Advancing the understanding of preoperative factors and patient experiences related to pain and physical function after total knee arthroplasty

Doctoral Thesis

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Contents

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Unni Olsen

Thesis at a glance

Paper	**Aim**	**Method**	**Main Findings**
Paper 1	Synthesize evidence on preoperative and intraoperative factors associated with pain 12 months after TKA (primary outcome), and 6 and 3 months after TKA (secondary outcomes)	Systematic review and meta-analysis	More pain catastrophizing, more symptomatic joints and more severe pain preoperatively were correlated with more pain one year after TKA, while more severe osteoarthritis preoperatively was correlated with less pain one year after TKA.
Paper 2	Synthesize evidence on preoperative and intraoperative factors associated with physical function 12 months after TKA (primary outcome), 6 and 3 months after TKA (secondary outcomes)	Systematic review and meta-analysis	Higher preoperative BMI was correlated with worse physical function after TKA, while better physical function and more severe osteoarthritis preoperatively were correlated with better physical function after TKA.
Paper 3	Examine the strength of associations between selected preoperative factors for pain and pain-related functional impairment five years after TKA	Prospective observational study	More severe pain, more painful sites, and more severe anxiety symptoms preoperatively were associated with moderate to severe pain five years after TKA, while more severe osteoarthritis was associated with less pain five years after surgery. More severe anxiety symptoms preoperatively were associated with moderate to severe pain-related functional impairment five years after surgery, while male sex was associated with less pain-related functional impairment five years after surgery.
Paper 4	Explore previous painful or stressful life experiences in patients reporting no improvement in pain one year after TKA	Explorative-descriptive qualitative study	Participants told stories of living with painful conditions and emotional challenges. Participants faced a dual burden from physical discomfort and psychological distress, leading them to endure substantial difficulties in years before TKA.

Summary in English

Introduction

Total knee arthroplasty (TKA) is a commonly performed surgical procedure in patients with osteoarthritis. Despite its success in reducing pain and improving physical function, a considerable proportion of patients continue to experience pain and functional limitations after surgery. The aim of this study was to advance the understanding on factors associated with short- and mid-term pain and physical function outcomes after TKA, and explore patients experiences before TKA.

Methods

In this thesis, three different methodological approaches were utilized. The first approach involved conducting systematic reviews and meta-analyses to synthesize current evidence on preoperative and intraoperative factors associated with pain and physical function 12 months after TKA (primary outcome) and 3 and 6 months after TKA (secondary outcomes). The second approach utilized a prospective observational study to analyze the association between pre-selected factors and pain and pain-related functional impairment five years after TKA. Lastly, a qualitative study was performed to explore stories of painful or stressful life experiences before TKA in a cohort of patients who reported no improvement in pain one year after TKA. To conduct these different studies, a range of statistical and analytical techniques were applied. Random-effect meta-analyses were used to synthesize evidence in the systematic reviews and meta-analyses. Multivariate logistic regression was used in the prospective observational study to estimate associations between preoperative factors and outcome, while a qualitative content analysis was applied in the qualitative study.

Results

The systematic review and meta-analysis of pain estimated correlations between preoperatively more pain catastrophizing, more symptomatic joints, and more pain one year after TKA, while more severe osteoarthritis preoperatively was correlated with less pain one year after TKA. The systematic review and meta-analysis of physical function estimated correlations between preoperatively higher preoperative BMI and worse physical function 12 months after TKA, while better physical function and more severe osteoarthritis preoperatively were correlated with better physical function 12 months after TKA. The analyses of secondary outcomes showed

similar results as the primary outcome, except that some factors did not meet the predetermined correlation threshold. Sensitivity analyses confirmed the results for both pain and physical function outcomes. In the prospective observational study, preoperative anxiety was associated with moderate to severe pain and pain-related functional impairment five years after TKA surgery. In addition, preoperative pain, number of painful sites, and osteoarthritis severity were associated with the pain outcome, while male sex was associated with pain-related functional impairment. In the qualitative study, two main themes emerged, painful years that reflected the burden of living with long-lasting pain and living with psychological distress. The participants reported severe and long-lasting knee pain, as well as pain in other locations or from comorbidities, and had experiences of psychologically stressful life events prior to surgery.

Conclusion

To improve patient outcomes after TKA, a comprehensive approach is needed that considers patient perspectives throughout the clinical decision-making process. The systematic reviews and meta-analyses identified factors associated with pain and physical function at different time points in the first year after TKA. Additionally, the prognostic observational study provided evidence on associations between preoperative factors and outcomes for pain and pain-related functional impairment five years after TKA. These factors should be included and evaluated in further prediction models to identify patients at higher risk of pain and impaired physical function after TKA. Patients' perspectives and experiences can provide useful information for guiding a future prediction model that captures the multidimensionality of patients' experiences.

Patient's descriptions of the burden of living with long-lasting pain, and the impact of psychological distress on aspects of daily living highlight the multifaceted and complex nature of preoperative pain. The findings from this thesis also emphasize the importance of effective preoperative pain management strategies and targeted interventions should be offered to patients with modifiable prognostic factors. Patient education, pain management, and guidance on physical activity should be offered to patients before TKA to improve outcomes and reduce the impact from osteoarthritis symptoms. Further research is needed to identify other possible factors that might be impacting TKA outcomes. In conclusion, the findings from this thesis contribute to a growing body of evidence on knowledge about TKA and provide a basis for future research to improve patient outcomes after TKA.

Summary in Norwegian

Innledning

Total kneartroplastikk (TKA) er en vanlig kirurgisk prosedyre for pasienter med kneartrose. Til tross for at de fleste pasienter opplever redusert smerte og forbedret fysisk funksjon etter operasjonen, er det en betydelig andel av pasientene som har vedvarende smerte og funksjonsbegrensninger. Målet med denne studien var å øke kunnskapen om faktorer knyttet til smerte og fysisk funksjon på kort og mellomlang sikt etter TKA, samt å utforske pasienters opplevelser før TKA.

Metode

I denne avhandlingen ble det tatt i bruk tre forskjellige metodiske tilnærminger. Den første tilnærmingen innebar å gjennomføre systematiske oversiktsstudier og meta-analyser for å oppsummere gjeldende forskning om preoperative og intraoperative faktorer knyttet til smerte og fysisk funksjon 12 måneder etter TKA (primært utfall) og 3 og 6 måneder etter TKA (sekundære utfall). I den andre tilnærmingen ble det benyttet en prospektiv observasjonsstudie for å analysere sammenhengen mellom forhåndsvalgte faktorer og smerte samt smerters påvirkning på fysisk funksjon fem år etter TKA. Til slutt ble det gjennomført en kvalitativ studie for å utforske tidligere smertefulle eller stressende livshendelser hos en gruppe pasienter som rapporterte ingen forbedring i smerte ett år etter TKA. Flere statistiske og analytiske metoder ble tatt i bruk for å gjennomføre studiene. Random-effekt meta-analyser ble anvendt for å oppsummere forskningen i de systematiske oversiktene og meta-analysene. Multivariat logistisk regresjon ble brukt i den prospektive observasjonsstudien for å estimere sammenhengen mellom preoperative faktorer og utfall, mens en kvalitativ innholdsanalyse ble brukt i den kvalitative studien.

Resultater

I den systematiske oversikten og metaanalysen av smerte ble det identifisert korrelasjoner mellom økt smertekatastrofisering, flere symptomatiske ledd og mer smerte før operasjonen, mens mer alvorlig grad av kneartrose før operasjonen var korrelert med mindre smerte ett år etter TKA. Den systematiske oversikten og metaanalysen av fysisk funksjon identifiserte korrelasjoner mellom høyere preoperativ BMI og dårligere fysisk funksjon 12 måneder etter TKA, mens bedre fysisk funksjon og mer alvorlig kneartrose før operasjonen var korrelert med

bedre fysisk funksjon 12 måneder etter TKA. Analyser av sekundære utfall ga lignende resultater som for primært utfall, men med unntak for noen få faktorer der korrelasjonen var svak. Sensitivitetsanalyser bekreftet resultatene for begge utfallene. I den prospektive observasjonsstudien var preoperativ angst assosiert med moderat til alvorlig smerte og smertebetinget funksjonsnedsettelse fem år etter TKA-operasjonen. I tillegg var preoperativ smerte, antall smertefulle områder og alvorlighetsgraden av kneartrose assosiert med mer smerte, mens mannlig kjønn var assosiert med mindre smertebetinget funksjonsnedsettelse. I den kvalitative studien fremkom to hovedtemaer: smertefulle år, som gjenspeilte byrden med å leve med langvarig smerte og byrden av å leve med psykisk stress. Deltakerne rapporterte om alvorlig og langvarig knesmerte, samt smerte i andre områder eller fra andre samsykdommer. Flere deltagere rapporterte å ha opplevd psykisk belastende livshendelser før operasjonen.

Konklusjon

For å forbedre pasientresultatene etter TKA er det behov for en helhetlig tilnærming som tar hensyn til pasientenes perspektiver gjennom hele den kliniske beslutningsprosessen. De systematiske oversiktene og metaanalysene identifiserte faktorer assosiert med smerte og fysisk funksjon på ulike tidspunkter det første året etter TKA. I den prospektive observasjonsstudien ble det identifisert assosiasjoner mellom preoperative faktorer og smerte og smertebetinget funksjon fem år etter TKA. Disse faktorene kan inkluderes og testes i fremtidige prediksjonsmodeller for å identifisere pasienter med økt risiko for smerte og redusert fysisk funksjon etter TKA. Pasientenes perspektiver og erfaringer kan gi nyttig informasjon for å veilede en fremtidig prediksjonsmodell som fanger opp flerdimensjonaliteten i pasientenes opplevelser.

List of papers

1. Olsen U, Lindberg MF, Rose C, Denison E, Gay C, Aamodt A, Brox JI, Skare Ø, Furnes o, Lee K, Lerdal A. Factors correlated with pain after total knee arthroplasty: a systematic review and meta-analysis. *PloS One.* 18(3):e0283446. [1]

2. Olsen U, Lindberg MF, Rose C, Denison E, Gay C, Aamodt A, Brox JI, Skare Ø, Furnes O, Lee K, Lerdal A. Factors Correlated With Physical Function 1 Year After Total Knee Arthroplasty in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2022;5:e2219636. [2]

3. Olsen U, Sellevold VB, Gay, CL, Aamodt A, Lerdal A, Småstuen M, Dihle A, Lindberg MF. Preoperative factors associated with pain and functional impairment five years after total knee arthroplasty. Submitted to *J. Orthop. Surg. Res*. [3]

4. Sellevold VB, Olsen U, Lindberg MF, Steindal S.A, Aamodt A, Lerdal A, Dihle A. "I am accustomed to something in my body causing pain": a qualitative study of knee replacement non-improvers' stories of previous painful and stressful experiences. *BMC Musculoskeletal Disorders*. 2023;24(1):305. doi:10.1186/s12891-023-06423-9. [4]

Abbreviations

ASA	American Society of Anesthesiologists Physical Status Classification
BMI	Body mass index
CI	Confidence interval
COREQ	Consolidated criteria for reporting qualitative research checklist
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICF	International Classification of Functioning, Disability and Health framework
IMMPACT	Initiative on Methods, Measurement, Pain Assessment in Clinical Trials
KOOS	Knee injury and Osteoarthritis Outcome Score
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NRS	Numeric Rating Scale
OR	Odds ratio
OMERACT	Outcome Measures in Rheumatology
PEOS	Population-Exposure-Outcome-Study
PICO	Population, Interventions, Comparators, and outcomes
PROM	Patient-Reported Outcome Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
QUIPS	Quality in Prognosis Studies
RCT	Randomized controlled trial
TJA	Total joint replacement (combination of hip- and knee replacement)
TKA	Total knee Arthroplasty
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1.0 Introduction

Total knee arthroplasty (TKA) is considered a clinically successful procedure for treating end-stage osteoarthritis in the knee that causes pain and immobility.[5-9] However, a considerable number of patients report severe pain (6-34%) and experience limitations in physical function (18-24%) a year or more after surgery.[10-14] This subset of patients with chronic post-surgical pain and impaired knee function is more likely to undergo revision surgery, which is costlier and yields inferior patient outcomes compared to primary TKA.[8,15-19]

To address variability in patient outcomes, there has been a growing emphasis on shared decision-making involving patients and surgeons, where patients are informed about the potential risks and benefits of surgery before reaching a shared decision to proceed.[8] Uncertainty persists regarding which factors are prognostic for pain and physical function outcomes, leaving surgeons to rely on their clinical judgment to select patients that might benefit from TKA surgery. However, a study demonstrated that surgeons' ability to predict which patients would improve and which would not was no better than chance.[20] This highlights the limitations of subjective patient selection, which can increase the risk of overutilizing the TKA procedure, and underscores the need to identify prognostic factors associated with poor outcomes after TKA.[21] Comprehensive knowledge is crucial for developing predictive models to identify patients at higher risk for chronic post-surgical pain and impaired physical function.[22-24]

Patients awaiting TKA surgery may have endured prolonged and debilitating knee pain, which can cause psychological distress.[25-27] However, there seems to be a lack of knowledge regarding the preoperative experiences of patients who later develop chronic post-surgical pain. This warrants further research to address potential areas of concern and provide personalized preoperative care that targets modifiable factors.

Advancing the understanding on factors and patients' experiences related to pain and physical function is essential for improving patient selection and developing personalized preoperative care. This thesis aims to develop knowledge about preoperative and intraoperative factors and patient experiences related to pain and physical function after TKA.

2.0 Background

2.1. Osteoarthritis of the knee

Osteoarthritis in the knee is a leading cause of disability due to pain and impaired mobility. Globally, an estimated 654 million people are affected by knee osteoarthritis, and this number is expected to rise due to aging populations and higher obesity rates. [28,29] Iincidence rates of knee osteoarthritis vary across regions and sociodemographic groups, with lower rates often being reported in more deprived areas. [28] Women are more likely than men to develop knee osteoarthritis, and its prevalence increases with age, particularly after 50 years. [28,30] Several factors, including genetics, joint malalignment, obesity, prior joint trauma, and occupational factors, such as frequent knee bending or squatting, have been suggested as important contributors to the progression of knee osteoarthritis. Osteoarthritis also increases the risk for cardiovascular diseases, falls, and shorter life span due to factors such as physical inactivity, use of anti-inflammatory medication, frailty, and disability. [31,32]

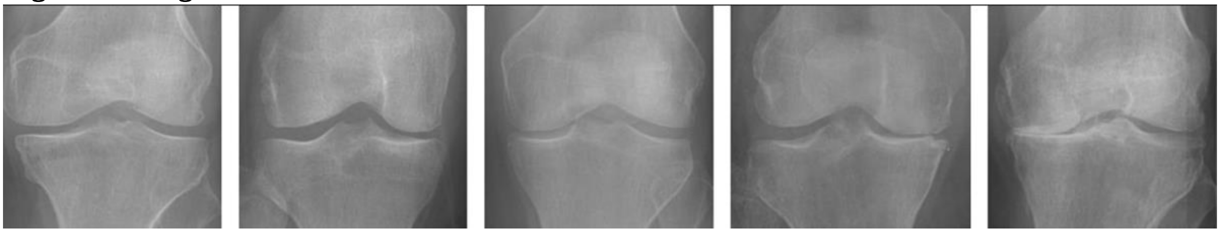
The cause of osteoarthritis is not completely understood, but it is believed to result from a combination of factors including changes in articular cartilage, bone, synovium, ligaments, adipose tissue, muscles, and meniscus, as well as alterations in the neurologic pathway important for pain processing. [33,34] The structural damage can cause symptoms such as pain, stiffness, swelling, limited joint mobility, and muscle weakness. [34-36] The progression of knee osteoarthritis varies among individuals and can vary over time. The diagnosis of knee osteoarthritis is determined by a combination of the patient’s history, physical examination, and radiographic assessment of the knee. The Kellgren Lawrence classification is the most widely used system to assess the severity of osteoarthritis in both clinical practice and research. [37,38] Although this classification system was intended for use in several joints it is mostly used to classify osteoarthritis in the knee. The Kellgren-Lawrence entails a 5-grade classification scheme, but numerous variations have been used since the original description in 1957. This classification system ranges from 0 to 4, and a description and radiographic images for each grade are provided in Table 1 and Figure 1, respectively. [29,35,37,39]

Table 1 Kellgren-Lawrence classification

Grade	Description
0	No joint space narrowing or reactive changes
1	Doubtful joint space narrowing and possible osteophytic lipping
2	Definite osteophytes and possible joint space narrowing
3	Moderate osteophytes, definite joint space narrowing, sclerosis, and possible bony deformity
4	Large osteophytes, marked joint space narrowing, severe sclerosis, and definite bone end deformity

The combination of more symptoms and altered radiographic findings is generally considered to represent a more severe disease burden. [40] Nonetheless, it is worth acknowledging the possibility of a discrepancy between symptom severity and radiographic findings. [30]

Figure 1 Kellgren Lawrence classification scale



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2.2. Treatment options for knee osteoarthritis

Currently, there is no effective treatment for regenerating damaged cartilage. [33,42] To postpone or avoid the need for TKA, several professional guidelines recommend non-surgical approaches as the first-line treatment before considering surgery. [43-47] Among these guidelines, The Osteoarthritis Research Society International (OARSI) has proposed a stepwise approach for the management of osteoarthritis. Their approach encompasses patient education, structured land-based exercise programs, weight management (when applicable), physical activity or exercise, physical therapy, and utilization of walking aids and orthoses, in combination with non-steroidal anti-inflammatory drugs (NSAIDs) or intraarticular glucocorticoids, if necessary. [46-48]

When pain and joint-related symptoms are no longer controllable with non-surgical approaches treatment modalities, surgical treatment should be considered. [30,34,42,47] Various surgical options exist for treating knee osteoarthritis, and the choice of treatment depends on the severity, extent, and location of the joint disease. [49] One option is a joint-preserving procedure that includes osteotomy that realigns the mechanical axis to unload the diseased knee joint.

Arthroscopic debridement and/or partial meniscectomy were previously widely used to treat mild or moderate knee osteoarthritis, but the use of such treatment has declined. [42] Other surgical options include joint-preserving procedures such as osteotomy that realigns the mechanical axis of the lower extremity to unload the diseased part knee joint. [50] Joint replacement is, however, the most common surgical procedure to treat advanced osteoarthritis of the knee. In unicompartmental knee arthroplasty one compartment is replaced, whereas in TKA, all articular surfaces are replaced with metal and polyethylene prosthetic components. [50] The main indications for knee replacement are severe pain that restricts activities, loss of physical function, radiographic changes, and failed conservative treatment. [8,9,50,51]

2.3. Total knee arthroplasty

Total knee arthroplasty (TKA) has improved greatly since its first procedure in 1890, overcoming challenges due to material and antiseptic conditions. [52,53] Advancements have resulted in more durable prostheses. [52,53] Recent technological innovations, including precise component placement and computer-aided navigation, have further improved outcomes. [52,54] In addition to these technological advancements, perioperative care has also undergone notable evolution. The implementation of fast-track surgery, multimodal pain control, decreased blood loss, and reduced operation time have all contributed to more successful TKA outcomes. [9,55] These developments have also led to shorter hospital stays, with most patients now discharged within zero to five days post-surgery. [9,52]

Despite these advances, there is still a need to understand the factors and experiences influencing pain and physical function outcomes after TKA, as some patients continue to report suboptimal results. [56-60] This thesis aims to contribute to the existing knowledge by investigating such associations and patient experiences, building on historical advancements in TKA. Furthermore, the increasing demand for TKA driven by the aging population, a growing number of younger patients undergoing the procedure, and the rising prevalence of obesity highlight the importance of furthering knowledge in this area. [5-8] In the USA, TKA is ranked among the most commonly performed inpatients procedures. [61] In Norway, the number of primary TKA reached a record high of 7,478 in 2021, which reflect the growing need for this procedure. [62] These trends underscore the importance of better understanding the factors and experiences that influence pain and physical function outcomes after TKA.

2.4 Pain and physical function

2.4.1 Pain

Pain theories have undergone notable historical development, transitioning from early models focused on physiological factors to more comprehensive approaches. The prominent gate control theory, introduced by Melzack and Wall, addressed the limitations of unidimensional models by incorporating both psychological and physiological factors. [63,64] Additionally, the neuromatrix theory expanded on this understanding by encompassing stress, physiological, and psychological factors in pain perception. [63,64]

As research revealed the high prevalence of patients experiencing severe pain after surgery, a more comprehensive approach to pain management became necessary. [65] In response to this, Macrae proposed a working definition with criteria for chronic post-surgical pain that incorporates the principles of the gate control and neuromatrix theories. [66,67] In 2014, Werner and Kongsgaard [68] introduced the term "persistent post-surgical pain" and refined the criteria for chronic post-surgical pain, aiming to distinguish pain that persists beyond the expected healing time. Subsequently, in 2019, the International Association for the Study of Pain (IASP) introduced criteria and a definition for chronic post-surgical pain, reflecting advancements in pain research. [69] The IASP states that chronic post-surgical pain is "pain that develops after a surgical procedure or a tissue injury and persists at least three months after surgery or tissue trauma." [70] As shown in Table 2, there is difference between the Werner et al. [68] criteria proposed for persistent post-surgical pain and the IASP criteria for chronic post-surgical pain. [69] The former includes pain duration of "at least three to six months" and its development as a continuation of acute post-surgery pain or after an asymptomatic period, while the criteria from the latter involves pain that persists beyond the healing process, at least three months after surgery." [71] In this thesis, the IASP 2019 definition of chronic post-surgical pain has been adapted, aligning with internationally recognized criteria set by the IASP. [69] This approach is useful for capturing the persistence of pain of three months or longer after TKA.

Table 2 Evolution of diagnostic criteria for chronic or persistent post-surgical pain

Diagnostic criteria 2002 Macrae et al[66]	Diagnostic criteria 2014 Werner and Kongsgaard[68]	Diagnostic criteria 2019 IASP[71]
Chronic post-surgical pain	Persistent post-surgical pain	Chronic post-surgical pain
The pain should be of at least 2 months duration.	The pain should be of at least 3–6 months' duration and significantly affect the patient's health related quality of life	Persists beyond the healing process, i.e., at least 3 months after surgery or tissue trauma
The possibility that the pain is continuing from a preexisting problem must be explored and exclusion attempted.	The pain is either a continuation of acute post-surgery pain or develops after an asymptomatic period.	
Other causes for the pain should have been excluded (i.e., continuing malignancy or chronic infection).	Other causes of the pain should be excluded, i.e., infection or continuing malignancy in cancer surgery.	Other causes of pain including infection, malignancy etc. need to be excluded
	The pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in the surgical field, or referred to a dermatome	Localized to the surgical field or area of injury, projected to the innervation territory of a nerve situated in this area, or referred to a dermatome

2.4.2 Physical function

Physical function is a crucial component of overall health and well-being, and in the context of patients undergoing TKA. Physical function can be conceptualized in various ways, and in this thesis physical function are conceptualized according to The International Classification of Functioning, Disability and Health framework (ICF) of the World Health Organization (WHO). [72-74] The ICF framework considers an individual's level of functioning to be a dynamic interaction between health-related factors, including body functions and structure, activities, and participation, and contextual factors, which all can be influenced by environment and personal factors. Body function and structure refer to the physiological and psychological functions of body systems and anatomical parts and involves for example the knee joint or muscle strength, while activity refers to task execution and involves patients' ability to perform activities related to daily living. Participation encompasses the individual's engagement in social, occupational, and recreational activities, while environmental factors include assessment of physical, social, and attitudinal environment factors, that can either facilitate or hinder rehabilitation While the ICF acknowledge personal factors, they are not explicitly described in the framework. [72,75] Addressing these various aspects of physical function can be considered crucial as it provides valuable insight into the functional capacities before and after TKA.

2.5 Pain and physical function outcomes after total knee arthroplasty

Despite the primary goal of total knee arthroplasty (TKA) being the alleviation of pain and restoration of physical function in patients with osteoarthritis, a significant number of individuals still experience residual pain and impaired physical function even after undergoing the procedure. [10-14] Most patients experience substantial improvement within the first three months after undergoing TKA, followed by a gradual improvement up to one year. However, the trajectory of recovery varies, and some patients may still experience worsening of pain and physical function after the initial improvement period. [12,13,57,76-80] Although several studies have studied the factors correlated with short-term outcomes after TKA, often yielding inconclusive results, the factors contributing to the trajectory of recovery beyond the one year have received less attention. It is thus possible that additional factors, distinct from those associated with short-term outcomes, influence longer-term outcomes. Within the scope of this thesis, short-term follow-up is the first postoperative year after TKA, while mid-term refers to five years after TKA. [81] By delineating specific time points, this thesis emphasizes the importance of considering both short-term and mid-term follow-up outcomes.

It is important to recognize that surgery itself is a risk factor for chronic post-surgical pain. It is suggested that the trauma caused by the surgical procedure triggers immune and inflammatory reactions within the tissues leading to the sensation of pain. [82,83] Also, pain can interfere and hinder a person's physical function, but pain and physical function are only modestly correlated. [84-86] Therefore, it is essential to investigate the relationship between previous painful and stressful experiences and TKA outcomes to better understand the factors contributing to chronic post-surgical pain and functional impairment after surgery.

2.6 Prognostic factors for pain and physical function after total knee arthroplasty

Identifying prognostic factors associated with poor pain and physical function outcomes is critical for improving patient care and optimizing the use of healthcare resources. In this thesis, prognostic factors are defined as any measure that is associated with a subsequent clinical outcome among people with a given health condition. [24,87] In the following sections an overview of the literature on factors associated with pain and physical function for short-term and mid-term outcome will be provided at the inception of the thesis (August 2017). These searches were updated to ensure the inclusion of the most recent studies and thus provide an up-to-date overview of the existing knowledge in the field. Furthermore, relevant studies' reference lists were examined to identify any other pertinent studies.

Searches were conducted in Medline (Ovid) and Embase (Ovid) for previous systematic reviews and meta-analyses on patients with OA scheduled for TKA and prognostic factors to pain and physical function at short term after TKA. This search revealed a considerable volume of research already existing on this topic. Systematic reviews and meta-analyses play a critical role in evidence-based medicine, guiding clinical decision-making and serving as valuable tools for synthesizing existing knowledge.[89] Systematic reviews and meta-analyses are traditionally regarded as to be on the top of the evidence-based hierarchy, followed by randomized controlled trials (RCTs) and cohort studies, with less robust designs positioned at lower stages.[88-90] However, it is important to acknowledge the unique contributions and value of different study designs within this framework.[23,91,92] The implementation of methodological standards including recommendations from the Cochrane Handbook for Systematic Reviews of Interventions,[93] Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA),[94,95] Quality in Prognosis Studies (QUIPS),[96] and Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)[97] has further enhanced the rigor and reliability of these studies. However, several systematic reviews and meta-analyses, were conducted prior to the implementation of these standards or without adhering to rigorous methods, and therefore do not meet the current recommended criteria.[98-109] Some of these studies analyzed pooled data from different follow-up periods, which might lead to imprecise and misleading conclusions.[56,100,101,103,105,106,110] Additionally, some studies combined results from prospective and retrospective studies, which can introduce recall bias and produce inaccurate results.[102,105,109,110] Interestingly, the results from these previous studies were inconsistent and there was a lack of agreement between some of the factors studied. The limitations and uncertainties in previous studies emphasized the need for additional studies to investigate prognostic factors to pain and physical function after TKA.

The literature search conducted to assess prior studies investigating factors associated with pain and physical function five years following TKA, was carried out on the Medline (Ovid) database with a combination of key words and text words, arthroplasty, replacement/ or arthroplasty, replacement, knee, activities of daily living, mobility limitation, chronic pain, persistent pain, persistent postsurgical pain, prognosis, predictor, association, and correlation. As shown in Table 3, this strategy yielded six studies that were published between 2007 and 2017. [12,111-115] Four of these were prospective observational studies, [111-113,115] one was a retrospective observational study, [116] and two were register studies. [12,114] Samples size ranged from 83[115] to 7139. [114] The majority of studies investigated factors associated with both the pain and physical function, [12,111-115] with the exception of one study that examined solely factors associated with pain. [114]

None of the studies reported a correlation between preoperative pain and pain five years after TKA. [12,111,112,114] For other factors, the findings were inconclusive. More comorbidities were associated with more severe pain in some studies, [12,112,114] but not in all. [111] Furthermore, the influence of mental health on pain outcomes exhibited varying outcomes, with two studies reported that worse mental health was associated with more severe pain at five years, [12,112] while another study did not find such an association. [111] One study found that mental health, depression, and anxiety were associated with higher odds of more severe knee pain, but no such associations were identified in others. [112,113,115] Similarly, age yielded conflicting results, as two studies reported worse pain outcomes with advancing age, [111,112] while another study did not report any significant associations. [12] Pain catastrophizing was studied once, but no associations were identified. [113]

Worse preoperative physical function was associated with worse preoperative function five years after TKA in two studies, [12,112] but these results were inconsistent with those from another. [111] There were also discrepancies in study results for the factors of worse mental health, [112,115] older age, [12,112] and comorbidities, [12,112,114] where some studies reported associations with worse physical function, while others did not. [111,113] Obesity was associated with worse physical function in the two studies examining it. [12,112]

Interpretation of the results from some of these studies may be limited due to several methodological constraints. For instance, one study had a small sample size of fewer than one hundred patients. Moreover, this study included patients who underwent a subsequent TKA, resulting in the inclusion of patients twice. Furthermore, this study excluded patients with symptoms of depression, potentially affecting the generalizability of the findings. [115] Another study had a relatively low follow-up rate of 29% at five years after TKA, raising concerns about the representativeness of the sample and potential attrition bias. [113] Lastly, one study utilized register data, where the aim and data were likely determined and collected retrospectively. [115] This raises potential concerns about potential biases associated with retrospective data collection methods. These methodological limitations and inconsistencies in prior research findings underscore the need for further research to improve patient care and optimize healthcare resources to enhance the knowledge on prognostic factors for pain and physical function five years after TKA. A systematic review on trajectories and predictor groups revealed one study that investigated factors associated with the outcome. [12,117] This study was previously identified during our primary search and supported our findings, emphasizing the limited number of studies specifically addressing this aspect within the given context.

Table 3. Summary of studies that examined factors associated with pain and physical function five years after TKA

Authors, years	Aim	Sample, (N)	Design, statistics	Prognostic factor	Outcome	Findings
Brander, 2007[115]	Examine influence of psychosocial factors on 5-year TKA outcomes	83	Prospective cohort. Linear multivariate analysis	Knee pain, function, depression, anxiety	Pain, physical function	Lower function: preoperative pain and depression Pain: No association identified
Dowsey, 2015[12]	Determine risk factors for 1- and 5-year pain and function outcomes	689	Register study. Latent class analysis. Logistic regression	Sex, mental health, physical function, comorbidity, computer navigation, patellar resurfacing, prosthesis type, contralateral TKA, knee pain, knee function, osteoarthritis severity, obesity (function), smoking status, etiology	Pain, physical function	Moderate pain trajectory class: mental health, physical function, comorbidities, absence computer-navigation. Poor function trajectory class: female sex, older age, physical function, obesity, comorbidities.
Jiang, 2017[112]	Identify predictors of pain and function outcomes after TKA.	2252	Prospective cohort. Multi-level, mixed-effects linear regression	Sex, age, marital status, BMI, social deprivation, health status, pain, physical function, mental health, ASA status, prior knee surgery, comorbidities,	Pain, physical function	Worse pain: Age ≥80, males ≥80, BMI >35, preoperative pain, SF-12 MCS ≥50, comorbidities Worse physical function: Age ≥80, BMI >35, preoperative OKS function score, SF-12 MCS ≥50, worse ASA grade, comorbidities
Nils-dottir 2009[111]	Identify preoperative characteristics predicting 5-year TKA outcomes	102	Prospective cohort. Analysis of covariance	Age, gender, comorbid conditions, physical function, bodily pain, mental health	Pain, physical function	More postoperative pain: older age Physical function: No predictors were identified.
Singh 2013[114]	Examine associations between comorbidities and 5-year TKA outcomes	7139	Register study. Logistic regression	Heart disease, peripheral vascular disease, renal disease, chronic obstructive pulmonary disease, diabetes, anxiety, depression, CTD	Pain	Moderate to severe pain: heart disease, depression, and anxiety
Wylde, 2017[113]	Identify preoperative psychosocial risk factors for 5-year TKA outcomes	266	Prospective cohort. Multiple linear regression	Preoperative depression, anxiety, catastrophizing, pain self-efficacy, social support	Pain. Physical function	No psychosocial factors were associated with any of the outcome measures at 5 years postoperatively.

Abbreviations: ASA, American Society of Anesthesiologists Physical Status Classification; BMI, body mass index; KSS, Knee Society Score; OKS, Oxford Knee Society Score; SF-12, The Short Form Health Survey

2.7 Patient experiences before total knee arthroplasty

In the field of total knee arthroplasty (TKA), understanding patients' experiences leading up to TKA is important for gaining insight into their preoperative trajectory and identifying potential areas for enhancing patient care. Therefore, we conducted a comprehensive search using a combination of keywords and search terms: arthroplasty, replacement/ or arthroplasty, replacement, knee, experience or perception, attitude, view, incident, occurrence, event, narratives, stories, chronic or persistent pain. This search covered the period from 1946 through January 2019 and was updated in May 2023. The reference lists of relevant studies were scrutinized to ensure comprehensive coverage of the literature.

Our search strategy yielded three potentially relevant studies: Leov et al.(2017), [26] Demierre et al.(2011) [118] and a systematic review by Wallis et. al (2019). [27] Although the identified studies did exclusively target TKA patients, their findings may still provide some insights into the preoperative experiences of individuals undergoing orthopedic surgery. The study by Leov et al., [26] aimed to investigate participants' experiences with pain through interpretive phenomenological analysis, involving 20 patients with osteoarthritis undergoing total joint arthroplasty. In this study pain was conceptualized as debilitating and relentless, perceiving it as a purely physical phenomenon. [26] Similarly, Demierre et al.'s study[118] conducted a thematic discourse analysis to explore the experiences of patients with hip, shoulder, and knee osteoarthritis before surgery. The findings highlighted the impact of living with pain on quality of life and its functional and social consequences. Wallis et al. [27] conducted a systematic review of 21 qualitative studies that focused on the experiences of individuals living with knee osteoarthritis. The authors described that pain and to manage the pain predominates the lived experience before surgery that impacted on emotions, activity, participation, and social activities. [27] None of these studies have explored experiences in patients that do not improve in pain after TKA. To address this knowledge gap, further research is needed to explore the perspectives of these patients. Such research could potentially enhance patient care by identifying areas for improvement and addressing the specific needs of this subgroup.

2.8 The biopsychosocial model

The biopsychosocial model are important concepts in healthcare, especially when it comes to understanding pain and physical function. Previous studies investigating the causes of osteoarthritis (OA) have been criticized for their biomedical perspective, focusing mainly on physiological variables contributing to articular cartilage degeneration. [119]

The biomedical model was the leading paradigm, originating from the ancient Greeks and later adopted by Descartes, and viewed the mind and body as separate entities, resulting in a dualistic view of somatogenic or psychogenic symptoms. [63] The biomedical view assumes that pain is caused by a specific disease or pathology, and thus medical interventions aim to resolve or cure the pathology. [63] This reflects a Cartesian mind-body dualistic view, with either somatogenic or psychogenic symptoms. [63] However, the inadequacy of the dualistic biomedical model that conceptualized the mind and body as separate entities led to the development of the biopsychosocial model proposed by Engel. [120] In the biopsychosocial model, health and disease are recognized as complex phenomena influenced by a range of biological, psychological, and social factors. [63,120-122] The model distinguishes between disease and illness, with disease referring to objective biological events, such as e.g. articular cartilage degeneration in the knee, that impact the body's functions. Illness refers to the subjective experience of symptoms or disability, which can be influenced by physical, behavioral, and psychosocial factors. [63,120,123,124] The biopsychosocial model is thus relevant in this thesis, as in order to understand pain, not only physical aspects but also psychosocial factors need to be considered.

The integration of the biopsychosocial model and evidence-based medicine has profoundly impacted the understanding of pain and physical function in TKA. However, there is still a gap in knowledge that require attention. To address these gaps, it is crucial to adapt to the biopsychosocial model to investigate this patient population and their outcomes.

2.9. Current knowledge gap

The demand for TKA is projected to rise due to the aging population, patients undergoing TKA at a younger age, and rising obesity rates. However, a significant proportion of patients continue to have residual pain and impaired physical function after TKA. Previous studies report significant inconsistency in defining prognostic factors associated with poor pain and physical function outcomes for short- and medium-term outcomes. Additionally, there is a notable gap in understanding the preoperative experiences of patients who later develop chronic post-surgical pain.

There is a need for the development of effective predictive models for identifying patients at higher risk for poor outcome after TKA, and to gain a deeper understanding of patients experiences prior to surgery, which can potentially affect long term outcomes. Therefore, further research is essential to advance the understanding of the factors associated with pain and physical function after TKA, as well as to explore patient` preoperative experiences, aiming to improve patients' outcomes and optimize preoperative care.

3.0 Aims of the study

The overall aim is to advance the understanding of preoperative and intraoperative factors and patients experiences related to pain and physical function after TKA.

Specific aims

Paper 1

To synthesize current evidence on preoperative and intraoperative factors associated with pain 12 months after TKA (primary outcome) and 3 and 6 months after TKA (secondary outcomes).

Paper 2

To synthesize evidence on preoperative and intraoperative factors associated with physical function 12 months after TKA (primary outcome) and 3 and 6 months after TKA (secondary outcomes).

Paper 3

To examine associations between preoperative selected factors and pain and pain-related functional impairment five years after TKA in patients with knee osteoarthritis.

Paper 4

To explore stories of previous painful or stressful experiences in life in a cohort of patients who reported no improvement in pain one year after total knee arthroplasty.

4.0 Methods

In this thesis, different methodological approaches were used to obtain a more advanced understanding of preoperative factors and patient experiences related to pain and physical function after total knee arthroplasty. The application of various methodologies was considered useful for the purpose of this thesis, as different methodologies provide diverse types of knowledge that can contribute to a more comprehensive and nuanced understanding of the research topic. [125,126]

4.1 Study design and procedures

Papers 1 and 2 conducted systematic reviews and meta-analyses to synthesize evidence from primary studies. [1,2] In Paper 3, a prospective observational study design was used to examine the associations between preoperative factors and pain and pain-related functional impairment five years after TKA. [3] Paper 4 employed an exploratory-descriptive qualitative design to explore the stories of patients who reported no improvement in pain one year after TKA regarding their previous painful or stressful life experiences. [4] Table 4 provides an overview of the thesis methods, data collection period, and analyses.

Table 4 Overview of methods, data collection and analyses

Paper	Study methods	Outcomes & aims	Data collected	Analysis
1	Systematic review & meta-analysis	Pain at 12 months (primary). Pain at 3 and 6 months (secondary)	2018-2022	Random-effect meta-analysis
2	Systematic review & meta-analysis	Physical function at 12 months (primary). Physical function at 3 and 6 months (secondary)	2018-2023	Random-effect meta-analysis
3	Prospective observational design	Pain five years (primary) Pain-related functional impairment (secondary)	2012-2017	Logistic regression
4	Explorative-descriptive qualitative design	Explore stories of previous painful or stressful life experiences in a cohort of patients who reported no improvement in pain one year after total knee arthroplasty.	2018-2020	Qualitative content analysis

4.1.1 Systematic reviews and meta-analyses (Papers 1 and 2)

To address reliable evidence on prognostic factors for pain and physical function outcomes, we conducted a systematic review and meta-analysis of each outcome. [1,2] A systematic review and meta-analysis cannot be considered as a design, but rather a research synthesis tool used for collating evidence based on pre-specified eligibility criteria that includes the appropriate study design to address the research question.[127,128] Systematic review and meta-analysis are recommended for identifying knowledge gaps before primary studies are conducted.[128] Including observational studies examining prognostic factors in systematic reviews present distinct challenges compared to randomized controlled trials (RCTs).[23,87,92] Thus, to ensure the validity of study findings, we followed rigorous methods outlined in the Cochrane Handbook,[128-130] starting with careful study planning.[128] To promote transparency, the methods were described in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018079069), a peer-reviewed protocol,[95] and in a preprint.[131] We conducted the study and reported the findings according to the PRISMA guidelines.[132-134] One of the key features of a systematic review and meta-analysis is the formulation of a well-defined review question.[128] In our systematic reviews and meta-analyses, we posed the research question: What preoperative and intraoperative factors are correlated with chronic pain or with impaired physical function following TKA? When these standards are met, systematic review and meta-analysis are considered powerful tools for examining and synthesizing available evidence.[127,130]

4.1.2 Prospective observational study (Paper 3)

If there is uncertainty about the potential factors associated with an outcome, such as for prognostic factors for pain and physical function after TKA, prospective observational studies are recommended to evaluate the strength of association between prognostic factors and the outcome.[23,87] Within this thesis context, this involves evaluate associations between preoperative and intraoperative factors and pain and physical function after TKA.[23,87] Reporting of this analysis is in accordance with the "STrengthening the Reporting of OBservational studies in Epidemiology" (STROBE) initiative and checklist.[135]

4.1.3 Explorative-descriptive qualitative study (Paper 4)

To explore patients' stories of previous painful or stressful life experiences, an exploratory-descriptive qualitative approach was utilized.[136] This design is considered appropriate when limited information is available on a phenomenon, such as in this study about patients with chronic post-surgical pain and their prior experiences of pain or stressful life events.[136] The reporting of this paper adheres to the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist guidelines.[137]

4.2 Sample and setting

4.2.1 Systematic reviews and meta-analyses (Papers 1 and 2)

Before conducting a systematic review and meta-analysis, careful consideration should be given to determining the appropriate sample to include. This determination is primarily based on the review question and the aim. [128] Cochrane recommends using the PICO framework to predetermine clear review questions with consideration of the PICO elements: the Population, Intervention, Comparators, and Outcomes. However, this strategy was modified in our study as our aim was not to examine the effect of interventions. Thus, we applied a Population-Exposure-Outcome-Study (PEOS) design strategy, with patients 18 years or older with osteoarthritis and scheduled for primary TKA as the population (P), preoperative or intraoperative factors as the exposures (E), pain and function assessed at 12, 6 and 3 months after TKA as outcomes (O), and prospective observational studies or the randomization arm of RCTs as the study design (S).

4.2.2 Prospective observational study (Paper 3)

Patients were consecutively enrolled in a longitudinal observational study on pain, physical function, and quality of life, completed in 2014. [11,77] The current study is a five-year follow-up from the original study. Data were collected between 2012 to 2017. Patients were included if they were scheduled for primary unilateral TKA for osteoarthritis at Lovisenberg Diaconal Hospital, aged 18 or older, and able to read, write, and understand Norwegian. Exclusion criteria included unicompartmental knee arthroplasty, revision surgery, or dementia diagnosis. [11,77] Patients who participated in this initial study and met the inclusion criteria were invited to participate in the prospective observational follow-up study at five years after TKA. Consenting patients signed a new consent form. [3]

4.2.3 Explorative-descriptive qualitative study (Paper 4)

Participants included in the qualitative study, Paper 4, [4] were included from the longitudinal observational study described in Paper 3. This follow-up qualitative study employed a purposive sampling to recruit patients from a specific subgroup, which consisted of 45 patients (22%) who reported no improvement in pain with walking one year after TKA from a total sample of 202 in the inception study. The same eligibility criteria as described for Paper 3 were applied, with the addition that patients were considered eligible if they participated in their five-year follow-up appointment and had less than a two-hour drive from Lovisenberg Diaconal Hospital. [4] In qualitative research, information power, or the amount of relevant information held by each participant, is more important to consider than sample size. [125,126,138] Therefore, we used Malterud et al.'s theoretical model of information power to determine the appropriate sample size for this study. [138]

4.3 Outcomes

4.3.1 Systematic reviews and meta-analyses (Papers 1 and 2)

As pain and physical function are moderately associated, [95] two distinct outcomes, pain, and physical function, were outlined in the protocol for this study. [95] The primary outcome was pain or physical function 12 months after TKA. The secondary outcomes were pain or physical function 3 and 6 months after TKA. [1,2]

4.3.2 Prospective observational study (Paper 3)

Pain severity was the primary outcome and pain-related functional impairment was the secondary outcome five years after TKA. Pain severity and pain-related functional impairment outcomes were measured by using the Brief Pain Inventory (BPI).

4.3.3 Explorative-descriptive qualitative study (Paper 4)

No outcome was set for the qualitative study, but the aim of this study was to deepen the understanding and explore stories of previous painful or stressful life experiences in patients with osteoarthritis who reported no improvement in pain one year after total knee arthroplasty.

4.4 Measures of prognostic factors and outcomes (Paper 3)

We used the Brief Pain Inventory (BPI) to measure the primary outcome, pain severity, and the secondary outcome, pain-related functional impairment. [139] Pain severity was assessed using four BPI items, pain right now, and average, worst, and least pain over the past 24 hours. Pain-related functional impairment was assessed using the pain-related interference with function index, which included seven items of interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. The BPI employs a numeric rating scale (NRS) ranging from 0 to 10, where higher scores indicate more severe pain or greater interference with function. [139] The mean of the seven interference items was calculated following the BPI manual, with at least four items answered. [139] We utilized the established cut-points for average pain ratings in TKA patients, none/mild (0-3), moderate (4-6), and severe (7-10). [140,141]

As cut-points for the BPI pain interference index in TKA patients are not yet established, we adopted cut-points from a study involving patients with low back pain: none/mild (0-3), moderate (4-5), and severe (6-10), [142] which were dichotomized into none to mild (0-3) and moderate to severe interference with function (4-10). The BPI has been translated to Norwegian and exhibits acceptable psychometric properties when assessing pain in patients with osteoarthritis awaiting total hip or knee arthroplasty. [143,144]

The selection of variables for the logistic regression model was guided by prior evidence from systematic reviews and meta-analyses, including our own research. [1,2,98,145,146] This approach is recommended in the literature, and ensures that the selection of factors for a model is based on well-justified reasoning. [147,148] The BPI was used preoperatively to assess average pain levels and identify the number of pain sites using the BPI body diagram. The BPI interference index was also employed to measure preoperative pain-related functional impairment. The severity of osteoarthritis was evaluated using radiographs and the Kellgren-Lawrence (K-L) classification, a grading system ranging from 0-4, where higher grades indicate more severe osteoarthritis. [37] Scores were dichotomized in accordance with scores used in a previous study, with mild to moderate (K-L grades 2 or 3) or severe osteoarthritis (K-L grade 4). [39] Symptoms of anxiety and depression were evaluated by using the Hospital Anxiety and Depression Scale (HADS), which previously demonstrated excellent psychometric properties in a large Norwegian population study. [149] The HADS consists of seven items each for assessing anxiety and depression symptoms, with subscale scores ranging from 0-21, with higher scores indicating more symptoms. [150] In this study, at cut-off score ≥8 indicated clinically significant symptoms. Clinical data were collected from medical records, including body mass index (BMI), comorbidities, American Society of Anesthesiologists (ASA) physical status classification, medication, and osteoarthritis severity. Comorbidities were categorized into four groups (0, 1, 2, ≥3), and BMI was calculated as kg/m2. Sociodemographic information was gathered using the Socio Now Pop questionnaire.

4.5 Data collection

4.5.1 Systematic reviews and meta-analysis (Papers 1 and 2)

The search strategy was developed collaboratively with experienced research team members and medical librarians. Following Cochrane Handbook recommendations, one research librarian designed the search strategy, which was then reviewed by the second librarian and the first author for accuracy. [128] The search covered the period from January 2000 to October 2021 and was updated in February 2023 to ensure relevance. Multiple databases, including Medline (Ovid), Embase (Ovid), CINAHL (EBSCO), Cochrane Library and Physiotherapy Evidence Database (PeDRO), were comprehensively searched using a combination of text words and subject headings, described in our protocol and papers. [1,2,95] Language limitations were not applied to encompass relevant studies, which is in accordance with Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards. [151] To account for the possibility of changes in treatment modalities for TKA, the search was restricted to studies published after year 2000. The software program used to manage references was EndNote V.X8 (Clarivate Analytics, Philadelphia, Pennsylvania, USA).

Following Cochrane guidelines, two authors conducted independent and blinded screening of title, abstract, and full text to select relevant studies. [95,128] Disagreements were resolved through consensus discussions and involvement of a systematic review and meta-analysis expert when needed. Studies meeting the inclusion criteria were thoroughly assessed during full-text assessment. Data extraction was conducted using a pilot-tested standardized form based on Cochrane recommendations. [128] One author entered the data and another verified the extracted items against the original article. For data-extraction of statistical data, the same procedure was performed, but in addition, data were controlled by the statistician. Studies that failed to meet one or more of the inclusion criteria were excluded from the review. Transparency was highlighted, and reasons for exclusion are provided in the supplementary material for the Paper 1[1] and Paper 2. [2]

4.5.2 Prospective observational study (Paper 3)

Data were collected between October 2012 and December 2017 at a high-volume orthopedic clinic in Norway. Eligible patients were approached by a nurse at the ward on the day of admission and given written information about the study. After reviewing the details of the study, patients signed the written informed consent and completed a baseline questionnaire that included demographic, clinical, symptom-related, and psychological characteristics, as well as preoperative pain and pain-related interference with physical function. Most patients were given the opportunity to complete the questionnaires on iPads on-site at the hospital at their five-year appointment, but some were given the option to complete the questionnaires on paper at their homes. These were then returned to the researchers using pre-paid sealed envelopes. If a questionnaire was not received in due time, the researchers would send a reminder, either via telephone or mail, to encourage its return.

4.5.3 Explorative-descriptive qualitative study (Paper 4)

Data for this study was collected between February 2018 and August 2020. Data was collected through qualitative semi-structured individual interviews, which might facilitate a deeper understanding of each patient's experiences, allowing them to share their stories without interruption, while also enabling the interviewer to ask follow-up questions as necessary. [125,136]

The first three interviews were performed by the senior author experienced in qualitative interview technique, while the first author who had limited experience with qualitative interview techniques, observed. Subsequently, the first author conducted interviews alongside the senior researcher, and for the 16 last interviews, the first author conducted all interviews independently. Participants could choose the location of the interview, either at the hospital or their home, and each interview lasted between 45 and 70 minutes. A semi-structured interview guide, based on previous research on factors associated with chronic post-surgical pain[152,153] and key topics from the longitudinal study, [154,155] was developed to facilitate reflection and conversation. [125] The guide included questions about the history of knee pain before the operation and important life events, such as what patients themselves considered to be important, but also on past physically or psychologically painful experiences. Follow-up questions allowed participants to reflect on issues they perceived as important. [125] The interview guide was pilot tested with three patients, and no modifications were needed. All interviews were audio-recorded.

4.6 Analysis

4.6.1 Systematic reviews and meta-analyses (Papers 1 and 2)

To be included, studies had to report associations as odds ratios, risk ratios, linear model coefficients, or correlations measured on discrete or continuous scales. Correlation coefficients were meta-analyzed on the arctangent scale, thereafter back-transformed to the correlation scale. [156] We combined and synthesized results from eligible studies at three, six-, and twelve months post-surgery, in line with descriptions in our pre-specified protocol. [95] We anticipated between-study heterogeneity, distinct studies that all estimated correlation for a given risk factor may have defined and hence estimated slightly different estimands by virtue of defining the risk factor in different ways. We therefore used random-effects meta-analysis to estimate mean (average) correlations between risk factors and a given outcome. We used a multivariate meta-analysis model to account for any correlation between the mean correlations.

We quantified heterogeneity using I^2 statistics, which quantify the percentage of variability in effect estimates that can be attributed to heterogeneity between different studies. [128,157] We computed a P score (cf. p-value) for each risk factor[128] to assess the strength of evidence that the risk factor is superior to all other risk factors (i.e., that the true mean correlation has the largest magnitude). [158] Protocol deviations are noted below, in the Discussion and in the Methods in the Supplements to Paper 1 and 2. [1,2] The study explored how estimates may depend on the choice of model and performed sensitivity analyses on pain at twelve months, excluding studies judged to have high risk of bias. The analysis was performed using Stata 16 (StataCorp), and mean correlations with 95% confidence intervals were reported. While hypothesis testing was not predefined, 2-sided p-values were reported for completeness. [1,2]

We assessed risk of bias using the Quality in Prognosis Studies (QUIPS) tool, which is the recommended tool for evaluating bias in prognostic factors studies. [96,159] QUIPS assesses various domains including study participation, attrition, prognostic factor measurement, statistical analysis and reporting, confounding, and outcome measurement. This was particularly important as prognostic factor studies are acknowledged to have high risk of bias due to poor design, conduct and analyses. [91,128] Additionally, we followed the Cochrane recommendation and employed the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) to assess certainty of evidence for each prognostic factor. [160-162] Evidence for each factor was evaluated by the five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. By evaluating these domains, an overall assessment was made to determine the quality of evidence, which could be classified as high, moderate, low, or very low. [128] This approach allowed us to systematically evaluate the strength of the evidence supporting each prognostic factor.

4.6.2 Prospective observational study (Paper 3)

The study's sample characteristics were calculated using means with standard deviations (SD) for continuous variables and frequencies and proportions for categorical variables. We assessed missing data and compared baseline characteristics between those who were lost to follow-up and those who remained in the study at five years. Univariate logistic regression models were used to investigate the associations between each pre-selected factor and the dependent variables. Age, sex, and comorbidity were also evaluated in univariate models. Factors with $p<0.05$ were included in the multivariate logistic regression model, which followed a backward elimination procedure to remove factors with a p-value ≥ 0.10 in each step. Model assumptions, linearity between independent variables and the log odds of the dependent variable were assessed. The dependent variables, pain, and pain interference with function, were dichotomized into NRS <4 or ≥4, while the independent variables were analyzed as continuous or dichotomous. Sensitivity analyses were conducted after the removal of extreme outliers.

There is no consensus on the ideal sample size for achieving sufficient statistical power in logistic regression. [125,147,148] We adhered to the recommendations described in Tabachnick and Fidell with minimum sample size of 50 participants, and to add at least 8 times the number of predictors to ensure adequate statistical power. [148] Using this formula (50 + [8 x10]), we calculated that we could include up to 10 factors for the analysis for both pain and physical function. IBM SPSS Statistics version 28 was used for data analysis.

4.6.3 Explorative-descriptive qualitative study (Paper 4)

In this study we followed the strategy for qualitative inductive content analysis suggested by Graneheim et al. [163,164] The interviews were transcribed verbatim by a professional transcriber and then verified by one author against the recordings. The analysis was conducted by two authors, who independently read all the transcripts to identify meaning units related to patients' previous painful or stressful life experiences. [125,164,165] These meaning units were condensed and coded closely reflecting the text[165] and patterns and similarities were identified and sorted into categories. The categories were then organized into themes for re-contextualization, [165] with input and critical questions provided by co-authors. All authors engaged in the discussion to ensure that all relevant data were included in the analysis. [164] There was agreement among authors on final themes. We recruited a diverse sample, consisting of both sexes and individuals ranging from 48-84 years at the time of surgery, to enhance the study's credibility. The interview guide used during data collection allowed participants to confidently tell stories about their prior experiences and enabled participants to speak freely on topics particularly important for them. Follow-up questions were asked during interviews to ensure accuracy and validate participants' statements. Co-authors discussed preconceptions to enhance reflexivity, and researcher triangulation was used to facilitate different perspectives in the analysis. Detailed descriptions and relevant quotes were included to enhance transferability of study findings.

4.7 Ethics

This study was planned and conducted according to the principles of the Helsinki declaration, the Norwegian act on medical and health research. [166] The study was approved by the Regional Medical Research Ethics Committee of Health South-East of Norway (#2011/1755) and the data protection officer at Lovisenberg Diaconal Hospital. Informed written consent was obtained from all patients. Data was stored on secured servers at Lovisenberg Diaconal Hospital.

5.0 Main findings

5.1 Systematic reviews and meta-analyses (Papers 1 and 2)

The primary search for studies identified 12 052 primary studies that investigated pain or physical function after TKA at three or six or twelve months in patients with osteoarthritis. [167-186] However, there was a need to update the search for the pain article, which resulted in 1 588 additional studies for the systematic review and meta-analysis on pain.

5.1.1 Systematic review and meta-analysis on pain (Paper 1)

The systematic review and meta-analysis on pain are based on literature searches that identified 13 640 studies, of which 29 were included with a total sample of 10 360 patients. [167,168,170,171,173-176,179,181,184,186-203] Among these, 25 studies were included for quantitative meta-analyses. [167,168,170,171,173-176,179,181,186,188-192,194-199,201-203] The studies varied in sample size from 26[193] to 5 309, [176] mean age from 63[190] to 73[196] years and the percentage of females ranged from 49%[181] to 95%.[190] The majority of the studies were conducted in European countries, [171,173-175,179,182,183,187,189-196,198] and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was the most commonly used instrument to measure pain. [168,170,173,175,179,181,186,188,197,198]

For the primary outcome of pain at twelve months, 15 studies, with a total of 3 241 participants, reported estimates for 34 factors associated with pain twelve months after TKA. [167,168,170,171,173,187-196] The two most frequently reported factors were preoperative pain, which was described in nine studies, [167,170,173,188-192,195] and mental health (consisting of anxiety, depression, psychological distress), which was reported in six studies. [167,168,170,171,173,189] Synthesized findings are shown in Tables 5a and 5b. [2] Preoperatively, higher levels of pain catastrophizing, symptomatic joints, and pain were correlated with more pain after TKA, while more severe osteoarthritis was correlated with less pain. The strongest mean correlation estimate was for the factor pain catastrophizing and more pain one year after TKA. In the sensitivity analysis the estimated correlation coefficients remained approximately similar for all factors. However, the estimated mean correlation for more temporal summation was obscured due to the removal of high-risk studies in the sensitivity analysis. For the secondary outcome of pain six months after TKA, 11 studies examining 34 potential factors were included with a total of 6 078 participants. [174-176,181,186,187,198-202] More preoperative pain was correlated with more postoperative pain, while better preoperative mental health was correlated with less postoperative pain. For the other secondary outcome, pain three months after TKA, five studies that included 1 786 patients and reported estimates 14 factors were included. In the multivariate meta-analysis, more preoperative pain was correlated with more postoperative pain. None of the intraoperative factors were included in multivariate meta-analysis, due to the fact that they were studied once.

Table 5a Preoperative factors correlated with more pain at 12, 6 and 3 months after TKA

Factors	12 months	6 months	3 months
	Mean correlation, CI 95%	Mean correlation, CI 95%	Mean correlation, CI 95%
More pain catastrophizing	0.36, 95% CI: 0.24 to 0.47, moderate certainty evidence. [170,188,196]	Did not reach correlation treshold	Factor not studied
More symptomatic joints	0.15, 95% CI: 0.08 to 0.23, Moderate certainty evidence. [173,188 170,188,196]	Did not reach correlation treshold	Factor studied once
More preoperative pain	0.13, 95% CI: 0.06 to 0.19, very low certainty evidence. [167,170,173,188-192,195]	0.20, 95% CI: 0.12 to 0.28, low certainty evidence. [175,176,198,199,202]	0.27, 95% CI: 0.13 to 0.39, low certainty evidence. [179,197,203]

Table 5b Preoperative factors correlated with less pain at 12 and 6 months after TKA

Factors	12 months	6 months
	Mean correlation, CI 95%	Mean correlation, CI 95%
More severe osteoarthritis	-0.15, 95% CI: -0.23 to -0.08, low certainty evidence. [167,194,195]	Factor not studied
Better mental health	Did not reach correlation treshold	-0.13, 95% CI: -0.24 to -0.02, moderate certainty evidence. [175,176,198,199,202]

*Multivariate random-effects meta-analyses were used to estimate mean correlations (95% CIs) between preoperative factors and postoperative pain. **No multivariate meta-analysis was conducted for the 3-months outcome.

5.1.2 Systematic review and meta-analysis of physical function (Paper 2)

In the systematic review and meta-analysis on physical function, 20 studies with a total sample size of 11 317 patients were included. [167-186] Of these, 17 studies were synthesized in multivariate meta-analyses. [167-178,180,181,183,186] Study sample sizes ranged from 49[181] to 5 309. [176] Mean age of participants ranged from 63 years[181] to 75 years, [176] while the proportion of females ranged from 49.3% [184] to 90.0%.[177] Most of the studies included for both systematic reviews and meta-analyses were conducted in European countries. [171,173-175,179,182,183,187,189-196,198] The most commonly studied preoperative factor was preoperative function (six studies) and mental health (eight studies) and the most commonly used physical function measure was the WOMAC.

As shown in Tables 6a and 6b, we identified that higher preoperative BMI, was correlated with worse physical function, while better physical function and more severe osteoarthritis preoperatively were correlated with better physical function twelve months after TKA. [2] Due to limited evidence and wide confidence intervals, we could not determine whether the other 15 factors had clinically significant correlations or not. The mean coefficient estimated in the sensitivity analysis was larger for better preoperative physical function but approximately similar for the other factors. For the secondary outcome, physical function 6 months after TKA, 20 factors reported in nine studies that involved 5 743 participants were identified. We did not perform multivariate meta-analysis for the three months outcome due to certain factors being studied only once or considered inappropriate for pooling estimates. Since there were no intraoperative factors that were studied more than once, they were not included in the multivariate meta-analysis

Table 6a Preoperative factors correlated with better physical function 12 and 6 months after TKA

Factors	**12 months**	**6 months**
	Mean correlation, CI 95%	Mean correlation, CI 95%
Better preoperative physical function	0.14, 95% CI,0.02,0.26, low-certainty evidence. [167,169-171,173,182]	0.37, 95% CI, 0.27, 0.46, moderate-certainty evidence
More severe osteoarthritis	0.10, 95% CI, 0.01, 0.19, high-certainty evidence. [167,195]	Factor not studied

Table 6b Preoperative factors correlated with worse physical function 12 and 6 months after TKA

Factors	**12 months**	**6 months**
	Mean correlation, CI 95%	Mean correlation, CI 95%
Higher preoperative BMI	−0.15, 95% CI, −0.24, −0.05, moderate-certainty evidence [167,170,171]	Factor studied once
More catastrophizing	Factor studied once	–0.19, 95% CI, –0.35, –0.01, very low–certainty evidence
Walking aid use	Factor not studied	–0.31, 95% CI, –0.45, –0.17, high-certainty evidence

*Multivariate random-effects meta-analyses were used to estimate mean correlations (95% CIs) between preoperative factors and postoperative physical function. **No multivariate meta-analysis was conducted for the 3-months outcome.

5.2 Prospective observational study (Paper 3)

Initially, 245 patients were invited to participate in the inception cohort study of which 202 patients were included. Further details on the enrolment process are described elsewhere. [77] For this prospective observational five-year follow-up study, we were unable to enroll six patients due to death or lack of contact information, leaving 196 patients eligible for participation. Out of 196 patients invited to participate in the study 136 (67%) were included in the final analysis. The study sample had a mean age of 67.7 years at the time of inclusion. Most patients were female

(68%), and most lived with a partner (61%). Baseline characteristics of the cohort are presented in Paper 3. [3] There were no significant differences observed between patients included in the five-year follow-up study and those who were not included in terms of preoperative age, sex, ASA classification, comorbidities, pain, pain-related function impairment, or symptoms of anxiety or depression. However, patients included in the follow-up had a significantly lower preoperative BMI (mean 28.6, SD 4.2) compared to those not included (30.3, SD 5.6, p=0.03).

5.2.1 Pain

The mean rating of average pain decreased from 5.2 (SD 1.8) before surgery to 2.7 (SD 2.3) at the five-year follow-up. The majority of the patients had moderate to severe pain before surgery, and the proportion decreased to one third after surgery. We assessed the associations of preoperative pain, painful sites, anxiety symptoms, K-L grade 4, sex, age, and comorbidities with pain twelve months after TKA in univariate logistic regressions. The significant variables from this analysis, K-L grade, anxiety symptoms, average pain, painful sites, were included in a backward multivariate logistic regression model. Higher preoperative pain was the strongest prognostic factor for moderate to severe pain five years following TKA, with odds increasing by 34% for each one-point increase in preoperative pain rating. Each additional painful site increased odds by 28%, while each one-point increase in HADS anxiety score increased odds for moderate to severe pain five years after TKA by 14%. Severe osteoarthritis was associated with 87% lower odds of moderate to severe pain at five years, compared to moderate to mild osteoarthritis.

5.2.2 Pain-related functional impairment

For the secondary outcome, pain-related functional impairment, the mean score improved from 4.4 (SD 2.0) before surgery to 1.9 (SD 2.1) five years after surgery. At five years, a total of 18% (n=24) of patients reported moderate to severe pain-related functional impairment, while 82% (n=111) of patients had no or mild impairment. We evaluated the univariate associations between each of the individual preoperative variables, age, comorbidity, BMI, K-L grade, sex, anxiety symptoms, pain interference with function and moderate to severe pain-related functional impairment five years after TKA. Our results showed significant associations between preoperative sex, anxiety, and pain interference with function and pain related functional impairment. These variables were further evaluated in a multivariate logistic regression model, which revealed that male sex and preoperative anxiety remained as prognostic factors to pain-related functional impairment five years after TKA. For each one-point increase in preoperative anxiety score, the odds of having moderate to severe pain-related functional impairment at five years increased by 25%. Males had a 77% lower likelihood than females of having moderate to severe pain-related functional impairment at five years. We also performed sensitivity analyses and removed five outliers, which confirmed our main findings.

5.3 Explorative-descriptive qualitative study (Paper 4)

Out of the initial 31 eligible participants, 23 individuals were included in the study after excluding eight participants due to death and illness. [4] The sample consisted of 13 women and ten men. The median age of participants in this sample was 67 years (interquartile range 48-84). Six participants reported the presence of at least one chronic illness, while 16 participants reported experiencing pain in two or more sites prior to undergoing TKA. After analyzing the data, two main themes emerged related to the experiences of patients who developed chronic post-surgical pain after TKA and their perceptions of pain and stress before the operation. The first theme highlighted that the participants had endured years of pain leading up to the surgery, which they perceived as a burdensome experience. Many told stories of long-lasting knee pain caused by osteoarthritis, and some also experienced additional painful comorbid conditions, such as migraine, endometriosis, and rheumatism. Furthermore, some participants had symptomatic joints beyond the knee, such as in the shoulder or hip, contributing to their overall pain burden. Additionally, a subset of participants had encountered traumatic and painful incidents, such as motor vehicle accidents or work-related injuries, resulting in trauma to various body parts. One participant described a severe traumatic work accident, not described in the paper, where hospital treatment and appropriate pain-relieving medication was unavailable. The pain was described as excruciating and unbearable without any pain relief. The study participants described these long-lasting painful conditions as a burden, affecting their quality of life, leading to sleepless nights and distress. The double burden of pain in multiple locations was emphasized, leading to a stressful and troublesome experience for the participants. Participants also expressed that their quality of life was significantly reduced due to physical inactivity and sleepless nights caused by the pain. [4]

The second theme that arose was the burden of living with psychological distress. Participants described stories of psychologically stressful events, such as the loss of a close relation and grief, as well as difficult marriages – even a description of an abusive marriage – divorces, and family relations. In addition, the emotional distress caused by these events was described as leaving participants with emotional scars, including anxiety and fear of undergoing surgery. Grief and mourning were common themes among those who had lost loved ones, and some expressed feelings of abandonment and lack of control. Seeking help to overcome emotional struggles was common for some, but others internalized their distress, and it stayed with them for years. Fear and anxiety related to surgery were also described, with some participants postponing surgery due to traumatic experiences or concerns about uncontrolled postoperative pain. In conclusion, the study findings provide a detailed account of the burden of living with long-lasting pain and psychological distress in patients with osteoarthritis undergoing TKA surgery.

6.0 Discussion

This thesis aimed to develop knowledge about factors and experiences relevant to pain and physical function after TKA through four papers that aimed to identify preoperative and intraoperative factors associated with short- and mid-term pain and physical function outcomes following TKA and to explore psychosocial factors that may affect TKA outcomes.

6.1 Methodological considerations

Three different methodological approaches were used in this study: systematic reviews and meta-analyses, a prospective longitudinal observational study, and a qualitative study. [1-4] Each of these approaches provide insight into the research question and have their own strengths and limitations that need to be considered when interpreting the findings. These considerations include assessments of internal and external validity and trustworthiness.

6.1.1 Design

Systematic reviews and meta-analyses (Papers 1 and 2)

Our selection of prognostic designs is in accordance with recommended practices for this type of research question. [91,92,128] By selecting prognostic designs, we aimed to ensure internal validity and reduced between-study heterogeneity. Although we initially intended to include the TKA arm of RCTs, none met our inclusion criteria. However, the stringent inclusion criteria employed in randomized controlled trials (RCTs) may inadvertently exclude studies who could offer valuable insights into prognostic factors. In this regard, our study benefits from a wider patient population, potentially providing an advantage in exploring these factors. [162] Despite an extensive search and screening numerous articles, it is important to acknowledge that our review may not have captured all relevant reports published beyond standard bibliographic databases. This includes gray literature sources, such as findings from government agencies and dissertations. This potential limitation may have introduced publication bias, as the included findings may systematically deviate from those omitted. [92,128] This issue, and small-studies effects can be explored by using funnel plots. However, this approach is not recommended when there are fewer than ten studies, as indicated in both the recommended guidelines and our own protocol for the systematic reviews and meta-analyses. [91,92] Given that no factor was studied in ten or more studies, we followed our protocol and did not make funnel plots. [95]

Prospective observational design (Paper 3)

Our decision to employ a prognostic design in our study aligns with established best practices for investigating research questions of this nature, ensuring internal validity.[87,125] This design allowed for the follow-up of a cohort of patients with osteoarthritis undergoing TKA over an extended time period (from prior to surgery to five years post-surgery) and allowed for the examination of potential differences in outcomes (pain and pain-related function five years after TKA) based on patient's characteristics assessed before surgery.[87,125] The prospective approach, with predetermined primary factors and outcomes, is regarded as a strength, as it minimizes the potential for data dredging and ensures a more robust analysis.[87] Prospective designs are generally considered stronger and thus preferred over retrospective designs, as data are collected before the outcome of interest, reducing the risk of recall biases.[24,125,160]

Exploratory-descriptive qualitative approach

For Paper 4, an exploratory-descriptive qualitative design was utilized for collecting data on the patients' experiences of painful or stressful life events prior to surgery and in a sample of patients who reported chronic post-surgical pain one year after TKA. The design is particularly suited for contexts where empirical knowledge about a phenomenon remains underdeveloped, which was the situation within our field, with an absence of pre-existing studies exploring patient experiences preceding TKA.[125,136] This design allows for a deeper understanding of individual experiences through semi-structured interviews, as individual interviews enable participants to share their stories without interruption and allow for follow-up questions from the interviewer when necessary.[125,136]

6.1.2 Sample

The process of selecting a study sample is a crucial step in the research process since it determines the patients who will be included in the study and can have a substantial impact on the generalizability or transferability of the study findings.[125,204]

Systematic review and meta-analyses (Papers 1 and 2)

Defining the target population is a crucial component of ensuring internal validity in systematic reviews and meta-analyses.[87,128] The systematic reviews and meta-analyses were carefully designed with a specific focus on patients with osteoarthritis, who underwent primary TKA arthroplasty within a defined timeframe.[1,2,95,131] This targeted approach allowed us to include a more homogenous sample, thereby reducing potential heterogeneity and enhancing the reliability of the synthesized evidence. To ensure the comparability of included studies, we established inclusion criteria guided by the PEOS criteria strategy, which were applied during the search process and article assessment. This approach contrasted to previous systematic reviews and meta-analyses, which often encompassed diverse study designs, follow-up durations, and patient populations, potentially resulting in systematic reviews that disagree with one or another. [56,91,92,98,103-105,107-110,145,146,205-209] Despite the availability of newer criteria to define research question and search strategy in prognosis studies, the Population, Index Prognostic Factor, Comparator Prognostic Factors, Outcome, Timing, and Setting (PICOTS) framework, [91,92] our eligibility criteria based on the PEOS framework, effectively guided the development of the scope, and search strategies. We believe that our approach would yield comparable results to those obtained through the newer PICOTS design, as the elements in both approaches are similar.

Sample size is an important consideration in meta-analysis of prognostic factors studies, impacting the precision and reliability of results. [161,162] Small sample sizes might report both larger and smaller estimates, but due to the play of chance. [91,92] Consequently, we rated down confidence in estimates for factors with wide confidence intervals around the pooled estimate, which again was important for a more cautious interpretation of results. Sample size can also influence the detection of between-study heterogeneity. With a small sample size, it may be more difficult to detect variations in study outcomes due to differences in study design, methodology, or other factors. In contrast, a larger sample size can increase the ability to identify and assess between-study heterogeneity, which is a critical consideration in meta-analysis. [91,92] I^2 increases as the estimates reported by the studies become more precise (i.e., as sample sizes increase). This can result in a very large I^2 value that does not correspond to meaningfully large heterogeneity, and I^2 should thus be interpreted cautiously. [160,162]

Prospective observational study (Paper 3)

The longitudinal study described in Paper 3 utilized a non-probability sampling procedure, selected, and guided based on the study's aim of examining associations between preoperative factors and outcomes. [125] Consecutive sampling was utilized to select participants who met specific inclusion criteria in a predetermined order, further reducing the potential for selection bias. We considered the number of factors used in our multivariate analysis to be appropriate for achieving adequate statistical power in multivariate logistic regression, given that our sample size exceeded the number of patients and factors calculated according to the descriptions by Tabachnick and Fidell. [148] Therefore, we consider the risk of overfitting to be limited. However, we acknowledge that a larger sample would be beneficial as this could increase the statistical power, decreasing the risk of committing Type II error, failure to identify true associations. [125]

Explorative-descriptive qualitative study (Paper 4)

In the exploratory qualitative study, we utilized purposeful sampling. With this recommended approach, we strategically chose participants who were likely to possess direct experience of the research topic, with an intention to illuminate the research question and offer a comprehensive description of the phenomenon being studied. [126,136,163] Determining sample size in qualitative studies is a critical step. We guided this decision by adhering to Malterud et al.'s theoretical model on information power, which addresses factors that influence on information power like study objectives, sample specificity, use of theory, dialogue quality, and analysis strategy. [126,138] We focused on a specific subgroup that showed no pain improvement one year after TKA. We anticipated dense information from the participants, thereby increasing information power. The adoption of the biopsychosocial model as a theoretical framework in this study, the interviewer's prior experience with orthopedic patients, along with pre-interview training augmented the quality of dialogue was all factors contributing to a higher information power in our study. [138]

In terms of our analysis strategy, we focused on identifying patterns rather than covering every aspect of the phenomenon, allowing for a detailed examination of patients' experiences. We conducted a preliminary analysis and assessed the information power of our study. Based on these evaluations, we determined that our initial sample size of 15 participants might not be sufficient to yield rich description of the phenomenon studied. To address this concern, we made the decision to expand our sample size to 23 participants. The participants were interviewed about their preoperative experiences five to seven years after their surgery. It is important to acknowledge that this time lapse between their preoperative experiences and the interviews could introduce recall bias. However, as we aimed to gain insight into the participants perceptions of their stories, and the aspects they illuminated as important for them in their lives,we believe that their recollections of prior experiences shed light on the real-life issues that were important to them during their preoperative process.

6.1.3 Data collection

Systematic review and meta-analyses (Papers 1 and 2)

To enhance internal validity in data collection for our systematic review and meta-analyses, we employed a predefined and recommended strategy to minimize bias, ensure accuracy, completeness, and transparency. [1,2,91,92,95,128] This strategy included standardized data extraction, clear eligibility criteria, comprehensive search methods, independent data extraction, and assessment of risk of bias and quality of evidence. These measures enhanced the internal consistency of our studies. Some of the decisions had to be made at analysis time, such as whether to pool factors or define them as being distinct risk factors. Other researchers might have made different decisions. We acknowledge that personal judgment may have influenced certain decisions despite the use of the rigorous data collection methods.

Prospective observational study (Paper 3)

Throughout the study, efforts were made to maintain data completeness and follow-up. Patients who did not return questionnaires were contacted via telephone or mail. This was to encourage questionnaire completion and enhance the overall response rate. By implementing such reminder strategies, the research team aimed to minimize missing data and maximize complete and reliable information. Reminders can mitigate potential biases introduced by non-response or missing data. [210]

Explorative-descriptive qualitative study (Paper 4)

Data collections are fundamental for study quality also in qualitative studies and influence the depth and validity of findings. Reflexivity, the researcher's self-awareness of their personal values and how these might influence on the data they collect, analysis and interpretation of the data is a key aspect to enhance quality, but also transparency in the research. [125, 211] Both the first and second authors, having previously worked with patients undergoing TKA, were aware of the potential influence of their preconceptions. In response to this, we followed best practices and held reflective discussions within the research team to address these biases and enhance rigor in the research. [163,164] However, the interviewer's familiarity and experience with patients undergoing TKA enabled the researcher to ask follow-up questions, that facilitated richer description of patients experiences. This deepened the understanding and added value by capturing more nuanced understanding of the phenomenon that otherwise could be challenging to uncover. To ensure that interviews were conducted in a skilled and consistent manner, the experienced senior author mentored the less experienced first author in qualitative interview techniques, which is recommended approach.[212] While the interview guide ensured that key topics were addressed consistently across interviews, the semi-structured nature of the interviews provided flexibility for participants to shape the discussion according to their priorities and interests the semi-structured nature of the interviews allowed participants to guide the discussion to the topics that were important to them.[125] Follow-up questions allowed participants to reflect on issues they perceived as important. The interview guide was pilot tested with three patients, and no modifications were needed.

6.1.4 Measurement of main outcomes

Pain and physical function were the main outcomes for Papers 1 and 2, while pain and pain-related function were primary and secondary outcomes in Paper 3.

Systematic review and meta-analyses (Papers 1 and 2)

In the original studies included in the systematic reviews, several instruments were used to measure the outcomes, which can introduce heterogeneity and make it difficult to combine the results of original studies in the meta-analyses. To mitigate this expected effect, we used random-effects meta-analysis, which assumes that the true effect size may vary across the included studies due to differences in the study population, intervention, and outcome measures. This method takes into account both within-study and between-study variability, and produces a pooled estimate of the effect size that incorporates this variability.[87,128] Although we could have chosen to perform analysis based on specific instruments, such as focusing solely on studies using the WOMAC instruments, we selected for a more comprehensive approach to capture a broader range of studies.

Prospective observational study (Paper 3)

In Paper 3, the BPI was used to measure the primary outcome pain five years after TKA and the secondary outcome of pain's impact on physical function five years after TKA.[139,143,144] The limitation of using cut-points developed for a different patient population, patients with low back pain, may not be ideal for generalization of study findings to the populations undergoing TKA. [142] However, these cut-points still provided valuable information on how pain affected physical function and broader aspects of daily living, which goes beyond symptom reduction. Moreover, by using these cut-points, we were able to identify a group of patients (18%) who reported moderate to severe pain-related functional impairment five years after TKA. Therefore, the BPI remains a useful tool to assess pain and pain's impact on function following TKA surgery. However, it is important to emphasize the need for further validation of these cut-points to ensure their reliability and applicability in patients undergoing TKA.

Studies indicate a modest correlation between pain and physical functioning, underscoring the need to assess both outcomes individually, as done in our study. [84,213] In line with the IMMPACT recommendations, we utilized the BPI to measure the impact of pain on physical function, which incorporated aspects of daily living such as household chores, walking and relations to others. [84,214] Furthermore, the BPI is a patient-reported outcome measure (PROM), which enabled the patients to report, without any interpretation, their own experiences of pain and physical function. [215-217] Self-report is particularly beneficial for measuring pain intensity as it is considered a subjective experience that is difficult to measure objectively. Therefore, patients' perceptions of pain intensity levels should be assessed directly by patients themselves. [218]

6.1.5 Data analysis

Systematic reviews and meta-analyses (Papers 1 and 2)

Our study highlights the importance of adhering to rigorous methodological standards in meta-analyses and critically evaluating study findings. While sensitivity analysis is recommended by Cochrane guidelines, its utilization in this area of research appears to be relatively rare, as evidenced by our limited findings of prior meta-analyses employing this approach. [56,128] However, due to data sparsity (informally, many risk factors but relatively few studies), we deviated from the protocol and used a frequentist version of the Bayesian multivariate model, described by Rose et al. [131] which provided valuable insights into our research question. Overall, our study highlights the importance of flexibility and adaptability in statistical approaches, particularly when dealing with sparse or heterogeneous data. We also made a deliberate choice to utilize a random effects model rather than a fixed-effect model, considering our expectation of heterogeneity within the data. This decision was based on the belief that a random effects model would better account for the variability observed. [95,128,156]

Prospective observational study (Paper 3)

We addressed several statistical issues regarding the statistical analyses, which strengthened the reliability of our findings. One important aspect was incorporating findings from prior meta-analyses, which allowed us to build upon existing evidence and select relevant factors to evaluate in our logistic regression models. This approach is recommended by experts in the field, including Field et al, [147] and Tabachnick and Fidell. [148] In our study, we employed a logistic conditional backward regression model, which is a recommended approach in prognostic research. [87] This method involved starting with a model that included the pre-selected factors and subsequently eliminating non-contributing factors based on their statistical significance. By doing this, we avoided overfitting the model and ensured that only the most relevant and significant predictors were retained. An alternative to our approach is linear regression, but as the outcomes were dichotomous, linear regression would not be appropriate as it assumes a linear relationship between the factors and the outcome. [147]

Explorative-descriptive qualitative study (Paper 4)

In our explorative-descriptive qualitative study (Paper 4), we employed inductive qualitative content analysis to analyze the participants stories and identify meaning units. [126,163,219] Inductive content analysis is recommended when there is limited knowledge about the research question, which was particularly relevant in this study where little was known on prior experiences in a specific subgroup of patients that did not show improvement in pain after TKA. [163,219] By employing an inductive approach, start with the data and gradually develop a more theoretical understanding, we were able to generate new insights based on the participants' narratives. Alternatively, a deductive approach could have been employed, involving the testing of pre-existing theories or explanatory models against the obtained data. [126,163,219] However, considering the limited knowledge surrounding the specific sub-group under study, this deductive approach was deemed less suitable. Graneheim et al. [163] points out that there is a risk for researcher to not be able to go under the surface. However, we believe that our approach, closely examining the transcripts, condensing meaning units, identifying codes searching for patterns and similarities before sorting into categories, which then again were sorted in theme for de-contextualization, made us able to uncover and describe important themes that emerged from the data. [165]

6.1.6 External validity

External validity is a crucial consideration in research, encompassing both generalizability and applicability to other populations, conditions, and settings. [125,220,221] Both generalizability and applicability should be considered when planning or reporting a study. [221] To ensure external validity, sample size and representativeness of the study sample are important factors to consider. [221]

Systematic reviews and meta-analyses (Papers 1 and 2)

As we applied strict eligibility criteria for the systematic reviews and meta-analyses, we are confident that study findings are applicable for the target population, patients with osteoarthritis undergoing TKA. This was also confirmed by using the concept of directness from the GRADE tool. [128,161,162,222] However, the strict inclusion criteria may limit generalizability to other populations such as for example patients with rheumatoid arthritis, and for these, future research is needed to determine generalizability. [162] It is important to note that the findings from our systematic reviews and meta-analyses within the first year after TKA may not be generalized to longer-term follow-up. Unlike other studies that encountered difficulties in conducting meta-analyses due to between-study heterogeneity, our use of random-effects multi-variate meta-analyses strengthens the generalizability of our findings. [103,105,108,110,208,223,224] Observing high I^2 values for some factors, potentially influenced by large sample sizes which result in narrow confidence intervals, is not uncommon in meta-analysis studies and is an inherent property of the studies included. [1,2,160,162] To account for this heterogeneity, we employed a multivariate random-effects meta-analysis to estimate the mean correlation, which offers a more accurate and encompassing interpretation of our data. By performing a sensitivity analysis and excluding studies with high risk of bias at the statistical QUIPS domain, we were able to assess the varying strengths of correlation among different factors. This rigorous approach enhanced the external validity of our study by ensuring that biased factors, such as for temporal summation in the meta-analysis of pain, were not included in the final meta-analysis of pain. [1] By this credibility and generalizability of our study findings were increased.

Prospective observational study (Paper 3)

In evaluating the generalizability in the prospective observational study, several factors need to be addressed. This study was limited to patients diagnosed with knee osteoarthritis who were scheduled for primary unilateral TKA, which made the findings applicable for this particular patient group. However, results might not be generalized for other, such as those with rheumatoid arthritis or undergoing uni-compartment arthroplasty. Age distribution was similar to that of the Norwegian population, reported in the Norwegian Arthroplasty Register. [225] Our sample included fewer males (32% vs. 45% in general population), which could restrict the generalizability to the male population. [225] The median age in our study was 69.0 years, closely aligned with the median age of 67 years recorded in the general population. [225] However, our sample had a lower representation of males (32%) compared to the 45% reported in the registry data, which could potentially restrict the generalizability of our findings to the male population. [225] We did not include patients who were unable to read, write and understand Norwegian, or patients with cognitive impairment, and generalization of study findings to these patients should be done with caution. Our patient population was derived from a single surgical clinic, which could potentially influence the breadth of applicability of our findings. This is due to the possibility of diverse clinical practices among different hospitals and distinct patient characteristics varying by region. However, the inclusivity of patients from all health regions in our study might serve to offset this limitation, enhancing the generalizability of our results. Patients underwent TKA in a high-volume surgical hospital, which might affect generalizability, as high-volume clinics generally achieve better outcomes in terms of complication rates than low-volume clinics where surgeons have lower surgical volume. [226-228] On the other hand, patients were included from different regions in Norway, which again can increase generalizability of study findings.

To address potential bias due to loss to follow-up, we compared the characteristics of those who completed the five-year follow-up with those who did not. Although only a small difference in BMI was observed, it is still possible that those who completed the study had different characteristics than those who did not. Longitudinal studies like ours often experience an increase in attrition over time, which can lead to a misrepresentation of the original sample as the remaining participants may have different characteristics. [87,229,230] Although there is no consensus on an acceptable response rate for longitudinal studies, Grooten et al. [159] suggested a response rate of 67% as a cut-off for attrition rate in their study on inter-rater agreement of risk of bias assessment in prognostic studies. As such, the response rate in this study was 69% which might be considered adequate.

6.1.7 Trustworthiness in the explorative-descriptive qualitative study (Paper 4)

Maintaining trustworthiness in qualitative analysis is essential, reflecting the confidence that researchers place in their data and associated interpretations. Lincoln and Guba set forth five criteria to uphold trustworthiness in qualitative research, namely, credibility, dependability, confirmability, transferability, and authenticity. [125,230] These criteria parallel the quantitative research concepts of internal validity, reliability, objectivity, and external validity. [126] This thesis will lay emphasis on the criteria credibility, dependability, confirmability, and transferability.

Credibility pertains to confidence in the truth of the data and the interpretations derived from it. [125,163,164] To enhance credibility in our study, we employed various methods. We aimed to recruit a diverse sample of participants who had likely experienced the phenomenon under study. [125,163,164] A diverse sample consisting of both sexes and ages ranging from 48 to 84 years was recruited, and this approach facilitated rich descriptions of prior life experiences. We did not perform member checking with for example debriefing with informants, but used follow-up questions during interviews to clarify any potential misinterpretations of participants statements. [125] Moreover, while maintaining consistency by aligning questions with the interview guide, we acknowledged the unique perspectives of each participant, tailoring the interviews to their individual experiences. This approach allowed participants sufficient time and opportunity to provide in-depth descriptions of their personal narratives.

To ensure dependability, which is the stability or reliability of data over time and under different conditions, and to maintain consistency in data interpretation in terms of accuracy, relevance, and meaning among researchers, we employed several strategies. [125,126,164] Firstly, we utilized researcher triangulation, incorporating the analyses of two researchers to minimize potential bias arising from a single perspective. [4,125,163] Secondly, preconceptions were discussed within the research group, a practice that not only addressed confirmability but also fostered a more dependable research process by making our approach more consistent and transparent. Through these measures, we strived to represent the perspectives of patients more accurately, thereby enhancing both the dependability and confirmability of our study.

Transferability, or the applicability of the study results to other contexts or groups, was addressed by providing sufficient descriptions of the sample, data collection, and analytic processes, along with rich descriptions of results, including quotes illustrating the findings depicted in a decision trail. [125,163,164,231] This approach allowed readers to assess the relevance of the data in their context. [125] Moreover, we believe that our findings could inform the development of research hypotheses, especially regarding subgroups that do not see pain improvement post-surgery. However, given that our sample was specific, the extent to which our results could be applicable to different patient populations, remains unanswered.

6.1.8 Ethical considerations

All of the studies in this thesis were conducted on the basis of the general principles of the Helsinki declaration, which highlight the physician's and health works duty to safeguard the health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information for patients involved in research. [232]

Risk, burden, and benefit

The Helsinki declaration provides ethical principles for research involving human subjects. A key principle is that research should only be conducted if the potential benefits of the research outweigh the risks and burdens to the participants. [232] In our meta-analyses, we used data from primary studies that had already obtained ethical consent (Papers 1 and 2), and thus no approval from an ethical committee was needed. Patients included in the prognostic and qualitative studies received care in line with standard treatment and care plans. [233] To reduce the burden on patients, certain measures were implemented during the study (Paper 3). The baseline questionnaire, required approximately 45 minutes to complete, was administered the day prior to surgery where patients typically often had lengthy waiting times for appointments. In the qualitative study (Paper 4), patients had the choice of being interviewed either at home or at the hospital, providing flexibility that particularly benefited individuals experiencing chronic post-surgical pain or impaired physical function, reducing the burden of study participation.

Vulnerable groups and individuals

The Helsinki Declaration also recognizes the vulnerability of certain patient populations who may be at greater risk of harm from participating in research studies. The interviewer took precautions to establish a safe environment for the interview by starting with a brief introduction of the study that included information on confidentiality, followed by ice-breaking small-talk before the interview started. [125] Considering the qualitative interview focused on patients' experiences before TKA, it had the potential to evoke memories that some patients did not wish to remember. To mitigate this, precautions were taken during the interview process by using the interview guide carefully, using open-ended questions and not pressuring participants to elaborate on specific element. We did not invite participants with cognitive impairment, considering they might be unable to fully understand the information presented to them, such as the potential risk versus benefits. [232] Consequently, their ability to provide a truly informed consent could be compromised.

Privacy, confidentiality, and informed consent

All participants were informed about the details of the study and that participation was voluntary. The interviewer reassured participants that their stories would be kept confidential and anonymous. For these reasons and legal purposes, we altered or omitted personal details when presenting the findings in the papers. All included participants signed the informed content before inclusion in these studies. While we acknowledge that openness in sharing personal stories can be a meaningful and empowering experience for participants, it is important to recognize that individuals may have varying feelings and perspectives over time. Therefore, it is essential to respect and honor the participants' autonomy throughout the research process.

6.2 Discussion of main findings

The overall aim of this thesis was to advance the understanding about factors and patient experiences related to pain and physical function after TKA. The findings from the studies in the thesis will first be discussed individually, in relation to each other, and then in an evidence-based context.

6.2.1 Factors and patient experiences related to pain and physical function after TKA

Different prognostic factors may influence recovery at various time points after TKA. [12,234] As a result, three time points (three, six, and twelve months) were assessed to determine whether there were different prognostic factors for the outcomes in the systematic reviews and meta-analyses. [1,2] By doing so, we identified prognostic factors specific to each time point during the first postoperative year, but also at five years in the prospective observational follow-up study. [3] Our systematic review and meta-analysis differ from earlier studies due to our exclusive focus on prospective observational studies, specifically investigating set time points within the first postoperative year. [1,2,95] Prior studies, in contrast have combined results from prospective and retrospective studies and short- to mid- to long-term outcomes thereby posing limitations on the generalizability of their conclusions. [56,98,104,105,109,145,205,223,224,235] Conversely, our methodology, accentuates the applicability and relevance of our findings, particularly with respect to short-term pain and physical functionality following TKA.

Interestingly, in both our systematic reviews and meta-analyses, more severe osteoarthritis was prognostic for better pain and physical function one year after TKA. [1,2] Our findings are inconsistent with results from two other meta-analyses that did not find this association. [146,208] However, it is worth noting that these studies combined data for short- and long-term outcomes, which may not be optimal as longer-term results can be impacted by other health issues or the natural decline in health that comes with aging. [236] According to some authors, the intensity of osteoarthritis alone may not fully explain the presence of pain or reduced physical function after TKA, and suggest that other factors, such as pain modulation, may play a role in these outcomes. [110,194,195,237] Underlying factors leading to pain modulation are largely unclear, which suggests that more research is needed in this area. [237] For example, we identified a correlation between increased pain modulation (temporal summation) and chronic post-surgical pain which could be helpful to explain the discrepancy between the severity of symptoms and radiographic findings.

[192,194] However, temporal summation was excluded from the final meta-analysis due to insufficient reporting on QUIPS domains, implying that further research is needed to explore the potential correlation between this factor and postoperative pain. Some patients might have severe radiographic changes but are symptom free, which might be explained by structural damage that lacks nociceptive innervation. Others might have symptoms from osteoarthritis, but typical features such as osteophytes or joint space narrowing are still not present on radiographs. [34] We acknowledge the absence of intraoperative factors that we were unable to include in multivariate meta-analysis, highlighting the need for future studies to investigate the impact of these factors on pain and physical function after TKA. Furthermore, while this study did not focus on postoperative factors or effect of pre- or rehabilitation strategies, it is still important to recognize their potential influence on TKA outcomes. Further research is needed to gain a more comprehensive understanding of pain and physical function after TKA.

In our five-year follow-up study, we identified a notable number of patients who reported moderate to severe pain (32%) and pain-related functional impairment (18%) five years after TKA. These findings address the gap in knowledge concerning mid-term recovery after TKA. However, further investigations are needed to better understand recovery trajectories beyond the mid-term period after TKA surgery. This was demonstrated in a recent study on chronic post-surgical pain after TKA that identified a subgroup of 13% who reported chronic post-surgical pain at one year, where two-thirds of these patients had a slower recovery trajectory than those without chronic post-surgical pain. [57] Almost one-third experienced fluctuating pain over the five years, and only a small percentage (4%) experienced continuous chronic pain. These results indicate that a specific sub-group of patients may require more time to recover from the pain and may have characteristics that make them more susceptible to adverse outcomes.

6.2.2 Understanding factors and patient experiences for the outcome of pain

The systematic review and meta-analysis described in Paper 1 may be the first to provide evidence for preoperative pain as a prognostic factor for chronic post-surgical pain at the set time point one year after TKA. [1] Our findings are supported by results from other studies, but because results from these are combined with short- to long-term follow-up, this may limit the applicability of their results to specific postoperative periods. [56,98,104,145] Our meta-analysis identified that more preoperative pain was a significant prognostic factor for chronic post-surgical pain at all three time points within the first postoperative year. [1] Interestingly, in our prospective observational follow-up study at five years, more severe preoperative pain was associated with chronic post-surgical pain, [3] which was consistent with findings from the meta-analysis. [1,3]

Furthermore, the findings from the qualitative study gave new insight into a group of patients with chronic post-surgical pain after TKA. Their descriptions revealed a heavy burden of living with pain and stress in the years before TKA. The patients' narratives during the interviews highlighted the enduring nature of their burden, which contrasts with the limited scope of the Brief Pain Inventory (BPI) questionnaire that measures preoperative pain over the last 24 hours. [139] The findings suggested that pain prior to TKA was multifaceted and complex, with patients reporting severe pain in multiple joint locations and comorbidities such as endometriosis and migraine, creating a double burden that was exhausting to live with. [4]

Interestingly, more symptomatic joints were correlated with chronic post-surgical pain in both the multivariate meta-analysis and the prospective observational follow-up study, at both one and five years after TKA. [1,3] One systematic review, based on data from short-term to long-term follow-up identified symptomatic joints as a factor associated with chronic post-surgical pain, but the association did not persist in the multivariate meta-analysis. [98] No study has, to our knowledge, included this factor in an analysis of the five-year pain outcome. However, what makes this particularly interesting is the negative impact that severe persistent pain from osteoarthritis or from multiple locations had on patients' quality of life, as expressed by several participants in the interviews. [4] This finding was also confirmed by another qualitative study, where participants described enduring long-lasting and excruciating joint pain, and which seriously impacted their quality of life. [26] These results emphasize the critical role of preoperative pain levels in the development of chronic post-surgical pain after TKA. This also underscores the need for a more comprehensive approach to preoperative pain management that takes into consideration the diverse and complex nature of pain experienced by patients before TKA. [1,2,4]

In our meta-analysis, we identified that pain catastrophizing was correlated with chronic post-surgical pain one year after TKA, aligning with previous research, with exception from one recent contrasting study. [1,56,98,104,109,145] Notably, our study exclusively focused on prospective studies with follow-up durations exceeding one year. Additionally, more preoperative anxiety symptoms were associated with chronic post-surgical pain five years after TKA in the prospective observational study. [3] It is important to note that while both are psychological phenomenon and may overlap, pain catastrophizing and anxiety are two distinct concepts. Anxiety symptoms were evaluated through the Hospital Anxiety and Depression Scale (HADS) questionnaire, whereas pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS), although both measures contain some similar items. This observation is noteworthy and supported by Petrini et al.'s study, in which the authors contend that there is unclarity in the definition of pain catastrophizing, restricting its comprehension to only encompass these three elements. [238] Participants in our qualitative study described a general feeling of anxiety, but also magnification of thought, and some had so much fear of pain or complications from surgery that they postponed their surgery, even when it was strongly indicated. [4] Although patients' descriptions in the qualitative study did not clarify whether anxiety or pain catastrophizing was present, their stories revealed a richer understanding of the psychosocial challenges patients may experience before surgery.

6.2.3 Understanding factors and patient experiences related to the outcome of physical function

While some of the same factors or experiences were related to the pain outcomes through both the quantitative and qualitative studies, no such similarities were observed for physical function outcomes. [2,3] One explanation for this may be that fewer studies had reported factors associated with physical function at three and six months following TKA, and that among those that did, several did not meet our eligibility criteria. [2] Another explanation might be that although patient-reported outcomes are increasingly more common, previously the outcome after TKA was evaluated through objective measures such as range of motion or joint impairment. [74,217,239] In our meta-analysis, we identified an association between better preoperative physical function and better physical function at both six and twelve months. [2] However, in our prospective observational follow-up study at five years, there was no significant association between preoperative physical function and physical function five years after TKA, which contradicted results from other follow-up studies. [3,12,112] In this study, physical function was measured by the multi-dimensional pain interference with function index. [139] One possible explanation for this discrepancy is that the BPI interference index might be less responsive to change as it is a generic instrument, not a knee-specific measure of physical function.

A study investigating the impact of pain on physical function utilized pain interference as a mediator, demonstrating its relevance.[240] The study found that the association between pain intensity and physical function became non-significant when pain interference was included as a mediator. The authors suggest that the impact of pain on a person's life plays a more important role in their physical function than the actual level of pain intensity they experience. This finding corresponds with the principles in ICF, which acknowledge that individual's level of functioning is influenced by factors and their interactions.[72,74,240] It is also possible that validated knee-specific questionnaires, such as the physical function subscales of the Ontario and McMaster Universities arthritis Index (WOMAC) or Knee Injury and Osteoarthritis Outcome Score (KOOS), would have provided different results. The WOMAC was the most frequently used instrument to measure physical function in the meta-analysis. Therefore, further rigorously conducted studies using knee-specific questionnaires should be performed if the aim is to measure physical function. At the same time, the BPI pain interference index is more appropriate if the aim is to measure how pain influence function. Considering the thesis study findings, it seems clear that physical function is not a single construct but involves multidimensionality and context, as suggested by the ICF, and reflected in the biopsychosocial model.[2,3,72,74,119,124,240]

It is interesting to note that although pain catastrophizing is a frequently studied factor in pain research on this patient group, none of the included studies in the meta-analyses investigated its association with physical function.[2,56,104] While several studies reported on mental health, there were no associations found with physical function at any time point in the meta-analysis.[2] However, in the prospective observational study, more preoperative anxiety symptoms were associated with moderate to severe pain-related functional impairment five years following TKA,[3] which is similar to findings from a register study,[114] but not consistent with another prognostic study restricted by a low follow-up rate (29%) at five years.[113] In our interview study, patients were not explicitly asked about the influence of psychological or cognitive factors on their physical function.[4] The patients described debilitating knee pain, making it difficult to maintain and participate in work and social life. Many reported being less physically active and having to prioritize their activities and participation in social life. This suggests that pain interfered with patients' psychosocial and social well-being. These findings from the interview study are in line with a systematic review of qualitative studies, which emphasized the importance of empowering patients with information and self-management strategies to reduce the impact of knee osteoarthritis in combination with an exercise program, an approach that is also consistent with the OARSI recommendations. [27,46]

In our meta-analysis of physical function, higher BMI was a prognostic factor for worse physical function at 12 months, which aligned with results from another meta-analysis. [2,241] However, it is noteworthy that despite this association, patients with obesity still experience functional improvement after surgery. When considering the benefits and risks of surgery for patients with obesity, surgeons should take into account the potential for complications such as infections and wound healing problems, which are more prevalent in patients with severe or super obesity. [242-244] It is important to have an open discussion with each patient about these issues and encourage realistic expectations before proceeding with TKA.

6.2.4 Findings from an evidence-based perspective

The findings of this thesis have several implications for clinical practice and research. First, this thesis highlights the importance of incorporating patients' stories and subjective experiences, and qualitative perspectives alongside quantitative findings into clinical decision-making and research. Second, while this study has identified prognostic factors for pain and physical function outcomes as an essential first step, their direct applicability in clinical practice requires further validation before testing and integration into prediction models. [23] Third, findings from our qualitative study, as well as quantitative studies, can inform new research hypotheses and enable clinicians to make more informed decisions tailored to the individual's needs. This is in line with the perspective of Sackett et al. [245] who argue that making optimal clinical decisions involves considering multiple perspectives.

The traditional hierarchy of evidence, which typically prioritizes randomized controlled trials (RCTs) as the gold standard, proves inadequate when studying prognostic factors for outcomes. The studies in this thesis adhere to rigorous Cochrane methodologies, including selecting appropriate study designs to address the research question on prognostic factors, evaluating risk of bias, assessing certainty of evidence, and conducting sensitivity analyses. [128] Thus, we have identified reliable evidence for several prognostic factors associated with pain and physical function outcomes after TKA. This highlights the importance of considering a broader range of criteria beyond solely relying on RCTs when assessing the quality and importance of evidence. Of note, systematic reviews and meta-analyses can only be as good as the data on which they are based.[89] Several authors have pointed out that evidence from previous prognostic factor studies have methodological limitations, which can lead to inconsistent findings and conclusions.[23,24,89,91,92] Therefore, it is highly important to critically assess and synthesize the available evidence in order to provide reliable and robust conclusions. By utilizing such an approach, we could estimate with high certainty evidence that more severe osteoarthritis was correlated with better physical function one year after TKA.[2] In contrast, due to inconsistent reporting on the statistical QUIPS domain in the studies for the factor temporal summation, we were compelled to exclude temporal summation in our final multivariate meta-analysis for the pain outcome.[1] This underscores the importance of conducting systematic reviews and meta-analyses to identify robust evidence, even when individual studies may lack sufficient statistical power to detect significant effects.

The systematic review process is not immune to subjectivity, as the process includes several decisions based on personal judgment and expertise that can influence the review's findings.[246] While it is impossible to eliminate subjectivity entirely, several steps were taken to minimize the effect of idiosyncrasies, such as registration of our protocol, establishing clear eligibility criteria, utilizing tools for data extraction tools and appraising risk of bias and certainty of evidence.[1,2,95,246] Nonetheless, inconsistencies in study findings from our systematic reviews and meta-analyses might still arise, especially when comparing studies using diverse methodologies. Several previously published systematic reviews and meta-analyses were performed before the development of standardized tools to address the risk of bias and certainty of evidence, such as the QUIPS and GRADE tools. An example of such a meta-analysis is the one published by Santaguida et al.[108] in 2008, before the previously mentioned tools were developed. Similarly, there might be discrepancies between systematic reviews and meta-analyses that utilize rigorous Cochrane methodology and those performed with less standardized methods.[129] Our systematic reviews and meta-analyses using state-of-the-art methodology is therefore helpful to address the issues of inconsistent findings or under-reported factors. The fact that some factors were reported only by a single study suggests that there are still many factors that need further exploration to replicate or validate findings. This thesis aims to address these gaps in knowledge, which later can be areas for research aiming to provide a more complete understanding of prognostic factors for pain and physical function outcomes.

To expand on the evidence-based hierarchy discussed earlier, it is worth noting that the prospective observational study in Paper 3 is ranked lower than RCTs in the hierarchy. [88,89] Nevertheless, our findings can still be considered a significant source of evidence as this design provides important insights into the course of the condition. [3,87] Despite the high number of publications of prognostic factor studies, it is acknowledged that the methodology with regard to study design, analysis and reporting of prognostic factor studies is suboptimal. For these reasons, many published prognostic studies are considered to be at high risk of bias. [24,87,92] To address methodological limitations in prior studies, several steps were taken to improve study quality in our study. For instance, prognostic factors were selected and evaluated on the basis of prior evidence from systematic reviews and meta-analyses. This is a recommended approach as it involves using theoretical reasoning to determine which variables to include. [147,148] In our study, this approach was particularly important given the constraints of our sample size. Hence, our objective was to carefully choose variables that were relevant and could be subjected to hypothesis testing, while also ensuring that the model was not excessively complex or overfitted. There are other approaches used, for instance, Dowsey et al. [12] aimed to study recovery according to trajectory groups over five years after TKA, but did not provide a rationale for the selection of factors and found that poor preoperative physical function was a predictor for belonging to a moderate pain trajectory class, which was inconsistent with our study findings. [3]

While quantitative studies, such as systematic reviews, meta-analyses, and the longitudinal observational study, can provide valuable answers to quantitative research questions, they have limitations in capturing the full range of patient experiences. The questionnaires used, for example, did not provide a comprehensive understanding of the multi-dimensionality of living with pain before TKA and how that affects patients' lives. In contrast, the qualitative study provided vivid descriptions of how pain and stress profoundly affected patients' lives, even years after the stressful events had occurred. [4] For example, several of the participants described living with what can be characterized as chronic pain for several years before undergoing TKA. One participant told stories about living in a psychologically abusive marriage for years, which negatively influenced her with bodily pain and emotional wellbeing. Furthermore, another described a traumatic accident where the participant had to endure excruciating pain without appropriate pain-relieving medication for a whole week. Patients carry their life stories with them, [247,248] and in our qualitative study, several told how their experiences impacted their lives, physical function, and pain.

These are personal stories, which reflect the complex interplay between biological, psychological, and social factors and therefore provide a valuable complement to quantitative studies. A questionnaire is limited in its ability to capture the complexity from the patient's life experience, as shown in the examples provided from the qualitative study. For instance, the questionnaire used to collect data on socio-demographic variables had an item where patients could report recent life events such as marriage (not divorce) or death in the family or close relations. [3] However, patients were only allowed to report events that had occurred within the last four weeks, as the tool was designed to provide a picture of the patient's current situation. Patients were not given the opportunity to report other factors or experiences that may have influenced them or over a longer term, such as a divorce. These examples show how the biomedical reductionist falls short in fully understanding the complexity of pain and illness experienced by patients. [122] The limitations of the questionnaire and the rich description of the patient's personal stories illustrate the relevance of adapting a biopsychosocial model for the understanding and management of pain when doing research, as this model acknowledges the complex interplay between biological, psychological, and social factors in the experience of pain and the impact of pain on function. [119,122,249] One way to incorporate patients' perspectives and experiences is through qualitative research, which can enhance understanding of patients' experiences. However, clinical guidelines mainly rely on quantitative research, and a meta-analysis identified that only a small percentage (20%) of them included qualitative research to identify clinical research questions. [250,251] This suggests that there is a significant gap in the incorporation of patients' perspectives and experiences in the development of clinical guidelines.

We were able to identify some prognostic factors for pain and physical function after TKA, which is valuable evidence, but may also provide a narrow and simplistic understanding of what influences patients prior to TKA. Incorporating findings from the qualitative study provided an opportunity to delve deeper into the experiences of patients living with chronic post-surgical pain, revealing how psychological and social factors, such as trauma, stress, and life events, might be important for pain and physical function after TKA. This ultimately led to a more comprehensive and nuanced perspective of patients with osteoarthritis scheduled for TKA. The qualitative study provided, in combination with the quantitative studies, a more comprehensive approach, emphasizing the importance of selecting the best study design for answering each research question. [1-4] Using a methodology that utilizes several research designs can be advisable, as each design emphasizes different aspects. [126] Both quantitative and qualitative methods are based on the same principles and use consistent methods. In this thesis, different methodologies are successfully adopted.

7.0 Conclusions

This thesis aimed to advance knowledge on factors associated with short- and mid-term pain and physical function outcomes, as well as explore patients' experiences before TKA. Through specific aims in each paper, essential insights were obtained.

In Papers 1 and 2, we synthesized evidence from previous studies, and identified preoperative factors correlated with pain and physical function at 12, 6 and 3 months after TKA. [1,2] Our findings contribute to the existing evidence on prognostic factors for short-term pain and physical function outcomes after TKA. In Paper 3, we conducted a prospective observational study and identified several pre-selected preoperative factors that were associated with pain and pain-related functional impairment outcomes five years after TKA. [3] This study has provided valuable knowledge on mid-term pain outcomes and revealed that a significant proportion of patients continued to experience moderate to severe pain and pain-related functional impairment five years after TKA. Lastly, in Paper 4, we delved into the stories and experiences told by patients who reported no improvement in pain during walking one year after TKA. [4] The narratives shared by the patients suggested that many had endured years of painful and stressful life events before undergoing TKA.

Overall, this thesis has provided a deeper understanding of patients' experiences before TKA, offering opportunities for further research and improvements in clinical practice.

7.1 Research implications

Although our study has identified prognostic factors for pain and physical function, there are potentially other factors that remain unexplored or where the findings are uncertain. Future well-designed prognostic observational studies should investigate these factors and their association with pain and physical function outcomes. Integrating findings from these studies along with already established prognostic factors, including those found in our studies, holds potential for the development, testing, and implementation of future prediction models. When externally validated, these models can be used to identify patients at a higher risk for chronic post-surgical pain or impaired physical function after TKA, thereby guiding the development of tailored interventions to improve outcomes. Another step is to consider reliable evidence and confirm the causal pathway of the prognostic factors as predictors of pain or physical function outcomes following TKA.

The findings from the qualitative study emphasize the importance of adopting a more comprehensive approach to preoperative pain management strategies that consider the diverse and complex nature of pain experienced by patients before TKA. Thus, further research on pain management strategies is needed to improve patient outcomes. Additionally, there is a gap in understanding of painful and stressful experiences and the transition leading to chronic post-surgical pain, and this should be addressed in future studies. We are at a turning point.

Multi-dimensional measurement tools like the BPI may not cover patients' diverse and complex experiences before TKA. Therefore, conducting qualitative and quantitative studies focusing on a sub-group of patients with adverse outcomes is advisable to gain deeper insights. Considering our finding that a significant proportion experience pain and impaired physical function in the mid-term outcome, future research is needed to analyze the trajectory from preoperative to mid-term outcome and to explore variation within the trajectories. Future studies should adhere to updated methodological standards to ensure the validity and reliability of study results and advance the knowledge in the field.

Finally, although this thesis did not address postoperative prognostic factors or prehabilitation or rehabilitation strategies, it is essential to recognize the importance of including these aspects in future research. A comprehensive research strategy encompassing preoperative and postoperative prognostic factors, interventions, and experiences is vital for a deeper understanding of pain and physical function outcomes after TKA.

7.2 Clinical implications

To further improve patient outcomes after TKA, a comprehensive approach is needed that incorporates patient perspectives and experiences throughout the clinical decision-making process. While meta-analyses can identify important patient factors, such as BMI, osteoarthritis severity and pain catastrophizing, it is important to validate these factors through prediction models and individual patient assessment. Patients with high BMI or catastrophizing thoughts can still have good outcomes from surgery and should not be denied the option of being offered TKA when indicated. In addition to offering TKA, we also have a moral responsibility to take care of the whole patient. This includes considering physical, psychological, and social factors, which necessitates a multidisciplinary approach from primary healthcare to inpatient care at the hospital. Acknowledging the difficulties that patients may face allows for tailored preoperative care. Providing patient education, advice on pain management, and guidance on physical activity can aid in maintaining patient health and well-being before their scheduled TKA. Adhering to guidelines such as those set by OARSI can improve patient outcomes. The findings from the thesis papers highlight important factors and experiences that contribute to a better understanding of the diverse and complex nature that patients with osteoarthritis in the knee may have before TKA.

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RESEARCH ARTICLE

Factors correlated with pain after total knee arthroplasty: A systematic review and meta-analysis

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Abstract

Main objective

Systematically review and synthesize preoperative and intraoperative factors associated with pain after total knee arthroplasty (TKA) in patients with osteoarthritis.

Methods

Based on a peer-reviewed protocol, we searched Medline, Embase, CINAHL, Cochrane Library, and PEDro for prospective observational studies (January 2000 to February 2023) investigating factors associated with pain after TKA. The primary outcome was pain twelve months after TKA. Pain at three and six months were secondary outcomes. Multivariate random-effects meta-analyses were used to estimate mean correlation (95% CIs) between factors and pain. Sensitivity analysis was performed for each risk of bias domain and certainty of evidence was assessed.

Results

Of 13,640 studies, 29 reports of 10,360 patients and 61 factors were analysed. The mean correlation between preoperative factors and more severe pain at twelve months was estimated to be 0.36 (95% CI, 0.24, 0.47; P < .000; moderate-certainty evidence) for more catastrophizing, 0.15 (95% CI; 0.08, 0.23; P < .001; moderate-certainty evidence) for more symptomatic joints, 0.13 (95% CI, 0.06, 0.19; P < .001; very low-certainty evidence) for more preoperative pain. Mean correlation between more severe radiographic osteoarthritis and less pain was -0.15 (95% CI; -0.23, -0.08; P < .001; low-certainty evidence). In sensitivity analysis, the estimated correlation coefficient for pain catastrophizing factor increased to 0.38 (95% CI 0.04, 0.64). At six and three months, more severe preoperative pain was associated with more pain. Better preoperative mental health was associated with less pain at six months.

Conclusion and relevance

More pain catastrophizing, more symptomatic joints and more pain preoperatively were correlated with more pain, while more severe osteoarthritis was correlated with less pain one year after TKA. More preoperative pain was correlated with more pain, and better mental health with less pain at six and three months. These findings should be further tested in predictive models to gain knowledge which may improve TKA outcomes.

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Introduction

Total knee arthroplasty (TKA) is one of the most common surgical procedures [1, 2], and is considered as an effective procedure in relieving pain and restore physical function in patients with end-stage osteoarthritis (OA). Although TKA surgery is effective for most, one in five patients may experience chronic postsurgical pain [3, 4]. Chronic postsurgical pain is typically defined as pain that develops after a surgical procedure and persists at least three months [5, 6]. Chronic postsurgical pain is associated with lower patient satisfaction and higher societal and health care expenses due to resource-intensive revision surgery and long-term recovery [4, 7–10].

A comprehensive understanding of factors associated with poor pain outcomes is imperative for the development of a prediction model needed to identify patients at higher risk for chronic postsurgical pain [11, 12]. Although numerous preoperative and intra-operative factors have been studied, synthesizing the available evidence has yielded contradictory findings, perhaps related to certainty of evidence, merging data from short- and long-term outcomes, or pooling estimates from prospective and retrospective study designs [13–21]. Some authors did not perform meta-analysis due to heterogeneity in design and methods [14, 22–24]. Thus, we aimed to build from previous reviews and synthesize current evidence between preoperative and intraoperative factors associated with pain twelve months (primary outcome) and three and six months (secondary outcomes) after TKA.

Methods

We performed our systematic review and meta-analysis according to an a priori peer-reviewed protocol and a preprint [25, 26]. The study was registered in International Prospective Register of Systematic Reviews (PROSPERO; CRD42018079069) [26]. We followed Cochrane Handbook guidelines [27], and reported the study using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting guideline (S1 Checklist).

Search strategy and data sources

Two researchers (UO, MFL) and research librarians developed the search strategy with input from the research team [25]. The research librarian performed a systematic search for publications in MEDLINE (Ovid), Embase (Ovid), Cumulative Index to Nursing and Allied Health

Literature (CINAHL; EBSCO), Cochrane Library and Physiotherapy Evidence Database between January 1, 2000, and February 6, 2023. No language restrictions were set. References were imported to Endnote X8 Software version 20.2.1 (Clarivate Analytics).

Eligibility criteria

We included peer-reviewed published studies that reported estimates of association between preoperative or intraoperative factors and pain at three, six and twelve months after TKA. Studies were eligible if participants were 18 years or older, diagnosed with osteoarthritis, and scheduled for primary TKA. Eligible study designs were prospective longitudinal observational studies and randomized clinical trials that provided estimates of association. Conference abstracts, retrospective studies, case-control studies, studies of uni-compartmental surgery and studies that lacked clear pain outcome measures were not eligible. Studies that merged data from mixed patient populations or did not report separate data for the osteoarthritis or TKA population were excluded

Outcomes

The primary outcome was pain at twelve months following TKA. Secondary outcomes were pain at three and six months.

Study selection and data extraction

We used a standardized data extraction form customized to the research question as explained in the published protocol [25] which included study design, country, participant characteristics, sample size, measures and outcomes, statistical analyses, and estimates of association. Two reviewers (UO, MFL) independently screened titles and abstracts for relevance, assessed full-text publications against eligibility criteria and assessed risk of bias. Disagreements were resolved by consensus or by consulting a third author (ED).

Methodological quality

The Quality in Prognosis Studies (QUIPS) tool [28] was used to systematically evaluate risk of bias in the retrieved studies according to the protocol [25]. The six QUIPS domains include study participation, study attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting [27].

Certainty of evidence

We assessed certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework [29]. Two researchers (UO and MFL) judged certainty of evidence, with a third researcher involved in discussing cases of disagreement (ED). GRADEpro GDT (McMaster University) was used to manage and summarize the evidence.

Statistical analysis

We synthesised results from all included studies at three, six, and twelve months post-surgery according to our pre-specified protocol [25], with the exception that we used a multivariate random-effects meta-analysis that accounts for the sparse data (many factors relative to the number of studies), as in our recent review of factors for post-surgical function [30]. Further protocol deviations are noted below, in the discussion and in the Methods in the Supplement.

The included studies reported associations as odds ratios (ORs), risk ratios (RRs), linear model coefficients (including differences), or correlations using discrete or continuous scales to measure factors and outcomes. Correlation coefficients were meta-analyzed on the arctangent scale [31], and estimates were back-transformed to the correlation scale for reporting.

We expected within-study correlation and between-study heterogeneity and therefore used a multivariate random-effects model to estimate mean rather than common correlations between factors and pain.

Heterogeneity was quantified by using I^2 statistics. P scores were calculated to evaluate the certainty that the mean correlation for each factor is larger in magnitude than the mean correlations for all other factors [32]. We also explored how estimates may depend on the choice of model: we removed factors supported by few studies (to decrease the impact of sparsity) and compared estimates from the two multivariate models and univariate meta-analyses for consistency. We then performed sensitivity analyses on pain at twelve months, and excluded studies judged to have high risk of bias for each QUIPS domain and re-ran the multivariate meta-analysis (S4 Appendix).

Statistical analyses were performed using Stata 16 (StataCorp LLC, College Station, Texas, USA). Mean correlations with 95% confidence intervals (CIs) are reported. Hypothesis testing was not predefined, but 2-sided P values are reported for completeness.

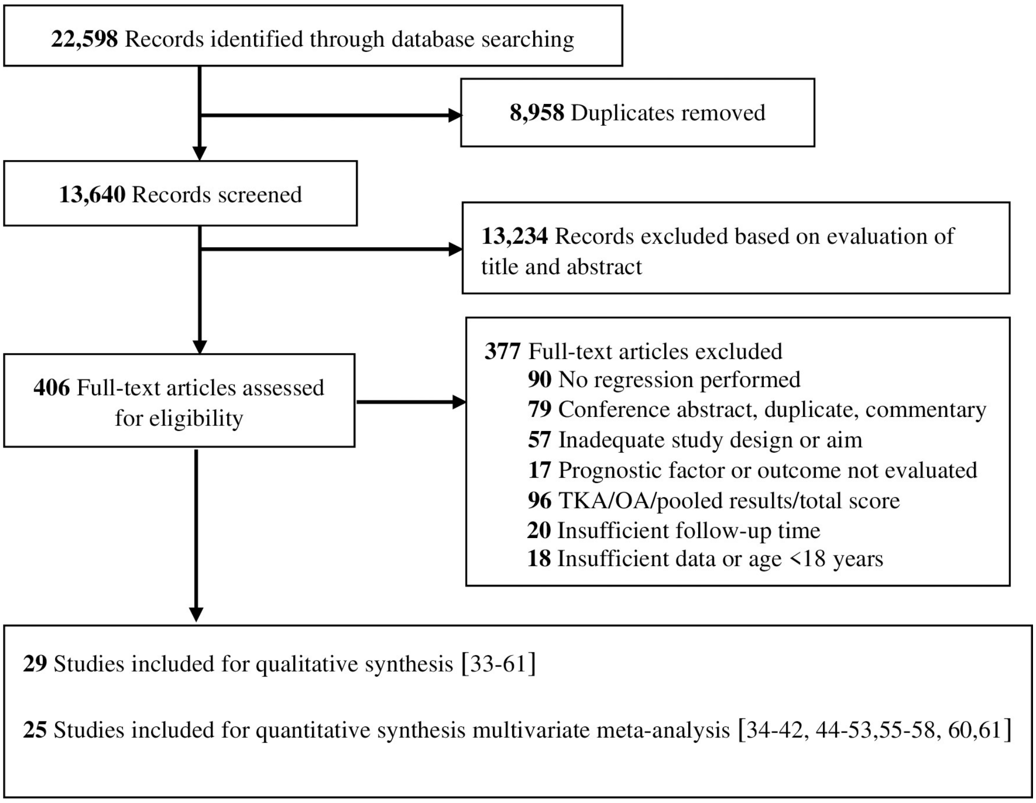
Results

The search yielded 13,640 studies. After title and abstract screening, 406 studies were assessed in full text and 374 were ineligible, leaving 29 studies [33–61] with a total sample of 10,360 patients (Fig 1). Sample sizes ranged from 26 [43] to 5309 [50]. We excluded eight studies from analysis because attempts to obtain missing data from authors were unsuccessful or insufficient [62–69]. The search strategy, subject headings and keywords customized for all databases is presented in S8 Appendix and reasons for study exclusion are in S9 Appendix.

In all, 61 preoperative and intraoperative factors were identified in the 29 studies [33–61]. All studies used prospective longitudinal observational designs, and most were single-center studies [33, 36–45, 48–51, 54, 55, 58–61] and conducted in European countries [33, 37, 39–48, 52, 57, 61]. No randomized trial met inclusion criteria. Mean age ranged from 63 [40] to 73 years [48], and the percentages of women in the samples varied from 49% [58] to 95% [40]. As shown in the Table 1, most studies used the Western Ontario and McMaster Universities Arthritis Index (WOMAC) to measure pain [34, 35, 37, 38, 47, 49, 51, 52, 58, 61].

We present separate estimates of mean correlations between preoperative and intraoperative factors and the three-, six- and twelve- month pain outcomes in multivariate meta-analysis (Figs 2–4). Multivariate meta-analytical estimates of correlation at each postoperative follow-up time are shown in Fig 2 and S1 Appendix. Descriptions of potential inconsistencies at three, six and twelve months are in S2 Appendix, and univariate meta-analyses for associations between individual factors and the outcomes are in S4 Appendix. Results from sensitivity analysis are presented in S1 Appendix. We provide a full glossary of labels for included factors in the Table in S5 Appendix. We report all estimates between preoperative and intraoperative factors and pain during the year (three, six and twelve months) after TKA as mean correlations, with positive correlations indicating more postoperative pain.

A total of 15 studies with 3,241 participants [33–46, 48] reported estimates for 34 factors correlated with pain twelve months after TKA (Fig 2). The two most common factors were preoperative pain [34, 36–42, 46] reported in nine studies and mental health (including anxiety, depression, psychological distress) reported in six studies [35–39, 45]. Most of these studies were judged as having high risk of bias on one or more domain (S6 Appendix).



TKA indicates total knee arthroplasty, OA, osteoarthritis.

Fig 1. Flow chart of included studies.

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Mean correlation between preoperative pain catastrophizing and pain twelve months after TKA was estimated to be 0.36 (95% CI, 0.24 to 0.47; $P < .001$; P score = 80.2%; three studies [34, 38, 48]; moderate-certainty evidence and substantial heterogeneity among reported estimates of association [$I^2 = 72.4\%$], while mean correlation for more temporal summation was estimated as 0.21 (95% CI, 0.05 to 0.36; $P < .000$; P score = 61.1%; two studies [42, 44]; very low-certainty evidence and heterogeneity among reported estimates of association might not be important [$I^2 = 0\%$]), more symptomatic joints was estimated to be 0.15 (95% CI, 0.08 to 0.23; $P < .001$; P score = 51.3%; two studies [34, 37]; moderate-certainty evidence and heterogeneity among reported estimates of association might not be important [$I^2 = 0\%$]), and more preoperative pain was estimated to be 0.13 (95% CI, 0.06 to 0.19; $P < .001$; P score = 44.6%; nine studies [34, 36–42, 46]; very low-certainty evidence and considerable heterogeneity among reported estimates of association [$I^2 = 97.0\%$]).

In contrast, mean correlation for more severe osteoarthritis and pain at twelve months was negative. The estimated correlation was -0.15 (95% CI, -0.23 to -0.08; $P < .001$; P score = 51.6%; three studies [36, 44, 46]; low-certainty evidence and heterogeneity among reported estimates of association might not be important [$I^2 = 0\%$]),

Results from the prespecified sensitivity analysis (S4 Appendix), estimated a mean correlation of 0.38 (95% CI, 0.04 to 0.64) between pain catastrophizing and more pain, compared to 0.28 (95% CI, 0.11 to 0.43) when including all studies. The mean correlation estimate was 0.15

Table 1. Characteristics of reviewed studies.

Study, country	Country	Design	Patients analyzed, No.	Data collection	Follow-up, mo	Baseline Age, y	Patients, No./Total No (%) Female	Male	Analysis	Factors measured	Outcome measure
Cremeans-Smith et al, 2016[a] [49]	United States	PC	101	NA	3	Mean, 69	75/110 (68)	35/110 (32)	Hierarchical linear regression	Education (level), pain (WOMAC), Cortisol (level), anaesthesia type (general vs spinal)	WOMAC
Lindner et al, 2018 [61]	Germany	PC	61	NA	3	Mean, 67	37/61 (61)	24/61 (39)	Stepwise multiple linear regression	Pain (WOMAC)	WOMAC
Lingard et al, 2007 [35]	UK, US, Canada, Australia	PC	676	1997–1999	3	Distress: median, 70 Non-distress: median, 71	574/676 (85)	102/676 (15)	Repeated measures	Psychological distress (SF-36)	WOMAC
Luo et al,2019 [59]	PC	PC	471	2017–2018	3	Mean, 64	357/471 (76)	114/471 (24)	Pearson correlation	Sleep dysfunction (PSQI), daytime sleepiness (ESS), sleep quality (self-developed scale)	KSS
Perruccio et al,2019 [60]	Canada	PC	477	2014–2016	3	Mean, 65	279/477 (58)	198/477 (42)	Linear regression	Age (y), sex (men/women), BMI, comorbidity (AAOs comorbidity Scale), symptomatic joint count, pain (KOOS), low back pain (yes/no), depression (HADS)	KOOS
Attal et al, 2012[a] [33]	France	PC	81	2008–2011	6	Mean, 69	58/89 (65)	31/89 (35)	Stepwise logistic regression	Trail Making Time (TMT-B time)	Brief Pain Inventory (BPI)
Bossman et al, 2017 [52]	Germany	PC	47	NA	6	Mean, 69	37/56 (66)	19/56 (34)	Analysis of variance (bootstrap)	Age (y), sex (men/women), BMI, pain (WOMAC), conditioned pain modulation (pressure pain algometry), heart rate variability (SDNN), temporal summation (pin-prick stimulator), pain catastrophizing (PCS), Sympathetic/parasympathetic activity (LogLF)	WOMAC
Bruehl et al, 2023 [54]	US	PC	91	NR	6	Mean, 67	57 (63)	34 (37)	Generalized linear density ratio model	Ischemia duration (blood sample), oxidative stress (blood sample)	MPQ-2
Bugada et al, 2017 [57]	Italy	PC	563	2012–2015	6	Median, 72	421/606 (69)	185/606 (31)	Logistic regression	Age (y),	NRS
Chen et al, 2021 [55]	China	PC	220	2019–2020	6	Pain ≥4: median, 70 Pain <4: median,71	102/220 (46)	118/220 (54)	Logistic regression	Age (y), serum angiotensin II Type 2 receptor (AT_2R), temporal summation (PD-Q), Anxiety and depression (HADS), disability (WOMAC). pain expectation (NRS), pain sites (count)	VAS

(*Continued*)

Table 1. (Continued)

Study, country	Country	Design	Patients analyzed, No.	Data collection	Follow-up, mo	Baseline Age, y	Patients, No./Total No (%) Female	Male	Analysis	Factors measured	Outcome measure
Edwards et al, 2022 [56]	US	PC	248	NA	6	Mean, 65	147 (59.5)	101 (40.5)	Backwards selection regression	Pain (BPI), State catastrophizing (PCS), catastrophizing (PCS), opioid use, sleep efficiency (PSQI), other chronic pain sites (count), painful areas (count), anxiety (PROMIS), agreeableness (NEO Inventory)	BPI
Engel et al, 2014 [58]	US	Case-control	54	NA	6	Mean, 68	36/74 (49)	38/74 (51)	Multiple hierarchical regression	Arthritis helplessness (AHI), coping efficacy (scale)	WOMAC
Escobar et al, 2007 [47]	Spain	PC	640	1999–2000	6	Mean, 72	473/640 (74)	167/640 (26)	General linear model	Age (y), sex (men/ women), social support (yes/no), comorbidity (CCI), pain (WOMAC), low back pain (yes/no), mental health (SF-36)	WOMAC
Fitz-simmons et al, 2018 [53]	Canada	PC	74	2014	6	Mean, 65	67/99 (68)	32/99 (32)	Multiple linear regression	Suspected neuropathic pain (SNEP), Preoperative pain (ICOAP), Pain catastrophizing (PCS), depression (PHQ, comorbidity (count)	ICOAP
Pua et al, 2019 [50]	Singapore	PC	4026	2013–2017	6	Mean, 68	3003/4026 (75)	1023/4026 (25)	Proportion-al odds regression	Age (y), Sex (Men/ women), BMI, education (primary, secondary, tertiary), ethnicity (Chinese, Indian, Malay, other), social support (yes/no), comorbidities (yes/no), contralateral knee pain (KSS), pain (OKQ), Knee extension and flexion (goniometer), physical function (categories), depression (SF-36)	OKQ
Yang et al, 2019 [51]	US	PC	107	2010–2011	6	Mean, 65	55/107 (51)	52/107 (49)	Multiple logistic regression	Mental health (SF-36), Pain catastrophizing (PCS), use device (yes/ no)	WOMAC
Attal et al, 2012a [33]	France	PC	69	2008–2011	12	Mean, 69	58/89 (65)	31/89 (35)	Stepwise logistic regression	Recall (ROCF)	BPI
Dave et al, 2017 [34]	United States	PC	241	2012–2014	12	Mean, 67	146/241 (61)	95/241 (39)	Poisson regression	Painful body regions (count), pain (WOMAC), pain catastrophizing (PCS)	WOMAC

(*Continued*)

Table 1. (Continued)

Study, country	Country	Design	Patients analyzed, No.	Data collection	Follow-up, mo	Baseline Age, y	Patients, No./Total No (%) Female	Male	Analysis	Factors measured	Outcome measure
Dowsey et al, 2012 [36]	Australia	PC	473	2006–2007	12	Mean, 71	331/473 (70)	142/473 (30)	Multivariate linear regression	Age (y), sex (men/ women), BMI, comorbidity (CCI), pain (IKSS), physical function (IKSS), mental health (SF-12), Osteoarthritis severity (K-L grade), cruciate retaining, patella resurface	IKSS
Getachew et al, 2020 [39]	Norway	PC	185	2012–2014	12	Mean, 68	137/202 (68)	65/202 (32)	Multiple logistic regression	Age (y), Sex (men/ women), Pain (NRS), fatigue (LFS) Sleep quality (PSQI), depression (HAD)	BPI
Giordiano et al, 2020 [41]	Denmark	PC	136	NR	12	High pain relief: mean, 69 Low pain relief: mean, 68	82/136 (60)	54/136 (40)	Linear regression	Pain (VAS), circulating micromiRna-146a-5p (venous blood)	VAS
Hardy et al, 2022 [48]	France	PC	103	2014–2015	12	Mean, 73	67/36	65/35	Logistic regression	Catastrophizing (PCS)	VAS
Kornilov et al, 2018 [40]	Russia	PC	79	2014	12	Mean, 63	75/79 (95)	4/79 (5)	Logistic regression	Pain (BPI), physical activity (HUNT 2 physical activity score)	BPI
Lingard et al,2007a [35]	UK, US, Canada, Australia	PC	676	1997–1999	12	Distress: median, 70 Non-distress: median, 71	574/676 (85)	102/676 (15)	Repeated measures	Psychological distress (SF-36)	WOMAC
Petersen et al, 2015 [42]	Denmark	PC	78	NA	12	Low pain: mean, 68 High pain group: mean, 72	50/78 (59)	28/78 (41)	Multi-variate logistic regression	Pain (VAS), temporal summation (von Frey stimulator)	VAS
Petersen et al, 2017 [44]	Denmark	PC	130	NA	12	Chronic pain: mean, 69 Normal recovery: mean, 68	Chronic pain: 14/ 19 (74) Normal recovery: 59/105 (56)	Chronic pain: 5/19 (26) Normal recovery: 46/105 (44)	Linear regression	Temporal summation (von Frey stimulator), K-L grade, warm detection-/heat pain threshold	VAS
Petersen et al, 2020 [43]	Denmark	PC	26	2011–2012	12	High pain: Mean, 64 Low pain: mean, 70	14/26 (54)	12/26 (46)	Pearson correlation	Synovial membrane thickness (CE-MRI), degree perfusion (voxels*ME), volume perfusion (IRE), synovitis severity	VAS
Tilbury et al, 2018 [45]	Netherlands	PC	146	2011–2012	12	Mean, 67	101/146 (69)	87/146 (31)	Multi-variate linear regression	BMI, mental health (SF-36), outcome expectancies (HSS)	KOOS

(*Continued*)

Table 1. (Continued)

Study, country	Country	Design	Patients analyzed, No.	Data collection	Follow-up, mo	Baseline Age, y	Patients, No./Total No (%) Female	Male	Analysis	Factors measured	Outcome measure
Sullivan et al, 2011 [38]	Canada	PC	120	NA	12	67 (mean)	73/120 (61)	47/120 (39)	Multiple regression	Age (y), sex (men/ women), BMI, comorbidity (CCI), pain (WOMAC), pain catastrophizing (PCS), depression (PHQ-9), kinesophobia (TSK), surgery duration (minutes)	WOMAC
Van de Water et al, 2019 [46]	Netherlands	PC	559	2012–2015	12	Mean, 67	378/559 (68)	181/559 (32)	Multi-variate linear regression	Pain (KOOS), K-L grade	KOOS
Wylde et al, 2012 [37]	United Kingdom	PC	220	NA	12	Median, 70	136/220 (62)	84/220 (38)	Ordinary least squares regression	Age (y), sex (men/ women), comorbidity (SCQ), pain (WOMAC), depression (HADS), anxiety (HADS), pain-self efficacy (PSEQ)	WOMAC

AAOS comorbidity Scale, American Academy of Orthopaedic Surgeons comorbidity scale; AHI, Arthritis Helplessness Index; AT_2R, Angiotensin Type 2 receptor; BMI, Body Mass Index; BPI, Brief Pain Inventory; CCI, Charlson Comorbidity Index; CE-MRI, contrast-enhanced magnetic resonance imaging; ESS, Epworth; Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; HSS, Hospital for Special Surgery; HUNT 2, The Trøndelag Health Study 2; ICOAP, Intermittent and Constant Osteoarthritis Pain; IKSS, International Knee Society Score; IRE, Initial Rate of Enhancement; K-L Grade, Kellgren Lawrence Grade; KOOS, Knee Injury and Osteoarthritis Outcome Score; KSS, Knee Society Rating System; LFS, Lee Fatigue Scale; LogLF; Low-Frequency Power (log-transformed); ME, Maximum Enhancement; MPQ-2, short Form-McGill Pain Questionnaire-2; NA, not applicable; Neo Inventory, NEO Personality Inventory; NRS, Numerical Rating Scale; PCS, Pain catastrophizing Scale; PROMIS, Patient-Reported Outcomes Measurement Information System (PROMIS); OKQ, Oxford Knee Questionnaire; PC, prospective cohort; PCS, Pain Catastrophizing Scale; PD-Q, Pain Detect Questionnaire; PHQ, Patient Health Questionnaire; PSEQ, Pain Self-Efficacy Scale; PSQI, Pittsburgh Sleep Quality Index; ROCF, Rey Osterreich Complex Figure; SCQ, Self-Administered Comorbidity questionnaire; SDNN, standard deviation RR-intervals; SF-12, 12-Item Short-Form Health Survey; SF-36, 36-Item, Short Form Health Survey; SNEP, Self-Leeds Assessment of Neuropathic Symptoms and Signs; TMT-B time, Trail Making Time; TSK, Tampa Scale of Kinesophobia; TUG, Timed Up and Go; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

[a] Study with 2 follow-up time

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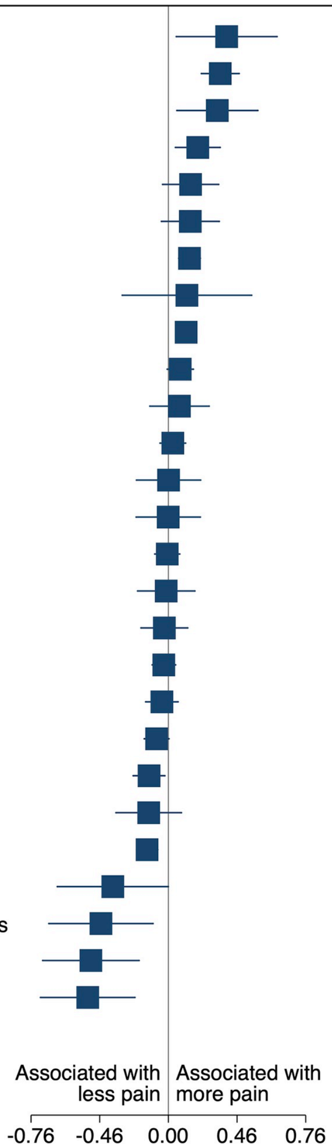
(95% CI 0.06 to 0.24) for symptomatic joints compared to 0.15 (95% CI 0.07 to 0.23) when including all studies. The mean correlation estimate was 0.16 (95% CI -0.00 to 0.25) for level of pain compared to 0.13 (95% CI 0.06 to 0.19) when including all studies. Mean correlation estimate was -0.15 (95% CI -0.24 to -0.06) for more severe osteoarthritis compared to -0.15 (95% CI -0.23 to -0.08) when including all studies. The association for temporal summation identified in the multivariate meta-analysis was obscured in the sensitivity analysis as the statistical analysis domain was judged high risk of bias.

There was 11 studies with 6,078 participants that included estimates for 34 potential factors associated with pain six months after TKA (Fig 3) [33, 47, 50–58]. Mean correlation with preoperative pain was 0.20 (95% CI 0.12 to 0.28; $P < .000$; P score = 66.1%; five studies [47, 50, 52, 53, 56]; low-certainty evidence and heterogeneity among reported estimates of association may not be important [$I^2 = 37.6\%$]). Mean correlation with better mental health was -0.13 (95% CI -0.24 to -0.02; $P = 0.01$; P score = 49.1%; six studies [47, 50, 52, 53, 56]; moderate-certainty evidence and heterogeneity among reported estimates of association may not be important [$I^2 = 29.1\%$]).



	Correlation	95% CI			*p*-value	Studies	*P*-score	*I*²
↑Fatigue	0.40	0.06	to	0.66	0.02	1	80.4%	.
↑Catastrophizing	0.36	0.24	to	0.47	0.00	3	80.2%	72.4%
↑ROCF Recall	0.34	0.06	to	0.57	0.01	1	75.7%	.
↑Temporal Summation	0.21	0.05	to	0.36	0.00	2	61.1%	0.0%
↑miRNA-146a-5p	0.16	-0.04	to	0.35	0.15	1	49.8%	.
↑Heat Pain Threshold	0.16	-0.05	to	0.35	0.17	1	49.3%	.
↑Symptomatic Joints	0.15	0.08	to	0.23	0.00	2	51.3%	0.0%
Worse Sleep Quality	0.13	-0.32	to	0.54	0.78	1	46.2%	.
↑Preoperative Pain	0.13	0.06	to	0.19	0.00	9	44.6%	97.0%
↑BMI	0.09	-0.01	to	0.18	0.07	3	33.6%	72.9%
↑Warm Detection Threshold	0.08	-0.13	to	0.29	0.65	1	36.4%	.
↑Comorbidity	0.03	-0.06	to	0.12	0.67	3	23.8%	0.0%
↑Kinesophobia	0.00	-0.23	to	0.23	1.00	1	20.0%	.
↑Surgery Duration	-0.00	-0.23	to	0.23	1.00	1	20.0%	.
Male Gender	-0.01	-0.10	to	0.08	0.97	4	29.9%	0.0%
↑Preoperative Function	-0.02	-0.22	to	0.19	0.98	2	40.5%	90.1%
↑Pain Self-Efficacy	-0.03	-0.20	to	0.14	0.91	1	32.7%	.
↑Age	-0.03	-0.12	to	0.05	0.61	4	23.1%	0.0%
Patella Resurfaced	-0.05	-0.16	to	0.07	0.60	1	27.4%	.
↑Mental Health	-0.09	-0.17	to	0.00	0.07	6	33.4%	69.0%
Cruciate Retaining	-0.14	-0.25	to	-0.03	0.01	1	47.2%	.
↑Outcome Expected	-0.14	-0.36	to	0.09	0.30	1	46.0%	.
↑K-L Grade	-0.15	-0.23	to	-0.08	0.00	3	51.6%	0.0%
↑Synovitis Severity	-0.38	-0.67	to	-0.00	0.05	1	77.3%	.
↑Synovial Membrane Thickness	-0.46	-0.70	to	-0.11	0.01	1	85.5%	.
↑Synovial Perfusion (Volume)	-0.51	-0.72	to	-0.21	0.00	1	90.7%	.
↑Synovial Perfusion (Degree)	-0.53	-0.73	to	-0.24	0.00	1	92.0%	.

Fig 2. Forest plot of factors associated with pain at twelve months.

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For the other secondary outcome, pain three months after TKA, five studies with 1786 patients provided pain outcome data at three months after TKA for 14 potential factors (Fig 4) [35, 49, 59–61]; Mean correlation with preoperative pain was 0.27 (95% CI 0.13 to 0.39; $p <$ .001; P score = 81.0%; three studies [49, 60, 61]; low-certainty evidence and heterogeneity among reported estimates of association may not be important [$I^2 = 0\%$]).

Meta-analytical estimates for the other factors do not exclude the possibility of no correlation with pain at three, six, and twelve months. It is plausible that these factors are uncorrelated with pain, but also possible that important correlations exist but cannot be estimated with much precision.

	Correlation	95% CI			*p*-value	Studies	*P*-score	I^2
↑Oxidative Stress	0.33	0.12	to	0.52	0.00	1	84.5%	.
↑Trail Making Time	0.32	0.06	to	0.54	0.01	1	81.4%	.
↑Arthritis Helplessness	0.27	-0.02	to	0.52	0.08	1	71.8%	.
↑Walking Aid Use	0.25	-0.15	to	0.58	0.29	1	64.0%	.
↑AT2R Level	0.23	0.07	to	0.38	0.00	1	70.4%	.
↑Preoperative Pain	0.20	0.12	to	0.28	0.00	5	66.1%	37.6%
Other Chronic Pain	0.16	0.00	to	0.31	0.03	1	55.2%	.
Opioid Use	0.15	-0.01	to	0.30	0.05	1	52.6%	.
↑Low Back Pain	0.14	0.03	to	0.24	0.01	1	49.7%	.
↑Temporal Summation	0.13	-0.03	to	0.28	0.11	2	46.8%	0.0%
↑Catastrophizing	0.09	-0.03	to	0.21	0.16	4	36.5%	0.0%
↑Heart Rate Variability	0.08	-0.29	to	0.43	0.87	1	44.3%	.
↑Comorbidity	0.08	0.00	to	0.16	0.04	3	34.4%	25.0%
↑Symptomatic Joints	0.08	-0.04	to	0.20	0.22	2	34.4%	74.2%
↑Knee Flexion	0.08	0.01	to	0.15	0.03	1	33.3%	.
↑Education	0.07	-0.15	to	0.28	0.75	1	37.4%	.
↑Preoperative Function	0.06	-0.16	to	0.27	0.81	1	37.0%	.
↑Contralateral Knee Pain	0.04	-0.04	to	0.12	0.29	1	23.2%	.
↑Pain Expected	0.04	-0.14	to	0.21	0.86	1	32.9%	.
↑Knee Extension	0.00	-0.07	to	0.07	1.00	1	12.6%	.
↑BMI	-0.01	-0.08	to	0.06	0.92	2	19.7%	0.0%
Male Gender	-0.02	-0.09	to	0.06	0.81	3	19.3%	74.2%
↑Age	-0.03	-0.09	to	0.04	0.55	5	20.7%	52.3%
↑Social Support	-0.08	-0.15	to	-0.00	0.05	2	33.3%	0.0%
↑Disability	-0.10	-0.27	to	0.07	0.32	1	40.3%	.
↑Mental Health	-0.13	-0.24	to	-0.02	0.01	6	49.1%	29.1%
↑Sleep Effiency	-0.15	-0.30	to	0.01	0.05	1	52.3%	.
↑Ischemia Duration	-0.16	-0.40	to	0.09	0.29	1	52.4%	.
↑Agreeableness	-0.18	-0.34	to	-0.00	0.04	1	57.8%	.
Suspected Neuropathic Pain	-0.19	-0.44	to	0.09	0.24	1	57.1%	.
↑Sym/Parasym Activity	-0.28	-0.56	to	0.07	0.13	1	70.5%	.
Chinese Ethnicity	-0.35	-0.51	to	-0.16	0.00	1	86.9%	.
↑Pain Self-Efficacy	-0.35	-0.57	to	-0.08	0.01	1	84.8%	.
↑Pain Modulation	-0.38	-0.62	to	-0.08	0.01	1	86.9%	.

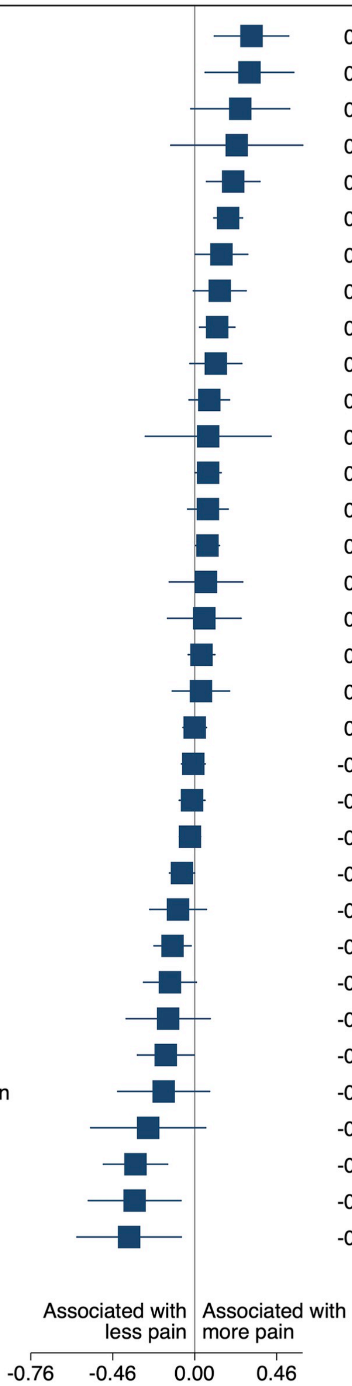

Fig 3. Forest plot of factors associated with pain at six months.

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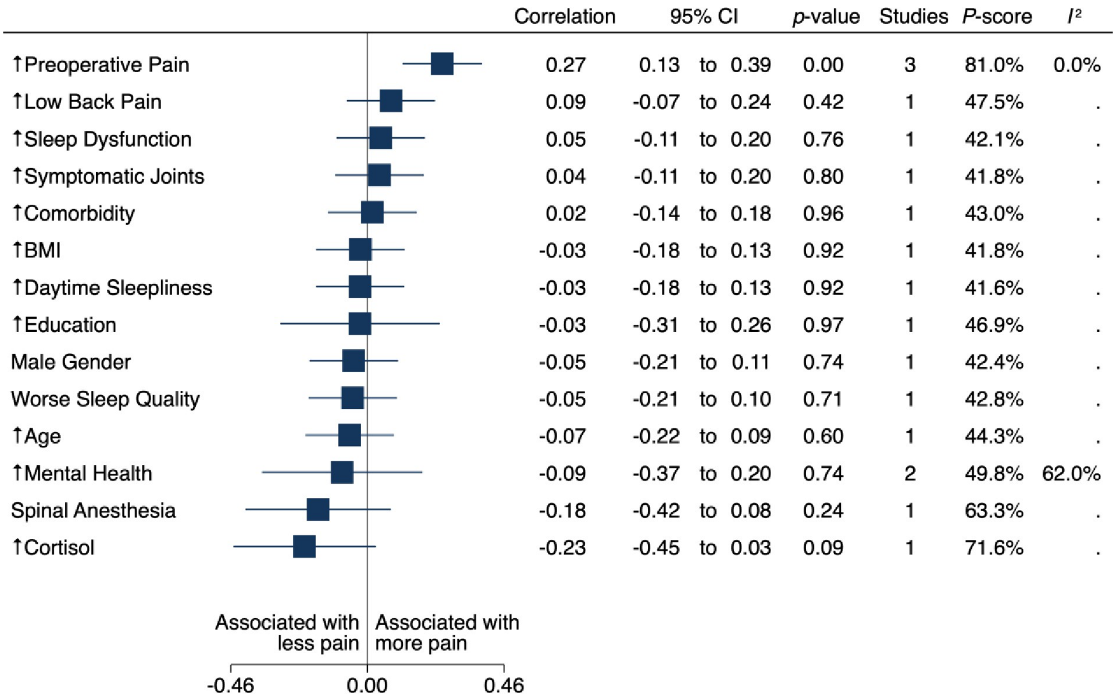

Fig 4. Forest plot of factors associated with pain at three months.

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We compared meta-analytic estimates from three models and there was reasonable consistency between the univariate and multivariate meta-analysis for all factors with respect to direction of association (S2 Appendix).

Decisions regarding risk of bias for each QUIPS domain are shown in S4 Fig in S1 Appendix. We judged the included studies to be generally low risk of bias for prognostic factor measurement (n = 16) and outcome measurement (n = 21). In contrast, some studies were judged high risk of bias for study participation (n = 12), study attrition (n = 16), and statistical analysis (n = 13).

Full details of our certainty of evidence (GRADE) judgements are provided in S7 Appendix. Risk of bias and imprecision were the most common reasons for downgrading the certainty of evidence.

Discussion

To our knowledge this is the first systematic review and meta-analysis examining factors correlated with pain at three, six and twelve months after TKA that also evaluated certainty of evidence. For the primary outcome at twelve months and based on at total sample of 3,241 patients, we estimated that pain catastrophizing, more symptomatic joints, and higher level of preoperative pain were correlated with worse pain outcomes, while more severe radiographic osteoarthritis were correlated with better pain outcome twelve months later. Our findings suggest that more severe preoperative pain is correlated with worse pain outcomes and that better mental health is associated with better pain outcomes at three and six months. It is worth noting that our findings do not indicate that the individual patient with a poor risk profile will experience chronic postsurgical pain if they undergo TKA surgery. Findings simply suggest that the identified factors were correlated with less or worse pain in an absolute sense. Thus, our results should be interpreted accordingly.

We estimated moderate-certainty evidence that pain catastrophizing is correlated with worse pain outcomes at twelve months. The correlation was larger in sensitivity analysis where we removed a study with high risk of bias. Our findings are similar to results from prior systematic reviews or meta-analyses [18, 22, 70]. However, our study differs in two critical ways: our results are entirely based on prospective studies, and we did not pool results from studies with short-term and longer-term follow-up. Efficacy for cognitive behavioral therapy to enhance skills for coping with pain remains unknown [71, 72], and still TKA surgery may be the most effective intervention, giving more pain relief, than non-operative treatment.

We found moderate-certainty evidence that a higher number of symptomatic joints was associated with more pain twelve months after TKA, with equal correlation in the sensitivity analysis. This result is supported by findings from a previous univariate meta-analysis that identified multiple painful sites as a factor influencing the pain outcome [18] but the association was not significant in the multivariate meta-analysis. Degenerated cartilage and subchondral bone are removed during surgery; however, pain may also be generated from other structures or tissue surrounding the knee, which might influence pain outcome.

We found positive correlations between more preoperative pain and pain severity at twelve months (very-low certainty evidence). Positive correlations were also identified for the secondary outcomes at three and six months (low-certainty evidence). Our findings are in consistency with other reviews and meta-analysis [13, 18]. There is emerging evidence that improvement in pain for most patients usually follows a steep trajectory in the first three to six postoperative months, before pain levels seems to plateau at twelve months [73–75]. Accordingly, we have added new evidence on preoperative factors correlated with adverse pain outcomes at three, six and twelve months after TKA. There were no intraoperative factors that correlated with pain outcomes at three, six or twelve months.

We found a negative correlation between severity of osteoarthritis and pain at twelve months, i.e., the more severe the osteoarthritis before surgery, the lower the pain severity twelve months later. Although the evidence was rated as low-certainty, the correlation persisted in the sensitivity analysis. Another meta-analysis has shown that patients with mild radiographic osteoarthritis reported more pain after TKA [16]. In contrast to our study, evidence was not graded and retrospective study designs with follow-up from one to six years were included. Results from our and their meta-analyses indicate that patients with severe osteoarthritis might gain more from TKA surgery than patients with less severe osteoarthritis. Non-operative treatment options should be considered to all patients with low-grade radiographic OA findings before surgery [76].

This study had many strengths, including up-to-date robust methods that followed Cochrane Handbook guidelines with descriptions in a pre-specified peer-reviewed protocol [25], a preprint [26], assessing risk of bias using QUIPS, and judging certainty of evidence using GRADE. We included only longitudinal prospective studies with associations reported at pre-defined time points in the first postoperative year and applied multivariate meta-analysis when the number of variables was large relative to number of studies [26].

There are some limitations that need to be addressed. First, we included studies that were largely heterogeneous for measurement of factors. Less heterogeneity existed in postoperative pain measures, with WOMAC being the most common. We used a number of exploratory statistics to estimate associations. Researchers either opt for narrow eligibility criteria and risk excluding potentially useful evidence, or wider eligibility criteria that require appropriate methods to address the heterogeneity [27]. We chose the latter, but results should be interpreted carefully due to underlying heterogeneity. Some included studies had large sample sizes that resulted in narrow CIs, and I^2 for the pooled results tend to be very high and might be misleading [29]. Our estimates may also be biased by including several studies judged high risk of bias. To address this issue, we performed pre-specified sensitivity analyses excluding studies with high risk of bias for each QUIPS domain. We were unable to perform planned analyses of non-reporting bias and small study effects, or planned subgroup analyses, because the number of included studies did not meet our pre-specified criterion. We had also planned leave-one-study-out sensitivity analysis to explore the influence of each study on meta-analysis results, but this was not feasible. Many of the studies in our review had limitations that resulted in downgrading our certainty of the evidence. This does not necessarily indicate that those studies were of poor quality, but that important areas requiring documentation according to methodological standards were not reported. The importance of consistent reporting following these standards should be stressed so that evidence can be evaluated with high certainty. We suggest that researchers design studies using tools such as QUIPS to minimize risk of bias. We did not address the magnitude of change in pain score, which probably would be the most interesting for the patients, but only the degree of pain at twelve months.

Conclusions

Our findings suggest that the preoperative factors of pain catastrophizing, symptomatic joints, pain, and radiographic osteoarthritis are correlated with pain one year after TKA. Pain are correlated with the six- and three- months pain outcomes, while mental health is correlated with pain at six months. However, our result highlights the need for further investigation on several factors that have been evaluated only once or in studies with small sample sizes. These factors should be considered when developing predictive models to identify patients most likely to experience chronic post-surgical pain. Accurately identifying factors associated with the pain outcome will be crucial for the development of effective predictive models.

Supporting information

S1 Checklist. PRISMA 2020 checklist.
(PDF)

S1 Appendix. Methods and results multivariate meta-analyses.
(PDF)

S2 Appendix. Exploring potential inconsistency.
(PDF)

S3 Appendix. Univariate meta-analysis.
(PDF)

S4 Appendix. Sensitivity analysis.
(PDF)

S5 Appendix. Definition and labels of the factors.
(PDF)

S6 Appendix. Risk of bias.
(PDF)

S7 Appendix. Grading of recommendation assessment, development and evaluation.
(PDF)

S8 Appendix. Search strategy.
(DOCX)

S9 Appendix. Reason for exclusion of individual studies.
(DOCX)

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Factors Correlated With Physical Function 1 Year After Total Knee Arthroplasty in Patients With Knee Osteoarthritis
A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE More than 1 in 5 patients do not experience improved physical function after total knee arthroplasty (TKA). Identification of factors associated with physical function may be warranted to improve outcomes in these patients.

OBJECTIVE To identify preoperative and intraoperative factors associated with physical function at 12 months after TKA in a systematic review and meta-analysis.

DATA SOURCES Data from January 2000 to October 2021 were searched in Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, and Physiotherapy Evidence Database (PEDro). No language restrictions were applied.

STUDY SELECTION Prospective observational studies or randomized clinical trials on factors associated with physical function after TKA in adult patients with osteoarthritis were selected. A prespecified peer-reviewed protocol was followed.

DATA EXTRACTION AND SYNTHESIS Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline, 2 reviewers independently screened titles and abstracts and judged risk of bias using Quality in Prognosis Studies (QUIPS). Multivariate random-effects meta-analyses were performed to estimate mean correlations between factors and physical function with 95% CIs. Sensitivity analyses were conducted for each QUIPS domain. Certainty of evidence was evaluated using Grading of Recommendations, Assessment, Development and Evaluations (GRADE). This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO).

MAIN OUTCOMES AND MEASURES The primary outcome was physical function 12 months after TKA. Secondary outcomes were physical function 3 and 6 months after TKA. All estimates are mean correlations between factors and postoperative function. Positive correlations correspond to better function.

RESULTS Among 12 052 articles, 20 studies (including 11 317 patients and 37 factors) were analyzed. Mean correlation with higher BMI was estimated to be −0.15 (95% CI, −0.24 to −0.05; *P* = .33; moderate-certainty evidence), while mean correlation with better physical function was estimated to be 0.14 (95% CI, 0.02 to 0.26; *P* = .03; low-certainty evidence) and mean correlation with more severe osteoarthritis was estimated to be 0.10 (95% CI, 0.01 to 0.19; *P* = .17; high-certainty evidence). In sensitivity analyses, mean correlation with better physical function was estimated to be 0.20 (95% CI, 0.04 to 0.36; *P* = .02), and so perhaps a larger coefficient than in the main analysis, while mean

(continued)

Key Points

Question What preoperative and intraoperative factors are correlated with physical function after total knee arthroplasty (TKA)?

Findings In this systematic review and meta-analysis of 20 studies that included 11 317 patients with osteoarthritis, higher preoperative body mass index (BMI) was correlated with worse physical function, while better preoperative physical function and more severe osteoarthritis were correlated with better physical function 1 year after TKA.

Meaning These findings suggest that presurgical BMI, physical function, and osteoarthritis severity may be important factors to include and test in models predicting TKA outcomes.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

correlations were estimated to be similar for other factors (BMI: −0.17; 95% CI, −0.28 to −0.06; $P < .001$; osteoarthritis severity: 0.10; 95% CI, −0.01 to 0.20; $P = .05$).

CONCLUSIONS AND RELEVANCE This study found that higher presurgical BMI was correlated with worse physical function (with moderate certainty) and that better physical function (low certainty) and osteoarthritis severity (high certainty) were correlated with better physical function after TKA. These findings suggest that these factors should be included when testing predictive models of TKA outcomes.

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Introduction

Total knee arthroplasty (TKA) has become the third most common inpatient surgery in the United States, with 750 000 yearly procedures projected to double in the next decade.[1,2] TKA is regarded as a cost-efficient and effective treatment for restoring physical function in patients with end-stage osteoarthritis.[3] However, more than 1 in 5 patients do not regain physical function after TKA.[4] Nonimprovement of physical function is a risk factor associated with more expensive revision surgery and an immense burden at individual, health care system, and socioeconomic levels.[5,6]

Factors identified in predictive models using high-quality evidence could improve patient outcomes, particularly for those who are unlikely to benefit from surgery or who have unrealistic expectations. Evidence on factors associated with physical function has been reviewed previously, but findings were contradictory, limited in scope, based on pooled data across short-term and longer-term outcomes, or did not address certainty of evidence.[7-13] Thus, there is need for a new synthesis of evidence on short-term TKA outcomes that uses current systematic review methods and captures recently published studies. The aim of this systematic review and meta-analysis was to synthesize evidence on preoperative and intraoperative factors associated with physical function 12 months after TKA (primary outcome) and 3 and 6 months after TKA (secondary outcomes).

Methods

In this systematic review and meta-analysis, we followed a prespecified peer-reviewed protocol[14] and a preprint[15] registered in International Prospective Register of Systematic Reviews (PROSPERO; CRD42018079069), designed and conducted according to Cochrane Handbook guidelines.[16] Results are reported according to the recently revised Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

Search Strategy and Data Sources

The search strategy was collaboratively developed by researchers (U.O. and M.F.L.) and research librarians, with feedback from the research team.[14] Published studies from January 1, 2000, to October 8, 2021, were systematically searched, with no language restrictions, in Medline (Ovid), Embase (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCO), Cochrane Library, and Physiotherapy Evidence Database. References were managed using Endnote X8 software version 20.2.1 (Clarivate Analytics). Subject headings and keywords for each database are described in eTable 5 in the Supplement, and full search strategies for each database are defined in the protocol.[14]

Eligibility Criteria

To be maximally inclusive, studies had to include estimates of association between preoperative or intraoperative factors and physical function at 3, 6, or 12 months after TKA. We considered studies eligible if participants were adults diagnosed with osteoarthritis scheduled for primary TKA. Prospective longitudinal observational studies and randomized clinical trials that provided sufficient estimates of association were eligible. We excluded retrospective and case-control studies, as well as conference abstracts. We also excluded studies with mixed patient populations (eg, rheumatoid arthritis, total hip arthroplasty, or unicompartmental arthroplasty) if separate outcome data were not reported for osteoarthritis and TKA.

Outcomes

The primary outcome was physical function at 12 months after TKA. Secondary outcomes were physical function 3 and 6 months after TKA.

Study Selection and Data Extraction

Data from included studies were extracted to a standardized extraction form, with details in the published protocol.[14] Data included study design, sample size, country, age, sex, body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]), outcome measures used, data collection time points, statistical analyses, and estimates of association. One reviewer performed data extraction (U.O.), while another reviewer checked data accuracy against source material (M.F.L.). Two reviewers (U.O. and M.F.L.) evaluated titles and abstracts for applicability, then read and checked full-text publications against eligibility criteria. Another author (E.D.) was involved in resolving disagreements.

Methodological Quality

Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool,[17] following the strategy described in the protocol,[14] in which 2 reviewers (U.O. and M.F.L.) independently assessed risk of bias and had consensus discussions before arriving at consensus. In cases of disagreement, E.D. was involved in the final decision. QUIPS has 6 risk domains: study participation, attrition, prognostic factor measurement, statistical analysis and reporting, confounding, and outcome measurement.

Certainty of Evidence

Two researchers (U.O. and M.F.L.) rated certainty of evidence by consensus discussion using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.[18,19] In some cases, a third researcher (E.D.) was involved in discussions. Certainty of evidence was graded as high, moderate, low, or very low. We used GRADEpro GDT (McMaster University) to summarize evidence.

Statistical Analysis

Findings for all included studies were synthesized by outcomes at 3, 6, or 12 months after TKA as described in the protocol.[14] We were unable to complete planned multivariate random-effects meta-analysis because extracted data were too sparse (with a large number of factors reported by relatively few studies). Accordingly, we used a frequentist version of the bayesian multivariate model.[15] Additional protocol deviations are explained in eMethods in the Supplement.

To quantify associations between potential factors and the outcome, we extracted odds ratios (ORs), risk ratios (RRs), linear model coefficients (including differences), or correlations using discrete or continuous scales. We meta-analyzed hyperbolic arctangent–transformed correlation coefficients,[20] which under reasonable assumptions can be imputed for these measures of association and are invariant under linear transformation. This approach allowed inclusion of studies using various measurement tools and analyses in the meta-analysis.

We anticipated that studies would use different instruments and statistical methods that could lead to between-study heterogeneity. Therefore, multivariate random-effects meta-analysis was conducted to estimate mean correlations (ie, not common correlations) between factors and postoperative physical function.

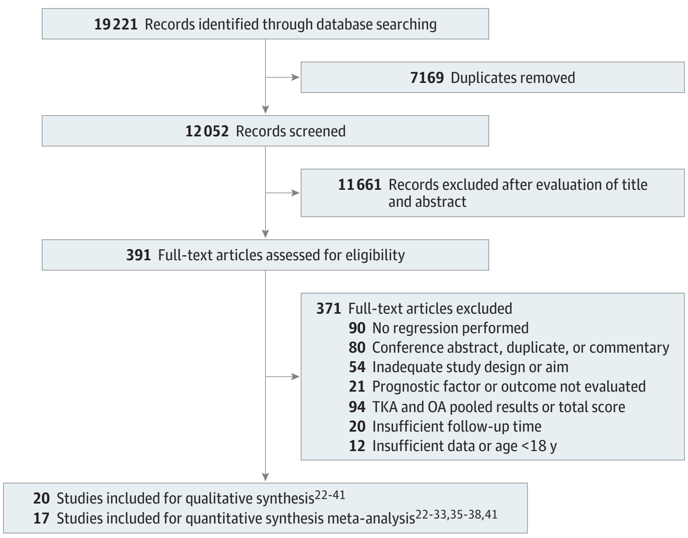
Heterogeneity was quantified using I^2 statistics. We used *P* scores that measured the certainty that the mean correlation for a factor was larger than those for all other factors.[21] We also performed exploratory univariate meta-analyses and multivariate meta-analyses (after removing factors supported by few studies to reduce the problem of sparsity of estimation). Estimates from 3 models were compared for consistency. Finally, sensitivity analyses on physical function at 12 months after TKA were conducted for each QUIPS domain by excluding studies judged as high risk of bias and rerunning multivariate meta-analysis.

Statistical analyses were performed using Stata statistical software version 16 (StataCorp). We report mean correlations with 95% CIs. We did not prespecify any hypothesis testing but report 2-sided *P* values for completeness.

Results

The **Figure 1** study flow diagram outlines study selection and reasons for exclusion.[22-41] From 12 052 articles screened for title and abstracts, 391 articles were selected for full-text examination, with 20 studies[22-41] (total sample = 11 317 patients) for qualitative analysis at 3, 6, and 12 months and 17 studies[22-33,35-38,41] for quantitative analysis at 6 and 12 months. Individual study characteristics are detailed in the **Table**.[22-41] All were prospective longitudinal observational designs; no randomized trial met inclusion criteria. We identified 37 factors across 20 studies. There were 8 studies[26-30,34,37,38] conducted in Europe, 6 studies[24,31-33,39,40] in Asia, 4 studies[25,35,36,41] in North America, and 1 study[22] in Australia, and 1 study[23] was multicontinental (ie, Australia, Europe, and North America). Sample sizes ranged from 49 patients[36] to 5309 patients.[31] Mean age varied from 63 years[35] to 75 years,[32] and representation of women ranged from 49.3%[36] to 90.0%.[32] The most common physical function measure was the Western Ontario and McMaster Universities Arthritis Index (WOMAC). We excluded 6 studies from analysis.[42-47] owing to unsuccessful attempts to obtain missing data. Sedentary behavior,[40] lack of energy,[38] drowsiness,[38] sleeping difficulties,[38]

Figure 1. Flowchart of Included Studies



OA indicates osteoarthritis; TKA, total knee arthroplasty.

Table. Characteristics of Reviewed Studies

Source	Country	Design	Patients analyzed, No.	Data collection	Follow-up, mo	Baseline age, y	Patients, No./Total No. (%)		Analysis	Factors measured	Outcome measured
							Female	Male			
Berghmans et al,[37] 2019[a]	Netherlands	PC	146	NA	3	Mean, 66.4	79/150 (53)	71/150 (47)	Stepwise multiple linear regression	Mental health (SF-36), physical function (WOMAC), knee stiffness (WOMAC)	WOMAC
Lindner et al,[34] 2018	Germany	PC	61	NA	3	Mean, 67	37/61 (61)	24/61 (39)	Stepwise multiple linear regression	Pain (WOMAC)	WOMAC
Lingard et al,[23] 2007[a]	UK, US, Canada, Australia	PC	676	1997-1999	3	Distress: median, 70 Nondistress: median, 71	574/676 (85)	102/ 676 (15)	Repeated measures	Psychological distress (SF-36)	WOMAC
Luo et al,[39] 2019	China	PC	471	2017-2018	3	Mean, 64.3	357/471 (76)	114/471 (24)	Pearson correlation	Sleep dysfunction (PSQI), daytime sleepiness (ESS), sleep quality (self-developed scale [0-10])	KSS
Bugada et al,[29] 2017	Italy	PC	563	2012-2015	6	Median, 72	421/606 (69)	185/606 (31)	Logistic regression	Comorbidity (ASA Physical Status Classification System)	NRS
Engel et al,[36] 2004	US	PC	54	NA	6	Mean, 68	26/74 (49%)	28 /74 (51)	Multiple hierarchical regression	AHI	WOMAC
Escobar et al,[30] 2007	Spain	PC	640	1999-2000	6	Mean, 72	473/471 (74%)	167/471 (26)	General linear model	Age (y), sex (men/women), social support (yes/no), comorbidity (CCI), physical function (WOMAC), low back pain (yes/no), mental health (SF-36)	WOMAC
Hylkema et al,[35] 2019	US	PC	131	2012-2014	6	Mean, 61	114/ 183 (62)	69/ 183 (38)	Univariate linear regression	Pain catastrophizing (PCS)	WPAI:SHP
Oka et al,[40] 2020	Japan	PC	82	2017-2019	6	Mean, 72.1	67/82 (82)	15/82 (18)	Multiple linear regression	Sedentary behavior (MET)	New KSS
Pua et al,[31] 2019	Singapore	PC	4026	2013-2017	6	Mean, 68	3003/4026 (75)	1026/4026 (25)	Proportional odds ordinal regression	Age (y), sex (men/women), BMI, education (primary, secondary, tertiary), ethnicity (Chinese, Indian, Malay, other), social support (yes/no), comorbidities (yes/no) contralateral knee pain (KSS), pain (OKQ), knee extension and flexion (goniometer), physical function (categories), depression (SF-36)	OKQ
Sugawara et al,[32] 2017	Japan	PC	59	2011-2012	6	Mean, 75	53/59 (90)	6/59 (10)	Stepwise multiple regression	TSLS	JKOM
Taniguchi et al,[33] 2016	Japan	PC	81	2013-2014	6	Mean, 72	73/81 (90)	8/81 (10)	Multiple linear regression	TUG	TUG
Yang et al,[41] 2019	US	PC	107	2010-2011	6	Mean, 65	55/107 (51)	42/107 (49)	Multivariate logistic regression	Mental health (SF-36), pain catastrophizing (PCS), comorbidity (CCI), use device (yes/no)	WOMAC
Berghmans et al,[37] 2019[a]	Netherlands	PC	144	NA	12	Mean, 66.4	79/150 (53)	71/150 (47)	Stepwise multiple linear regression	Physical function (WOMAC), knee function (KSS)	WOMAC

(continued)

Table. Characteristics of Reviewed Studies (continued)

Source	Country	Design	Patients analyzed, No.	Data collection	Follow-up, mo	Baseline age, y	Patients, No./Total No. (%)		Analysis	Factors measured	Outcome measured
							Female	Male			
Dowsey et al,[22] 2012	Australia	PC	473	2006-2007	12	Mean, 71	331/478 (69)	142/478 (31)	Multivariate linear regression	Age (y), sex (men/women), BMI, comorbidity (CCI), pain (IKSS), physical function (IKSS), mental health (SF-12), K-L grade, cruciate retaining, patella resurface, multicompartment OA	IKSS
Lindberg et al,[38] 2020	Norway	PC	182	2012-2014	12	Mean, 67	124/ 182 (68)	58/182 (32)	Multivariate logistic regression	Age (y), sex (men/women), pain (BPI), lack of energy, drowsiness, sleeping difficulties, bloating, worrying, sexuality problems (MSAS-SF)	BPI
Lingard et al,[23] 2007[a]	UK, US, Canada, Australia	PC	676	1997-1999	12	Distress: median, 70	574/676 (85)	102/ 676 (15)	Logistic regression	Psychological distress (SF-36)	WOMAC
						Nondistress: median, 71					
Nankaku et al,[24] 2018	Japan	PC	115	2013-2015	12	Mean, 71	99/115 (86)	16/115 (14)	Stepwise multiple regression	Age (y), physical function (KSS), TUG	KSS
Sullivan et al,[25] 2011	Canada	PC	120	NA	12	Mean, 67	73/120 (61)	47/120 (39)	Multiple regression	Age (y), sex (men/women), BMI, comorbidity (CCI), physical function and pain (WOMAC), pain catastrophizing (PCS), depression (PHQ-9), kinesiophobia (TSK), surgery duration (min)	WOMAC
Tilbury et al,[26] 2018	Netherlands	PC	146	2011-2012	12	Mean, 67	101/146 (69)	87/146 (31)	Multivariate linear regression	BMI, mental health (SF-36), physical function (KOOS), outcome expectancies (HSS hip replacement and knee replacement expectations surveys)	KOOS
van de Water et al,[27] 2019	Netherlands	PC	559	2012-2015	12	Mean, 67	378/559 (68)	181/559 (32)	Multivariate linear regression	Pain (KOOS), K-L grade	KOOS
Wylde et al,[28] 2012	UK	PC	220	NA	12	Median, 70	136/220 (62)	84/220 (38)	Ordinary least square regression	Age (y), sex (men/women), comorbidity (SCQ), physical function (WOMAC), depression and anxiety (HADS), pain self-efficacy (PSEQ)	WOMAC

Abbreviations: AHI, Arthritis Helplessness Index; ASA, American Society of Anesthesiologists; BMI, body mass index; BPI, Brief Pain Inventory; CCI, Charlson Comorbidity Index; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; HSS, Hospital for Special Surgery; IKSS, International Knee Society Score; JKOM, Japanese Knee Osteoarthritis Measure; K-L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; KSS, Knee Society Clinical Rating System; MET, Metabolic Equivalent of Tasks; MSAS-SF, Memorial Symptom Assessment Scale Short Form; NA, not applicable; NRS, numerical rating scale; OKQ, Oxford Knee Questionnaire; PC, prospective cohort; PCS, Pain Catastrophizing Scale; PHQ-9, Patient Health Questionnaire; PSEQ, Pain Self-Efficacy Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SCQ, Self-Administered Comorbidity Questionnaire; SF-12, 12-Item Short-Form Health Survey 12; SF-36, 36-Item Short Form Health Survey; TSK, Tampa Scale of Kinesiophobia; TSLS, time single legged stand with eyes open; TUG, Timed Up and Go; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Study with 2 follow-up times.

bloating,[38] worrying,[38] and problems with sexuality were reported once[38] and were not included in the meta-analysis.

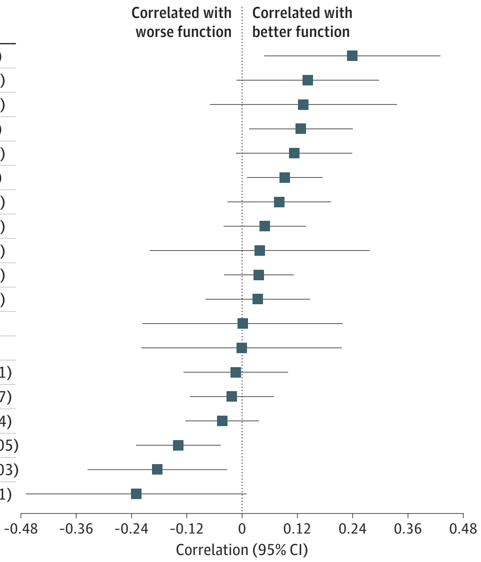
Estimates of correlations of factors with function are reported separately for 6-month and 12-month outcomes (**Figure 2** and **Figure 3**). Results from 2 or more studies that could be statistically combined in multivariate meta-analysis are reported subsequently. Explorations of sensitivity analysis are in eFigure 1 and eTable 1 in the Supplement, while explorations of potential inconsistencies and results from exploratory univariate meta-analyses are in eFigures 2 and 3 in the Supplement. Labels for included factors are defined in eTable 3 and reason for exclusion of the individual studies are described in eTable 6 in the Supplement. Positive correlations correspond to better function postoperatively.

There were 9 studies with 2637 patients that reported estimates for 25 potential factors for our primary outcome, physical function at 12 months after TKA.[22-28,37,38] Preoperative function (6 studies),[22,24-26,28,37] mental health (including anxiety, depression, and psychological distress [5 studies]),[22,23,25,26,28] and age (5 studies)[22,24,25,28,38] were the most frequently reported factors. Several studies were judged as at high risk of bias on 1 or more domains (**Figure 4**).[23-26,28-30,32,34-36,39] Multivariate meta-analytical correlation coefficient estimates are in Figure 2.[22-28,37,38]

Mean correlation with higher BMI was estimated to be −0.15 (95% CI −0.24 to −0.05; *P* = .33; *P* score = 70.0%; 3 studies[22,25,26]; moderate-certainty evidence and moderate heterogeneity among reported estimates of association [I^2 = 46%]). Mean correlation with better physical function was estimated to be 0.14 (95% CI, 0.02 to 0.26; *P* = .03; *P* score = 65.6%; 6 studies[22,24-26,28,37]; low-certainty evidence and substantial heterogeneity among estimates of association [I^2 = 90%]), while mean correlation with better mental health was estimated to be 0.12 (95% CI, −0.01 to 0.25; *P* = .10; *P* score = 60.0%; 5 studies[22,23,25,26,28]; moderate-certainty evidence and substantial heterogeneity among reported estimates of association [I^2 = 67%]) and mean correlation with more severe osteoarthritis was estimated to be 0.10 (95% CI, 0.01 to 0.19; *P* = .17; *P* score = 53.8%; 2 studies[22,27]; high-certainty evidence and heterogeneity between reported estimates [I^2 = 26%]).

Figure 2. Forest Plot of Factors Associated With Physical Function at 12 mo

Factor	Studies, No.	Correlation (95% CI)	*P* value	*P* score, %	I^2, %
Mobility[24]	1	0.25 (0.05 to 0.44)	.02	87.4	NA
Pain self-efficacy[28]	1	0.15 (-0.01 to 0.31)	.048	68.1	NA
Knee status[37]	1	0.14 (-0.08 to 0.35)	.28	63.3	NA
Preoperative function[22,24-26,28,37]	6	0.14 (0.02 to 0.26)	.03	65.6	89.6
Mental health[22,23,25,26,28]	5	0.12 (-0.01 to 0.25)	.10	60.0	67.4
K-L grade[22,27]	2	0.10 (0.01 to 0.19)	.17	53.8	25.9
Cruciate retaining[22]	1	0.09 (-0.03 to 0.21)	.21	48.6	NA
Male sex[22,25,28,38]	4	0.05 (-0.04 to 0.15)	.009	36.1	44.3
Outcome expected[26]	1	0.04 (-0.21 to 0.29)	.93	37.0	NA
Preoperative pain[22,25,27,38]	4	0.04 (-0.04 to 0.12)	.008	30.6	74.2
Patella resurfaced[22]	1	0.04 (-0.09 to 0.16)	.005	31.1	NA
Surgery duration[25]	1	0 (-0.23 to 0.23)	.004	26.7	NA
Kinesophobia[25]	1	0 (-0.23 to 0.23)	.004	26.7	NA
Multicompartment OA[22]	1	-0.01 (-0.14 to 0.11)	.004	24.2	NA
Comorbidity[22,25,28]	3	-0.02 (-0.12 to 0.07)	.84	25.8	26.1
Age[22,24,25,28,38]	5	-0.05 (-0.13 to 0.04)	.009	33.3	73.0
BMI[22,25,28]	3	-0.15 (-0.24 to -0.05)	.33	70.0	46.1
Symptomatic joints[28]	1	-0.20 (-0.35 to -0.03)	.31	79.1	NA
Catastrophizing[25]	1	-0.24 (-0.47 to 0.01)	.07	82.8	NA



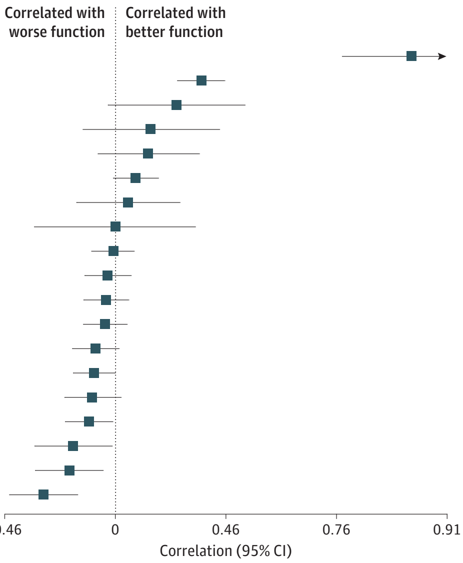
BMI indicates body mass index; K-L, Kellgren-Lawrence; NA, not applicable; OA, osteoarthritis. Direction of correlation: increased values of factors correlate with better postoperative function for all factors except dichotomous values (ie, cruciate retaining, male sex, patella resurfaced, and multicompartment OA), for which presence of factor correlates with better postoperative function.

High-certainty evidence and heterogeneity for osteoarthritis may not be important. We were unable to conclude that clinically meaningful correlations did not exist for the other 15 factors owing to limited evidence (ie, wide CIs).

In the prespecified sensitivity analysis (eTable 1 in the Supplement), mean correlation with better physical function was estimated to be 0.20 (95% CI, 0.04 to 0.36; *P* = .02 vs coefficient = 0.14; 95% CI, 0.02 to 0.26 when including all studies). Mean correlation with BMI was

Figure 3. Forest Plot of Factors Associated With Physical Function at 6 mo

Factor	Studies, No.	Correlation (95% CI)	*P* value	*P* score, %	I^2, %
Mobility[33]	1	0.87 (0.77 to 0.93)	<.001	100	NA
Preoperative function[30-32]	3	0.37 (0.27 to 0.46)	<.001	90.4	92.9
Pain self-efficacy[36]	1	0.27 (-0.03 to 0.53)	.09	73.1	NA
Education[31]	1	0.16 (-0.15 to 0.44)	.45	54.1	NA
Mental health[30,31,41]	3	0.15 (-0.08 to 0.36)	.28	53.5	80.9
Social support[30,31]	2	0.09 (-0.01 to 0.19)	.09	40.9	0
Preoperative pain[31]	1	0.06 (-0.17 to 0.28)	.83	32.8	NA
Arthritis helplessness[36]	1	0 (-0.35 to 0.35)	>.99	26.3	NA
Knee extension[31]	1	-0.0 1 (-0.11 to 0.09)	.96	16.4	NA
Male sex[30,31]	2	-0.03 (-0.14 to 0.07)	.74	22.6	83.2
Knee flexion[31]	1	-0.04 (-0.14 to 0.06)	.61	24.8	NA
BMI[31]	1	-0.05 (-0.14 to 0.05)	.53	26.0	NA
Comorbidity[29-31]	3	-0.09 (-0.19 to 0.02)	.13	39.7	5.5
Age[30,31]	2	-0.09 (-0.19 to 0.00)	.06	41.6	95.3
Low back pain[30]	1	-0.10 (-0.23 to 0.03)	.15	43.4	NA
Contralateral knee pain[31]	1	-0.12 (-0.22 to -0.01)	.03	48.7	NA
Catastrophizing[35,41]	2	-0.19 (-0.35 to -0.01)	.03	63.4	84.9
Indian ethnicity[31]	1	-0.20 (-0.35 to -0.05)	.005	68.1	NA
Walking aid use[31,41]	2	-0.31 (-0.45 to -0.17)	<.001	84.1	63.5



BMI indicates body mass index; NA, not applicable. Direction of correlation: increased values of factors correlate with better postoperative function for all factors except dichotomous values (ie, male sex, Indian ethnicity, and walking aid use), for which presence of factor correlates with better postoperative function.

Figure 4. Risk of Bias

Low risk of bias | Moderate risk of bias | High risk of bias

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis	Risk within a study
Berghmans et al,[37] 2019	Moderate	Low	Low	Low	Moderate	Low	Moderate
Bugada et al,[29] 2017	Moderate	Moderate	High	Moderate	High	High	High
Dowsey et al,[22] 2012	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Engel et al,[36] 2004	High	High	Moderate	Low	High	High	High
Escobar et al,[30] 2007	High	High	Low	Low	Moderate	Low	High
Hylkema et al,[35] 2019	Low	High	Low	Low	Moderate	Moderate	High
Lindberg et al,[38] 2020	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Lindner et al,[34] 2018	High	Moderate	Moderate	Low	High	High	High
Lingard et al,[23] 2007	Low	High	Low	Low	Low	Low	High
Luo et al,[39] 2019	Moderate	Low	Low	Moderate	High	High	High
Nankaku et al,[24] 2018	Moderate	High	Low	Low	High	High	High
Oka et al,[40] 2019	Moderate	Low	Low	Low	Low	Moderate	Moderate
Pua et al,[31] 2019	Low	Low	Low	Low	Moderate	Low	Moderate
Sugawara et al,[32] 2017	High	Low	Low	Low	High	High	High
Sullivan et al,[25] 2011	High	High	Low	Low	Moderate	High	High
Taniguchi et al,[33] 2016	Low	Low	Low	Low	Moderate	Moderate	Moderate
Tilbury et al,[26] 2018	Moderate	High	Low	Low	Moderate	Moderate	High
Van de Water et al,[27] 2019	Low	Low	Low	Low	Low	Moderate	Moderate
Wylde et al,[28] 2012	High	Moderate	Low	Low	Moderate	Low	High
Yang et al,[41] 2019	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate

estimated to be −0.17; 95% CI, −0.28 to −0.06; $P < .001$ vs coefficient = −0.15; 95% CI, −0.24 to −0.05 when including all studies), while mean correlation with mental health was estimated to be 0.13 (95% CI, −0.04 to 0.29; $P = .02$ vs coefficient = 0.12; 95% CI, −0.01 to 0.25 when including all studies), and mean correlation with osteoarthritis severity was estimated to be 0.10 (95% CI, −0.01 to 0.20; $P = .05$ vs coefficient = 0.10; 95% CI, 0.01 to 0.19 when including all studies).

For the secondary outcome, physical function 6 months after TKA, 9 studies with 5743 participants reported estimates on 20 potential factors.[29-33,35,36,40,41] Estimated correlation coefficients from multivariate meta-analysis are in Figure 3.[29-33,35,36,41] Mean correlation with more catastrophizing was estimated to be −0.19 (95% CI, −0.35 to −0.01; $P = .03$; P score = 63.4%; 2 studies[35,41]; very low–certainty evidence and substantial heterogeneity between reported estimates of association [I^2 = 85%]), while mean correlation with walking use was estimated to be −0.31 (95% CI, −0.45 to −0.17; $P < .001$, P score = 84.1%; 2 studies[31,41]; high-certainty evidence and substantial heterogeneity between reported estimates of association [I^2 = 63%]). Mean correlation with better physical function was estimated to be 0.37 (95% CI, 0.27 to 0.46; $P < .001$; P score = 90.4; 3 studies[30-32]; moderate-certainty evidence and substantial heterogeneity among reported estimates of association [I^2 = 93%]), while mean correlation with better mental health was estimated to be 0.15 (95% CI, −0.08 to 0.36; $P = .28$; P score = 53.5; 3 studies[30,31,41]; high-certainty evidence and substantial heterogeneity among reported estimates of association [I^2 = 81%]). We were unable to conclude that clinically meaningful correlations did not exist for the other 15 factors owing to limited evidence (ie, wide CIs). For the 3-month outcome, we were unable to perform multivariate meta-analysis, as shown in eTable 2 in the Supplement.

QUIPS domains most frequently assessed as at low risk of bias were prognostic factor measurement (16 studies[23-28,30-33,37-41]) and outcome measurement (17 studies[22-28,30-38,40]). For high risk of bias, QUIPS domains most often assessed were attrition (7 studies[23-26,30,35,37]) and statistical analysis (7 studies[24,25,29,32,34,36,39]), as shown in Figure 4.

Our GRADE certainty of evidence judgements are included in previously listed data and in eTable 4 in the Supplement. The most common reasons for downgrading certainty of evidence were risk of bias and imprecision.

Discussion

To our knowledge, this study is the first prespecified systematic review and meta-analysis using wide eligibility criteria and evaluating certainty of evidence to identify preoperative and intraoperative factors correlated with physical function at 12 months after TKA. Evidence from 7 observational studies[22,24-28,37] suggested that higher BMI was correlated with poorer physical function 12 months after TKA and that better preoperative physical function and more severe osteoarthritis were correlated with better physical function 12 months after TKA. Importantly, our findings did not suggest that individual patients with a poor risk factor profile will not experience functional improvement if they undergo TKA. Our findings merely suggest that identified factors were correlated with poorer or better physical function in an absolute sense and may therefore be useful for guiding expectations about TKA outcomes.

We found moderate-certainty evidence for a correlation between higher preoperative BMI and worse function at 12 months, with equal correlation in the sensitivity analysis, in which studies judged to be at high risk of bias were removed. This finding is similar to that of another meta-analysis,[13] in which participants without obesity reported lower rates of disability than participants with obesity. The evidence was not graded, however, and the study included retrospective studies with follow-up at 6 months to 10 years. Although we found a correlation between obesity and poorer physical function after TKA, patients with obesity still experience improved function from baseline[48] and should thus be considered for surgery. However, the surgeon needs to consider the functional benefit against the risk for complications (eg, septic revisions are more prevalent in patients with severe obesity and super obesity[49]) for each patient and discuss these issues with the patient to encourage realistic expectations before proceeding with TKA.[49]

We found a correlation between better preoperative and better postoperative function at 12 months (low-certainty evidence) and 6 months (moderate-certainty evidence). The correlation remained, with increased coefficients, in the sensitivity analysis. It is not surprising that patients who were healthier before surgery may also have been healthier after surgery. However, our results conflict with those of a systematic review[8] concluding that lower preoperative function was associated with better function 12 months after TKA. To resolve these conflicting findings, evidence is needed from well-conducted studies using standardized methods to measure factors and outcomes. We also estimated a correlation between more severe osteoarthritis (Kellgren-Lawrence grade) and better physical function at 12 months (high-certainty evidence) in multivariate meta-analysis and sensitivity analysis. These findings are consistent with those of a systematic review[8] that included retrospective studies with follow-up extending to 1 year. Uncertainty remains regarding evidence for osteoarthritis severity as a factor associated with the outcome at 12 months.[50,51]

Major strengths of our study include following the recently revised Cochrane Handbook[16] and guidelines for peer-reviewed protocols,[14] including longitudinal prospective studies reporting associations at predefined times after TKA, and using multivariate meta-analysis when the number of factors was large compared with the number of studies.[15] Several previous systematic reviews were unable to perform meta-analysis owing to heterogeneity associated with measurement issues, and others used vote counting, a method discouraged in current guidelines.[16] We used recommended tools to assess risk of bias (QUIPS) and certainty of evidence (GRADE). Additionally, we prioritized transparency with the systematic use of prespecified methods documented in the protocol,[14] preprint,[15] and this article's supplemental materials.

Limitations

This study has several limitations. To obtain trustworthy estimates without prejudging which factors may have been associated with the outcome, we included a wide range of factors but only from prospective studies reporting associations at specific postoperative times. This necessarily included estimates from studies measuring factors using a range of methods, and so we accounted for heterogeneity in our random-effects meta-analyses. Less heterogeneity was observed across studies using a common measure, particularly 9 studies that used WOMAC to measure physical function. Narrower inclusion criteria could increase the potential for excluding important evidence.[16] Some studies had large sample sizes and therefore provided precise estimates (ie, narrow CIs). I^2 may be misleading when study estimates are very precise because it is statistically easier to distinguish (ie, detect heterogeneity) between study estimates. In this situation, it is important to consider the degree to which study estimates vary from one another and whether this is clinically important, rather than relying solely on I^2. In particular, I^2 from prognostic studies may be misleading so I^2 statistics should be interpreted cautiously.[18] Because studies with high risk of bias can lead to biased main results and heterogeneity, we performed prespecified sensitivity analyses and excluded studies assessed as high risk for each QUIPS domain.[14] We planned to perform analyses of nonreporting bias, small study effects, and subgroup analyses,[14] but the number of included studies did not meet our prespecified threshold.

We also downgraded certainty of evidence if we judged studies to be at risk of bias. Several studies[11,52-54] had insufficient reporting of important QUIPS domains (such as attrition and statistical analysis), thus lowering the certainty that study estimates were unbiased. We suggest that researchers use tools like QUIPS at the study design stage to encourage low risk of bias in their findings regarding prognostic factors. This review identified some key areas for future research. Uncertainty remains regarding which patients may benefit most from TKA. Because patient preoperative status (ie, BMI, physical function, and osteoarthritis severity) may be correlated with overall outcomes, evidence from high-quality studies is fundamental for developing a prediction model to better identify patients at increased risk of poor outcomes after TKA. Prehabilitation interventions to improve modifiable factors (eg, better mental health) are not well-established.[55,56] We could not synthesize data for a number of factors given that they were studied only once. For these and other factors and outcomes, such as associations between physical function during the first year after TKA and biomechanical aspects of surgery (eg, implant) or pain management, evidence is lacking, highlighting the need for research from these perspectives with appropriate design and power. Additionally, our study provided evidence at the population level not at the level of individual patients. Our results are important for investigating factors to include in predictive models but should be used with caution at the individual level.

Conclusions

This study found that there is evidence (with moderate certainty) that higher BMI was correlated with worse physical function and that better physical function (low-certainty evidence) and more severe osteoarthritis (high-certainty evidence) were correlated with better physical function 12 months after TKA. Our findings suggest that these factors should be included in development of predictive models aimed at identifying patients at increased risk of poor function after TKA.

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III

III

Factors associated with pain and functional impairment five years after total knee arthroplasty: a prospective observational study

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Abstract

Background:

Few studies have evaluated the associations between preoperative factors and pain and physical function outcomes after total knee arthroplasty (TKA) from a mid-term perspective. Identification of such factors is important for optimizing outcomes following surgery. Thus, we examined the associations between selected preoperative factors and pain and pain-related functional impairment five years after TKA in patients with knee osteoarthritis.

Methods:

In this prospective observational study, all patients scheduled for primary unilateral TKA for osteoarthritis were consecutively recruited. Preoperative factors associated with pain and physical function were included from previous meta-analyses to assess their associations with pain severity and pain-related functional impairment five years after TKA. Pain severity was the primary outcome, while pain-related functional impairment was the secondary outcome. The Brief Pain Inventory was used to evaluate outcomes five years post-TKA. Statistically significant factors from univariate regressions were entered into a multiple logistic regression model to identify those with the strongest associations with pain or pain-related functional impairment five years after TKA.

Results:

A total of 136 patients were included, with a mean age of 67.7 years (SD 9.2) and a majority being female (68%). Severe preoperative pain defined as ≥6 on a 0-10 scale (OR=1.34, 95% CI [1.03 to 1.74]), more painful sites (OR=1.28., 95% CI [1.01 to 1.63]), and more severe anxiety symptoms (OR=1.14., 95% CI [1.01 to 1.28]) were associated with increased likelihood of moderate to severe pain five years after TKA surgery, while more severe osteoarthritis (OR=0.13, 95% CI [0.03 to 0.61]) was associated with *reduced* likelihood of moderate to severe pain five years after TKA. More severe anxiety symptoms (OR=1.25, 95% CI [1.08 to 1.46]) were also associated with *increased* likelihood of moderate to severe pain-related functional impairment five years after surgery, while male sex (OR=0.23, 95% CI [0.05 to 0.98]) was associated with *reduced* likelihood of pain-related functional impairment five years after surgery.

Conclusion:

The identified factors should be included in larger prognostic studies evaluating the associations between preoperative factors and mid-term pain and physical function outcomes after TKA surgery.

Keywords: Knee arthroplasty, Pain, Chronic pain, Function, Osteoarthritis, Prognosis

Background

Total knee arthroplasty (TKA) is a widely accepted and cost-effective surgical procedure intervention for end-stage knee osteoarthritis (1, 2). However, one in five patients experience persistent knee pain and limited functional improvement following TKA (3, 4). Most of the improvement in pain and physical function levels occurs and plateaus during the first year after TKA, followed by smaller gains or even worsening in pain and physical function levels thereafter (3, 5-10). Ongoing pain and impaired physical function not only necessitate the consideration of revision surgery but also impose significant burdens on affected individuals (11, 12) and substantial demands on healthcare (11-13). By better understanding the factors associated with these poor outcomes, we aim to enhance postoperative care and optimize long-term outcomes for patients undergoing TKA.

Prior meta-analyses have identified that preoperative pain catastrophizing, mental health, number of painful sites, and severity of osteoarthritis are associated with persistent pain (14-17), while preoperative physical function, mental health, body mass index, and severity of osteoarthritis are associated with persistent impairment in physical function (14, 16, 18). Few studies have evaluated factors associated with the mid-term outcome (five years) after TKA and their results have been conflicting. As in the previously mentioned meta-analyses, preoperative mental health was associated with both pain and physical function five years after TKA (19). However, anxiety and depression were associated with pain five years after TKA in one study (20), but no associations were found in another (21). These inconsistencies in results may be explained by low follow-up rates, and considerable heterogeneity in how the prognostic factors, pain, and physical function were measured and analyzed (19-21). Thus, uncertainty remains regarding the factors correlated with pain and physical function after TKA, extending beyond one year after TKA.

To address this knowledge gap, we selected preoperative factors associated with pain and physical function in prior meta-analyses (14-18) to examine the strength of associations between these and pain and pain-related functional impairment five years after TKA. We hypothesized that preoperative pain, number of painful sites, anxiety, and severity of osteoarthritis are associated with moderate to severe pain five years after TKA. Additionally, we hypothesized that preoperative pain-related functional impairment, BMI, anxiety, and severity of osteoarthritis are associated with moderate to severe pain-related functional impairment five years after TKA.

Methods

Data were collected from October 2012 to December 2017 from patients who underwent TKA at Lovisenberg Diaconal Hospital in Oslo, Norway. This study is a five-year follow-up study stemming from a longitudinal study on pain, functioning and quality of life completed in 2014 (6). Methodological details are described in a prior report from the same research group (6). Reporting of the current analysis is in accordance with the **“**STrengthening the Reporting of OBservational studies in Epidemiology” (STROBE**)** initiative and checklist (22).

Study sample and procedures

Patients were consecutively recruited and included in the original study if they were scheduled for primary unilateral TKA for osteoarthritis at Lovisenberg Diaconal Hospital, were 18 years or older, were able to read, write and understand Norwegian. Patients were excluded if they underwent an unicompartmental knee arthroplasty or a revision surgery or had a diagnosis of dementia. Patients completed a baseline questionnaire prior to surgery that included sociodemographic characteristics and preoperative symptoms and clinical factors. Data on body mass index (BMI), comorbidities, American Society of Anaesthesiologists' physical status classification (ASA) (23), medication and osteoarthritis severity were obtained from medical records. The anaesthesiologist performed the ASA assessment prior to surgery. A posterior cruciate-retaining fixed modular-bearing implant (The Profix Total Knee System (Smith and Nephew, Memphis, USA) was used in all surgeries, and patients were treated according to a standardized protocol with regard to anaesthesia, surgical procedures, pain management, postoperative mobilisation and physical therapy, as previously described in detail (6, 24).

For the current five-year follow-up study, all participants from the original study were invited to participate. Those who agreed to participate signed a new consent form. Most patients were scheduled for a five-year appointment at the hospital and were given the option to complete the questionnaires on iPads on-site or on paper at home. Those who completed paper questionnaires returned them by mail in pre-paid sealed envelopes. Patients who did not complete the questionnaire received one reminder either by telephone or mail.

Measures

The Brief Pain Inventory (BPI) was used to measure pain severity (primary outcome) and pain-related functional impairment (secondary outcome). The BPI consists of four items to measure pain severity (pain right now, as well as average, worst, and least pain in the past 24 hours). Additionally, the BPI includes seven items to rate pain interference with function (general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). Furthermore, the BPI incorporates a body map to determine the number and location of painful sites. The BPI is scored on a 0-10 numerical rating scale (NRS), from no pain or no interference with function to pain as bad as you can imagine or total interference with function (25). We used the average pain item from the BPI to measure pain five years after TKA, and as recommended by IMMPACT panel (26), we used the BPI pain interference with function index to measure pain-related functional impairment. We followed the recommendations in the BPI user guide and calculated the mean of the seven interference items, as long as at least four of the seven items were answered (25). The Norwegian version of the BPI has shown acceptable consistency, reliability, construct validity and responsiveness in the assessment of pain in a sample of patients with osteoarthritis waiting for total hip arthroplasty (27). Optimal cut-points for average pain ratings in TKA patients are: none/mild (0-3), moderate (4-6) and severe (7-10) (28, 29). Cut-off values points for the BPI pain interference index are not established for patients undergoing TKA. We therefore used the cut-points identified in a study of patients with low back pain: none/mild (0-3), moderate (4-5) and severe (6-10) (30). BPI scores for pain and pain interference with function index five years after surgery were dichotomized into none to mild (0-3) and moderate to severe (4-10) for analysis.

Measurement of selected preoperative variables

The selected preoperative variables hypothesized to be associated with pain and function at five-year follow-up are shown in Table 1. The factors were selected based on evidence from prior meta-analyses (14-18).

Table 1. Selected preoperative factors identified in prior meta-analyses

	Pain	Physical function
Possible associated factor	Pain (14, 15)	Functional impairment (16)
Possible associated factor	Osteoarthritis severity (16, 17)	Osteoarthritis severity (16, 17)
Possible associated factor	Anxiety (13, 14)	Anxiety (13)
Possible associated factor	Number painful sites (14, 15)	Body Mass Index (kg/m^2) (16)
Control factor	Age	Age
Control factor	Sex	Sex
Control factor	Comorbidity	Comorbidity

The BPI was used to measure patients' preoperative average pain severity, and their number of pain locations was measured using the BPI body diagram. Osteoarthritis severity was determined by classifying the patients' preoperative radiographs using the Kellgren-Lawrence (K-L) classification system (31). An experienced musculoskeletal radiologist and an orthopedic surgeon who were blinded to the clinical data evaluated the radiographs. The K-L grades range from 0-4, with higher grades indicating more severe osteoarthritis. K-L grade was dichotomized into mild to moderate osteoarthritis (K-L grades 2 or 3) or severe osteoarthritis (K-L grade 4). In our analysis, we dichotomized the K-L grade used in the logistic regression model into mild to moderate (K-L grades 2 or 3) or severe osteoarthritis (K-L grade 4) using the same cut-off as a previous study (32). Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS), which consists of seven items for measuring anxiety and seven items for depression (33). Scores for each subscale range from 0 to 21, with higher scores indicating more symptoms of depression or anxiety. A dichotomized HADS score was used in the analysis, with a HADS score <8 indicating less symptoms, and a score ≥8 indicating more symptoms (34). The tool has been evaluated in a large Norwegian population study and was found to have excellent psychometric properties (35). Body mass index (BMI) was calculated as kg/m^2. Comorbidities were counted and divided into four categories (0, 1, 2, ≥3).

Statistical analyses

Summary statistics for the sample characteristics were calculated and presented as means with standard deviations (SD) for continuous variables and frequencies and proportions for categorical variables. Data were checked for missing values, and baseline characteristics for those who were lost to follow-up were compared to those who remained in the study at five years.

For analyses of associations, we dichotomized the pain and pain interference with function outcomes (dependent variables) as <4 (none or mild, coded 0) or ≥4 (moderate to severe, coded 1). For the preoperative factors (independent variables), sex (male or female), and K-L grade (2-3 or 4) were dichotomous, while all others were treated as continuous. We first examined univariate associations using a logistic regression model between each of the selected preoperative factors identified in prior meta-analyses and the pain and pain interference with function outcomes. In addition, we evaluated age, comorbidity and sex in univariate models. Variables that were statistically significant in univariate analyses ($p<0.05$) were entered into a multivariate logistic regression model using a conditional backward selection model. The factor with the least significant p-value (≥0.10) was removed from the model, followed by a refit with the remaining factors in the next step. This process was repeated until all the included variables were statistically significant ($p \leq 0.05$).

We investigated the effect of extreme observations (outliers), removed these, and performed sensitivity analyses. To evaluate the logistic regression model assumptions, we assessed linearity between independent variables and the log odds of the dependent variable. Multicollinearity was examined by analysing correlation coefficients between independent variables, and if two variables had a correlation of $r \geq 0.7$, one of them was excluded (36). All analyses were considered exploratory and no correction for multiple testing was done. P-values <0.05 were considered statistically significant and all tests were two-sided.

Data analyses were performed using SPSS for Windows, version 28 (IBM Corp, Armonk, NY).

Results

Demographic and clinical characteristics

In the original longitudinal study, 245 patients were invited to participate, of which 202 were included. Details regarding the enrolment process for the original study have been previously described (6). For the current follow-up study, we considered all 202 patients from the original study for inclusion, but as two patients had died, and four had no available contact information, we invited 196 patients to participate in the follow-up study. Of these, 60 did not return the questionnaire, leaving 136 (67%) consenting patients for inclusion in the final analysis. Baseline characteristics of the cohort are presented in Table 2.

Table 2 Preoperative demographic and clinical characteristics (N=136)

Demographic characteristics	n	Statistics	
		Mean	***SD***
Age in years	136	67.7	9.1
		n	**%**
Sex	136		
Male		44	32
Female		92	68
Cohabitation status	136		
Lives alone		53	39
Married/partnered		83	61
Education	135		
High school or lower		64	47
College/university		72	53
Clinical characteristics		**Mean**	***SD***
BMI	136	28.6	4.2
Number of comorbidities	136	1.2	1.0
ASA score (1-3)	136	2.0	0.5
Osteoarthritis severity	135		
Mild to moderate (K-L grade≤3)		107	79
Severe (K-L grade=4)		28	21
Number of painful sites	136	2.1	1.8
BPI pain ratings on 0-10 scale			
Worst pain	136	5.3	2.1
Average pain	135	5.2	1.8
Pain interference with function index	136	4.4	2.0
BPI pain categories (dichotomized)		**n**	**%**
Average pain	135		
None/mild (<4)		28	21
Moderate/severe (≥4)		107	79
Pain interference with function index	136		
None/mild (<4)		58	43
Moderate/severe (≥4)		78	57
HADS anxiety score	129		
Low (<8)		99	77
High (≥8)		30	23

HADS depression score	130		
Low (<8)		111	85
High (≥8)		19	15

Abbreviations: ASA, American Society of Anaesthesiologists' physical status classification; BPI, Brief Pain Inventory; BMI, Body Mass Index; K-L, Kellgren Lawrence; HADS, Hospital Anxiety and Depression Scale

In short, the mean age of this sample was 67.7 (SD 9.1) years, and most participants were female (68%) and lived with a partner (61%). Comparing patients who were included in the five-year follow-up with those who were not, there were no statistically significant differences in age, sex, ASA classification, number of comorbidities, number of painful sites, average pain, pain-related functional impairment or symptoms of anxiety or depression. Patients included in the five-year follow-up sample had statistically lower preoperative BMI (mean 28.6, SD 4.2) than those who were not included (mean 30.3, SD 5.6) (p=0.03).

Pain

The average pain score declined from a mean value of 5.2 (SD 1.8) preoperatively to 2.7 (SD 2.3) five years after surgery (Tables 2 and 3). The vast majority of the patients (79%) reported moderate to severe pain (BPI ≥4) prior to surgery and this proportion decreased to about one third (32%) five years after surgery.

Table 3. Descriptions of pain and functional outcome variables at five-year follow-up

Outcome variables	**n**	**Statistics**	
		Mean	***SD***
BPI average pain rating (0-10 scale)	136	2.7	2.3
BPI pain interference with function index (0-10 scale)	135	1.9	2.1
		n	**%**
BPI average pain rating (dichotomized)	136		
None/mild (<4)		92	68
Moderate/severe (≥4)		44	32
BPI pain interference with function index (dichotomized)	135		
None/mild (<4)		111	82
Moderate/severe (≥4)		24	18

Abbreviation: BPI, Brief Pain Inventory

As shown in Table 4, univariate logistic regression analyses revealed significant associations between pain five years after TKA and the following preoperative factors: pain, anxiety symptoms, radiographic osteoarthritis, painful sites and sex. Male sex and less severe radiographic osteoarthritis were associated with less pain. In the final multivariate regression model (Table 4), higher preoperative pain was the strongest prognostic factor for moderate to severe postoperative pain five years after TKA. For each 1-point increase in preoperative average pain rating, the odds for moderate to severe pain at five years increased by 34%, controlling for all other variables. Each additional painful site patients reported preoperatively increased the odds of having moderate to severe pain by 28%. In addition, each 1-point increase in the patient's HADS anxiety score was associated with 14% higher odds for reporting moderate to severe pain five years after surgery. Those with severe radiological osteoarthritis had 87% lower odds for experiencing moderate to severe pain at five years, compared to those with moderate osteoarthritis. Sex was not associated with moderate to severe pain at five years and thus was not retained in the final model (step 2).

Table 4 Associations between selected preoperative factors and moderate to severe average pain at 5-year follow-up

Preoperative factors	Univariate logistic regression				Multivariate logistic regression			
	OR	CI 95%		P value	OR	CI 95%		P value
K-L grade 4 (vs ≤3)	0.12	0.03	0.53	0.005	0.13	0.03	0.61	0.010
Anxiety symptoms	1.19	1.07	1.33	0.002	1.14	1.01	1.28	0.035
Average pain rating	1.36	1.09	1.69	0.005	1.34	1.03	1.74	0.028
Number of painful sites	1.26	1.03	1.54	0.024	1.28	1.01	1.63	0.045
Age	1.01	0.96	1.04	0.847				
Number of comorbidities	1.31	0.93	1.84	0.122				
Male sex (female reference)	0.42	0.18	0.97	0.043				

Abbreviations: K-L grade, Kellgren Lawrence grade.

Pain-related functional impairment

For the secondary outcome, pain-related functional impairment, the mean score improved from 4.4 (SD 2.0) before surgery to 1.9 (SD 2.1) five years after surgery (Table 2 and 3). Prior to surgery, 78 (57%) patients had moderate to severe pain-related functional impairment based on their pain interference with function index, and this proportion declined to 24 (18%) patients five years after surgery.

The univariate logistic regression analyses revealed significant associations between pain-related functional impairment five years after TKA and the following preoperative factors: sex, anxiety symptoms and preoperative pain interference with function (Table 5). Male sex was associated with less pain-related functional impairment. When all variables that were statistically significant in univariate analysis were entered into the multiple logistic regression model, male sex and anxiety remained independent prognostic factors for pain-related functional impairment. Each 1-point increase in the patient's preoperative anxiety score was associated with 25% higher odds for having moderate to severe pain-related functional impairment five years after TKA. Males were 77% less likely than females to have moderate to severe pain-related functional impairment. The removal of outliers did not substantially alter the overall results of the study.

Table 5 Associations between selected preoperative factors and pain-related functional impairment at 5-year follow-up

Preoperative factors	Univariate logistic regression				Multivariate logistic regression			
	OR	95% CI		P value	OR	95% CI		P value
Age	0.97	0.93	1.02	0.298				
Number comorbidities	1.17	0.78	1.76	0.434				
BMI	0.98	0.88	1.09	0.704				
K-L grade 4 (vs ≤3)	0.14	0.02	1.09	0.061				
Male sex (female reference)	0.24	0.07	0.87	0.029	0.23	0.05	0.98	0.047
Anxiety symptoms	1.30	1.13	1.50	<0.001	1.25	1.08	1.46	0.003
Pain interference function	1.45	1.14	1.83	0.002	1.20	0.90	1.60	0.20

Abbreviations: K-L grade, Kellgren Lawrence grade; BMI, body mass index.

Discussion

To our knowledge, this is the first study to investigate evidence-based preoperative prognostic factors' associations with moderate to severe pain and pain-related functional impairment five years after TKA. Our findings indicate that all of the preoperative factors identified in previous meta-analyses for pain, such as preoperative pain, painful sites, anxiety symptoms, and osteoarthritis severity, were also significantly associated with mid-term pain outcomes five years following TKA (14-17). However, the same was not true for physical function, as BMI, preoperative functional impairment, and severity of osteoarthritis, which were identified as preoperative factors in prior meta-analyses, were not significantly correlated with physical function five years after TKA (16, 18). Notably, a considerable proportion of the patients reported moderate to severe pain (32%), and pain-related functional impairment (18%) five years after TKA. Our findings largely confirm and clarify that certain factors have enduring effects on pain and physical function outcomes. These findings also contribute to addressing the gap in knowledge on the recovery course five-years after TKA.

Interestingly, more anxiety symptoms were a prognostic factor for both moderate to severe pain and moderate to severe pain-related functional impairment. Consistent with our findings, results from a registry study (Mayo Clinic Total Joint Registry) indicated that more severe anxiety increased the odds for more severe pain, but also for impaired physical function years after TKA (20). In another prospective study, no correlations were identified between preoperative anxiety symptoms and pain or physical function outcomes at five years (21). These conflicting results may be due to the low follow-up rate of 29% at five years in the latter study. High preoperative pain levels in OA patients have been correlated with higher levels of anxiety (37). If untreated, anxiety and pain catastrophizing may hamper surgical outcomes as problems with pain catastrophizing, avoidance and worrying may complicate the recovery process for these patients (14, 38-40). While the presence of anxiety symptoms should not be used as a criterion for patient selection, identifying patients at high risk before surgery and developing effective targeted psychological interventions that facilitate recovery after TKA may be important as such approaches are still lacking (41, 42).

Among all factors, higher preoperative pain had the strongest association with moderate to severe pain five years after TKA surgery. Our results for the five-year outcome are supported by results from previous well-conducted systematic reviews and meta-analyses (15, 17, 43). Furthermore, we found that more painful sites before surgery were associated with moderate to severe pain five years after surgery, which is in line with findings from other studies (15, 44, 45). Fibromyalgia is a disorder characterized by multiple pain sites, and findings from Brummet et al. (45) indicate that patients with this condition have less improvement than patients with fewer pain sites.

We also found that more severe radiographic osteoarthritis was associated with less pain five years after surgery, which aligns with findings from recent systematic reviews and meta-analyses (16, 17). Klasan et al. (46) identified a subgroup of patients that had a combination of high preoperative pain and less severe osteoarthritis and were more likely to have higher levels of pain one year after TKA. The authors suggested that the aetiology of pain in this subgroup is multifaceted and more independent of osteoarthritis-specific pathology, highlighting the complex pain mechanism after surgery. Patients with severe radiographic osteoarthritis might be more affected by disease symptoms than patients with less severe osteoarthritis, potentially explaining why they tend to benefit more from TKA surgery than patients with milder osteoarthritis (47). It is important to note that patients with less severe osteoarthritis can still obtain significant benefits from TKA surgery. However, Osteoarthritis Research Society International (OARSI) guidelines to postpone surgery until first-line treatments for osteoarthritis are no longer helpful might be especially relevant for these patients (48).

For the secondary outcome, pain-related functional impairment five years after surgery, we found that more severe preoperative anxiety symptoms was associated with moderate to severe pain-related functional impairment, while male sex was associated with less pain-related functional impairment five years after TKA. We did not find any correlation between preoperative and postoperative pain-related functional impairment, which perhaps was surprising, as other studies, including a meta-analysis, identified a correlation between worse preoperative and postoperative function at one (18) and five years (3, 19). This discrepancy suggests that additional factors might influence pain-related functional impairment five years after TKA, which needs to be addressed in future studies.

Limitations and strengths

Our study, like many longitudinal follow-up studies, encountered attrition over time. While there is no consensus on an acceptable attrition rate in prospective observational studies, Grooten et al. (49) proposed a response rate of 67% as a cut-off for attrition in their study on inter-rater agreement of risk of bias assessment in prognostic studies. In our study, the response rate exceeded this cut-off, reaching 69%, within an acceptable range according to their suggestion. Prior prospective observational studies have reported response rates of 29% (21) and 57% (20), highlighting the variability in low response rates among studies with longer-term follow-up. The respondents and non-respondents did not differ on the baseline characteristics of age, sex, ASA status, number of comorbidities, painful sites, average pain, pain-related functional impairment, or anxiety symptoms. However, we observed that the patients included in the analysis had a significantly lower mean BMI (28.6, SD 4.2) than those lost to follow-up (mean 30.3, SD 5.6). Although this difference was statistically significant ($p=0.03$), its clinical significance may be limited. Our results can therefore still be generalised to the patients with osteoarthritis scheduled for primary TKA. Our statistical model was based on hypotheses, and we used the logistic conditional backward regression model, a recommended model in prognosis research (50). A common pitfall is to overfit the logistic regression model, but as we used the principle described in Tabachnick and Fidell (51) with minimum sample size of 50 participants, and to add at least 8 times the number of predictors to ensure adequate statistical power, we believe the our model is not overfitted.

In this study, we have used evidence-based factors to identify prognostic factors for pain and pain-related functional impairment five years after TKA. The results indicate several factors that should be considered for inclusion in future prognostic models with the aim to identify the best set of prognostic factors for predicting patients' risk for unfavourable TKA outcomes. We found that one out of three patients had persistent pain and nearly one in five had pain-related functional impairment five years after TKA. A recent study suggests that there is a subgroup of patients that fluctuates in and out of a chronic pain pattern during the five-year follow-up period (8). There is therefore a need to establish the course of recovery for non-improvers in pain and physical function, but also to investigate whether there are certain preoperative characteristics that predispose these patients to adverse pain and physical function outcomes so that targeted interventions can be developed to facilitate their recovery.

Conclusion

In this study, more preoperative anxiety symptoms were associated with moderate to severe pain and pain-related functional impairment five years after TKA surgery. In addition, preoperative pain, number of painful sites, and osteoarthritis severity were factors associated with moderate to severe pain five years after TKA. Male sex was associated with less pain-related functional impairment five years after TKA. The factors identified in this study should be used to develop prognostic models for mid-term pain or pain-related functional impairment outcomes after TKA surgery.

Abbreviations

ASA	American Society of Anesthesiologists' physical status classification
BPI	Brief Pain Inventory
BMI	Body mass index
CI	Confidence interval
HADS	Hospital Anxiety and Depression Scale (HADS)
NRS	Numerical Rating Scale
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
SD	Standard deviation
TKA	Total knee arthroplasty

Declarations

Ethics approval

The study was approved by the Regional Medical Research Ethics Committee of Health South-East of Norway (#2011/1755) and the data protection officer at Lovisenberg Diaconal Hospital.

Consent for publication

Not applicable.

Availability of data and materials

The datasets utilized in this study are not publicly accessible to ensure the protection of individual privacy and adhere to legal restrictions. However, upon reasonable request and with approval from the Regional Committee in Ethics in Medical Research in South-East

Norway (REC) and the hospitals' Data Protection Officers, a minimal dataset may be made available by the authors.

Competing interests

None

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Authors' contributions

UO, VBS, CG, AA, AL, MFL collaborated about the study conception and design. MFL acquisition of data. UO, CG, MS analyzed and interpreted data. UO, VBS drafted the manuscript, while CG, AA, AL. MS, AD, and MFL critically revised the article for important intellectual content. All authors, UO, VBS, CG, AA, AL, MS, AD, and MFL, read and approved the final manuscript.

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RESEARCH **Open Access**

"I am accustomed to something in my body causing pain": a qualitative study of knee replacement non-improvers' stories of previous painful and stressful experiences

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Abstract

Background Approximately 20% of total knee arthroplasty patients experience persistent postsurgical pain one year after surgery. No qualitative studies have explored previous stories of painful or stressful life experiences in patients experiencing persistent postsurgical pain after total knee replacement. This study aimed to explore stories of previous painful or stressful experiences in life in a cohort of patients that reported no improvement in pain one year after total knee arthroplasty.

Methods The study employed an explorative-descriptive qualitative design. Data was collected through semi-structured interviews five to seven years after surgery, with patients who reported no improvement in pain-related interference with walking 12 months after total knee replacement. The data was analyzed using qualitative content analysis.

Results The sample consisted of 13 women and 10 men with a median age of 67 years at the time of surgery. Prior to surgery, six reported having at least one chronic illness and 16 reported having two or more painful sites. Two main themes were identified in the data analysis: Painful years - the burden of living with long lasting pain, and the burden of living with psychological distress.

Conclusions The participants had severe long lasting knee pain as well as long lasting pain in other locations, in addition to experiences of psychologically stressful life events before surgery. Health personnel needs to address the experience and perception of pain and psychological struggles, and how it influences patients' everyday life including sleeping routines, work- and family life as well as to identify possible vulnerability for persistent postsurgical pain. Identifying and assessing the challenges enables personalized care and support, such as advice on pain management, cognitive support, guided rehabilitation, and coping strategies both pre-and post-surgery.

Keywords Interviews, Pain stories, Persistent postsurgical pain, Total knee arthroplasty, Qualitative research.

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Background

Patients with advanced knee osteoarthritis (OA) are considered eligible for total knee arthroplasty (TKA) if they have pain and reduced function of the knee that are not relieved with other treatments [1]. However, there are conflicting guidelines on when to recommend knee replacement and the decision should also be based on individual and patient-specific factors [2]. Substantial growth in the number of TKA procedures over the next decade is expected [3, 4]. However, approximately 20% of TKA patients experience persistent postsurgical pain (PPP) one year after surgery, with 15–19% reporting severe pain [5–7]. Some patients with PPP one year after surgery have been shown to have a prolonged pain recovery after surgery achieving satisfactory pain levels five to seven years after surgery [8].

PPP is defined as pain that develops or increases in intensity after a surgical procedure, lasts for at least 3–6 months and significantly affects health-related quality of life (HRQOL) [7]. A considerable body of quantitative research suggests that long lasting preoperative pain, pain catastrophizing and pain in anatomical sites other than the knee are the strongest predictors of PPP [9–11]. In a real-life setting, these risk factors may indicate that patients with PPP following TKA have struggled with other painful conditions, with pain coping or have had a more complex history of pain than those who do not experience PPP. Pain and symptoms that are unrelated to the knee may also persist following TKA and may interfere with rehabilitation. For example, in a recent study, patients struggling with higher pain and symptom burden, often unrelated to the knee, were more likely to be non-improvers after TKA [12].

With the high and increasing number of TKA surgeries being performed, targeting, exploring, and gaining more qualitative insight into risk factors for developing PPP are warranted. A previous qualitative study explored the path leading to hip and knee arthroplasty. The patients' quality of life (QOL) deteriorated as their knee pain increased, until the point where it was experienced as "unbearable" [13]. Another qualitative study which explored the decision-making process leading to TKA surgery, showed that the participants' description of their knee pain varied from just a nuisance to excruciating pain [14]. However, to our knowledge, no qualitative studies have explored stories of previous painful or stressful life experiences in patients experiencing PPP after TKA. Stories could provide insights into the lived life behind the numbers, representing the patient perspective, as "Language, words, and stories are the currency of the humanities—they are fundamental to the human experience" [15]. With their stories, the participants can share their experiences and we can learn from the stories and make sense of their world [15]. Stories communicate in a way that includes both the particpants as well the reader [16]. Therefore, the stories invites the readers into what is experienced as important real life issues and struggles for a group of non-improvers after TKA surgery. Through stories, nurses, physicians and physiotherapists may better connect and relate to the experiences these patients had earlier in life [16]. Studies have shown that healthcare professionals have limited knowledge of their patients as persons, including previous stories of painful and stressful events in life. The lack of insight into the patient´s life experiences can jeopardize tailoring patient-centered care [17–19]. TKA patients' previous painful conditions and stressful experiences may prove to be important for preoperative counseling and for designing a more tailored rehabilitation to improve outcomes. Therefore, this study aimed to explore stories of previous painful or stressful life experiences in a qualitative study of a cohort of patients reporting no improvement in pain one year after TKA [5, 8].

Methods

Study design

This study employed an explorative-descriptive qualitative design [20] and data was collected using semi-structured individual interviews. This design is suitable when there is little knowledge on a phenomenon, such as the experiences of painful or stressful events earlier in life for patients with PPP. Individual interviews allow for a more focused understanding of each patient's experiences and permit each participant to elaborate on their own stories without interruptions. The interviewer may also pose follow-up questions when needed [20]. This paper is reported according to the Consolidated criteria for reporting qualitative research (COREQ) checklist [21].

Participants

This follow-up study focuses on a subgroup of 45 (22%) of 202 patients who participated in a previous longitudinal study of pain, symptoms and HRQOL, and reported no improvement of pain-related interference with walking 12 months after TKA [5, 8, 22]. Patients were invited in the longitudinal study if they were ≥18 years, literate in Norwegian, scheduled for primary TKA for OA and had no diagnosis of dementia. Patients undergoing unicompartmental or revision surgery were not included [5]. We recruited a purposive sample [23] of participants from this non-improver subgroup, and those who attended their five-year follow-up and lived within a two-hour drive from the hospital were eligible for inclusion in this study (n=31).

Data collection

Two of the authors (AD, VBS) conducted individual semi-structured interviews at one timepoint, between

February 2018 and August 2020. The senior qualitative researcher (AD) trained the first author (VBS) in the interview approach. The first author (VBS) observed while the senior researcher (AD) interviewed the first participants. Next, the first author interviewed with the senior researcher present. The last 16 interviews were conducted by the first author only. The interviewers did not have a private or professional relationship with any of the participants prior to the interviews. Each interview lasted 45–70 min. The participants were free to choose where they wished to be interviewed, either in a private room at the hospital or in their home. To facilitate reflection and conversation, a semi-structured interview guide with follow-up questions was developed based on previous research on risk factors for persistent pain [10, 24] and key topics from the previous longitudinal study from which the patients were recruited [5, 25]. The interview guide contained questions concerning the history of "knee pain prior to the operation", i.e., the character and severity of the knee pain, and duration before the operation. Questions concerning "events in life" included thoughts on what the participants regarded as meaningful or important things/events in life, as well as any previous physically or psychologically painful life experiences. Follow-up questions gave participants the opportunity to elaborate on issues that were important to them. We pilot-tested the interview guide on three patients, and no changes were considered necessary. We audio-recorded all interviews.

As part of the previous longitudinal study, participants self-reported their number of painful sites through the Brief Pain Inventory (BPI) questionnaire and their chronic illnesses or long lasting sequalae after injuries through the *Socio now pop* (SNP) questionnaire prior to surgery.

Analysis

A professional transcriber transcribed the interviews verbatim. The first author (VBS) checked and validated the transcripts against the recordings. The data was then analyzed by inductive qualitative content analysis [26, 27]. Two of the authors (VBS, USO) independently read all transcripts to get an overview of the data. Guided by the study aim, they independently identified meaning units containing the stories and expressions of the patients' earlier painful or stressful life experiences. The authors discussed the meaning units, which were then condensed and coded using descriptions close to the text [26]. The codes were searched for patterns, similarities and differences and sorted into categories. This is a process that involves abstraction and interpretation of the codes, highlighting the unique experiences expressed by patients. Ultimately, the categories were sorted into themes for re-contextualization [26]. The first and second authors (VBS, USO) analyzed the data while three of the co-authors (SAS, AD, MFL) posed critical questions during the analytical process to explore alternative interpretations. Discussion between the authors also ensured that no relevant data had been excluded and that no irrelevant data was included in the analysis [27]. All of the authors agreed on the final themes. The audit trail of the analysis and the findings are shown in Table 1.

Trustworthiness

Credibility was enhanced by recruiting a sample including both sexes and ages ranging from 48 to 84 years at the time of surgery. This contributes to a rich variation of experiences earlier in life. The interview guide enabled participants to communicate, tell stories and emphasize issues that were important to them. Member checking was not carried out, however, during the interviews, follow-up questions were asked for validation and allowed the participants to clear up any misinterpretations of their statements. All participants were asked questions according to the themes in the interview guide, to ensure consistency during data collection. However, the participants' unique experiences form each individual interview and follow-up questions were tailored to each individual participant, enabling them to elaborate, describe and have additional time to tell their individual story.

The first and second authors are registered nurses with clinical experience on orthopedic wards. Their preconception of patients with persisting pain was that these patients often are vulnerable persons with high levels of stress due to pain. To enhance reflexivity and transparency, these authors' preconceptions were discussed with the co-authors. Researcher triangulation (VBS, USO, MFL, SAS, AD) was applied to facilitate different perspectives in the analytical process [28]. To enhance dependability, the first author (VBS) received training from a senior qualitative researcher (AD) on how to conduct interviews and a semi-structured interview guide was used. To facilitate the transferability of our findings [29], presentations of the sample, data collection and analytical process and rich descriptions of the findings illustrated with relevant quotes were provided. This was to enable the reader to consider whether the findings are relevant and applicable to their context.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (reference number 2011/1755) and the Data Protection Officer at Lovisenberg Diaconal Hospital. Patients were informed about the study in writing and verbally. All participants signed an informed consent form before the quantitative longitudinal study and another regarding the qualitative interviews. Participants had the right to withdraw from

Table 1 Illustration of the analytical process

Meaning unit	Condensed meaning unit	Code	Category	Theme
I had pain for about ten years, I think. I was limping around 3–4 months of the year. It came in periods. It was very painful (Haakon)	I had pain for about ten years	Pain for years	Long lasting knee pain	Painful years -the burden of living with long lasting pain
I was on 50% disability benefits because of my fibromyalgia (Randi)	I was on disability benefits because of fibromyalgia	Reduced work capability because of widespread pain	The difficult balance of pain and work- and social life	
I had surgery a couple of times on my back too. It has been pretty major operations. And when the knees started to hurt too, I was pretty miserable for a while there (Dagny)	I had surgery a couple of times on my back too. When the knees started to hurt too, I was pretty miserable for a while	Back pain and knee pain	Double burden of pain in multiple locations	
Well, I got rheumatism at the age of 24. It was terribly painful for a long time, coming and going, before it burnt out so to speak. So, I am used to having pain (Signe)	I got rheumatism at the age of 24. It was terribly painful for a long time. So, I am used to having pain	Resolved long lasting painful condition as a young adult	Suffered from long lasting painful condition	
I have been so low in my life because of a very difficult marriage. And it was all about destroying me as the open-hearted person I was. So, it has been a pain so great in my life. But it was impossible for me to leave him, it was dreadful (Ingeborg)	I have been in a very difficult marriage. It was all about destroying me as the open-hearted person. It has been a pain so great	A painful marriage	A life of distress and unhappiness	The burden of living with psychological distress
I was very worried about the analgesia if it would work and such. No, that was very tough. I was afraid and anxious and such (Einar)	I was very worried about the analgesia if it would work and such. I was afraid and anxious and such	Afraid and anxious before surgery	Preoperative anxiety	
My mother, she was old when she had me. She had so much pain, she became all twisted and crippled and she took so much pain medications and became odd from them. In addition: my parents had a bad marriage. I think her pains got worse from it. So, I have seen her, and I just did not want to end up like her (Inger)	My mother had so much pain, she became odd from pain medications, and she had a bad marriage. So I have seen her, I did not want to end up like her	Growing up with a mother in pain	Emotional struggles of difficult family relations	

the study at any time until the findings were published. Their confidentiality and anonymity were safeguarded according to local and national regulations.

Results

Of the 31 eligible patients, two had died, and six patients declined to participate due to illness. The final sample consisted of the remaining 13 women and 10 men, with a median age of 67 (48–84) years at the time of surgery. Prior to surgery, six reported having at least one chronic illness and 16 reported having two or more painful sites. Patient characteristics are shown in Table 2. We have assigned each participant an alias to ensure anonymity. Two themes were identified from the data analysis: painful years - the burden of living with long lasting pain, and the burden of living with psychological distress.

Painful years - the burden of living with long lasting pain

Long lasting painful conditions

Nearly all the participants experienced living with painful comorbid conditions, such as migraine, back pain, endometriosis, fibromyalgia, and rheumatism, in addition to their long lasting OA knee pain. Of note, some of these were not reported in the preoperative questionnaires (Table 2). Others had additional symptomatic joints such as a painful shoulder, ankle, hip, or contralateral knee. Several had experienced traumatic and painful accidents, such as falls due to ski accidents, motor vehicle accidents or work accidents with trauma to different body parts, that led to hospitalization, and some struggled with sequelae after the accidents. Gjermund experienced long lasting severe pain after a trauma to his hip: “I was up on the roof shoveling snow off the roof, and suddenly I was hanging by one arm from the barge board, and of course I had already cleared the terrace for snow. So, I fell 4 meters down on the terrace on the side. I tore tendons and broke my hip in three places. It was a dreadful pain. That pain in the hip lasted for such a long time, luckily it has become better now.”

Migraine and recurrent headaches were experienced as severe impediments in everyday life and were described as a violent pain leaving them nauseous and unable to function for days at a time. Audun described living with long lasting pain like this: “I’ve had a lot of migraines throughout my life. That has nothing to do with my knee, but it has to do with pain. And that means that I’ve been accustomed, really, to something in my body causing me pain”.

Several female participants suffered from endometriosis, fibromyalgia, and rheumatism, illnesses characterized by multiple painful locations that impaired and restricted them in everyday life. Randi, for example, struggled with endometriosis from adolescence to the age of 40: “Imagine, from I was 15 years old until 40, having all that pain”.

Table 2 Overview of participants' preoperative characteristics

Participant alias	Sex	Cohabitation status	Chronic illness	Number of painful sites
Amund	M	Lives with others	No	2
Astrid	F	Lives with children	No	4
Audun	M	Lives with partner /spouse	No	2
Dagny	F	Lives with partner /spouse	-	2
Ingeborg	F	Lives with partner /spouse	Yes	6
Liv	F	Lives with partner /spouse	-	1
Arne	M	Lives with partner /spouse	No	1
Brynjar	M	Lives alone	No	3
Erlend	M	Lives alone	No	1
Gjermund	M	Lives alone	No	1
Solveig	F	Lives alone	-	3
Inger	F	Lives alone	No	4
Harald	M	Lives with partner /spouse	Yes	5
Signe	F	Lives with partner /spouse	No	1
Ragnhild	F	Lives alone	Yes	5
Sigrid	F	Lives with partner /spouse	No	1
Randi	F	Lives with partner	Yes	3
Idunn	F	Lives with partner /spouse and children	No	4
Olav	M	Lives with partner /spouse	No	1
Sonja	F	Lives with partner /spouse	No	2
Haakon	M	Lives alone	Yes	8
Martha	F	Lives alone	Yes	10
Einar	M	Lives with partner /spouse	No	2

Definitions: - = missing

She expressed that she was not taken seriously by doctors or at school as a young adult. She felt left to her own devices with long lasting and severe pain that limited her to such a degree that she missed out on social activities and school. She was later diagnosed with fibromyalgia.

Several had experienced severe back pain, described as crippling, leaving them immobilized. Brynjar explained that he had internalized a special walk for several years, bending over, to ease the pain from his spinal stenosis before he finally underwent spinal surgery. These participants continued to compare migraine and back pain to new painful experiences in life, describing them as the worst pain they had ever experienced, and more painful than the knee pain.

The double burden of pain in multiple locations

Pain in other joints was also expressed as problematic and exhausting by several participants. Typically, they had endured these other painful conditions for many years, sometimes long before they started to experience osteoarthritic knee pain. These participants emphasized the double burden of having pain in multiple locations. Living with multiple pain locations was described as troubling and stressful. When the knee pain started to manifest itself, these previous pain conditions became especially difficult to endure. As Liv expressed: "You know, I have had a lot of back pain too, I had terrible back pain for many years, but it all got a bit too much for me, when my knees started hurting at the same time ".

The difficult balance of pain and work and social life

Most of the participants had memories of many increasingly painful years, one up to 13 years before surgery. As a result of enduring pain over a long period of time, many expressed in different ways that their QOL was significantly reduced. They found themselves worried about the future, sleepless and distressed. Working and keeping a social life at the same time was described as difficult due to exhausting pain. As a result of debilitating knee pain, many participants were not able to participate fully in their personal or work life. Some prioritized work over having a social life because working was a necessity to feel normal. However, after work they had no energy left, leaving them isolated and excluded from participating in social activities with the important people in their lives. Furthermore, several participants described their sleep quality deteriorating because of pain. Sleepless nights also harmed their QOL and left them tired and unable to participate in activities during the day. Harald described his knee pain as very troublesome for 3–4 years, to such a degree that it disturbed his sleep. He and others described the time with pain before surgery as difficult, tough, or trying and some used metaphors to describe their frustration and exhaustion. Two described their experience of pain like "almost hitting a wall" and another described painful nights as "tossing and turning in bed " indicating the challenges they faced in dealing with the pain.

Physical inactivity

Many participants expressed that they had become physically inactive due to pain. This left them frustrated and feeling out of touch with their normal selves, as typically physically active Norwegians. Amund described his experiences like this: "As long as I had this pain, I could do nothing, I couldn't bend the knee, I couldn't walk, so it was a rough time before surgery. This lasted for about two years before I had the knee surgery".

Enduring long lasting pain in addition to OA pain, and then, postsurgical pain

At the time of TKA surgery, some participants (n=5) no longer had pain in other locations - it had resolved. This was especially the case with some of the participants who endured back pain due to spinal stenosis or disc herniation, and one participant with rheumatic pain conditions that had "burned out" before their knee operation. However, most of the participants still suffered from pain elsewhere, thus they experienced the double burden of OA pain combined with other painful sites. This double burden of pain continued into the postoperative period when postoperative pain and other painful sites interfered with rehabilitation. Despite years of suffering from painful comorbid diseases, many participants displayed a strong mindset and a perseverance. They told their stories with a sense of humor and trying to make sense of their different painful experiences. A recurrent comment among the participants was "I think I've a very high tolerance for pain."

The burden of living with psychological distress

Emotional struggles

Participants described stories of psychologically stressful events, such as the loss of a close relation and grief, as well as difficult marriages, divorces, and family relations. The participants expressed that they had not discussed such experiences with others, and that these experiences had left them with emotional scars. Some of them still struggled emotionally and had yet to process and come to terms with their experiences.

After losing the closest person in their life, patients described stories of grief and mourning, and a feeling of abandonment and lack of control over what happened to them. Gjermund, who had several experiences of the loss of people close to him, both early and later in life, expressed it like this: "Grief work is tough work. I´m still not done with those months from when my wife got sick and until she died. I struggle with that. And that doesn't make things better."

Some had sought help to get over their emotional struggles, while others had internalized their emotional distress. It stuck with them, and they never truly got over it, even years after the events. Martha expressed her experience of a difficult break-up like this: "I experienced a divorce that I never truly got over. (…) People around me said I should be done with it, and I took that …well, that went on inside of me, so, I had to seek therapy in the end for that. (…). I think it got stuck in my body because I didn't breathe properly and such." Others told stories of difficult and stressful family relations due to parents with painful illnesses and extensive use of pain medications, expressing how this shaped their view on pain medication and pain behavior - they did not wish to become like their parents in this respect.

Anxiety and fear

A few participants told stories about a general feeling of anxiety, fear, and reluctance to undergo surgery because of previous experiences with uncontrolled postoperative pain. Erlend described going through an earlier TKA surgery with inadequate pain management. He elaborated: "I was in so much pain that I almost cried. They would only give me paracetamol, so I walked out into the hospital corridor. I remember tossing my crutch because I was so angry and in pain, but they wouldn´t get me anything but paracetamol. That has stuck with me, in my head." Previous stressful events in life were also described as a reason for feeling anxious and reluctant to undergo surgery. Some postponed surgery because they were concerned about the possibility of something going wrong. Ingeborg had a traumatic experience with the school dentist as a child, which stayed with her into adulthood. She explained: "I'm a sissy when it comes to pain. I don't know, but when someone else is doing this to you, that's the worst. When I moved to the city to live on my own, I didn't dare go to the dentist for two years".

Discussion

This qualitative study aimed to explore stories of previous painful or stressful life experiences in a cohort of patients that reported no improvement in pain one year after TKA. We found that most of the patients shared stories of years of struggles with painful comorbid diseases and painful sequelae after accidents prior to surgery, in addition to symptomatic joints. Furthermore, they emphasized life experiences that included loss, grief, and difficult family relations. Thus, their stories also revealed experiences of heavy burdens of psychological distress prior to surgery, unrelated to their painful knee. Furthermore, several expressed a general feeling of anxiety and fear about undergoing new surgeries. We also found inconsistency in what the participants reported through questionnaires, (Table 2) versus their stories of painful conditions during interviews. Those with resolved painful conditions, did not report these, even if the previous long lasting pain had influenced their lives for a long period of time.

Some of our participants had painful symptomatic knees for many years, one even up to 13 years, prior to their TKA surgery. This finding corresponds with one of the strongest independent predictors of PPP, namely preoperative long lasting pain [10, 30]. In addition, participants shared stories of severe pain experienced in relation to accidents. These experiences were highlighted as memories that had stuck with the participants throughout life. Some of the participants continued to struggle with painful sequelae after their accidents. In addition to painful knees, many participants had struggled with other painful conditions for years. Earlier experiences of pain and earlier stressful experiences may lead to a more sensitized pain perception [31–33] although the underlying factors in the complex matter of pain sensitization are still unclear [34].

Several of the female patients in our study were diagnosed with fibromyalgia. Brummett et al. [35] found that fibromyalgia independently predicts poor total knee and hip arthroplasty outcomes, even for patients scoring below the threshold for diagnosing the condition. Three of our participants who underlined the burden of living with rheumatism or other chronic disabilities in the interviews had failed to report these conditions in the preoperative questionnaires (Table 2). If patients are to be identified for possible pain vulnerability prior to surgery, as suggested by Schug and Bruce [9], health personnel may need to ask the patients directly about earlier painful conditions as the patient may not self report these in questionnaires. In the case of our participants, if the conditions had been resolved by the time of surgery, they may have considered the information irrelevant when asked to fill in the questionnaire, or they may not have understood how this information is relevant in a new context. Our participants expressed limitations in physical activities due to pain in two phases: several years prior to TKA surgery due to OA pain and later, due to PPP. Inactivity deteriorated their QOL, leaving them frustrated and feeling out of touch with their physically active lives. Being physically active may also involve an element of expectations of one´s cultural and personal identity which is essential to feeling whole as a person [36, 37] Importantly, physical inactivity is contradictory to the recommendations for optimal treatment of OA by the Osteoarthritis Research Society International (OARSI), which emphasize the combination of non-pharmacological treatments such as exercise, pacing of activities and weight reduction, if needed [1].

Our findings suggest that pain interfered greatly with participants' social life and psychological wellbeing. In particular, participants still working expressed difficulties prioritizing between work, or social and family life due of the exhausting pain. A systematic review indicates that patients with chronic pain who wait more than six months for treatment experience increased physical and psychosocial problems, deterioration in HRQOL and increased depression scores [38]. As a result, pain may lead to social isolation, and for younger patients, difficulties working, which can also lead to depression and low self-esteem [39] Furthermore, several of our participants experienced poor sleep quality due to pain. Studies have raised the issue of the bidirectional relationship between pain and sleep [40]. In line with a previous study [41], our participants with excessive preoperative pain seemed to experience a cycle of pain and deteriorating health. In addition, poor preoperative sleep quality has been shown to have a negative impact on PPP [42].

Participants shared stories and expressed that they still struggled with loss, grief, difficult family relationships and distress. Some said they had not shared their stories of psychological hardship with others before, leaving them alone with their thoughts and struggles. A systematic review and a meta-analysis highlight the poor outcome after TKA for patients who struggle with psychological health and distress, i.e. depression and anxiety [11, 43]. Psychological stress is a known risk factor associated with postsurgical persistent pain after TKA [10, 30, 43]. We found that these additional psychological stress experiences added to the burdens already carried by our participants. The double burden, thus, is expressed by multiple layers of struggles visualized in both biological and psychological and social components [44] (Fig. 1). Holding stressful experiences in life can complicate the postoperative pain experience and leave individuals more vulnerable to the perception of pain [33]. When considering our findings from a biopsychosocial viewpoint, it is important to consider the passage of time and any experiences that have had a lasting impact in regard to pain and persistent pain.

Some of our participants described a general feeling of anxiety and reluctance to undergo surgery. Some even postponed their surgery due to fear of complications or expectations of severe postoperative pain. Some expressed a sense of helplessness in their painful situation; they no longer felt they could do something to relieve the pain, they felt like they had hit a wall, and they felt exhausted, worried, and distressed. High levels of anxiety may be a reason some patients are more attentive to pain [33]. These descriptions may indicate that some participants tend to catastrophize pain. Pain catastrophizing is defined as an expectation or worry about major negative consequences during an actual or anticipated painful experience. Magnification and helplessness are among the components described [45]. A recent meta-analysis concludes that OA patients should be screened for anxiety and depression for better pain management and to increase clinical awareness around the association between psychological aspects and persistent pain [46]. However, eligibility for surgery should not be influenced by preoperative anxiety or depression symptoms [47, 48]. In addition, OARSI guidelines suggest that patients' clinical status may improve before surgery if they are contacted regularly by phone [1]. Importantly, patients with PPP have reported a feeling of abandonment post-operatively, expressing a need for more support after TKA [49]. A tailored supplement to treatment such as internet

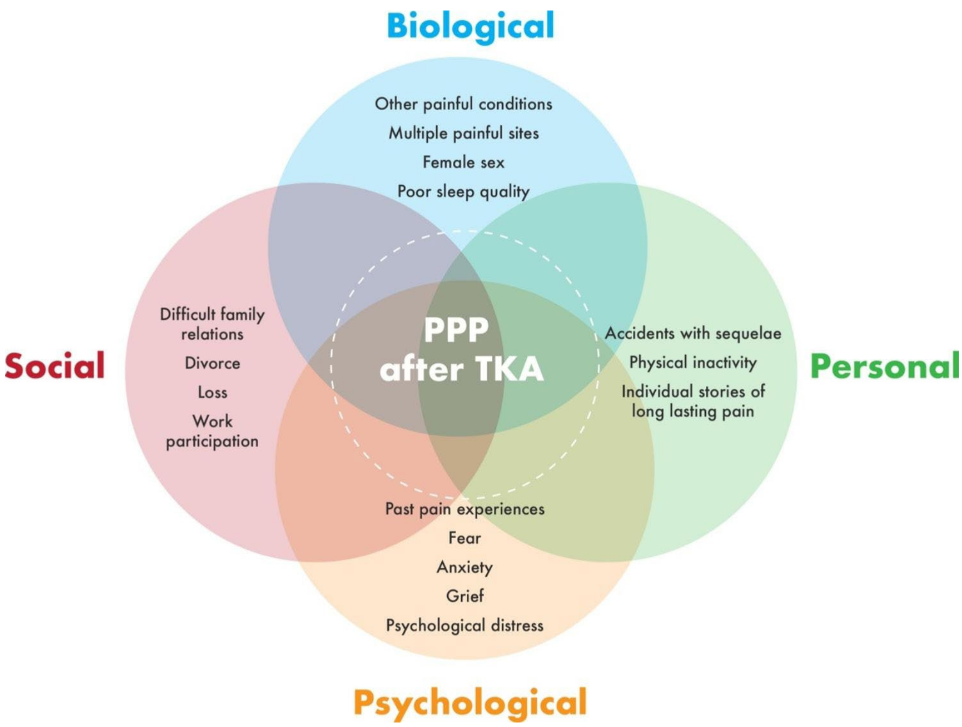

Fig. 1 Illustrates the elements in painful experiences from a biopsychosocial pain perspective

delivered follow-up may also be a way to improve outcomes for vulnerable patients [50].

The first and second authors' preconception of patients with persistent pain was that these patients are often vulnerable with high levels of stress. However, our participants showed perseverance and a strong mindset. This was unexpected. Participants sometimes had a humorous twist or tone when telling their stories of painful or stressful experiences. Having in mind that these patients may be reluctant to share their experiences with healthcare personnel [51], humor may be a way of modifying and presenting their stories in a more listener-friendly way.

The perception of pain may be influenced by physical health problems, such as painful conditions and multiple painful sites, one's psychological state, such as fear, expectations, earlier pain history, family relations and work-life [33]. Thus, several factors are at play and must be considered when exploring the complexity of persistent pain after TKA. The biopsychosocial model [39, 44, 52] is a useful theoretical model for understanding and explaining what our participants highlighted as important memories and experiences, in this context of pain, before their TKA surgery. The model illustrates the complexity of elements that can influence the perception of pain in patients.

Strengths and limitations

Our study employed purposive sampling of participants from a larger longitudinal quantitative study, which allowed us to conduct this follow-up study targeting an already identified subgroup of patients who did not improve one year after TKA. However, in this follow-up study the participants were interviewed only at one timepoint 5–7 years postoperatively as part of a 5 year follow-up. Stories from years prior to surgery may lead to recall bias. However, we aimed to investigate the participants' own perception of painful stories and what was important and meaningful to them. We believe that the real-life issues and struggles important to the participants were highlighted through their sharing of stories of earlier incidents in life. What participants remember is influenced by time and by the painful experience itself [53, 54]. However, we believe that we achieved what we aimed to; namely explore earlier painful and stressful experiences considered important and meaningful to the participants in the context of experiencing pain [23]. When discussing the findings within a biopsychosocial perspective, the passing of time and highlighting experiences that have stuck with them, is in fact highly relevant in the context of pain perception and persistent pain [33, 54].

Having data from questionnaires and interviews allowed us to detect inconsistency in what patients report on painful conditions. We found that patients excluded information on painful accidents with sequelea and painful comorbidity in questionnaires while elaborating on them in interviews. The theoretical model of information power was employed to evaluate sample size [55]. The sample size generated sufficient information power as the participants´ characteristics were highly specific for the aim. The interview dialogue and setting enabled the participants to share their stories undisturbed in a safe and quiet environment, consequently, generating rich data [8, 55]. The participants are all from one single orthopedic unit in Norway. The unit is however one with the highest volume of TKA surgery in Norway, allowing for a subgroup of non-improvers of a certain number.

Conclusion

Participants in this study told stories of lives with emotional struggles and long lasting painful conditions. The double burden of more painful conditions often in addition to psychological stress left the participants struggling, often years before surgery. Their stories described a vicious cycle of pain and deteriorating QOL, physically, socially, and psychologically prior to TKA surgery.

Implications for clinical practice and further research

The study highlights the importance of considering patients' preoperative stories of pain, as well as their psychological and social struggles, for better identification of those at risk of PPP. Nurses, physiotherapists, and physicians may tailor healthcare for these patients if their challenges are identified preoperatively. Identifying and assessing the challenges enables personalized care and support, such as advice on pain management, cognitive support, guided rehabilitation and coping strategies both pre- and post-surgery. Addressing patients´ high levels of pain and related or unrelated psychological struggles before surgery can thus improve outcomes and reduce the risk of PPP.

The present study provides insight into the non-improver TKA patients as individuals and offers new approaches for identifying those patients who will benefit from individualized perioperative pain management. These findings could be subject to further quantitative investigations.

Abbreviations

BPI	Brief Pain Inventory
HRQOL	Health Related Quality of Life
OA	osteoarthritis
OARSI	the Osteoarthritis Research Society International
PPP	Persistent post-surgical Pain
TKA	Total Knee Arthoplasty

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Author contributions

All authors discussed the findings and commented on the manuscript. Study conception and design: V.B.S., U.O., M.F.L., S.A.S., A.L., A.D. Acquisition of data: V.B.S., M.F.L., A.A., A.D. Analysis and interpretation of data: V.B.S., U.O., M.F.L., S.A.S., A.D. Drafting of the article: V.B.S., U.O Critical revision of the article for important intellectual content: V.B.S., U.O., M.F.L., S.A.S., A.A., A.L., A.D. Final approval of the article: V.B.S., U.O., M.F.L., S.A.S., A.A., A.L., A.D. All authors reviewed the manuscript.

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Data Availability

The datasets generated and analyzed during the current study are not publicly available due to not compromise individual privacy and legal restrictions. A minimal dataset may however be available from the authors upon reasonable request and with permission from the Regional Committee in Ethics in Medical Research in South-East Norway (REC) and the hospitals' Data Protection Officers.

Declarations

Ethics approval and consent to participate

The study was approved by the Regional Committee for Medical and Health Research Ethics (reference number 2011/1755) and performed in accordance with the Declaration of Helsinki. Written consent was obtained from all participants before inclusion into the study. All methods and storing of research data were performed in accordance with the Regional Committee in Ethics in Medical Research in South-East Norway (REC) and the hospitals' Data Protection Officers guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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