University of Antwerp

Faculty of Medicine and Health Sciences
Department of Rehabilitation Sciences and Physiotherapy
Research group MOVANT

Maastricht University

Faculty of Health, Medicine and Life Sciences
Department CAPHRI, functioning, Participation and Rehabilitation

Heterogeneity in individuals with knee osteoarthritis awaiting total knee arthroplasty and its impact on outcome from a biopsychosocial perspective

Heterogeniteit bij personen met knie artrose die een totale knie prothese ondergaan en de impact op therapie uitkomst vanuit een biopsychosociaal perspectief

Sophie Vervullens

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Heterogeneity in individuals with knee osteoarthritis awaiting total knee arthroplasty and its impact on outcome from a biopsychosocial perspective

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Sophie Vervullens

Born 14 July 1995 in Wilrijk

PROMOTORES:

Prof. Dr. Mira Meeus, Antwerp University, Wilrijk, Belgium/Pain in Motion International Research Group (PiM)

Prof. Dr. Rob J.E.M. Smeets, University, Maastricht, The Netherlands/CIR Clinics in Revalidatie, location Eindhoven, The Netherlands/Pain in Motion International Research Group (PiM)

Prof. Dr. Jonas Verbrugghe, Antwerp University, Wilrijk, Belgium/Hasselt University, Hasselt, Belgium

ASSESSMENT COMMITTEE MAASTRICHT UNIVERSITY:

Prof. Dr. Jeanine Verbunt, Maastricht University, Maastricht, The Netherlands (Chair)

Prof. Dr. Filip Struyf, Antwerp University, Wilrijk, Belgium

Prof. Dr. André Wolff, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Dr. Eva Huysmans, Vrije Universiteit Brussel, Belgium/Pain in Motion International Research Group (PiM)

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INTERAL PHD COMMITTEE ANTWERP UNIVERSITY:

Prof. Dr. Eric Van Breda, Antwerp University, Wilrijk, Belgium (Chair)

Prof. Dr. Jeanine Verbunt, Maastricht University, Maastricht, The Netherlands

Prof. Dr. Filip Struyf, Antwerp University, Wilrijk, Belgium

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List of abbreviations

30CST= 30-Second Timed Chair Stand Test
ANOVA= Analysis Of Variance Analysis
AUC= Area Under The Curve
BIC= Bayesian Information Criterion
BMI= Body Mass Index
CBT= Cognitive Behavioural Therapy
CDT= Cold Detection Threshold
CI= Confidence Interval
CIR= Clinics In Revalidatie
CPM= Conditioned Pain Modulation
CPT= Cold Pain Threshold
CRP= C-reactive Protein
CS= Central Sensitisation
CSI= Central Sensitisation Inventory
DDPR= Dutch Dataset Pain Rehabilitation
DN-4= Douleur Neuropathique – 4
EBRO= Evidence-Based Guideline Development
ECRL= Extensor Carpi Radialis Longus
EDT= Electrical Detection Threshold
EIH= Exercise Induced Analgesia
EM= Estimated Mean
EPT= Electrical Pain Threshold
EULAR= The European League Against Rheumatism
HADS = Hospital Anxiety And Depression Scale
HbA1c= Glycated Haemoglobin
HPT= Heat Pain Threshold
IASP= International Association For The Study Of Pain
ICD-11= International Classification Of Diseases, 11th Revision
IMMPACT= The Initiative On Methods, Measurement, And Pain Assessment In Clinical Trials
IMPT= Interdisciplinary Multimodal Pain Treatment
IPQR= The Illness Perceptions Questionnaire Revised
K&L Scale= Kellgren & Lawrence Scale
KOA= Knee Osteoarthritis
KOOS= Knee Injury And Osteoarthritis Outcome Score
KSSS= The Knee Society Scoring System
LP= Linear Predictor
LPA= Latent Profile Analysis
M2SENS= Sensory Functioning Lab
MCIC= Minimal Clinically Important Change
MCID= Minimal Clinically Important Difference
MREC= Medical Research Ethics Committee

MSK= Musculoskeletal
NRS= Numeric Rating Scale
OA= Osteoarthritis
OARSI= Osteoarthritis Research Society International
OCEBM= Oxford Centre For Evidence-Based Medicine
PCS = Pain Catastrophizing Scale
PDI= Pain Disability Index
PICO= Patient Intervention Comparison Outcome
PPT= Pressure Pain Threshold
PPTT = Pain Pressure Tolerance Threshold
PRISMA= Preferred Reporting Items For Systematic Reviews And Meta-Analyses
PROMS= Patient Reported Outcome Measurements
QST= Quantitative Sensory Testing
QUIPS= The Quality In Prognostic Studies
Rcts= Randomized Controlled Trials
Rob= Risk Of Bias
ROB-II= The International Cochrane Risk Of Bias Checklist For Randomized Controlled Trials
ROBINS-I= The International Cochrane Risk Of Bias Checklist For Nonrandomized Controlled Trials
ROC= Receiver Operating Characteristic Curve
SD= Standard Deviation
SPS= Somatosensory Processing System
SPSS= Statistical Package For Social Sciences
STROBE= Strengthening The Reporting Of Observational Studies In Epidemiology
THA= Total Hip Arthroplasty
Tidier= Template For Intervention Description And Replication
TKA= Total Knee Arthroplasty
TRIPOD= Transparent Reporting Of A Multivariable Prediction Model For Individual Prognosis Or Diagnosis
TS= Temporal Summation
TSA= Total Shoulder Arthroplasty
VDT= Vibration Detection Threshold
VLMR= Vuong-Lo-Mendell-Rubin Likelihood Ratio Test
WDT= Warmth Detection Threshold
Wos= Web Of Science

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Chapter 1: General introduction

This dissertation explores the clinical heterogeneity present in individuals affected by (knee) osteoarthritis and mainly those awaiting total knee arthroplasty (TKA). The central objective is to investigate the association between this heterogeneity and treatment outcomes from a biopsychosocial perspective.

The general introduction is organized into five sections. The *first section* provides information about the epidemiology, pathogenesis, clinical manifestation and current treatment of knee osteoarthritis (KOA). The *second section* explores the heterogeneity across individuals with KOA, addressing topics such as phenotyping, pain mechanisms, and chronic pain definitions. The *third section* elaborates on identifying KOA treatment response based on predictive factors for (in)sufficient treatment outcome. The *fourth section* informs on stratified preoperative rehabilitation (further called 'prehabilitation') care. Lastly, the *fifth section* summarizes the research objectives and outline of the dissertation.

1. Knee osteoarthritis

Epidemiology and pathogenesis

Osteoarthritis is the third most common musculoskeletal pain condition in the world, with an annual incidence of 12.5% and prevalence of 7.6%. It currently affects approximately 595 million people worldwide, 60% of whom are female and 73% over the age of 55 (1–4). KOA ranks as the most common form of osteoarthritis, accounting for at least two-thirds of individuals with osteoarthritis (3,4). In addition, KOA results in an economic burden in e.g. the Netherlands of €27 million due to sick leave (5), and e.g. in the United States of €25 billion due to healthcare expenditures (6) each year. A continued rise of these numbers is anticipated due to the global trends in ageing and obesity rates (4,7).

KOA is a chronic condition involving structural and functional failure of the synovial knee joints driven by an active dynamic process of imbalance between joint tissue destruction and repair. Integrity loss and changes in the composition of cartilage tissue lead to higher synthetic activity, which in turn activates matrix degeneration and an increase in pro-inflammatory mediators (8). To date, osteoarthritis can be considered as a 'whole-joint' condition, affecting the ligaments, subchondral bone, periarticular muscles, synovium, and capsule, and not just the articular cartilage structures of the joint (9). The development and cause of KOA remain very complex, multifactorial and heterogeneous, resulting from a combination of various underlying mechanisms such as systemic (ageing, hormonal, metabolic and central nervous system disturbances), genetic (predisposition), biomechanical (joint shape, alignment, mechanical overload, post-traumatic) and environmental influences (physical inactivity, dietary changes, smoking, stress, etc.) (10–14). Therefore, the focus on individuals with osteoarthritis must go beyond the 'whole-joint' condition itself and requires the integration of all other biological, psychological and social factors of the individual (11). Thus, to date, adopting a 'whole person' approach is considered necessary to understand this complex condition.

‘Whole person’ clinical manifestation

At the individual level, KOA also has an enormous impact, caused by the experience of pain, reduced function and range of motion, stiffness, joint instability, swelling, crepitus, and deformity (15). Pain is by far the most important symptom of KOA and guides most clinical-related decisions (16). The perception of pain varies, ranging from more predictable intermittent activity-related pain in early stages to constant, unpredictable pain in advanced stages of KOA (17). As KOA is a chronic condition, the experience of chronic pain (i.e. pain lasting three months or more (18)) is almost inevitable. The pain experience itself is influenced not only by the peripheral joint (biological factor), but also by external elements such as psychological, social and neural factors (16). Therefore, the International Association for the Study of Pain (IASP) defines pain as ‘an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage’ and emphasises that each pain experience is personal and a combination of biological, psychological and social factors (19). This means that in addition to the cause and the development of KOA, there is also a great variability in the clinical manifestation of KOA (13).

Current treatment strategies

To date, conservative management of KOA is still primarily focused on symptom relief to improve function and quality of life (20), as no disease-modifying treatment has been identified yet (21). First-line conservative treatment mainly focuses on education, exercise, weight management, walking aids or braces, and pharmacological treatment (22). Interdisciplinary multimodal pain treatments (IMPT) that focus more on the whole biopsychosocial model have also shown positive effects on pain and disability in individuals with osteoarthritis, and are currently conditionally recommended by several guidelines (22–24). Inadequate management of these conservative treatments, meaning that individuals with KOA continue to experience persistent pain and symptoms that affect their quality of life, is one of the main reasons to perform TKA surgery (25,26). Corresponding to the increased prevalence of KOA, the escalating number of TKA surgeries presents an additional societal problem due to its financial and individual impact (27,28).

Despite the positive outcomes of both the conservative and surgical treatment, the effect sizes of the conservative treatments remain only small to moderate at best (29,30), and 20% of patients undergoing TKA still experience postoperative pain (31–33). This variance in treatment outcome may be explained by the fact that current guidelines and most clinical trials still do not take into account the inherent heterogeneity seen in the development, cause and clinical manifestation of KOA (34–36). To date, guidelines still recommend a stepped care approach for KOA patients (20,24), implying that all KOA patients should start with the same treatment approach, and that a change in treatment is only necessary if the prior step proves unsuccessful. However, it has been postulated that adopting a stratified care approach, where the treatment is more tailored to the pain perception and ‘whole person’ clinical manifestation related to KOA’s biopsychosocial-related heterogeneity, would result in greater benefit (37,38).

2. Towards stratified treatment: delving into heterogeneity

Phenotyping in KOA

Despite the extensive research into the pathogenesis, mechanisms and (conservative and surgical) treatments of KOA, all of which have highlighted its heterogeneity, unravelling and targeting this heterogeneity still remains a challenge (13). An attempt to clarify the heterogeneity in the clinical and structural presentation of KOA is the use of phenotyping (12,13,39). Phenotypes can be defined as combinations of different observable traits or states (resulting from different genetic and environmental factors) that identify and characterise subgroups within a given patient population (12,13). Phenotyping can be based on disease or syndrome aetiology, clinical manifestation, progression, or treatment response, but phenotyping based on clinical manifestation and treatment response is considered to be the most useful to improve the current conservative and surgical management of KOA (12). A couple of reviews have been published on phenotyping individuals with KOA (12,40–43), but only one systematic review (Dell'Isola et al.) attempted to summarise and bundle the results of all original clinical phenotype studies in KOA into more 'general' phenotypes and identified six subgroups including a chronic pain, an inflammatory, a metabolic syndrome, a bone and cartilage metabolism, a mechanical overload, and a minimal joint disease phenotype (12). However, the classification of Dell'Isola et al. (12) is currently under debate and also other reviews emphasise the importance of further research in this area (39,43). This further research also includes prescriptive phenotyping, which identifies characteristics of phenotypes that are more or less likely to respond adequately to treatment, thereby helping to target and improve treatment outcomes (39). Depending on the identified phenotype, different treatment approaches are suggested (e.g. diet intervention for individuals with a metabolic syndrome phenotype, anti-inflammatory approach for individuals with an inflammatory phenotype, etc.). This first attempt of a summary of KOA phenotypes showed that most research only focused on specific risk factors and/or parts of the biopsychosocial model to subgroup individuals with KOA, without considering the 'whole person' clinical manifestation (12). In addition, findings of previous phenotype research have shown that the number and characteristics of the phenotypes are also very heterogeneous depending on the variables included in the phenotype construct (12,39,41,43–46).

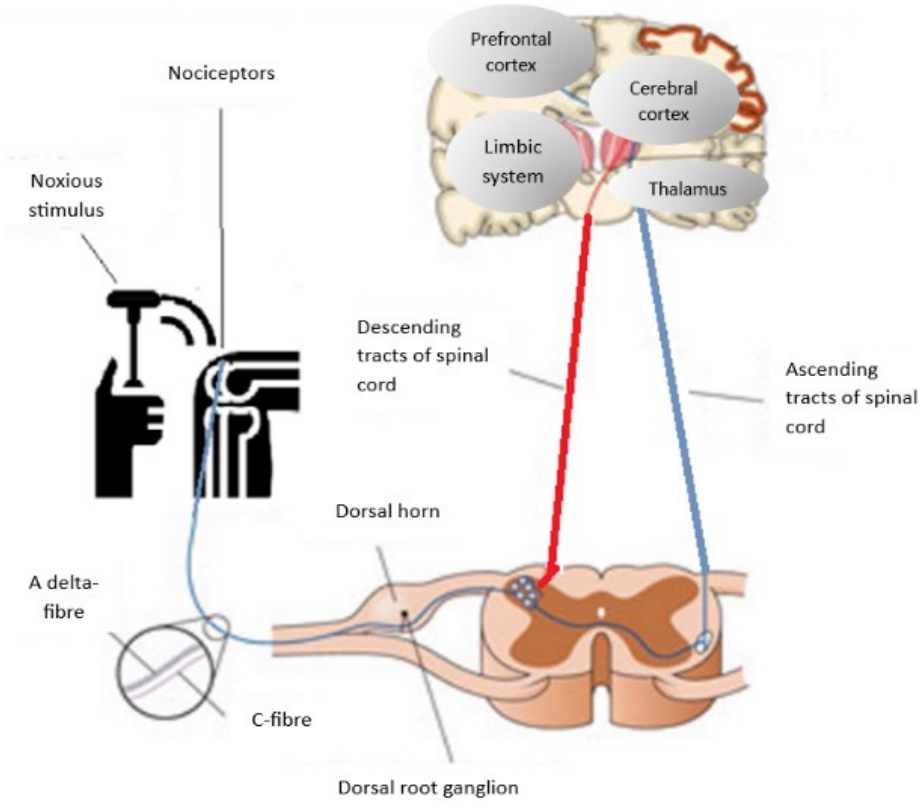
The focus on pain

As previously mentioned, the experience of (chronic) pain is the most common symptom of KOA and the main reason why individuals with KOA seek medical help (16). Moreover, different mechanisms determine the pain perception in KOA, and therefore, research on pain phenotyping specifically has become very popular (13). The fact that one of the summarised phenotypes in the systematic review by Dell'Isola et al. was a 'chronic pain phenotype', characterized by disturbed somatosensory functioning and psychological distress, and the fact that some reviews specifically focus on pain phenotyping studies (41,43), highlights the extent and importance of research into phenotyping individuals with KOA based on pain characteristics (12). To ensure clear understanding of the neuro- and pathophysiology of pain, this is briefly discussed in *Information box 1*.

Information box 1*: *the neuro- and pathophysiology of pain

The somatosensory functioning system includes the peripheral (nerves and nerve endings) and central nervous system (brain and spinal cord), and is responsible for the processing of all somatosensory signals in our body (i.e. touch, vibration, temperature, chemical, and noxious stimuli) (51). Focusing on the noxious stimuli (i.e. 'harmful' stimuli), nociceptors become activated when the threshold of the afferent Aδ- and C-fibre nerve endings is exceeded. These activated nociceptors send out an electrical signal (i.e. transduction) that stimulates the primary and secondary order afferent neurons in the dorsal horn of the spinal cord through synaptic contact (i.e. transmission). This signal is then transmitted from the dorsal horn of the spinal cord to the brainstem and the thalamus through the spinothalamic tract. The thalamus acts as a relay system and sends the signal further to the higher cortical regions (52), which analyse and interpret the nociceptive signal (body location and intensity – bottom-up or ascending mechanism) according to their cognitive, affective and emotional function (top-down or descending mechanism). Thereafter, the feeling of 'pain' can be generated (53). This pathway is activated in both acute (i.e. pain lasting less than three months) and chronic (i.e. pain lasting three months or longer) pain (18).

Figure 1: somatosensory pathways involved in pain experience.



Descending (i.e. cognitive emotional sensitisation and impaired endogenous pain inhibition) and ascending (i.e. nerve ending hypersensitivity and increased synaptic transmission) facilitatory mechanisms may contribute to dysfunctional somatosensory functioning (52). This can lead to peripheral and central sensitisation (primary and secondary hyperalgesia and allodynia, respectively). Hyperalgesia is increased sensitivity to painful stimuli, whereas allodynia is increased sensitivity to non-painful stimuli. Peripheral sensitisation also occurs in acute pain where the injured site becomes hypersensitive as a temporary adaptive protective mechanism of our peripheral somatosensory nervous system (temporary hypersensitivity of local C-fibres). However, the presence of both peripheral and central sensitisation can occur in chronic pain, where both injured and uninjured sites can become hypersensitive as a result of generalized hypersensitivity of the somatosensory system (54).

Therefore, phenotyping individuals based on pain mechanisms seems to be another approach to further unravel the heterogeneity in this population and become a step closer to successful treatment allocation (43). The IASP classifies pain according to three different pain mechanisms: nociceptive, neuropathic and nociplastic pain (or a combination) (19,47). These pain mechanisms are also proposed to improve stratified care, as different treatment approaches are recommended based on the heterogeneity in pain mechanisms, such as a localised approach in case of a predominant nociceptive pain mechanism, a central nervous system-targeted approach in case of a nociplastic pain mechanism, or a peripheral nerve-targeted approach in case of a neuropathic pain mechanism (47–49). These three pain mechanisms can occur separately, but can also be present in a combination, which results in the presence of a mixed pain mechanism. Therefore, these pain mechanisms should be considered as a continuum, including a predominant pain mechanism. Features of all the three mechanisms are thought to be present in KOA and more 'general' proposed criteria for defining the predominant mechanism are listed in *Table 1* (50). However, these characteristics are still very vague and require further clarification, making the identification of the predominant pain mechanism a real challenge in current research and clinical practice.

Nociplastic pain is the most recently added pain mechanism (47), and therefore, further detailed description and identification of the biopsychosocial characteristics and the treatment outcome that reflect this pain mechanism in KOA is warranted. Altered nociception and disturbed somatosensory functioning (i.e. peripheral and central sensitisation) are currently thought to be the underlying mechanisms of nociplastic pain (57,58). Peripheral and central sensitisation are defined as "increased responsiveness of nociceptive neurons in the peripheral and central nervous system to their normal or subthreshold afferent input" according to the IASP (19). Somatosensory dysfunction manifests as an imbalance between facilitatory and inhibitory ascending and descending activity in the central nervous system (59,60). As *mentioned in Information box 1,* impaired endogenous pain modulation and cognitive emotional sensitisation can influence this descending activity, the latter by the presence of disturbed psychological factors (i.e. anxiety, depression, pain catastrophizing) (61). The presence of psychological disturbances and insufficient outcomes of localised treatment approaches are also proposed as features to discriminate nociplastic pain from the other pain mechanisms (62).

Table 1: Pain mechanisms according to the International Association for the Study of Pain in knee osteoarthritis (19,50,55,56)

	Nociceptive	Neuropathic	Nociplastic
Definition International Association for the Study of Pain	'Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.'	'Pain caused by a lesion or disease of the somatosensory nervous system.'	'Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.'
Intensity	Proportional to structural damage (osteoarthritis) seen on medical imaging and normal expected response to physical provocation tests (palpation)	Related to damage on peripheral nerve endings innervating subchondral bone in the knee joint (or nerve damage after TKA surgery) (infrapatellar branch of tibial nerve, obturator nerve and saphenous nerve)	Disproportional, not related to structural or peripheral nerve damage or abnormal expected response to physical provocation tests (palpation)
Type	More intense predictable intermittent activity-related pain in combination with constant aching pain, but pain in rest is possible in later stages	Shooting, burning, varying, intermittent	Unpredictable, varying, constant pain
Pain distribution	Local, discrete pain around the knee joint (medial, lateral knee joint, patellar, lower femoral and higher tibial pain)	Neuro-anatomical pattern of the damaged peripheral nerves	More regional or even widespread, diffuse pain, not restricted to the knee joint
Pain duration	< or > 3 months	< or > 3 months	> 3 months
Somatosensory dysfunction	Local hyperalgesia and possible allodynia	Hyper- and/ or hypoalgesia, and possible allodynia following the neuro-anatomical pattern	Local and/ or widespread hyperalgesia and allodynia, possible disturbed pain modulation
Treatment response	Good response to osteoarthritis targeted treatments (conservative treatments like local agent medication, exercise, weight management etc. in early stage KOA, TKA surgery in end-stage KOA)	Better treatment response with centrally acting agent medication ass addendum to osteoarthritis targeted treatments	No or less response to osteoarthritis targeted treatments, unpredictable response

Abbreviations: TKA= total knee arthroplasty, KOA= knee osteoarthritis

To date, there is no gold standard for assessing somatosensory functioning, but quantitative sensory testing and questionnaires (e.g., Central Sensitisation Index [CSI] or Pain Sensitivity Questionnaire) are currently used (60,63,64). Previous research has shown that this disturbed somatosensory functioning is present in a proportion of the KOA (63,65–67) and TKA population (68,69), manifesting as local and widespread hyperalgesia and allodynia (indirectly measurable with pain thresholds), hyperexcitability of the afferent neurons (indirectly measurable with temporal summation), inefficient endogenous pain inhibition (indirectly measurable with conditioned pain modulation), and self-reported symptoms of central sensitisation (measurable with CSI) (67,70).

Preoperative disturbed somatosensory functioning has also been of interest as a potential risk factor for chronic pain after TKA surgery (65,71–73). To date, KOA pain is classified as chronic secondary musculoskeletal pain in the International Classification of Diseases, 11th Revision (ICD-11). This means that the pain and (possible) disturbed somatosensory functioning are a symptom resulting from persistent nociception of, and directly related to, the KOA (musculoskeletal disorder) itself (18). This is different from chronic primary musculoskeletal pain, in which pain is or has become the condition itself, not directly related to a known musculoskeletal disease or injury (74,75). Other examples of chronic secondary musculoskeletal pain are pain arising from a musculoskeletal injury (e.g., ankle sprain), rheumatoid arthritis, etc. (18). Examples of chronic primary musculoskeletal pain are non-specific musculoskeletal conditions (e.g., non-specific low back pain, neck pain, fibromyalgia, etc.) (74).

The substantial number of individuals with chronic pain after TKA (31–33) and the discrepancy between the presence of worse radiological signs and worse pain complaints (76) suggest that not all KOA pain may be inherently ‘secondary’. Some studies have also shown that patients with persistent pain after treatments targeting the nociceptive source of KOA (e.g., TKA surgery) still experience disturbed somatosensory functioning (77,78). The central nervous system is dynamic and it is therefore postulated that (possible) disturbed somatosensory functioning may indeed be caused by the peripheral source of nociception (peripherally driven disturbed somatosensory functioning or chronic secondary musculoskeletal pain) in a subgroup of individuals with KOA (79) but may be more independent of the identified KOA itself (centrally driven disturbed somatosensory functioning) in another subgroup (18,74,75). The persistence of disturbed somatosensory functioning could (additionally) be interpreted as a sign of chronic primary musculoskeletal pain. Next to disturbed somatosensory functioning, significant emotional distress presents as one of characteristics (74,75) and is also identified as an important possible preoperative risk factor for chronic pain after TKA (73,80). To date, it is not confirmed yet whether a subclassification of centrally and peripherally driven disturbed somatosensory functioning is present in individuals with KOA.

3. Towards stratified treatment: treatment response

The identification of predictive factors for (in)adequate treatment success (e.g., sufficient or insufficient pain relief based on e.g. the minimal clinically important change, patient acceptable state or cut-off value of a certain treatment outcome) seems to be a crucial step towards successful treatment allocation and stratified care management (31,32). In recent years, there has been extensive research into possible predictive factors for chronic pain after TKA. A recent umbrella review provided an overview of the results of all previous systematic reviews and meta-analyses focusing on this topic and identified factors covering the entire biopsychosocial model (demographic, functional, social, psychological, pain-related, structural, comorbidities and metabolic/inflammatory variables) (73). In addition, possible predictors of (in)sufficient treatment success have also been reported for IMPT in various musculoskeletal pain populations (lower baseline levels of negative psychological factors and disability, and higher levels of physical functioning), but also some specific for individuals with osteoarthritis (younger age, lower baseline body mass index, and presence of KOA compared to hip osteoarthritis) (81–83). However, to date, it still remains a challenge to identify the most important predictive factors that have a consistent relationship with treatment outcome (80). Consistent findings of multivariable regression models are necessary to identify the real and causal predictive factors (84). In line with the previous paragraph, current research also highlights the importance of prescriptive phenotyping, which includes the identification of subgroups that are more or less likely to experience adequate treatment response based on identified possible predictors for insufficient treatment outcome as a crucial step for stratified treatment approaches (31,39). If correctly identified, future stratified care management could target these predictive factors and characteristics of subgroups that have less treatment success to investigate whether this approach would lead to a better treatment outcome.

4. Stratified treatment in prehabilitation before total knee arthroplasty

To optimise TKA outcomes, prehabilitation has been proposed as a potential strategy to target and improve possible preoperative risk factors for poor surgical outcomes (85,86). Prehabilitation typically includes physiotherapy-supervised exercise, home-based exercise (both of which tend to focus on strengthening and mobility), and education (85,87). Research has shown that prehabilitation improves risk factors, however only regarding preoperative or short-term postoperative outcomes (87). Long-term postoperative outcomes research has shown no or, at best, small positive effects (85–91). As a result, to date, current guidelines do not make specific recommendations regarding the use of prehabilitation (25,92). Remarkably, previous systematic reviews and meta-analyses did not consider whether the previous original prehabilitation studies used a more stratified or patient-tailored approach (85–91). The lack of strong positive effects of long-term postoperative outcome could possibly be attributed again to the heterogeneity present in KOA. Comparable to the hypothesis of better treatment response with stratified treatment in other treatment strategies of KOA (37,38), it is postulated that more stratified prehabilitation care would result in better long-term post-TKA outcomes.

5. Research objectives and outline of the dissertation

Objectives

The overall aim of this dissertation is to gain better insight into the heterogeneity in individuals with KOA, especially those awaiting TKA and its impact on outcome from a biopsychosocial perspective. Therefore, the current dissertation is divided into three sub-aims, resulting in three parts within the dissertation.

1) **AIM 1:** Future phenotype research should focus on the 'whole person' clinical manifestation (11), encompassing a large number of variables from the whole biopsychosocial model (39,43). Furthermore, the identification of pain phenotypes specifically, based on pain mechanisms (to identify the nociplastic pain mechanism in KOA) and somatosensory functioning (to identify peripherally and centrally driven disturbed somatosensory functioning in KOA), is also highly relevant, as pain is the main symptom of KOA (see *section 2*). Last, phenotyping individuals with KOA awaiting for TKA specifically and determining their response to TKA surgery is warranted, as previous research has shown that 20% of patients experience chronic pain after TKA (31–33). Therefore, the **first aim** is to identify and characterize subgroups based on different biopsychosocial variables, pain mechanisms and somatosensory functioning within a KOA population awaiting TKA and compare their long-term treatment response.
2) **AIM 2:** Consistent predictors for chronic pain after TKA in individuals with KOA are lacking because previous research has not included a broad range of possible biopsychosocial-related predictors in one multivariable regression model with one-year follow-up (80). This may shed light on which factors are the most influential and may distinguish those that may overshadow or 'filter our' the others. In the context of IMPT, possible predictors of (in)sufficient treatment success have also been identified, but a clinical prediction model that can be used in clinical practice to indicate whether an individual with osteoarthritis is likely to benefit from IMPT is currently lacking. Therefore, the **second aim** is to identify predictors of (in)sufficient treatment outcome in individuals with KOA undergoing TKA and individuals with osteoarthritis (not restricted to KOA) admitted to IMPT.
3) **AIM 3:** To date, it is not known whether prehabilitation trials specifically targeted preoperative risk factors and as such gave more stratified interventions in their prehabilitation. As a result, there is currently no evidence whether prehabilitation with a more stratified care approach would lead to better long-term outcomes after TKA compared to prehabilitation with a more one-size-fits-all approach. Therefore, the **third aim** is to provide an overview of all previous stratified and non-stratified prehabilitation studies in KOA patients awaiting TKA and their differences in long-term outcomes after TKA.

Dissertation outline

The present dissertation is divided into three parts (corresponding to the three sub-aims), each of which contains one to four chapters. These three parts are followed by a general discussion including the impact paragraph, an English and Dutch summary, the appendices, the curriculum vitae of the PhD candidate, and acknowledgments.

Before outlining the flow of the three parts included in the dissertation, an overview in *Information box 2* is given of the different studies from which data were analysed.

Information box 2: different studies included in the dissertation

Chapters 2, 3, 5 and 6 *present data from the same multicentre prospective cohort study conducted in four hospitals in Belgium (University Hospital of Antwerp and AZ Monica), and the Netherlands (University Hospital of Maastricht and St. Jans Gasthuis Weert) (prospective cohort study 1). Eligible candidates with KOA who underwent TKA at these hospitals were tested four weeks preoperatively, three months postoperatively, and one-year postoperatively. At these time point, participants completed self-reported questionnaires and underwent various physical examinations that included variables from the entire biopsychosocial model. This model was used to categorise all variables and to ensure a more complete overview of the KOA condition. These are shown in Figure 2. Preoperative and one-year postoperative data were used in* ***Chapter 2, 3, and 6****, while three months postoperative data was also used in* ***Chapter 5****.*

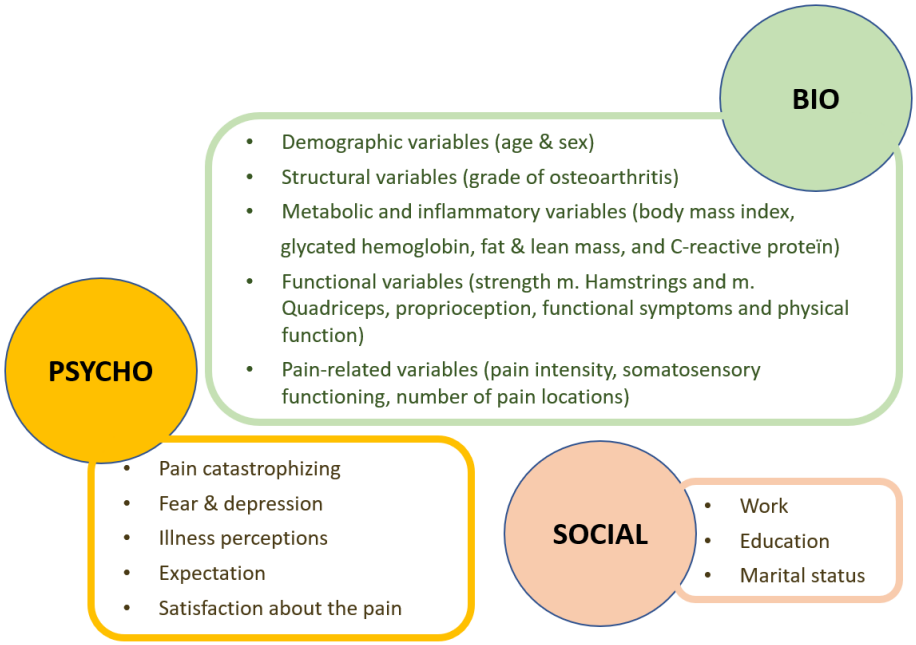
Chapter 7 *contains data from another multicentre prospective cohort study including individuals with osteoarthritis (not restricted to KOA) who received a 10-week individualized IMPT in six clinics in rehabilitation centres in the Netherlands (prospective cohort study 2). Participants completed self-reported psychosocial questionnaires at baseline, and treatment success was measured right after treatment (93).* ***Chapter 4 and 8*** *are systematic reviews.*

PART 1: AIM 1 was to identify and characterize subgroups based on different biopsychosocial variables, pain mechanisms and somatosensory functioning within a KOA population awaiting TKA and compare their long-term treatment response, and therefore comprises **Chapters 2 to 5**.

Chapter 2 presents a secondary analysis of the multicentre *prospective cohort study 1*, in which phenotypes were constructed using latent profile analysis (i.e. data-driven) based on a wide range of different preoperative biopsychosocial variables in KOA patients awaiting TKA. The identified phenotypes were also compared for their difference in pain scores one-year after TKA. **Chapter 3** presents another secondary analysis of the multicentre *prospective cohort study 1* that identified and proposed more refined criteria for a 'no', 'possible', and 'probable' nociplastic pain mechanism group by applying the IASP grading system for nociplastic pain in KOA patients awaiting TKA. The subgroups were also compared for differences in a wide range of preoperative biopsychosocial variables and in pain scores one-year after TKA. **Chapter 4** summarizes all studies that have investigated the evolution of

somatosensory functioning from pre- to postoperative in different musculoskeletal conditions (*systematic review 1*). This systematic review was conducted as a preparatory step for **Chapter 5**, which also includes data of the multicentre *prospective cohort study 1* investigating the evolution of pain intensity from pre- to postoperative in different somatosensory functioning evolution groups.

Figure 2: Biopsychosocial factors implemented chapter 2, 3, 5 and 6



PART 2: AIM 2 was to identify predictors of (in)sufficient treatment outcome in individuals with osteoarthritis and comprises **Chapters 6 and 7**.

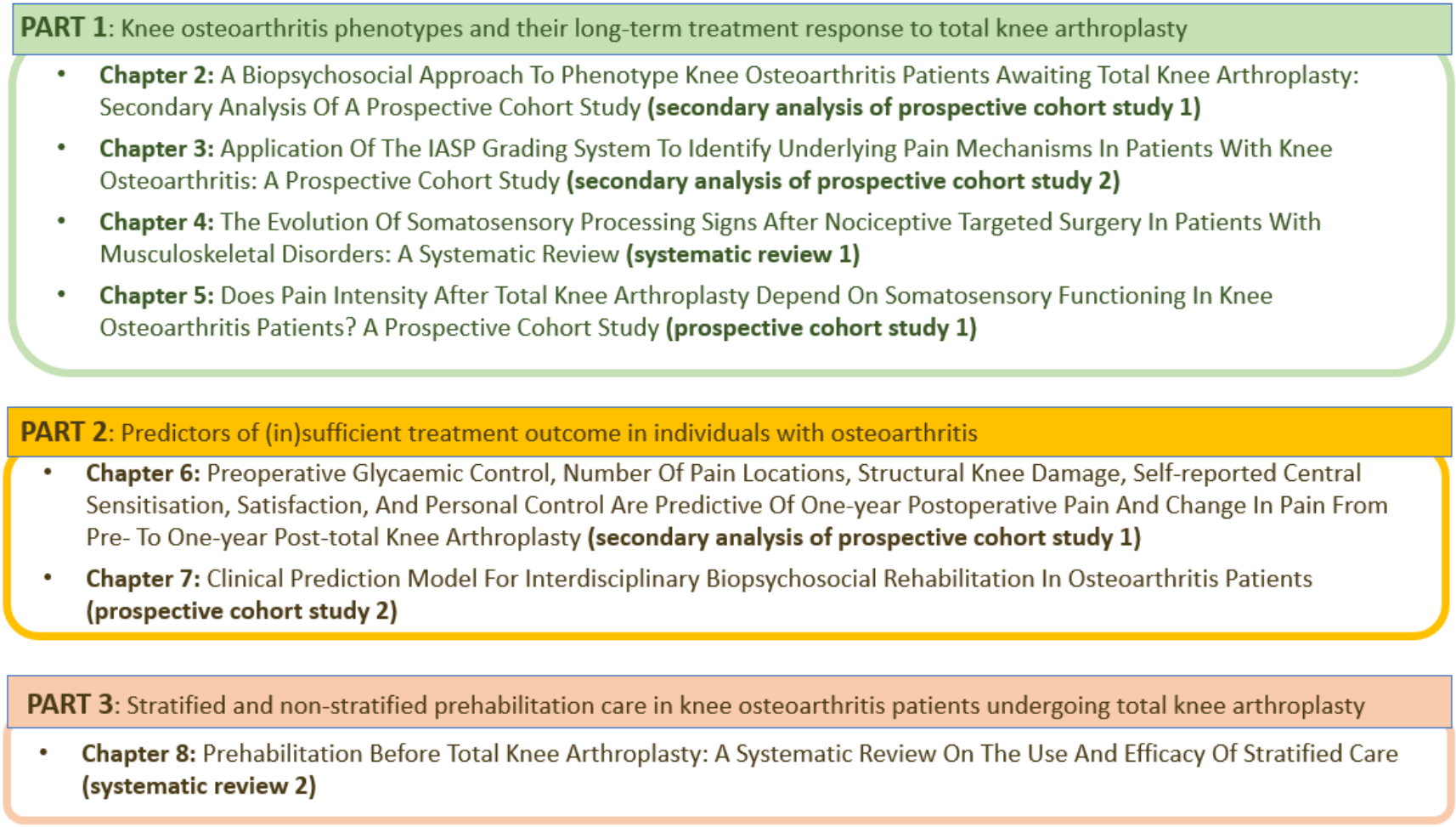
Chapter 6 includes again a secondary analysis of the multicentre *prospective cohort study 1* that performed a multivariable linear regression analysis of a wide range of previously identified possible preoperative biopsychosocial predictors of chronic pain after TKA. **Chapter 7** comprises data of the multicentre *prospective cohort study 2* and aimed to identify and internally validate a multivariable clinical prediction model to predict treatment success after IMPT based on predictors that are standardly measured before the treatment in clinics in rehabilitation (93).

PART 3: AIM 3 provides an overview of stratified and non-stratified prehabilitation care in KOA patients undergoing TKA and comprises one chapter (**Chapter 8**):

Chapter 8 summarises all conservative, non-pharmacological prehabilitation studies in KOA patients undergoing TKA that investigate their effect on long-term pain, satisfaction, function and quality of life (*systematic review 2*). In particular, the review focuses on the use of stratified or non-stratified prehabilitation treatment, and the differences between these approaches in terms of long-term outcomes.

Finally, **Chapter 9** contains the general discussion of the dissertation, including a comprehensive overview and critically review of the results found in **Chapter 2 to 8**, followed by the methodological considerations, valorisation and clinical implications (impact paragraph), suggestions for future research, and a general conclusion.

Figure 3: Overview of scientific publications in PhD dissertation



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PART 1: Knee osteoarthritis phenotypes and their long-term treatment response to total knee arthroplasty

Chapter 2: A biopsychosocial approach to phenotype knee osteoarthritis patients awaiting total knee arthroplasty: secondary analysis of a prospective cohort study

Sophie Vervullens[1,2,3] , Lotte Meert[1,2,3], Rob J.E.M. Smeets[2,3,4], Gavin van der Nest[5], Jonas Verbrugghe[1,8], Peter Verdonk[6], Frank Th.G. Rahusen[7], Mira Meeus[1,3]

[1]Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium

[2]Research School CAPHRI, Department of Rehabilitation Medicine, Maastricht University

[3]Pain in Motion International Research Group (PiM), www.paininmotion.be

[4]CIR Clinics in Revalidatie, location Eindhoven, The Netherlands

[5]Department of Methodology and Statistics, and Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, Netherlands

[6]ORTHOCA, Antwerp, Belgium and ASTARC department, Antwerp University, Belgium

[7]Department of Orthopaedics, St Jans Gasthuis Weert, The Netherlands

[8]REVAL-Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Hasselt, BELGIUM.

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Abstract

Background: Previous research showed chronic post-total knee arthroplasty (TKA) pain in 20% of people with knee osteoarthritis (KOA). Various preoperative biopsychosocial-related factors have been described, but phenotyping people with KOA awaiting TKA based on these factors is still lacking. This could be relevant to understand differences in their TKA surgery response.

Objective: To identify phenotypes in people with KOA awaiting TKA and their difference in post-TKA pain based on preoperative biopsychosocial factors.

Methods: People with KOA awaiting TKA in four hospitals in Belgium or the Netherlands were included. A cross-sectional latent profile analysis was conducted containing structural, metabolic, functional, pain-related, psychological and social variables. Concurrent validity was tested using 3-step multinomial logistic regression. The difference in one year post-TKA pain was examined with linear mixed model analysis.

Results: Two-hundred-seventeen participants were included in the latent profile analysis with a mean age of 65.5 (7.7), including 109 women. A model with two phenotypes differed in 14 out of 21 variables. Participants in phenotype 2 (28% participants) had higher body mass index (BMI), higher chance for having less structural damage (KOA grade), lower m. Quadriceps strength and physical function (Knee Society Scoring System functional and 30seconds chair stand test), higher pain intensity, number of pain locations, and indices of central sensitization (temporal summation, central sensitization inventory score, and lower pressure pain thresholds), higher pain catastrophizing, anxiety and depression, and more post-TKA pain intensity compared to phenotype 1 (72% of participants). Concurrent validity was confirmed in 3 out of 4 variables.

Conclusions: Phenotype 2 (28%) resembling nociplastic pain characteristics in combination with worse psychological factors, BMI, functional and structural factors, and phenotype 1 (72%) not representing these characteristics were identified. Phenotype 2 had worse pain intensity scores after TKA compared to phenotype 1. Attention to characteristics of phenotype 2 is warranted concerning post-TKA pain.

Introduction

Knee osteoarthritis (KOA) represents one of the most common forms of osteoarthritis (1). It affects a substantial part of the elderly with a huge impact on individuals' life, but also on society, due to the accompanying symptoms and costs related to treatment and participation problems (2). KOA is a heterogeneous disease, where individuals present with various aetiological backgrounds, disease progressions and clinical representations related to a complex combination of biopsychosocial factors (3). Various phenotypes (i.e., subgroups) can as such be expected based on biopsychosocial factors accompanied by the KOA diagnosis itself.

Apart from studying potential phenotypes in people with KOA in general, doing so in people with KOA awaiting TKA specifically in combination with comparing their response to TKA surgery would be relevant because 20% of people reports chronic post-TKA pain (4,5). Various biopsychosocial-related preoperative factors have already been described (6), but contradictions remain present, and consensus in combination with a determination of phenotypes based on these factors is still lacking (6). Moreover, current evidence about the indication criteria for performing TKA in people with KOA is scarce and based on pain symptoms, functionality and radiological changes without the inclusion of other possible biopsychosocial-related preoperative factors (7). This makes adequate selection of eligible people still very vague and challenging (8).

One of the first clinical phenotype studies in KOA used muscle strength, KOA grade, depression and body mass index (BMI) for their phenotype-construct and found five different phenotypes (9,10). In addition, a narrative review mentioning KOA phenotypes emphasized a structure, age and obesity phenotype (11). However, more recent reviews have given an overview of all clinical KOA phenotypes studied in previous research and show that the number and characteristics of phenotypes is highly different depending on the variables included in the phenotype construct (5,12–16). Various biopsychosocial-related variables such as metabolic (e.g., BMI and level of tissue inflammation), structural (e.g., KOA grade), psychological (e.g. pain catastrophizing, hypervigilance and depression), functional (e.g., strength, functional impairment and mobility), pain-related (e.g., pain intensity, pain distribution and somatosensory functioning [also known as central sensitization]), and social variables (e.g., social support, work and education) (5,12–17) were included, however, none of the previous studies included all biopsychosocial-related variables simultaneously in their phenotype-construct (5,12–17). Moreover, most research was restricted to non-latent clustering methods, which is assumed inferior to latent clustering because of not being able to adequately capture the rich heterogeneity in variables, less variation in estimated models, and less classification accuracy (18); focused on a general group of people with KOA (12,17); or did not include response to TKA surgery (5).

Clustering people with KOA awaiting TKA based on different preoperative biopsychosocial factors on the group level could reveal specific phenotypes with possible differences in TKA outcome in people with KOA undergoing TKA. Characteristics of the phenotypes with less favourable TKA outcome could in turn be valuable for future studies to predict TKA outcome

and could support the provision of stratified prehabilitation care strategies for TKA outcome optimization (19). This study is a secondary analysis of a prospective longitudinal study that investigated whether the change in pain intensity over time differs between somatosensory functioning evolution profiles in this population, which found that pain intensity over time was not improved in the group with unchanged self-reported symptoms of central sensitization over time.

Therefore, this exploratory study aims to identify phenotypes based on various biopsychosocial-related preoperative factors, including structural, metabolic, pain-related, psychologic and social variables in people with KOA awaiting TKA by using a cross-sectional latent profile analysis (LPA). The second aim is to examine the concurrent validity by describing possible phenotype membership differentiated by other, but similar biopsychosocial-related variables. The third aim is to compare pain scores one year post-TKA between the identified phenotypes.

Methods

This prospective cohort study was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (20).

Setting

This study is a secondary analysis of a multi-center longitudinal prospective project approved by the Ethical committee of the University Hospital of Antwerp and AZ Monica, Belgium (B300201319366); and the academic Hospital of Maastricht and St. Jans Gasthuis Weert, the Netherlands (NL6465408618). The protocol is registered at ClinicalTrials.gov (NCT05380648). The baseline values of this project, measured during March 2018 until July 2022, were used for the phenotype-construct. The one year post-TKA pain score, measured during March 2019 and July 2023, was used to compare TKA response between phenotypes.

Potentially eligible candidates were approached through face-to-face contact at the orthopedic department in the Netherlands through a nurse, or through telephone calls by one of the executive researchers (S.V. or L.M.) in Belgium. After having signed the informed consent form, participants filled out demographics and questionnaires on paper (if no computer was available) or via Qualtrics (www.qualtrics.com) without the presence of an investigator. Physical measurements were performed by two executive researchers (S.V. and L.M.) who had a practical skills training and used standard measurement forms. These measurements took place at the Sensoric Functioning Lab (M2SENS) at campus 'Drie Eiken' of the University of Antwerp for participants having surgery in Belgium, and at the orthopedic department of the academic Hospital of Maastricht and St. Jans Gasthuis Weert for participants having surgery in the Netherlands. The grade of KOA was scored by one of the participating orthopedic surgeons of the University Hospital of Antwerp (C.H.W.H.). Participants were measured a maximum of 4 weeks before surgery and asked to stop the intake of first-stage pain medication, coffee and alcohol 24 hours before testing.

Participants

Participants were included if diagnosed with KOA, aged ≥ 40 years old, and waiting for primary TKA surgery in one of the participating hospitals. They were excluded if they had neurological/systemic diseases that could possibly impact pain, and could not understand and speak Dutch.

Sample size

To date, no definite guidelines about the required sample size for using LPA exist, because this depends on the level of distinction between the phenotypes, complexity and number of indicators. Requirements are between 100 and 500 participants, with 200 to 250 participants seen as acceptable (18,21,22).

Variables considered for LPA and concurrent validation

To ensure clinical interpretability and examination of concurrent validity of the phenotypes, not all measured biopsychosocial-related baseline variables used for the prospective longitudinal cohort study were considered for the LPA itself. All baseline data were checked and variables to use in the LPA were chosen based on their prognostic value for TKA surgery (6), previous use in KOA phenotyping studies (5,12,17), the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for phenotyping of people with chronic pain (23), possible multicollinearity between the baseline data, and modifiable character. A combination of structural (KOA grade), metabolic and inflammatory (BMI, glycated hemoglobin, fat and lean mass, C-reactive protein), functional (strength, proprioception, functional symptoms and physical function), pain-related (pain intensity, symptoms, self-reported sensitization-associated symptoms, number of pain locations, pressure pain thresholds [PPT], temporal summation [TS], thermal allodynia, conditioned pain modulation [CPM]), psychological (pain catastrophizing, anxiety, depression, expectations, satisfaction about pain, illness perceptions), and social variables (work, education, marital status) were considered as possible variables to be included in the LPA. All variables were prospectively collected, except for C-reactive protein which was retrospective extracted out of the medical record.

Variables used for concurrent validation were chosen after the LPA to select variables that measure similar constructs to the ones that differed between the phenotypes. These variables were based on baseline data not included in the LPA itself. A detailed overview is given in Table 1. The chosen variables to include in the LPA and for concurrent validation are presented in the results section.

TKA response

The subscale pain of the Knee Injury and Osteoarthritis Outcome Score (KOOS) was used to define differences between phenotypes regarding one year post-TKA. The KOOS is a valid and reliable questionnaire, scored on a 5-point Likert scale and transformed to a score of 0 (extreme pain) to 100 (no pain) (24,25).

Table 1: Variables considered for analysis

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties	Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Structural factors						
Grade of KOA	-X-ray images in AP, profile and Rosenberg weight-bearing position (51). -Retrospectively extracted from the participant's record by the general practitioner of the participants or the participants themselves -If one of the images was not available, scoring was based on the available image(s). If no X-ray image was available, MRI in coronal and sagittal position were extracted. If none of the X-ray or MRI images could be found, this variable was recorded as missing value.	-K&L scale (52) or MRI grading system (53) -Ordinal variable -5-point Likert scale: 0 (no KOA) to 4 (worst grade of KOA) -K&L: Good reliability and validity in KOA (54) MRI grading: Good reliability and responsiveness (55)	X			-Previously used in KOA phenotype studies (12) -Prognostic value for chronic pain after TKA (6)
Metabolic and inflammatory factors						
BMI	-Length: demographic questionnaire -Weight: standing on an electronic scale at the moment of testing	-Formula: Weight/(length in cm)^2 -Continuous variable -kg/cm^2 -N/A	X			-Previously used in KOA phenotype studies (12) -Prognostic value for chronic pain after TKA (6)
HbA1c	-Sitting position -Taking a blood sample by pricking into a fingertip	-A1CNow+ system (*PTS Diagnostics, China*) and a fingerstick (56) -Continuous variable -% -Accurate measurement to detect diabetes (57)	X			-Prognostic value for chronic pain after TKA (6)
Fat mass **Lean mass**	-Supine lying position -Skinfold electrodes on hand and foot connected to the device	-Bioelectrical Impedance Analysis (Bodystat Quadscan 4000) -Continuous variable -N/A -Accurate measurement for body composition (58)			X X	>40% missing values due to measurements errors of the device

Table 1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties	Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Metabolic and inflammatory factors (continued)						
C-reactive protein	-Blood sample before surgery, retrospectively extracted from participant's record by executive researchers	-Blood sample -Continuous variable -mg/L -Reliable method (59)			X	>40% missing values due to missing values in medical record
Functional variables						
Strength m. Quadriceps	-Sitting position with hip and knee in 90°, upper leg fully supported by the table, and arm crossed over their chest. Isometric strength measurement was assured by using a traction belt.	-MicroFET 2 hand-held dynamometer (*ProCare, Groningen*) -Continuous variable -Kgf -Reliable and valid (60)	X			-Previously used in KOA phenotype studies (12) -Prognostic value for chronic pain after TKA (6)
Strength m. Hamstrings	-Perform flexion (Hamstrings) or extension (Quadriceps) of the knee against the device -3 times, highest value used for analysis			X		High correlation with strength m. Quadriceps
Proprioception	-Sitting position with hip and knee in 90°, upper leg fully supported by the table -Repositioning error during a knee joint position sense test (20°, 45° and 70° flexed knee) -Twice assessed, mean of 6 trials used for analysis	-Plurimeter *(Dr. Rippstein, Switzerland)* -Continuous variable -° of knee angle -Reliable (61)	X			Prognostic value for KOA treatment (49)
Functional symptoms	-Questionnaire: questions related to stiffness, noises and mobility of the knee	-KOOS subscale symptoms -Continuous variable -5-point Likert scale: 0 (no symptoms) to 4 (always symptoms) for question 1 to 5, 4 (always) to 1 (never) for question 6 and 7 -Valid and reliable (50)			X	To reduce amount of variables for better interpretability. Chosen for KOOS pain and other functional measurements

Table 1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties	Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Functional variables (continued)						
Physical function	-Questionnaire: asking questions related to different activities -Sum of subscales 'walking and standing', 'standard activities', 'advanced activities' and 'discretionary activities	-KSSS Functional Score -Continuous variable -Scored 0 (impossible to perform any activities) – 120 (possible to perform any activity) -Valid and reliable (62)	X			-Previously used in KOA phenotype studies (12) -Prognostic value for chronic pain after TKA (6)
	-Sitting position with arms resting next to the body -Standing up and again sitting down as much as possible without support in 30s	-30 CST -Continuous variable -Number of times to stand up -Reliable (63)	X			
Pain-related variables						
Pain intensity	-Questionnaire: questions related to pain intensity and specific movements during previous months	-KOOS subscale pain -Continuous variable -5-point Likert scale: 0 (no pain) to 4 (unbearable pain) -Valid and reliable (50)	X			-Previously used in KOA phenotype studies (12) -Prognostic value for chronic pain after TKA (6)
	-Scale to measure pain intensity in rest at one moment	-Numeric pain rating scale -Continuous variable -11-point Likert scale: 0 (no pain) to 10 (unbearable pain) -Valid and reliable (64)		X		KOOS pain was significant between phenotypes, this subscale has similarities
Pain symptoms	-3 scales related to pain during walking on ground, pain during walking on stairs and how 'normal' the knee feels	-KSSS Symptom Score -Continuous variable -Scored 0 (no pain) – 25 (worst pain) -Valid and reliable (62)			X	Same pain questions as KOOS subscale pain

Table 1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties		Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Pain-related variables (continued)							
Sensitization-associated symptoms	-Questionnaire: questions related to self-reported central sensitization -Total score was used for analysis	-Central Sensitization Inventory -Continuous variable -5-point Likert scale: 0 (no central sensitization present) to 4 (most central sensitization symptom present) -Reliable (65)		X			-IMMPAACT recommendations for pain phenotyping (23) -Prognostic value for chronic pain after TKA (6)
Number of pain locations	To draw their pain on a body chart by crossing all body parts that were painful during the last week	-Pain drawings on body chart -Continuous variable -Number of body parts -Valid and reliable (66)		X			-Previously used in KOA phenotype studies (12) -Prognostic value for chronic pain after TKA (6) -IMMPAACT recommendations for pain phenotyping (23)
Mechanical PPT	-Supine lying position -The probe (1cm2) was placed perpendicular to the test surface and pressure increased with a speed of 9.8 Newton/second until the participant reported a feeling of discomfort. -Repeated after 30s (2 trials), mean used for analysis	Medial joint-space dominant side	-Hand-held pressure algometer *(Wagner FDX 25 Force Gage, USA)* -Continuous variable -Newton/second -Reliable (67,68)	X			-Previously used in KOA phenotype studies (12) -IMMPAACT recommendations for pain phenotyping (23)
		Lateral joint-space dominant side			X		High correlation with PPT medial joint-space
		m. Tibialis Anterior dominant side				X	High correlation with PPT medial joint-space

Table 1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties	Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Pain-related variables (continued)						
Mechanical PPT (continued)		m. ECRL of non-dominant side -Hand-held pressure algometer *(Wagner FDX 25 Force Gage, USA)* -Continuous variable -Newton/second -Reliable (67,68)	X			-Previously used in KOA phenotype studies (12) -IMMPAACT recommendations for pain phenotyping (23)
		Forehead			X	High correlation with PPT m. ECRL
Thermal allodynia	-Supine lying position -At the skin overlying the medial and lateral joint-space of the affected knee and m. ECRL of non-dominant side -The executive researcher rolled the thermoroller for 10s over the skin and participant had to score their pain intensity (69)	-Thermal rollers (Rolltemp II) with a roller of 25°C and 40°C -Continuous variable -NRS: 0 (no pain) to 10 (unbearable pain) -Reliability unknown, but recommended to test abnormal thermal sensation			X	-To reduce amount of variables for better interpretability -Because of unknown reliability, chosen for the other somatosensory variables
Temporal summation	-Supine lying position -At the skin overlying the medial joint-space of the affected knee and the dorsal wrist of the affected side -30 repeated pinpricks with pace of 1 pinprick/s -Pain NRS score given by participant on first and last pinprick -The differences of the NRS scores were calculated and used for analysis.	-Von Frey monofilament 60g -Continuous variable -NRS: 0 (no pain) to 10 (unbearable pain) -Reliable (70,71)	X			-Previously used in KOA phenotype studies (12) -IMMPAACT recommendations for pain phenotyping (23) -Prognostic value for chronic pain after TKA (6)

Table 1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties	Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Pain-related variables (continued)						
Temporal summation	-After sensations after temporal summation -Pain NRS score given by the participant 15s after the stop of the pinpricks	-Von Frey monofilament 60g -Continuous variable -NRS: 0 (no pain) to 10 (unbearable pain)			X	-To reduce amount of variables for better interpretability (chosen for temporal summation without after sensations)
CPM	-Sitting position, lower arms supported, heat thermodes around the wrists -The device searched for a temperature equal to a pain intensity NRS score of 4/10 (until a maximum of 46°C). This identified temperature (or 46°C when the 4/10 on a NRS was not reached) was used as test stimulus. The participant had to score the test stimulus on a NRS 4 times. After a pause of 120 seconds, a conditioning stimulus (with a temperature of 0.5°C higher) was added for 65 seconds and 20 seconds after its initiation, the test stimulus was repeated. Again, the participants had to score their pain for 4 times, but only on the test site. If the NRS at 46°C and the mean of the NRS of test stimulus was equal to zero, the participant was excluded for analysis of this variable. -Percentage change ((absolute score/NRS score during test stimulus)*100) scores were used for analysis.	-Q-sense CPM (*Medoc, USA*) -Continuous variable -NRS: 0 (no pain) to 10 (unbearable pain) -Reliability to better confirmed (71)	X			-Previously used in KOA phenotype studies (12) -IMMPAACT recommendations for pain phenotyping (23) -Prognostic value for chronic pain after TKA (6)

Table 1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties	Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Psychological variables						
Pain catastrophizing	-Questionnaire: questions related to pain catastrophizing -Three subdomains: magnification, rumination and helplessness -Total score was used for the analysis	-Pain Catastrophizing Scale -Continuous variable -5-point Likert scale: 0 (not at all) to 4 (all the time) -Valid and reliable (72,73)	X			-Previously used in KOA phenotype studies (12) -IMMPAACT recommendations for pain phenotyping (23) -Total score used to reduce amount of variables for better interpretability -Prognostic value for chronic pain after TKA (6)
Depression Anxiety	-Questionnaire: questions related to depression and anxiety -Two subscales : depression and anxiety -Scores of two subscales were used for analysis	-Hospital Anxiety and Depression Scale -Continuous variable -4-point Likert scale: 0 to 3 (variable meaning per item) -Valid and reliable (74)	X X			-Previously used in KOA phenotype studies (12) -IMMPAACT recommendations for pain phenotyping (23) -Prognostic value for chronic pain after TKA (6)
Expectations	-Questionnaire: questions related to surgery result expectation -Subscale 'expectations' was used for analysis	-Knee Society Scoring System Score -Continuous variable -6-point Likert scale: 0 (no expectation) to 5 (high positive expectations) -Valid and reliable (62)	X			-Previously used in KOA phenotype studies (47) -Prognostic value for chronic pain after TKA (6)

Table 1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties	Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Psychological variables (continued)						
Satisfaction	-Questionnaire: questions related to satisfaction about knee complaint -Subscale 'satisfaction' was used for analysis	-Knee Society Scoring System Score -Continuous variable -5 items scored from 0 (no satisfaction) to 8 (high satisfaction) -Valid and reliable (62)			X	High correlation with KOOS subscale pain
Consequences	-Questionnaire: questions related to consequences of KOA complaint	-Illness perception questionnaire: subscales -Continuous variable			X	-To reduce amount of variables for better interpretability (otherwise 8 extra variables)
Timeline	-Questionnaire: questions related to acute/chronic timeline of KOA complaint	-6 items scored from 1 (strongly disagree) to 5 (strongly agree)			X	
Timeline cyclical	-Questionnaire: questions related to the cyclical timeline of KOA complaint	-Reliable, expect for subscale cohorence (75)				
Personal control	-Questionnaire: questions related to personal control over the KOA disease				X	-Not previously used in phenotype studies or in prognostic studies for chronic pain after TKA
Treatment control	-Questionnaire: questions related to treatment control over the KOA treatment				X	
Emotional representation	-Questionnaire: questions related to emotional representation			X		HADS was significant between phenotypes, this subscale has similarities
Illness coherence	-Questionnaire: questions related to illness coherence				X	-To reduce amount of variables for better interpretability (8 extra variables) -Not previously used in phenotype studies
Identity	-Questionnaire: questions related to experienced symptom related (or not) to the disease	-Illness perception questionnaire: subcale identity -Continuous variable -9 symptoms related to illness scored 0 (no) or 1 (yes) -Reliable (75)			X	

Table 1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties	Included in LPA	External validation	Not included	Reason for (not) including in LPA or external validation
Social variables						
Work	-Work level including pension, self-employed, white-collar worker, laborer, unemployed, or other	-Demographic questionnaire -Nominal variable -Scored from 1 to 6	X			-Prognostic value for chronic pain after TKA (6)
Education	-Educational level going from no degree, primary school degree, technical secondary school degree, higher secondary school degree, high school degree, university degree to other	-Demographic questionnaire -Ordinal variable -Scored from 1 to 7	X			-Prognostic value for chronic pain after TKA (6)
Marital status	-Marital status including married, divorced, single, widow(er) or other	-Demographic questionnaire -Nominal variable -Scored from 1 to 5			X	-To reduce amount of variables for better interpretability -Not previously used in phenotype studies

Abbreviations: 30CST = 30s timed chair stand test, AP = anterior-posterior, BPS = biopsychosocial, CPM = conditioned pain modulation, ECRL = Extensor capri radialis longus, g = grams, h = hour, HbA1c = glycated hemoglobin (presence of diabetes type 2), K&L scale = Kellgren and Lawrence scale, kgf = kilogram force, KOA = knee osteoarthritis, KOOS = Knee Osteoarthritis Outcome and Index Score, KSSS = Knee Society Scoring System, mg/l = milligrams/liter, MRI = magnetic resonance images, N/A = not applicable, BMI = body mass index, NRS = numeric rating scale, PPT = pressure pain threshold, s = second

Statistical methods

All steps were performed in IBM Statistical Package for Social Sciences Version 25 (SPSS, IBM Corporation, Armonk, NY), except for the LPA itself and concurrent validation, which were conducted in the statistical program MPlus version 8.7.

Preparation of the data

First, univariate outliers were checked and only deleted if unreasonable or due to data input mistakes. Second, missing data were examined and reported. Multivariate outliers were checked by using Mahalanobis Distances and participants were deleted if identified as multivariate outlier. Bivariate correlation analyses using Pearson and Wilcoxon rang sum-correlation tests were performed to test multicollinearity (26), and only one variable was chosen to include in the LPA when variables were highly correlated (correlation coefficient = ≥0.70 or ≤ -0.70) (27). Missing data was not imputed because LPA uses full-information maximum likelihood which mathematically accounts for missing data in the analysis (28).

Latent profile analysis

A cross-sectional LPA (which is a probabilistic model that clusters individuals based on the probability of belonging to a certain phenotype) was conducted. Both a model with classes having zero covariances on the one hand and fixed variances per class (model A) or class-variant variances per class (model B) were run up to 5 phenotypes. To decide the optimal number of phenotypes, several factors were taken into account: 1. Qualitative evaluation using theoretical plausibility, 2. Goodness of fit statistics (using the Bayesian information criterion (BIC) - the lower the better, the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) – low p-value supportive of current model relative to one with fewer phenotypes), and 3. Classification uncertainty (using scaled entropy value: 1 means perfect classification certainty, with a recommended threshold above 0.8) (26,29). Estimated mean values (continuous variables), estimated probability values (categorical variables), and 95% confidence intervals (CI) were given. Thereafter, normality of all residuals within the different phenotypes was checked. Significance level was $p<0.05$, and differences between variables across the phenotypes were considered significant when the 95%CI did not overlap. To guarantee a clear interpretation, continuous variables were also transformed into categorical variables (if reference values could be found in literature) and differences between phenotypes were examined based on Fisher's exact test, Pearson Chi-Square test and Mann-Whitney-U test where applicable, also with a significance level of $p<0.05$.

Concurrent validity

The concurrent validity was checked by comparing the phenotypes (independent variable) on a different but comparable set of auxiliary (dependent) variables (not used in LPA) using the 3-step multinomial logistic regression procedure for LPA to show that the phenotypes were differently associated with different criteria. This new set of dependent variables was used as possible predictors to describe phenotype membership (30–32).

Difference in pain intensity after TKA surgery

The 3-step multinomial logistic regression procedure for LPA was also used to check if the phenotypes were differently associated with age and sex, to decide if these variables should be added as covariates in the analysis. Multiple imputation (n= 10 imputed datasets) using predictive mean matching with the mice package in R was performed to impute KOOS subscale pain scores based on all other included variables to ensure all participants could be analyzed. A linear mixed model was applied to compare the difference between phenotypes in pain intensity scores one year post-TKA. Cluster (group) and baseline KOOS subscale pain score (covariate) were used as a fixed effects. Normality of residuals and homogeneity of variance was checked. The median p-value of all imputed datasets was calculated and a p-value<0.05 was significant (33). Least squares estimated means (EM) and 95%CIs were calculated and pooled according to Rubin's rules (34).

Results

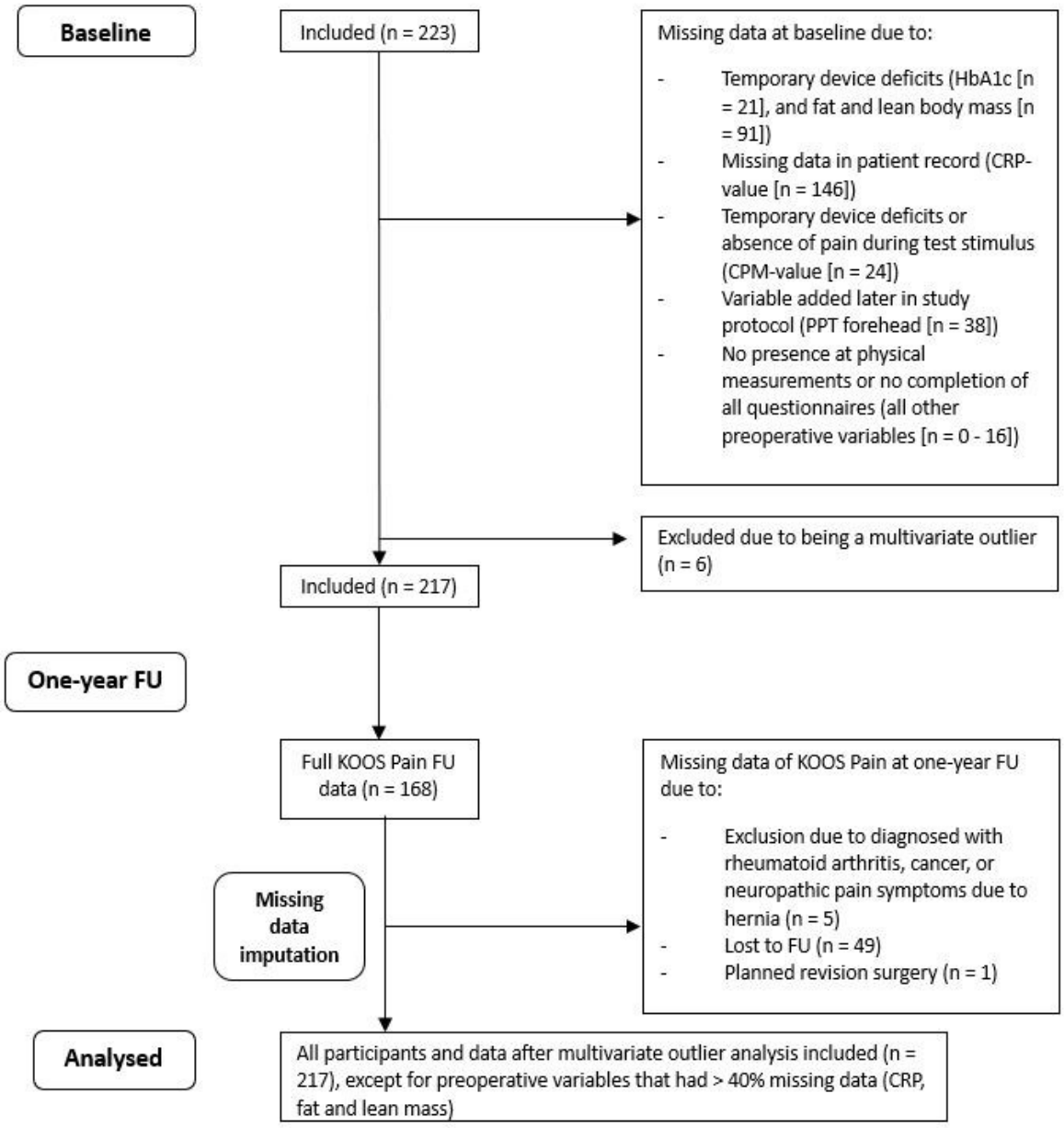
Number of participants and missing data analysis

After contacting all eligible candidates, 223 participants were included. Missing data and participant flow is presented in Figure 1. Eleven out of 24 (<5% of the total sample of 223) of the missing values of CPM were due to participants reporting no pain for the maximum temperature of the test stimulus. Participants reporting no pain did not differ in any of the variables included in LPA compared to the others (range p-values= 0.092; 0.638), except for a higher PPT score measured at the medial knee joint line in the group that reported no pain (p= 0.014). All mean, standard deviation (continuous variables), median, quartile one and three (categorical variables) and missing values of all variables can be found in supplementary Table S1. Fat and lean mass, and C-reactive protein value could not be included in the analyses due to >40% missing values.

Multivariate outlier analysis and characteristics of participants

After multivariate outlier analysis, six participants were additionally excluded and LPA was thus conducted for 217 participants with a mean age of 65.5 (7.7), including 109 women and 108 men (Figure 1). Thirteen participants were measured more than 4 weeks before surgery, due to surgery postponement because of COVID-19 flareups. The time of measurements of these participants was between 15 and 6 weeks before surgery. However, these participants did not differ in any of the variables (range p-values= 0.055; 0.958), except for a lower temporal summation score measured at the medial knee joint line in the group that was measured >4 weeks preoperative (p= 0.010).

Figure 1: Missing data and participant flow



Abbreviations: n = number of participants, FU = Follow-up, HbA1c = glycated hemoglobin, CRP = creatine phosphate, CPM = conditioned pain modulation, PPT = pressure pain threshold; KOOS = Knee Injury and Osteoarthritis Outcome Score

Multicollinearity analysis and variables not included in LPA

Supplementary Tables S2a-c show the results of the correlation analyses. Strength of the m. Hamstrings, Knee Society Scoring System (KSSS) subscale satisfaction, PPT measured at the lateral knee, at m. Tibialis anterior and at the forehead were not included in LPA, because of their high correlation with the other variables [35]. In addition, marital status, all subscales of the Illness Perceptions Questionnaire Revised (IPQR), numeric rating scale (NRS) for pain in rest, KSSS subscale symptoms, KOOS subscale symptoms, and all thermal hypersensitivity

measurements were not included in the LPA phenotype construct. This was done to have some back-up variables for the construct validation and to not include too many (or unnecessary) variables which would reduce the interpretability of the phenotypes. Despite the exclusion of the aforementioned variables, we made sure that the included variables covered all the biopsychosocial domains, which can be found in Table 1.

Variables included in LPA

As **structural variable**, the grade of KOA before TKA surgery was used. **Metabolic variables** consisted of BMI and HbA1c value. **Functional variables** included isometric maximal voluntary muscle strength of m. Quadriceps of the affected leg, proprioceptive accuracy of the affected leg, the 30-second timed chair stand test (30CST) and the functional score of the KSSS questionnaire. **Pain-related variables** were the subscale pain of the KOOS, number of pain locations, and somatosensory processing (central sensitization inventory [CSI]; and Quantitative Sensory Testing [QST], including mechanical PPTs, temporal summation and CPM). **Psychological variables** included pain catastrophizing, depression, anxiety and expectation of the surgery. Finally, **social variables** consisted of work and education level. More details can be found in Table 1.

Results of the LPA analysis

Deciding on optimal number of phenotypes

Supplementary Table S3 shows the model development of the LPA as the number of fitted phenotypes increased. Although model B had lower BIC-values, model B did not outperform model A considering the clinically meaningfulness and theoretical plausibility. Phenotypes in model A had a more realistic class size spread (max. +/- 30% of participants with sensitization-associated symptoms (35,36)) compared to phenotypes in model B (>50% with sensitization-associated symptoms (35,36)). Moreover, model A with 2 phenotypes had the lowest BIC-value compared to the higher amount of phenotypes in model A, a (scaled) entropy above the threshold of 0.8, and had a significant VLMR p-value (p= 0.006), which indicated that a model with more phenotypes was not better. Last, the CIs of model A with 2 phenotypes showed good distinction between various continuous indicators. Thus, based on these arguments, this model was further analyzed.

Description of phenotypes

Table 2 and 3 show the values and their 95%CI of the whole sample compared to the 2 phenotypes, while figure 2 and 3 show the differences graphically (continuous and categorical variables, respectively). Both phenotypes were clinically meaningful different in 13 out of 18 continuous variables. Phenotype 2 (28% of participants) had lower m. Quadriceps strength, KSSS functional score, 30CST score, local and widespread PPT; and higher BMI, pain intensity, number of pain locations, local temporal summation, CSI score, pain catastrophizing, anxiety and depression compared to phenotype 1 (72% of participants) regarding continuous variables. Concerning categorical variables, phenotype 1 was characterized by having a lower probability to have a lower Kellgren & Lawrence (K&L) scale (II) compared with participants in

phenotype 2. The probabilities of the other categorical variables did not differ between the two phenotypes.

Supplementary Table S4 represents the transformation of the continuous variables into categorical variables for better interpretation when cut-off values were available (see Table 2). Fewer participants in phenotype 2 had normal weight (5 vs 21%), and more had obesity (60 vs 44%), local (39 vs 16%) and widespread (46 vs 23%) hyperexcitability in the temporal summation measurement, central sensitization presence according to CSI (59 vs 3%), pain catastrophizing (23 vs 3%), fear (70 vs 9%), and depression (47 vs 9%) compared to phenotype 1. Differences between people with well or no-controlled HbA1c; or between inhibitors (anti-nociceptive CPM effect), facilitators (pro-nociceptive CPM effect) and non-responders (no difference between test- and conditioning stimulus score) regarding CPM score value remained absent.

Concurrent validity

The subscale 'emotional representations' of the IPQR (as a psychological variable), NRS for pain in rest, PPT measured at the later knee (as pain-related variables) and isometric maximal voluntary muscle strength of m. Hamstrings (as a functional variable) were chosen to test the concurrent validity of the phenotypes. No variable for the structural and metabolic domain could be used because K&L scale, BMI and HbA1c were the only structural and metabolic variables measured. The phenotypes exhibited concurrent validity by differentiating participants across 3 out of 4 variables (30). All but NRS for pain in rest were differently associated with phenotype membership (and as such showed differences between phenotypes). Odds estimates and 95%CI can be found in Supplementary Table S5. The odds of belonging to phenotype 1 increases by 1.281 (strength m. Hamstrings), 1.093 (PPT lateral knee) and 0.549 (subscale IPQR) times relative to the odds of belonging to phenotype 2.

Difference in pain intensity after TKA surgery

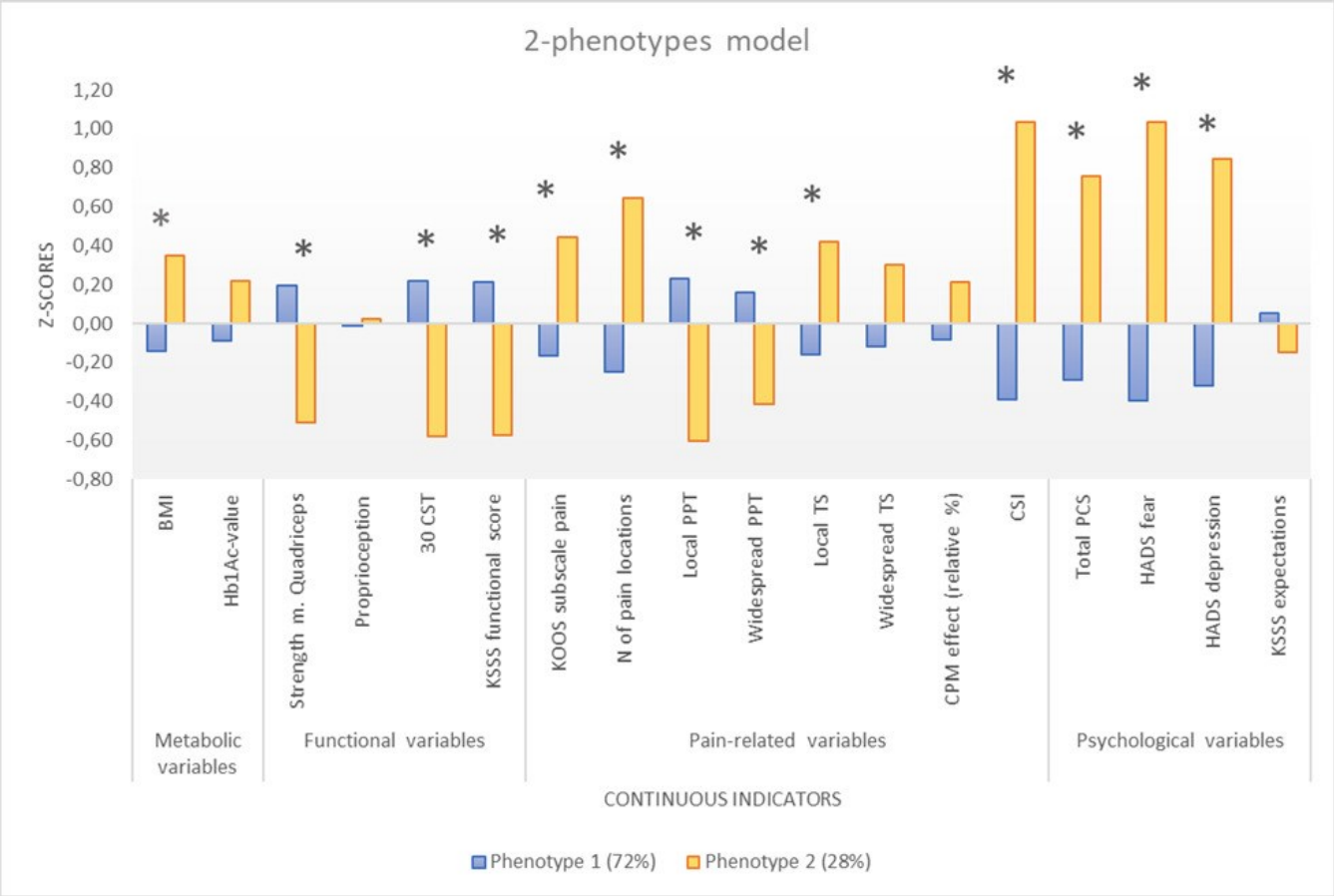
Age and sex were not differently associated with the two phenotypes (Table 4), and therefore not used as covariates in the analysis (1 included in 95%CI). Phenotype 2 had worse KOOS subscale pain scores (EM: 67.29, 95%CI 60.11; 74.47) one year after surgery compared to phenotype 1 (EM: 76.03, 95%CI 71.48; 80.58) (p=0.015).

Table 2: Mean and 95% confidence interval of continuous variables for whole group and 2-phenotype model A and response to TKA treatment

	Reference/normative values (ref)	N	Whole sample N = 217 (100%)	Phenotype 1 N = 156 (72%)	Phenotype 2 N = 61 (28%)
				Estimated Mean (95%CI)	
Metabolic variables					
BMI (kg/m²)	18-24.9 (76)	214	29.77 (28.98; 30.57)	29.21 (28.52; 29.91)*	31.55 (30.23; 32.86)
HbA1c-value (%)	<6.5 (57)	195	5.59 (5.50; 5.67)	5.54 (5.46; 5.62)	5.71 (5.56; 5.87)
Functional variables					
Strength m. Quadriceps (kgf)	>24.9 (77) §	214	27.05 (25.07; 29.02)	29.92 (27.90; 31.94)*	20.96 (17.69; 24.23)
Proprioception (°)	Lower = better	212	4.48 (4.15; 4.81)	4.47 (4.19; 4.76)	4.47 (3.93; 5.00)
30 CST (N)	>13 (78) §	211	10.67 (10.02; 11.32)	11.48 (10.92; 12.04)*	8.52 (7.50; 9.53)
KSS functional score (0-120)	>55.7 (79)	205	43.51 (41.35; 45.66)	46.99 (44.80; 49.18)*	35.35 (32.13; 38.57)
Pain-related variables					
KOOS subscale pain (0-100)	>88.1 § (80)	205	44.26 (42.18; 46.34)	46.90 (44.41; 49.39)*	37.25 (34.07; 40.43)
N of pain locations	Lower = better (81)	201	3.39 (3.09; 3.70)	2.83 (2.58; 3.09)*	4.84 (4.08; 5.60)
Local PPT (Newton)	Higher = better	214	41.32 (37.79; 44.84)	48.03 (44.14; 51.93)*	28.76 (24.33; 33.19)
Widespread PPT (Newton)	Higher = better	214	36.90 (34.17; 39.63)	40.80 (37.77; 43.83)*	30.70 (26.95; 33.86)
Local TS (Diff in NRS)	<2 (82)	214	0.70 (0.47; 0.91)	0.50 (0.28; 0.72)*	1.42 (0.93; 1.91)
Widespread TS (Diff in NRS)	<2 (82)	214	1.09 (0.82; 1.37)	0.88 (0.57; 1.19)	1.62 (1.03; 2.21)
CPM effect (relative %)	<0 (83)	201	9.76 (2.53; 16.98)	6.26 (-1.29; 13.80)	18.66 (6.86; 30.46)
CSI (0-100)	<40 (43)	205	28.18 (26.28; 30.07)	22.69 (21.11; 24.27)*	40.86 (36.39; 45.33)
Psychological variables					
Total PCS (0-52)	≤21 (44)	206	16.30 (14.78; 17.82)	12.90 (11.43; 14.36)*	23.26 (20.15; 26.38)
HADS fear (0-11)	≤7 (45)	207	5.29 (4.72; 5.85)	3.72 (3.22; 4.22)*	9.20 (7.80; 10.60)
HADS depression (0-11)	≤7 (45)	207	4.93 (4.48; 5.38)	3.97 (3.45; 4.49)*	7.38 (6.41; 8.35)
KSSS expectations (0-15)	Higher = better	204	14.14 (13.93; 14.35)	14.11 (13.91; 14.30)	13.85 (13.45; 14.24)

Mean values are all significantly different from 0 in each phenotype ($p < 0.05$), expect for CPM effect in phenotype 1 ($p = 0.171$). Significant difference means that 95%CI do not overlap. *= significant difference between phenotype 1 and 2. Lower values indicate better results, except for functional variables, PPT and KSSS expectations where higher values mean better results. §= lowest values for representative age group (both genders taken together). Full bibliography of references in this table are presented in appendix 1. Abbreviations: 30CST = 30 seconds chair stand test, BMI = body mass index, CI = confidence interval, CPM = conditioned pain modulation, CSI = Central Sensitization Index, Diff = difference, HADS = Hospital Anxiety and Depression Scale, Hb1Ac = glycated hemoglobin, KSSS = Knee Society Scoring System, kg = kilograms, kgf = kilogram force, KOA = knee osteoarthritis, KOOS = Knee Injury and Osteoarthritis Outcome Score, m. = musculus, m2 = squared meter, N = number, NRS = numeric rating scale, PPT = pressure pain threshold, PCS = Pain Catastrophizing Scale, ref = reference, TS = temporal summation, ° = degrees

Figure 2: Z-scores of continuous indicators in 2-phenotypes model



Lower values indicate better results, except for functional variables, PPT and KSSS expectations where higher values mean better results. Abbreviations: 30CST = 30 seconds chair stand test, BMI = body mass index, CPM = conditioned pain modulation, CSI = Central Sensitization Index, HADS = Hospital Anxiety and Depression Scale, HbA1c = glycated hemoglobin, KOA = knee osteoarthritis, KOOS = Knee Injury and Osteoarthritis Outcome Score, KSSS = Knee Society Scoring System, m. = musculus, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold, TS = temporal summation. *= significant difference between both phenotypes (95%CI do not overlap)

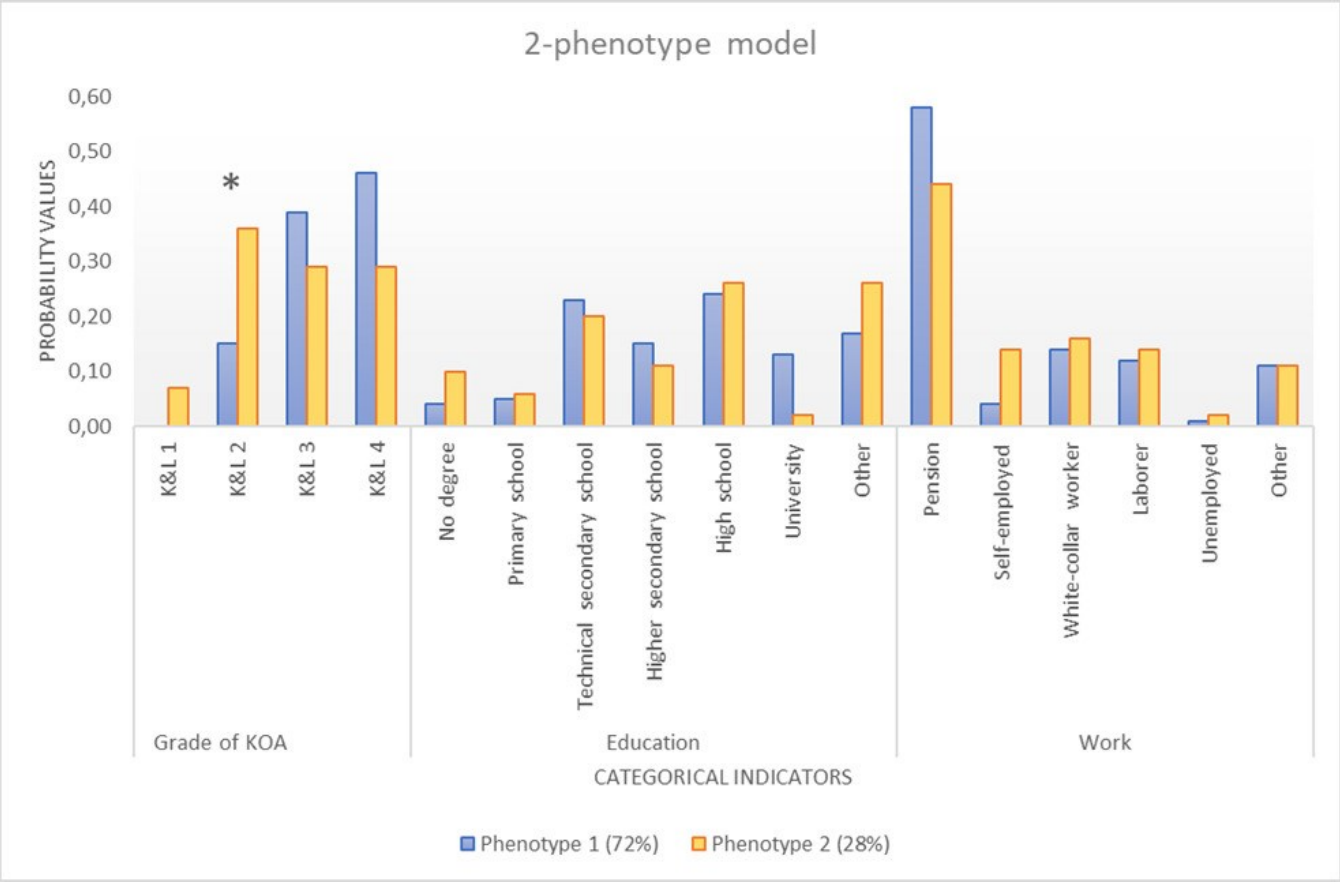
Table 3: Probability and 95% confidence interval of categorical variables for whole group, 2-phenotype model A

Categorical variables	Whole sample N = 217 (100%) N (%)	Phenotype 1 N = 156 (72%) Probability in % (95%CI)	Phenotype 2 N = 61 (28%) Probability in % (95%CI)
Structural variables			
Grade of KOA (N = 208)			
K&L 1	4 (2)	0.00 (0.00; 0.00)	0.07 (0.01; 0.13)
K&L 2	43 (20)	0.15 (0.09; 0.20)*	0.36 (0.24; 0.47)
K&L 3	75 (35)	0.39 (0.32; 0.46)	0.29 (0.18; 0.40)
K&L 4	86 (40)	0.46 (0.39; 0.54)	0.29 (0.15; 0.42)
Social variables			
Education (N = 205)			
No degree	11 (5)	0.04 (0.01; 0.06)	0.10 (0.03; 0.18)
Primary school	11 (5)	0.05 (0.02; 0.09)	0.06 (0.00; 0.13)
Technical secondary school	45 (21)	0.23 (0.17; 0.29)	0.20 (0.11; 0.29)
Higher secondary school	28 (13)	0.15 (0.09; 0.20)	0.11 (0.03; 0.19)
High school	50 (23)	0.24 (0.18; 0.30)	0.26 (0.16; 0.37)
University	20 (9)	0.13 (0.08; 0.18)	0.02 (0.00; 0.06)
Other	40 (18)	0.17 (0.12; 0.22)	0.26 (0.16; 0.36)
Work (N = 205)			
Pension	111 (51)	0.58 (0.51; 0.65)	0.44 (0.32; 0.56)
Self-employed	14 (7)	0.04 (0.01; 0.07)	0.14 (0.06; 0.23)
White-collar worker	29 (13)	0.14 (0.09; 0.19)	0.16 (0.06; 0.25)
Laborer	26 (12)	0.12 (0.07; 0.17)	0.14 (0.04; 0.23)
Unemployed	2 (1)	0.01 (0.00; 0.02)	0.02 (0.00; 0.05)
Other	23 (11)	0.11 (0.07; 0.16)	0.11 (0.03; 0.19)

Probability values are all significantly different from 0 in each phenotype ($p < 0.05$), expect for K&L 1 in both phenotype 1 and 2 ($p= 1.000$ and $p= 0.051$, respectively), 'unemployed' in phenotype 1 and 2 ($p=0.320$ and $p=0.374$, respectively), and 'primary school' and 'university' in phenotype 2 ($p= 0.160$ and $p= 0.517$, respectively). Significant difference means that 95%CI do not overlap. *= significant difference between phenotype 1 and 2. Higher values indicate more probability of belonging to a certain categorical level in the categorical variables.

Abbreviations: CI = confidence interval, K&L = Kellgren and Lawrence scale, KOA = knee osteoarthritis, N = number

Figure 3: Probability values of belonging to a certain category of categorical variables in 2-phenotypes model



Abbreviations: K&L = Kellgren and Lawrence scale, KOA = knee osteoarthritis. *= significant difference between both phenotypes (95%CI do not overlap)

Discussion

This exploratory study aimed to identify phenotypes based on biopsychosocial-related factors in people with KOA awaiting TKA and identify difference in pain scores one year after TKA. Our analysis found two distinct phenotypes: phenotype 2 (28%) that had lower m. Quadriceps strength, KSSS functional score, 30CST score, local and widespread PPTs; and higher BMI, pain intensity, number of pain locations, temporal summation, CSI score, pain catastrophizing, anxiety and depression scores; and a higher chance for less structural damage compared to phenotype 1 (72%). This study also confirmed the concurrent validity of the phenotypes based on differences in scores on m. Hamstrings strength, PPT measured at the lateral knee and the emotional representations subscale of the IPQR, as was expected because similar variables included in our phenotype construct were also different between phenotypes. Phenotype 2 had worse pain scores one year after TKA compared to phenotype 1.

Relation to previous findings and explanation for findings

This study used various biopsychosocial-related factors to construct phenotypes, which created a broader biopsychosocial-related overview compared to previous phenotype studies (12–14,16,17). The results of our study partly confirm findings of Kittelson et al.: they found a phenotype with higher knee joint sensitivity (24%), higher psychological distress (10%), higher cardiometabolic comorbidities (4%) and a lower K&L grade, better strength and lower knee joint pain sensitivity (62%) (37). We only identified two phenotypes, but our phenotype 1 is in line with their phenotype 4 including 62% of their participants, except for the lower K&L grade. Having less structural damage was associated with our phenotype 2 and not with phenotype 1. The study of Pan et al. (38) found both a group with less structural damage and low psychological distress (resembling phenotype 4 of Kittelson et al. (37)), and a group with less structural damage and high psychological distress (resembling our phenotype 2). However, both included all people with KOA, in contrast to our study that only included people with KOA awaiting TKA. More end-stage structural OA was as such present in our sample compared to the sample of Kittelson et al. (37) (75% had K&L grade 3 or 4 in our study versus 30%), and in the sample of Pan et al. (38) only 60% experienced radiographic confirmed OA. Therefore, it is possible that a subgroup with less structural damage and low psychological distress was absent in our findings (39). Our phenotype 2 seems to cover Kittelsons' other phenotypes (apart from their phenotype 4) (37), but no further distinction in separate phenotypes was found in our study. This could be due to some differences in methodology compared to Kittelsons' study (37): measurement of knee pain sensitivity (extensive QST protocol in our study versus joint palpation tenderness), registration of metabolic comorbidities (HbA1c-value in our study versus self-reported questionnaire), and the smaller and more specific sample size in our study (only people with KOA awaiting TKA in our study versus a bigger sample of all people with KOA). The smaller sample size in our study is, however, not a limitation. Previous research on sample sizes in LPA found that small sample sizes per phenotype (even 5 to 30 participants) were sufficient enough if more indicators (i.e. variables), good distinction between phenotypes, and less complex latent structure (we used raw values, instead of performing principal component analysis for reducing amount of variables) were present (21).

Next, the phenotypes and their proportions observed in our study are in line with the findings based on previous original studies in the review of Dell'Isola et al. (12), which also identified a phenotype characterized by disturbed somatosensory functioning and psychological variables. Furthermore, findings of previous non-data-driven phenotyping research found that +/- 30% of people with KOA presents with central sensitization (35,36). Central sensitization is the primary underlying mechanism of nociplastic pain, which is defined as 'pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain' (40). In addition, based on the results of our study and reference/normative values provided by previous literature (Table 2), participants in phenotype 2 resembled nociplastic pain characteristics (41), characterized by a combination of worse scores on somatosensory functioning (normative values have not yet been confirmed (42)) and presence of pain catastrophizing, fear, depression and self-reported sensitisation-associated symptoms (43–45). The review of Deveza et al. (5) also highlights the presence of a pain- (i.e. greater features of sensitization and more likely having persistent pain) and a structural endotype (i.e. related to ageing and cell senescence, greater KOA grade severity and differences in gene expression). Despite endotypes are based on pathobiological mechanisms (5), features of these endotypes seem to overlap with our clinical findings. Therefore, these could be potential names for our phenotype 1 (structural-phenotype) and phenotype 2 (pain-phenotype).

The reviews of Dell'Isola et al. (12) and Deveza et al. (17) also included studies that found metabolic syndrome-, minimal joint disease-, metabolic bone/cartilage-, mechanical overload, and inflammatory KOA phenotypes. These studies often only included characteristics examined with imaging and laboratory blood analyses and had the goal of only finding phenotypes based on one specific domain. We decided to include variables over the whole biopsychosocial domain, because KOA pain remains a biopsychosocial-related complaint. Thereupon, our construct includes multiple pain-related factors, because pain indeed remains one of the main symptoms in the KOA population and is an important reason for people to be dissatisfied after TKA (46).

Our study did not observe any differences in CPM scores between phenotypes (although categorical division between facilitators, inhibitors and non-responders almost reached significance), which contrasts with the results of Cruz-Almeida et al. (47). There may be several reasons for this disparity, such as differences in the methodology used to measure CPM (heat thermodes in our study versus cold immersion), in phenotype construct (various biopsychosocial factors in our study versus solely psychological factors), or in study sample characteristics (white Belgian and Dutch individuals in our study versus 50% African Americans and 50% Non-Hispanic whites (47,48)).

Glycated hemoglobin, expectations, proprioception, work- and education level seemed added no value to our phenotype construct. This leans upon the findings of both reviews that indicated these factors as non-relevant characteristics in KOA phenotypes (12,17). However, because people with KOA awaiting TKA normally present with other characteristics than people with KOA in general (i.e. non-response to conservative therapies and joint symptoms

significant enough to affect the quality of life (7)), and because aforementioned factors can still be associated with prognostic factors for musculoskeletal pain and/ or TKA outcome (6,49), these variables were included in our phenotype construct. Our findings suggest that these factors do not contribute in determining phenotype membership within this specific population, which is in line with characteristics of specific pain mechanisms that also do not indicate these variables as discriminative factors (41).

The current study was also the first study to examine difference in pain intensity scores after TKA surgery and found that phenotype 2 had more pain compared to phenotype 1. This finding can be interesting for future research and clinical practice in the sense that alertness to specific characteristics of this phenotype could be valuable to better understand, anticipate and treat post-TKA pain.

Future research should investigate this further for external validation. If confirmed, ideally, a minimal batch test-battery based on aforementioned differentiating variables could be designed, evaluated and validated and used as a convenient screening tool in clinical practice.

Strengths and limitations

This manuscript has several strengths, including being the first KOA phenotype study that specifically focuses on people with KOA awaiting TKA and the outcome after TKA, and building a phenotype construct based on a wide range of various biopsychosocial-related variables. Thereupon, LPA was used for constructing the phenotypes, enabling the combination of continuous and categorical variables and the use of auxiliary variables to describe and validate phenotype membership (26). Moreover, like only two previous studies (37,38), our study also implemented clinical and imaging characteristics of the participants in a phenotype construct, making it more comprehensive. One limitation of this study could be the measurement method for CPM. Originally, the test stimulus in the CPM measurement had to be a temperature that elicits a numeric pain rating score of 4/10, but we only excluded participants that reported no pain (0/10). It is possible that the noxious stimulus with a score scoring lower than 4/10 was too low to provoke a CPM effect. Two other limitations include the rather large and heterogenous size of phenotype 1 (72%) and the fact that TKA response was only investigated after phenotype-construct analysis. Ideally, prescriptive phenotyping is based on the response of TKA (5). Nevertheless, phenotype membership was still associated with post-TKA pain, which means that the characteristics of phenotype 2 (28%) can be of interest to improve our understanding of post-TKA pain in future research. The last limitation concerned the high C-reactive protein and lean- and fat mass missing data, which could therefore not be imputed. For all other missing data, full-information likelihood of multiple data imputation was used.

Conclusion

A model with 2 phenotypes in people with KOA awaiting TKA was described, of which phenotype 2 had characteristics resembling nociplastic pain characteristics (28%) in combination with worse results on structural variables, psychological variables, BMI, strength and physical function, and phenotype 1 having no nociplastic pain characteristics in combination with better results on these variables (72%). Phenotype 2 had worse pain scores

one year post-TKA. While this study represents a crucial first step in the characterization of KOA awaiting TKA phenotypes and their response to pain after TKA, external validation is necessary.

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Chapter 3: Application of the IASP grading system to identify underlying pain mechanisms in patients with knee osteoarthritis: a cross-sectional study

Sophie Vervullens[1,2,3] , Lotte Meert[1,2,3], Mira Meeus[1,3], Christiaan H.W. Heusdens[5], Peter Verdonk[6], Anthe Foubert[1,3,7], Emmanuel Abatih[8], Lies Durnez[1], Jonas Verbrugghe[1,9*], Rob J.E.M. Smeets[2,3,4*]

[1]Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium

[2]Research School CAPHRI, Department of Rehabilitation Medicine, Maastricht University

[3]Pain in Motion International Research Group (PiM), www.paininmotion.be

[4]CIR Clinics in Revalidatie, location Eindhoven, The Netherlands

[5]Department of Orthopedics and Traumatology, University Hospital of Antwerp, Antwerp, Belgium, and Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium

[6]ORTHOCA, Antwerp, Belgium and ASTARC department, Antwerp University, Belgium

[7]Faculté des Sciences de la Motricité, Université catholique de Louvain, Louvain-La-Neuve, Belgium

[8]DASS (Center for Data Analysis and Statistical Science), Ghent University, Krijgslaan 281 - S9, 9000 Gent

[9]REVAL-Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Hasselt, BELGIUM.

*= shared last-authorship

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Abstract

Objectives: This study aimed to apply the International Association for the Study of Pain (IASP) grading system for identifying nociplastic pain in knee osteoarthritis (KOA) awaiting total knee arthroplasty (TKA) and propose criteria to finetune decision-making. Additionally, the study aimed to characterize a 'probable' versus 'no or possible' nociplastic pain mechanism using biopsychosocial variables and compare both groups in their one-year post-TKA response.

Methods: A secondary analysis of baseline data of a longitudinal prospective study involving 197 KOA patients awaiting total knee arthroplasty in Belgium and the Netherlands was performed. Two approaches, one considering four and the other three pain locations (step 2 of the grading system), were presented. Linear mixed model analyses were performed to compare the 'probable' and 'no or possible' nociplastic pain mechanism groups for several preoperative biopsychosocial-related variables and one-year postoperative pain. Also, a sensitivity analysis, comparing the three pain mechanism groups, was performed.

Results: Thirty (15.22% - approach four pain locations) and 46 (23.35% - approach three pain locations) participants were categorized under 'probable' nociplastic pain. Irrespective of the pain location approach or sensitivity analysis, the 'probable' nociplastic pain group included more woman, were younger, exhibited worse results on various preoperative pain-related and psychological variables, and had more pain one-year post-TKA compared to the other group.

Discussion: This study proposed additional criteria to finetune the grading system for nociplastic pain (except for discrete/regional/multifocal/widespread pain) and characterized a subgroup of KOA patients with 'probable' nociplastic pain. Future research is warranted for further validation.

Introduction

Knee osteoarthritis (KOA) is a heterogeneous condition in which different phenotypes (based on disease trajectory, clinical presentation, etiology, treatment response etc.) are present, however without clear consensus yet (1,2). Phenotypes based on clinical representation are considered as the most useful for optimizing treatment selection (1,3). To date, the experience of chronic pain is still the primary symptom of KOA and the main reason why individuals seek medical care (4). Moreover, approximately 20% or KOA patients experience chronic pain after total knee arthroplasty (TKA) (5–7). Because different mechanisms determine the pain perception, pain phenotyping in particular has become very important in this population (8,9).

Previous research found that a subgroup of KOA patients experiencing chronic pain presents with disturbed somatosensory functioning, which includes mechanisms of peripheral and central sensitization (1,10–13). This can be observed in humans as primary and secondary hyperalgesia and allodynia, respectively. Central sensitization is accompanied by disturbances in the brain, nociceptors, and facilitatory and inhibitory ascending and descending pathways of the central nervous system (14). Interestingly, a recent umbrella review also found evidence that preoperative disturbed somatosensory functioning can be associated with chronic post-TKA pain (15).

Previous pain phenotyping research was mostly based on objective measurements and patient reported outcome measurements (PROMS) (9), but recently, also phenotyping based on pain mechanisms specifically has gained attention (16). The International Association for the Study of Pain (IASP) categorized musculoskeletal pain into three main pain mechanisms: nociceptive, neuropathic or nociplastic (or a combination) (17,18). Nociplastic pain is defined as 'pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain' (17). Moreover, having disproportionate pain, higher levels of negative psychological factors (pain catastrophizing, anxiety), disturbed somatosensory functioning (enhanced temporal summation) and other comorbidities (diabetes, heart disease) are thought to be related to nociplastic pain according to a Delphi consensus expert study (19) and seem to be predictors for worse musculoskeletal pain prognosis or KOA treatment outcomes (7,15,20,21). Therefore, it is postulated that nociplastic pain mechanisms contribute to the knee pain and are (or have become) the predominant pain mechanism in at least a subgroup of KOA patients.

Previous research has attempted to phenotype and characterize KOA or TKA patients according to pain mechanisms, however this was restricted to comparing KOA patients with nociceptive pain and neuropathic-like pain classified according to the (modified) PainDETECT questionnaire (22–24), or did not focus on the 'nociplastic' pain mechanism explicitly (25). Regarding the nociplastic pain mechanism, Shraim and colleagues attempted to define a group of typical nociplastic pain characteristics based on literature and a Delphi consensus expert study (19,26).

As such, to date, the identification of the predominant pain mechanism remains a challenge in research and clinical practice. Identifying the predominant pain mechanism and its response

to treatment is expected to improve patient-tailored care (27), which aims to optimize treatment outcomes or slow disease progression by tailoring interventions to individuals' specific characteristics (28). For example, studies found that KOA patients with more neuropathic-like pain had worse long-term pain outcomes after TKA (23,24). Therefore, different or additional treatment approaches are advised depending on whether patients have a predominant nociplastic (central nervous system targeted therapy such as cognitive behavioral therapy, central-acting drugs, pain neuroscience education), nociceptive (biomedical approach such as surgery, joint-targeted manual or exercise therapy), or neuropathic pain mechanism (peripheral nerve-targeted drug, exercise or manual therapy) (18,29,30).

Recently, a clinical decision tree grading system for identifying the nociplastic pain mechanism has also been proposed by IASP in collaboration with experts in this field (18). However, clear specific guidelines and cut-off scores are missing to decide whether the underlying pain mechanism is nociplastic or not. Hence, Kosek et al. (18) have highlighted the importance of applying and validating their IASP grading system in specific chronic pain populations using clinically useful and reliable diagnostic tests. Detailed information about their original grading system can be found in the article itself (18) and the methods section of current article.

This study aimed to investigate the application of the IASP grading system in KOA patients awaiting TKA, as well as to propose criteria and cut-offs specifically for KOA patients to finetune the decisions and different steps used in the grading system (AIM 1). Additionally, existing differences regarding various preoperative biopsychosocial factors were compared between individuals categorized as having 'no or possible' nociplastic pain compared to individuals having 'probable' nociplastic pain following the grading system to further characterize groups (26) (AIM 2). Last, the response to TKA one-year post-surgery was compared between groups using pain intensity scores (AIM 3).

Materials and methods

This study consists of a secondary analysis of a multi-center longitudinal prospective study and is conducted by applying the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (31).

Setting

The longitudinal prospective has been approved by the Ethical committees of the University Hospital of Antwerp and AZ Monica, Belgium (BE300201319366); and the academic Hospital of Maastricht and St. Jans Gasthuis Weert, the Netherlands (NL6465408618). The protocol was registered at ClinicalTrials.gov (NCT05380648). This study was already ongoing when the IASP grading system (18) was published, but through data of this study many variables were covered, allowing to apply the IASP grading system to a cohort of KOA patients awaiting TKA (see paragraph 'Different steps including methods to apply the IASP grading system in KOA patients'). Preoperative data of this project, measured during March 2018 until July 2022, was

used to answer AIM 1 and 2, while also the one-year post-TKA pain score, measured during March 2019 and July 2023, was used to answer AIM 3.

Participants

Knee osteoarthritis patients were either approached and checked for eligibility in person at the orthopedic department in the Netherlands by a nurse, or via phone by one of the executive researchers (S.V. or L.M.) in Belgium. Eligibility criteria are presented in Table 1. After giving their consent to participate, participants completed questionnaires to gather demographic information and health-related characteristics on paper or online via Qualtrics (www.qualtrics.com). All participants were instructed to refrain from first-stage pain medication, coffee, and alcohol 24 hours before the physical measurements, which were conducted at the Sensoric Functioning Lab at the University of Antwerp's campus 'Drie Eiken' (Belgian participants), or at the orthopedic department of the academic Hospital of Maastricht and St. Jans Gasthuis Weert (Dutch participants) by two executive researchers (S.V. or L.M.). Both researchers followed a practical skills training and used the same measurement forms to ensure standardization.

Table 1: Eligibility criteria knee osteoarthritis patients and healthy controls

Knee osteoarthritis patients	
Inclusion criteria	**Exclusion criteria**
- Diagnosis of KOA - ≥ 40 years old - Awaiting primary TKA	- Neurological, or systemic diseases possibly impacting pain (experiencing neuropathic-like pain symptoms according to patient interview part of DN-4, neurological diseases such as Parkinson, CVA, etc., and systemic diseases such as rheumatoid arthritis, polymyalgia rheumatica, cancer, etc.). - Not understanding or speaking Dutch
Healthy participants	
Inclusion criteria	**Exclusion criteria**
- Healthy adults - ≥40 years old - Free of current pain	- Pain/discomfort in >3 body regions pain/discomfort (NRS ≥ 3) for > 30 days during the past 12 months or at the moment of the testing NRS ≥ 3 (max 2/10) - Pregnant women or women giving birth or breast feeding <1 year ago - Having psychiatric, systemic, neurological or cardiovascular diseases - Had radio- or chemotherapy in the past - Intake of opioids, antidepressants, anticonvulsant medication <2 weeks before the test

Abbreviations: KOA= knee osteoarthritis, TKA= total knee arthroplasty, NRS= numeric rating scale, DN= Douleur Neuropathique – 4, CVA= cerebrovascular accident

AIM 1: Different steps and methods to apply the IASP grading system in KOA patients

All the different steps of the IASP grading system with the chosen methods and interpretation used in the present KOA sample will be explained below and are also presented in Figure 1. Interpretation and methods were based on previous literature in KOA patients, other chronic MSK populations, and expert opinions.

Step 1 - Chronic pain (> 3 months)

The Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale pain is a reliable and valid questionnaire (32), and was used to define the presence of pain in the knee that would undergo TKA. This subscale consists of nine questions of which the total score was transformed into a percentage score of zero (indicating the worst pain) to 100 (indicating no pain) (33). Roos et al. defines a score of 87.5 or higher as 'no pain' (34). This cut-off was chosen by Roos et al. based on their previous findings regarding the 'patient acceptable symptom state', which identifies patients who are satisfied with their condition or not (35). The KOOS subscale pain does not include a question of 'pain duration', however, because KOA is still a chronic disease and all included participants were on the waiting list for a TKA -which is the last treatment strategy in case of a non-response to conservative treatment strategies- (36), sufficient arguments were available that the included sample of this study had >3 months pain if scores were below the cut-off presented by Roos et al. (34).

Step 2 – Regional, multifocal or widespread rather than discrete pain

Participants had to mark all body parts that they perceived as painful during the last week on a pain drawing showing a full body. The number of pain locations was immediately counted and transferred to the digital database. Each large joint of the limbs (shoulder, elbow, wrist, hip, knee, and ankle, until the anatomical boundary of the joint), each finger and toe, a location between joints of limbs, cervical, thoracal, lumbar, sacroiliac or coccyx, head, jaw, and nose counted as one pain location (bilateral = two locations). As no specific cut-offs for separating regional, widespread or multifocal pain from discrete pain were provided by Kosek et al. (18), we followed different approaches.

MULTIFOCAL - APPROACH 1: Previous research used a modified definition of widespread pain in a KOA population: pain at the affected knee in addition to three other locations (four locations in total) (37,38). This modified definition was also used in current study for multifocal - approach 1. All participants who fulfilled this modified definition fulfilled step 2.

MULTIFOCAL - APPROACH 2 Because Kosek et al. (18) does not differentiate between the terms regional/widespread/multifocal, we also decided to present a less stringent approach: participants had to report pain at the affected knee and at two additional pain locations (three locations in total) to fulfil step 2.

RATHER DISCRETE PAIN: If participants reported pain at the knee with only one other location, the participant was categorized as having rather discrete pain. This approach was chosen because KOA patients frequently experience bilateral KOA (39,40), thus eliminating the risk of classifying these patients as having non-discrete pain. As such, these participants were categorized as having unlikely nociplastic pain.

The next steps will as such be evaluated considering the two approaches of multifocal pain.

Step 3 – Nociceptive pain cannot be entirely responsible for the pain

To date, there exist no grading systems or clearly defined criteria to decide whether nociceptive pain is fully responsible for the pain. Medical imaging, a thorough patient

interview and physical examination could be used to decide whether nociceptive pain is present, but still cannot rule out the presence of concurrent nociplastic pain (mixed pain mechanism). The interpretation of this interview and examination still depends of the clinical subjective judgement of an investigator (18). This study measured KOA grade with X-ray or Magnetic Resonance (if no X-ray was available) images from the medical record before TKA surgery (41,42). However, as confirmed KOA on medical imaging alone is insufficient to judge whether nociceptive pain if fully responsible for the pain, every participant who fulfilled step two was transferred to step four.

Step 4 – Neuropathic pain cannot be entirely responsible for the pain

The proposed grading system for neuropathic pain was used to judge this criterium (43). However, patients needed to have a history of relevant neurological lesion or disease to transfer to the next step to examine the presence of neuropathic pain. Because experiencing neuropathic-like pain (which was verbally checked if at least one of neuropathic pain symptoms according to the patient interview part of Douleur Neuropathique – 4 (DN-4) (44) was present) was an exclusion criteria of the current study, it was unlikely that neuropathic-like pain was present in the current KOA sample. Therefore, all KOA patients fulfilling step three were automatically transferred to step five.

Step 5 – Evoked pain hypersensitivity phenomena

The IASP grading system defined the presence of evoked pain hypersensitivity if this could be elicited clinically in the region of pain by any one of the following: (a) static mechanical allodynia, (b) dynamic mechanical allodynia, (c) painful after-sensations, or (d) heat or cold allodynia (18). Therefore, the following methods were used in the current study:

a) Static mechanical allodynia was measured with pressure pain thresholds (PPTs) that were taken at the medial and lateral joint-spaces of the knee with a hand-held pressure algometer (*Wagner FDX 25 Force Gage*, *USA*). The participant was lying supine while the probe ($1cm^2$) was placed perpendicular to the test surface. Pressure was increased with a speed of 9.8N/s until the subject reported a first feeling of pain/discomfort (1/10 on numeric pain rating scale) felt at the stimulus location. This was repeated after 30 seconds and the average of both measurements was taken. Measuring PPT is found to be reliable and valid (45).
b) No measurement for dynamic mechanical allodynia was available in the dataset. However, also a temporal summation measurement was performed in the region of pain (the knee awaiting TKA). Therefore, we decided to add this variable to the judgement of step 5. Thirty pinpricks were given at the skin overlying the medial tibiofemoral joint-line of the affected knee at a pace of 1 pinprick/second with a Von Frey monofilament of 60 grams. Together with the first and the last stimulus, the subject was instructed to give a pain score felt at the stimulus location on a numeric rating scale (NRS) ranging from zero to 10, where zero indicated ‘no pain’ and 10 ‘unbearable pain’. The differences of the NRS scores were calculated and used for analysis. This method is found to be reliable (46).

c) Painful after-sensations: after ending the 30 pinpricks with the Von Frey monofilament, a pause of 15 seconds followed, and after this pause, the patient had to score their pain felt at the stimulus location again on a NRS (without any stimulus given at that moment). This is also found to be reliable (46).
d) Heat/cold allodynia: thermal rollers (Rolltemp II Somedic Senselab) having a temperature of 25°C (cold stimulus) and 40°C (hot stimulus) were used. The rollers were passed 10 seconds at the skin overlying the medial and lateral tibiofemoral joint-line of the affected knee. After these 10 seconds, patients needed to score their sensation of pain again felt at the stimulus location on a NRS as described above. Thermal rollers have been used in previous research to test thermal allodynia in this population (25) as 25°C and 40°C do not normally activate nociceptors (47). This method is also recommended to test abnormalities in thermal sensation (48).

For applying this step, normative data (n = 38) from another ongoing project aiming to establish reference values for quantitative sensory testing in healthy people were used. This project was approved by the Ethical committee of the University Hospital of Antwerp (BE3002021000016). Eligibility criteria for these healthy people are also presented in Table 1. The exact same measurements as provided in the KOA population were also applied in these healthy subjects at the Sensoric Functioning Lab at the University of Antwerp. For each KOA patient, every value was compared to the mean and standard deviation of the healthy population based on z-scores. If a z-score exceeded a value of 1.96, the value was considered indicative of evoked hypersensitivity (49,50), meaning that the participant fulfilled step five and was categorized as having at least 'possible' nociplastic pain.

Step 6 – History of pain hypersensitivity and comorbidities

The IASP grading system defined the part 'a history of pain hypersensitivity' as fulfilled when participants mentioned any of the following during a patient interview with the executive researchers (Belgium) or nurses (the Netherlands): sensitivity to (a) touch, (b) pressure, (c) movement, or (d) cold or heat (18). The part 'presence of comorbidities' was defined as fulfilled when the participants presented with any one of the following: (a) increased sensitivity to sound and/or light and/or odors, (b) sleep disturbance with frequent nocturnal awakenings, (c) fatigue, or (d) cognitive problems such as difficulty to focus, attention, memory disturbances, etc.

In the current study, we had the opportunity to carry out an extensive quantitative sensory testing instead of a patient interview (which was included in the previous step). As such, we only considered the 'presence of comorbidities' part for the fulfillment of step six. As no validated methods or cut-off scores are defined yet, we followed the approach of Nijs et al. (30,51) and Foubert et al. (52). to assess and interpret this step by using the individual questions of the central sensitization index (CSI) part A. This questionnaire, in which every item is scored from zero (never) to four (always), is found to be reliable (53). The CSI questions suggested to be related to the proposed comorbidities (30,51) can be found in Table 3. Foubert et al. (52) defined the following cut-off criteria to objectively fulfill this criterium of 'probable' nociplastic pain: a score of ≥ three (often or always present) for ≥ two of the selected CSI questions (Table 3).

Table 2: Extra biopsychosocial variables used to compare no and 'probable' nociplastic pain groups (apart from variables used in the IASP grading system)

Biopsychosocial variable group	Variable	Measurement
Demographic variables	Age	Birth date until first physical measurement
	Sex	Man or woman
Metabolic and inflammatory variables	BMI	Weight/(length in cm)2
	HbA1c value	A1CNow+ system *(PTS Diagnostics, China)* and a fingerstick
	Fat and lean mass	Bioelectrical Impedance Analysis (*Bodystat Quadscan 4000*)
	C-reactive protein	Blood sample
Pain-related variables	Pain intensity	KOOS subscale pain and NRS pain in rest
	Pain symptoms	KSSS subscale symptoms
	PPT m. Tibialis anterior, forehead and m. ECRL	Hand-held pressure algometer *(Wagner FDX 25 Force Gage, USA)*
	Temporal summation m. ECRL	Von Frey Monofilament 60 grams
	Thermal allodynia at m. ECRL	Thermal rollers (Rolltemp II)
	CPM	Q-Sense CPM *(Medoc, USA)*
Functional variables	Isometric strength of m. Quadriceps and m. Hamstrings of the affected leg	MicroFET 2 hand-held dynamometer (*ProCare, Groningen*)
	Proprioception of the affected leg	Plurimeter *(Dr. Rippstein, Switzerland)*
	Functionality (symptoms and functional ability of performing activities)	KOOS subscale symptoms, 30s timed chair stand test, KSSS functional score
Psychological variables	Pain catastrophizing	PCS total score, subscale rumination, magnification and helplessness
	Depression	HADS subscale depression
	Anxiety	HADS subscale anxiety
	Expectations about the surgery	KSSS subscale expectations
	Satisfaction about their current pain	KSSS subscale satisfaction
	Illness perceptions	IPQR subscale identity, consequences, timeline, personal control, treatment control, illness coherence, emotional representations
Structural variables	Grade of OA	RX or MRI
Social variables	Work Educational level Marital status	Demographic questionnaire scored on different levels

Table 2. Abbreviations: BMI = body mass index, Hb1Ac = glycated hemoglobin, PPT= pressure pain threshold, ECRL= extensor carpi radialis longus, CPM= conditioned pain modulation, m.= musculus, OA = osteoarthritis, NRS= numeric rating scale, KOOS= Knee Injury and Osteoarthritis Outcome Score, KSSS= Knee society outcome score system, KOOS= knee injury and osteoarthritis outcome score, s= seconds, PCS= pain catastrophizing scale, HADS= hospital anxiety and depression scale, IPQR= illness perceptions questionnaire revised, RX= radiography, MRI= magnetic resonance imaging

AIM 2: Comparing biopsychosocial variables among participants with 'probable' and 'possible or no' nociplastic pain

Apart from comparing the above-mentioned variables, also differences in demographic, metabolic, functional, psychological, structural, social and other pain-related variables measured at baseline in the longitudinal study (see Table 2) were evaluated comparing patients with 'probable' vs 'no or possible' nociplastic pain to get an extensive overview of all biopsychosocial characteristics. Details about the measurements and their clinimetric properties used to assess these biopsychosocial variables can be found in the Supplementary Material.

AIM 3: The response to TKA one-year postoperative compared between groups

The KOOS subscale pain at one-year post-TKA was used to compare the response to TKA treatment (pain intensity score of operated knee) between the different identified 'probable' and 'possible or no' nociplastic pain groups.

Statistical analyses

All statistical analyses were performed using the IBM Statistical Package for Social Sciences Version 29 (SPSS, IBM Corporation, Armonk, NY), and R software (version 4.2.3) for multiple imputation. First, univariate outliers were checked with boxplots (< than quartile 1 – 1.5* interquartile range, or > than quartile 3 – 1.5* interquartile range), if present these were checked in the digital database and on the measurement form and only deleted if unreasonable (not in between the expected range). Second, subjects with missing data in one of the variables used in the grading system were deleted (as the subject could not be run through the whole grading system) (AIM 1).

Focusing on AIM 2 and 3, missing data were accounted using multiple imputations (n=10 imputed datasets) (54), except if more than 40% of data was missing (55). To compare all biopsychosocial variables between the two groups in each pain-location approach (3 or 4 pain locations), linear mixed model analyses were used (multinomial logistic regression for categorical variables of more than 2 categories). Group (3 or 4 pain locations), age and sex (covariates – except if age and sex were the independent variables themselves) were used as fixed effects (PART 2). Sex and age were used as independent factors, but also added as covariates for the other independent factors because we know sex and age can influence quantitative sensory testing (56,57), psychological and physical factors (58–60). In addition, the difference in TKA treatment between the groups was examined with linear mixed model analyses of which group (3 or 4 pain locations), age, sex and KOOS subscale pain preoperative score (covariates) were used as fixed effects (PART 3). Normality of the residuals and homogeneity of variance were checked. Based on the 10 imputed datasets, 10 different p-values were generated for each comparison per variable and their median value was reported (61). A Benjamini-Hochberg correction was applied to correct for multiple testing and the significance level was therefore set to $p<0.017$ (62). Data is presented as estimated mean and 95% confidence interval (95%CI) for continuous variables, and as frequency and percentage for categorical variables).

Finally, a sensitivity analysis was performed to strengthen our group separation choices by separating subjects with 'possible' nociplastic pain from the 'no' nociplastic pain group, and comparing the three groups. Statistical analyses were run again on all variables, however results will not be discussed in detail as this is beyond the scope of this article. Again, a Benjamini-Hochberg correction was applied to correct for multiple testing and the significance level was therefore set to $p<0.019$ (4 pain locations) and $p<0.017$ (3 pain locations) (62).

Results

AIM 1: result of IASP grading system in KOA patients

Preoperative data of 223 KOA patients were available to apply to the grading system. Of the 223 KOA patients, 11 had missing data for the KOOS subscale pain, 16 for the number of pain locations, and one for the CSI. This resulted in 197 included participants having full data necessary to run through the grading system (some had missing data on multiple variables). This sample had a mean age of 65.4 years +/- 7.7, and consisted of 95 women (48%).

The classification of nociplastic pain

The number of KOA patients fulfilling each step of the grading system is presented in Figure 1.

Step 1 - Chronic pain (> 3 months)

Apart from two patients (1%), all participants experienced significant pain (34). Therefore, sufficient arguments were available to transfer these 195 (99%) patients to the next step in the decision tree.

Step 2 – Multifocal rather than discrete pain

1. APPROACH 1 (knee + 3 additional pain locations): the pain of 73 (37.4%) participants was defined as widespread/regional, and that of 122 (62.6%) participants was discrete.
2. APPROACH 2 (knee + 2 additional pain locations): the pain of 120 (61.5%) participants was defined as regional, and that of 75 (38.5%) participants was discrete.

Step 3 – Nociceptive pain cannot be entirely responsible for the pain

As mentioned in the methods section, although all participants had confirmed KOA on medical imaging in combination with regional, widespread, or multifocal pain rather than discrete pain (discrete pain filtered out in previous step) does not exclude the presence of nociplastic pain (18). Therefore, all participants fulfilling step two (73 [37.6% of 194] and 120 [61.9% of 194], respectively) were automatically transferred to step four.

Step 4 – Neuropathic pain cannot be entirely responsible for the pain

As provided in the methods, none of the participants had neuropathic-like pain symptoms according to the DN-4 patient interview, because this was an exclusion criterion for current study. As both a neuroanatomically plausible location and neuropathic-like pain symptoms need to be present to examine if neuropathic pain is the definite pain mechanism (43), none

of the participants fulfilled this step. Therefore, all participants fulfilling step two and three (73 [37.6% of 194] and 120 [61.9% of 194], respectively) were also automatically transferred to the next step.

Step 5 – Evoked pain hypersensitivity phenomena

Table 3 gives an overview of the results and z-scores used for this criterion.

1. APPROACH 1 (knee + 3 additional pain locations): 50 (68.5% of 73) participants had evoked pain hypersensitivity and as such fulfilled step five, and 23 (31.5% of 73) experienced no hypersensitivity.
2. APPROACH 2 (knee + 2 additional pain locations): 82 (68.3% of 120) participants had evoked pain hypersensitivity and as such fulfilled step five, and 38 (31.7% of 120) experienced no hypersensitivity.

Step 6 – History of pain hypersensitivity and comorbidities

1. APPROACH 1 (knee + 3 additional pain locations): 30 (60.0% of 50) participants had at least two comorbidities and were therefore categorized as having 'probable' nociplastic pain. The other 20 (40.0% of 50) were categorized as having 'possible' nociplastic pain.
2. APPROACH 2 (knee + 2 additional pain locations): 46 (54.1% of 82) participants had at least two comorbidities and were therefore categorized as having 'probable' nociplastic pain. The other 36 (45.9% of 82) were categorized as having 'possible' nociplastic pain.

PART 2: Comparing biopsychosocial variables among participants with 'probable' and 'possible or no' nociplastic pain

Data preprocessing

Every variable used to assess differences between groups had no (n= 24 variables) or <4% (n= 21 variables) missing data, except for six variables: PPT forehead had 23 (11.86%) missing values (because this variable was added later in the study protocol), conditioned pain modulation (CPM) 15 (7.62%) (because of device deficits or some participants reporting no pain during the test-stimulus), and glycated hemoglobin (HbA1c) 16 (8.12%) (because of device deficits). Fat and lean mass and C-reactive protein had over 40% missing values and were as such not added for multiple imputation and analysis (55). Baseline values and amount of missing values for the KOA patients can be found in the Supplementary Material.

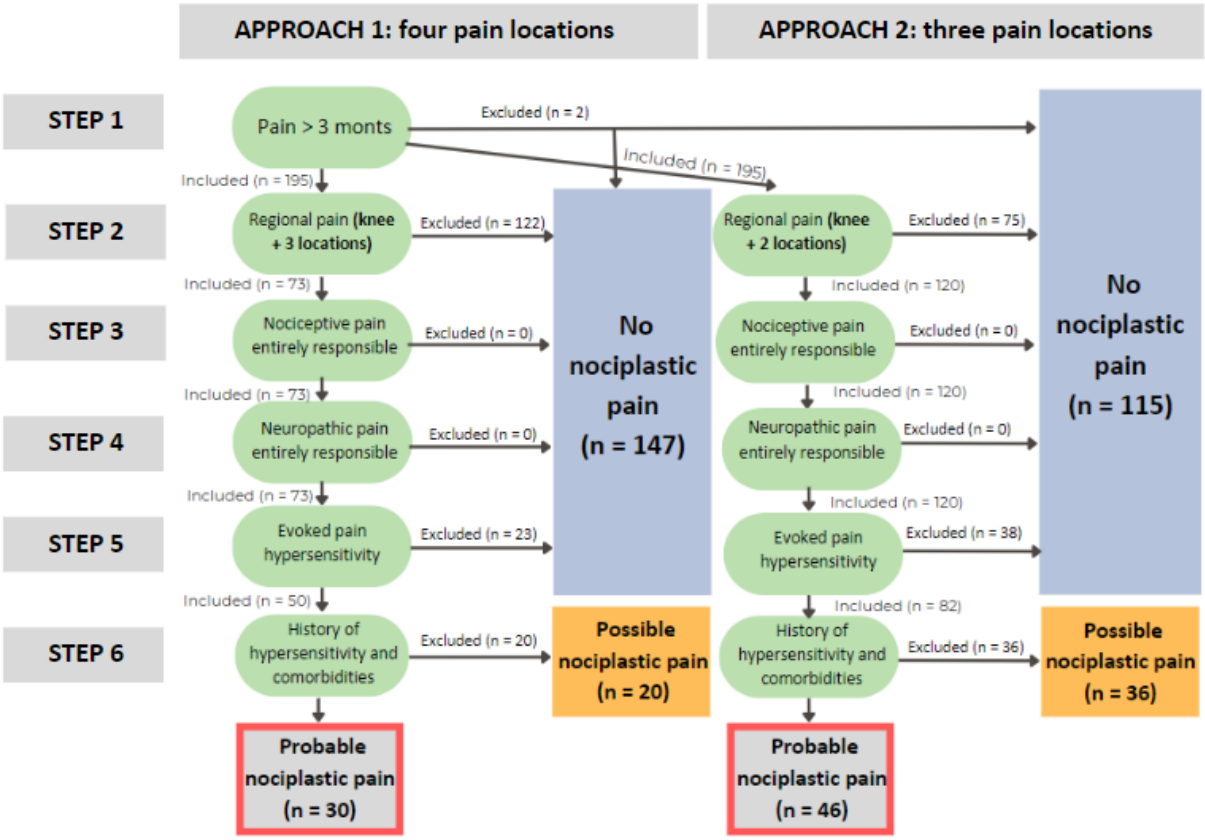
Table 3: Additional information for the results of step 5 and 6 of the IASP grading system

ADDITIONAL INFORMATION FOR STEP 5				
Approach 1: 4 pain locations	**KOA (n = 73) Mean +/- SD**	**Healthy (n = 38) Mean +/- SD**	**N (%) Z-score <-1.96* or >1.96****	**N (%) Z-score <-1.96* or >1.96** on ≥ 1 QST item**
PPT medial knee (Ne)*	36.45 +/- 20.90	64.87 +/- 33.10	0 (0)	**50 (68.49)**
PPT lateral knee (Ne)*	40.69 +/- 25.82	68.43 +/- 35.23	0 (0)	
TS(Diff in NRS)**	1.58 +/-2.25	0.30 +/- 0.55	34 (46.58)	
TS After sensation (NRS)**	0.81 +/- 1.55	0.08 +/- 0.22	20 (27.40)	
HPA medial knee (NRS)**	1.10 +/- 1.80	0.16 +/- 0.40	27 (36.99)	
HPA lateral knee (NRS)**	0.63 +/- 1.56	0 +/- 0	16 (21.92)	
CPA medial knee (NRS)**	0.58 +/- 1.09	0.01 +/- 0.08	19 (26.03)	
CPA lateral knee (NRS)**	0.49 +/- 1.17	0 +/- 0	15 (20.55)	
Approach 2: 3 pain locations	**KOA (n = 120)**	**Healthy (n = 38)**		
PPT medial knee (N)*	40.01 +/- 22.15	64.87 +/- 33.10	0 (0)	**82 (68.33)**
PPT lateral knee (N)*	44.38 +/- 25.69	68.43 +/- 35.23	0 (0)	
TS(Diff in NRS)**	1.32 +/-2.07	0.30 +/- 0.55	47 (39.17)	
TS After sensation (NRS)**	0.53 +/- 1.28	0.08 +/- 0.22	24 (20)	
HPA medial knee (NRS)**	0.92 +/- 1.57	0.16 +/- 0.40	42 (35)	
HPA lateral knee (NRS)**	0.42 +/- 1.25	0 +/- 0	21 (17.50)	
CPA medial knee (NRS)**	0.42 +/- 0.96	0.01 +/- 0.08	23 (19.17)	
CPA lateral knee (NRS)**	0.33 +/- 0.94	0 +/- 0	19 (15)	

ADDITIONAL INFORMATION FOR STEP 6			
Approach 1: 4 pain locations	**KOA (n = 50)**		
	CSI item	**N (%) with a score of ≥ 3**	**N that scored ≥ 3 on ≥ 2 CSI items**
Sound/light/odors	Item 7: I am sensitive to bright lights.	7 (14)	30 (60)
	Item 20: Certain smells, such as perfumes, make me feel dizzy and nauseated.	2 (4)	
Sleep disturbance	Item 1: I feel tired and unrefreshed when I wake up from sleeping.	23 (46)	
	Item 12: I do not sleep well.	21 (42)	
	Item 22: My legs feel uncomfortable and restless when I am trying to go to sleep at night.	16 (32)	
Fatigue	Item 8: I get tired very easily when I am physically active.	26 (52)	
	Item 17: I have low energy.	14 (28)	
Cognitive problems	Item 13: I have difficulty concentrating.	8 (16)	
	Item 23: I have difficulty remembering things.	8 (16)	
Approach 2: 3 pain locations	**KOA (n = 82)**		
Sound/light/odors	Item 7: I am sensitive to bright lights.	14 (17.07)	46 (54.12)
	Item 20: Certain smells, such as perfumes, make me feel dizzy and nauseated.	6 (7.32)	
Sleep disturbance	Item 1: I feel tired and unrefreshed when I wake up from sleeping.	35 (42.68)	
	Item 12: I do not sleep well.	31 (37.80)	
	Item 22: My legs feel uncomfortable and restless when I am trying to go to sleep at night.	21 (25.61)	
Fatigue	Item 8: I get tired very easily when I am physically active.	36 (43.90)	
	Item 17: I have low energy.	18 (21.95)	
Cognitive problems	Item 13: I have difficulty concentrating.	13 (15.85)	
	Item 23: I have difficulty remembering things.	15 (18.29)	

Table 3. Abbreviations: KOA= knee osteoarthritis, SD= standard deviation, BMI= body mass index, TS= temporal summation, PPT = pressure pain threshold, AS = after sensation, HPA = heat pain allodynia, CPA = cold pain allodynia, QST= quantitative sensory testing, Ne= Newton, Diff= difference, NRS= numeric pain rating scale 0-10, N= number.

Figure 1: Flowchart of IASP grading system for having probable nociplastic pain



Differences between groups

Details about group differences can be found in Table 4 and Table 5.

APPROACH 1: four pain locations

After running through the IASP grading system, 30 participants (15.23%) were classified as having 'probable' nociplastic pain. The 'probable' nociplastic pain group included more woman ($p=0.010$), and had a lower age ($p=0.006$), higher number of pain locations ($p<0.001$), lower PPT at medial ($p=0.003$) and later knee joint-line of affected knee ($p=0.010$), higher thermal allodynia seconds at the skin overlying the medial and lateral tibiofemoral joint-line of the affected knee (all $p<0.001$), higher temporal summation ($p=0.005$) and after sensation ($p<0.001$) at the skin overlying the medial tibiofemoral joint-line of the affected knee, higher temporal summation at medial wrist ($p=0.007$), higher heat allodynia measured at m. extensor carpi radialis longus ($p=0.004$), higher CSI scores ($p<0.001$), and higher anxiety ($p=0.008$) and depression scores ($p=0.001$) compared to the 'possible or no' nociplastic pain group. Other variables were non-significant ($p>0.05$). The sensitivity analysis revealed similar results, except that age and temporal summation measured at the skin overlying the lateral knee were not significantly different anymore ($p>0.019$). Post-hoc testing showed that differences were mostly present between the 'probable' and the 'no' nociplastic pain group (Supplementary material).

APPROACH 2: three pain locations

Using this method, 46 participants (23.35%) were classified as having 'probable' nociplastic pain. The 'probable' group included more woman (p=0.007), and had a lower age (p=0.003), a higher number of pain location (p<0.001), lower PPT (0.003) and higher cold (p=0.001) and heat (p=0.002) allodynia at the skin overlying the medial tibiofemoral joint-line of affected knee, higher temporal summation at medial wrist (p=0.010), higher CSI score (p<0.001), higher scores of the Illness Perceptions Questionnaire Revised (IPQR) subscale emotional representations (p=0.003), the subscale magnification (p<0.001), helplessness (p=0.001) and total score (p=0.002) of the Pain Catastrophizing Scale (PCS), subscale anxiety (p=0.010) and depression (p<0.001) of the Hospital Anxiety and Depression Scale (HADS), and lower m. Quadriceps strength (p<0.001) compared to the 'possible or no' nociplastic pain group. Other variables were not different between groups (p>0.05). The sensitivity analysis revealed similar results except for five variables: temporal summation (p=0.010) and after sensations (p=0.007) measured at the skin overlying the medial tibiofemoral joint-line of the affected knee, and the functional score of the Knee Society Scoring System (KSSS) (p=0.010), which appeared to be significantly different and were worse in the 'probable' nociplastic pain group. Temporal summation measured at the skin overlying the medial wrist and HADS fear were not significant anymore. Post-hoc testing showed again that differences were mostly present between the 'probable' and the 'no' nociplastic pain group (Supplementary material).

PART 3: The response to TKA one-year postoperative compared between groups

The KOOS subscale pain measured at one-year post-TKA had missing data for 41 participants (20.8%) because participants had no time for the measurements or were unreachable (n=40) or were planned for revision surgery (n=1). Baseline values and number of missing values can also be found in the Supplementary Material. The 'probable' group had lower KOOS subscale pain scores (= more pain) at baseline compared to the 'possible or no' nociplastic pain group (however, not significant after Benjamini-Hochberg correction), and was therefore used as a covariate in the analysis. For both pain locations approaches, the 'probable' group had lower KOOS subscale pain scores (= more pain) compared to the 'possible or no' nociplastic pain group (p=0.005 for approach 1 – 4 pain locations, p= 0.004 for approach 2 – 3 pain locations) one year post-TKA (Table 4). The sensitivity approach showed the same results (Supplementary material).

Table 4: Differences between knee osteoarthritis participants without and with 'probable' no nociplastic pain (continuous variables) at baseline and one-year postoperative

Variable	4 PAIN LOCATIONS		P-value	3 PAIN LOCATIONS		P-value
	Probable nociplastic pain (n = 30)	Possible + no nociplastic pain (n= 167)		Probable nociplastic pain (n= 46)	Possible + no nociplastic pain (n= 151)	
Continuous variables	**Estimated mean (95%CI)**			**Estimated mean (95%CI)**		
Demographic variable						
Age	61.83 (59.14; 64.53)	65.98 (64.84; 67.13)	0.006*	62.41 (60.24; 64.58)	66.25 (65.05; 67.44)	0.003*
Metabolic and inflammatory variables						
BMI (kg/m^2)	29.88 (27.94; 31.83)	29.99 (29.18; 30.80)	0.919	29.90 (28.32; 31.47)	30.00 (29.15; 30.86)	0.911
Hba1c value (%)	5.65 (5.41; 5.89)	5.57 (5.48; 5.67)	0.577	5.67 (5.47; 5.84)	5.56 (5.45; 5.66)	0.361
Pain-related variables						
Bodychart (N)	6.41 (5.72; 7.09)	2.95 (2.67; 3.24)	<0.001*	5.19 (4.59; 5.79)	2.96 (2.63; 3.28)	<0.001*
NRS pain in rest (0-10)	4.86 (3.88; 5.84)	4.57 (4.16; 4.98)	0.602	5.07 (4.28; 5.86)	4.47 (4.05; 4.90)	0.199
KOOS subscale pain (0-100)	38.09 (32.52; 43.56)	44.88 (42.60; 47.16)	0.027	39.12 (34.71; 43.53)	45.29 (42.87; 47.70)	0.019
PPT m. Tibialis anterior (Ne)	42.73 (35.08; 50.39)	50.97 (47.79; 54.15)	0.055	46.27 (40.05; 52.49)	5.75 (47.38; 54.13)	0.223
PPT MK joint-line (Ne)	31.03 (23.28; 38.78)	43.86 (40.64; 47.08)	0.003*	33.52 (27.26; 39.78)	44.46 (41.06; 47.86)	0.003*
PPT LK joint-line (Ne)	36.59 (28.17; 45.01)	48.77 (45.27; 52.27)	0.010*	41.11 (34.25; 47.96)	48.68 (44.95; 52.40)	0.063
PPT m. ECRL (Ne)	30.79 (25.19; 36.39)	37.97 (35.54; 40.30)	0.023	32.77 (28.23; 37.31)	38.12 (35.66; 40.59)	0.047
PPT forehead (Ne)	25.07 (20.48; 29.65)	31.02 (29.02; 33.02)	0.020	27.79 (24.01; 31.57)	30.81 (28.72; 32.91)	0.152
TS MK joint-line (Diff in NRS)	2.21 (1.51; 2.91)	1.10 (0.81; 1.38)	0.005*	1.76 (1.19; 2.33)	1.12 (0.81; 1.43)	0.060
After sensation medial knee (0-10)	1.13 (0.72; 1.53)	0.31 (0.14; 0.48)	<0.001*	0.73 (0.40; 1.07)	0.34 (0.16; 0.52)	0.049
TS medial wrist (Diff in NRS)	1.82 (1.23; 2.41)	0.93 (0.68; 1.17)	0.007*	1.62 (1.15; 2.10)	0.89 (0.63; 1.45)	0.010*
After sensation medial wrist (0-10)	0.26 (0.04; 0.49)	0.15 (0.06; 0.25)	0.391	0.26 (0.04; 0.49)	0.15 (0.06; 0.25)	0.867
Cold allodynia MK joint-line (0-10)	1.04 (0.69; 1.38)	0.25 (0.10; 0.39)	<0.001*	0.78 (0.49; 1.06)	0.24 (0.09; 0.40)	0.001*
Heat allodynia MK joint-line (0-10)	1.85 (1.31; 2.40)	0.71 (0.48; 0.93)	<0.001*	1.51 (1.07; 1.96)	0.69 (0.45; 0.93)	0.002*
Cold allodynia LK joint-line (0-10)	0.95 (0.61; 1.30)	0.19 (0.04; 0.33)	<0.001*	0.61 (0.32; 0.89)	0.21 (0.05; 0.37)	0.018

Table 4 (continued)

Variable	4 PAIN LOCATIONS			3 PAIN LOCATIONS		
	Probable nociplastic pain (n = 30)	Possible + no nociplastic pain (n= 167)	P-value	Probable nociplastic pain (n = 30)	Possible + no nociplastic pain (n= 167)	P-value
Continuous variables	Estimated mean (95%CI)			Estimated mean (95%CI)		
Pain-related variables (continued)						
Heat allodynia LK joint-line (0-10)	1.21 (0.80; 1.62)	0.27 (0.10; 0.45)	<0.001*	0.78 (0.44; 1.12)	0.31 (0.12; 0.50)	0.019
Cold allodynia m. ECRL (0-10)	0.51 (0.22; 0.81)	0.15 (0.03; 0.28)	0.029	0.35 (0.11; 0.59)	0..17 (0.04; 0.30)	0.182
Heat allodynia m. ECRL (0-10)	1.08 (0.65; 1.51)	0.39 (0.21; 0.57)	0.004*	0.84 (0.50; 1.19)	0.39 (0.20; 0.58)	0.027
CPM relative score (%)	7.24 (-17.29; 31.77)	16.41 (5.75; 27.07)	0.507	4.19 (-15.63; 24.02)	18.33 (7.11; 29.55)	0.207
CSI (0-100)	40.29 (36.12; 44.47)	26.33 (24.56; 28.07)	<0.001*	38.81 (35.53; 42.10)	25.30 (22.50; 27.08)	<0.001*
Functional variables						
Strength m. Quadriceps (kgf)	23.57 (19.54; 27.50)	27.94 (26.21; 29.57)	0.047	22.28 (19.18; 25.38)	28.81 (27.12; 30.50)	<0.001*
Strength m. Hamstrings (kgf)	10.00 (8.04; 11.96)	12.19 (11.37; 13.00)	0.048	10.48 (8.90; 12.07)	12.27 (11.41; 13.13)	0.058
Proprioception (°)	4.28 (3.51; 5.06)	4.49 (4.18; 4.81)	0.558	4.43 (3.90; 5.15)	4.44 (4.10; 4.78)	0.872
30s chair stand test (N)	9.87 (8.39; 11.35)	10.91 (10.29; 11.53)	0.210	9.46 (8.27; 10.65)	11.14 (10.50; 11.79)	0.017
KSSS symptoms (0-20)	8.12 (6.46; 9.79)	8.50 (7.81; 9.20)	0.685	8.07 (6.73; 9.42)	8.56 (7.83; 9.29)	0.542
KSSS functional score (0-100)	37.60 (32.18; 43.01)	44.01 (41.76; 46.27)	0.035	37.60 (32.18; 43.01)	44.01 (41.76; 46.27)	0.035
KOOS subscale symptoms (0-100)	9.87 (8.61; 11.13)	10.31 (9.79; 10.84)	0.534	9.99 (8.98; 11.01)	10.32 (9.77; 10.88)	0.578
Psychological variables						
IPQR identitiy score (0-14)	2.21 (1.69; 2.73)	2.11 (1.90; 2.33)	0.727	2.49 (2.08; 2.91)	2.01 (1.79; 2.24)	0.050
IPQR Timeline (6-30)	19.02 (17.08; 20.97)	17.65 (16.84; 18.46)	0.208	19.46 (17.90; 21.02)	17.37 (16.52; 18.22)	0.024
IPQR Consequences (6-30)	19.33 (17.80; 20.87)	19.46 (18.83; 20.10)	0.879	20.63 (19.41; 21.86)	19.08 (18.41; 19.74)	0.032
IPQR personal control (6-30)	19.81 (18.33; 21.28)	19.67 (19.06; 20.28)	0.872	19.62 (18.43; 20.80)	19.72 (19.07; 20.36)	0.886
IPQR treatment control (5-25)	17.85 (16.71; 18.98)	18.21 (17.74; 18.68)	0.568	17.67 (16.76; 18.58)	18.30 (17.81; 18.80)	0.240

Table 4 (continued)

Variable	4 PAIN LOCATIONS			3 PAIN LOCATIONS		
	Probable nociplastic pain (n = 30)	Possible + no nociplastic pain (n= 167)	P-value	Probable nociplastic pain (n = 30)	Possible + no nociplastic pain (n= 167)	P-value
Continuous variables	**Estimated mean (95%CI)**			**Estimated mean (95%CI)**		
Psychological variables (continued)						
IPQR Illness cohorence (5-25)	19.31 (18.53; 20.09)	18.63 (18.30; 18.95)	0.117	19.21 (18.58; 19.84)	18.59 (18.24; 18.93)	0.096
IPQR Timeline cyclical (4-20)	11.90 (10.49; 13.32)	11.97 (11.38; 12.56)	0.937	11.28 (10.14; 12.42)	12.17 (11.55; 12.79)	0.188
IPQR Emotional representations (6-30)	17.63 (15.98; 19.28)	15.49 (14.80; 16.17)	0.021	17.58 (16.26; 18.90)	15.28 (15.56; 15.99)	0.003*
PCS rumination (0-16)	7.43 (6.03; 8.83)	6.05 (5.47; 6.63)	0.078	7.30 (6.17; 8.42)	5.94 (5.33; 5.56)	0.042
PCS magnification (0-12)	3.67 (2.76; 4.61)	2.55 (2.17; 2.93)	0.028	3.86 (3.12; 4.59)	2.38 (1.98; 2.77)	<0.001*
PCS helplesness (0-24)	9.10 (7.26; 10.93)	7.05 (6.29; 7.82)	0.047	9.52 (80.6; 1098)	6.70 (5.90; 7.49)	0.001*
PCS total score (0-52)	20.21 (16.44; 23.98)	15.65 (14.08; 17.22)	0.031	20.67 (17.67; 23.68)	15.02 (13.38; 16.65)	0.002*
HADS fear (0-21)	7.10 (5.70; 8.49)	5.02 (4.44; 5.60)	0.008*	6.67 (5.54; 7.79)	4.93 (4.32; 5.54)	0.010*
HADS depression (0-21)	6.88 (5.73; 8.02)	4.74 (4.27; 5.22)	0.001*	6.55 (5.63; 7.47)	4.42 (4.11; 5.12)	<0.001*
KSSS satisfaction (0-40)	12.98 (10.35; 15.60)	15.80 (14.70; 16.89)	0.056	13.68 (11.55; 15.80)	15.88 (14.72; 17.04)	0.080
KSSS expectations (3-15)	13.48 (12.89; 14.07)	14.04 (13.49; 14.28)	0.090	13.60 (13.12; 14.07)	14.06 13.80; 14.32)	0.101
One year postoperative outcome variable						
KOOS subscale pain	60.23 (50.08; 70.37)	74.27 (69.94; 78.61)	0.005*	62.83 (55.14; 70.52)	74.97 (70.41; 79.53)	0.004*

Table 4. *significant difference (p<0.017). All variables are adjusted for sex and age (except age itself)

Abbreviations: BMI= body mass index. kg/m2= kilograms/squared meter. PPT= pressure pain threshold. m. = musculus. Ne= Newton. ECRL= extensor carpi radialis longus. TS= temporal summation. Diff= difference. NRS= numeric rating scale. CPM= conditioned pain modulation. kgf= kilograms force. Hb1ac= glycated hemoglobin. IPQR= illness perceptions questionnaire revised. PCS= pain catastrophizing scale. HADS= hospitality anxiety and depression scale. KSSS= knee society scoring system. KOOS= knee injury and osteoarthritis outcome scale. CSI= central sensitization inventory, MK= medial knee, LK= lateral knee.

Table 5: Differences between knee osteoarthritis participants without and with 'probable' no nociplastic pain (categorical variables)

Variable		4 PAIN LOCATIONS			3 PAIN LOCATIONS		
		Probable nociplastic pain (n = 30)	Possible + no nociplastic pain (n = 167)	P-value	Probable nociplastic pain (n = 46)	Possible + no nociplastic pain (n = 151)	P-value
Categorical variables		N (%)			N (%)		
Demographic variable							
Sex	Man	9 (30.00)	93 (55.69)	0.009*	16 (34.78)	86 (56.95)	0.008*
	Woman	21 (70.00)	74 (44.31)		30 (65.22)	65 (43.05)	
Structural variable							
Grade of KOA	K&L 1	1 (3.33)	2 (1.20)	0.116	3 (6.52)	0 (0.00)	0.063
	K&L 2	10 (33.33)	32 (19.16)		14 (30.43)	28 (18.54)	
	K&L 3	10 (33.33)	61 (36.53)		13 (28.26)	57 (37.75)	
	K&L 4	9 (30.00)	72 (43.11)		16 (34.78)	66 (43.71)	
Social variables							
Education	No degree	3 (10.00)	8 (4.97)	0.994	3 (6.52)	8 (5.52)	0.603
	Primary school	1 (3.33)	10 (6.21)		2 (4.35)	9 (6.21)	
	Technical secondary school	5 (16.67)	41 (25.47)		13 (28.26)	33 (22.76)	
	Higher secondary school	3 (10.00)	21 (13.04)		5 (10.87)	19 (13.10)	
	High school	9 (30.00)	39 (24.22)		10 (21.74)	38 (26.21)	
	University	3 (10.00)	13 (8.07)		3 (6.52)	13 (8.97)	
	Other	6 (20.00)	35 (21.74)		10 (21.74)	31 (21.38)	
Work	Pension	9 (30.00)	95 (59.01)	0.567	16 (34.78)	88 (60.69)	0.463
	Self-employed	5 (16.67)	9 (5.59)		6 (13.04)	8 (5.52)	
	White-collar worker	6 (20.00)	20 (12.42)		9 (19.57)	17 (11.72)	
	Laborer	4 (13.33)	21 (13.04)		6 (13.04)	19 (13.10)	
	Unemployed	0 (0.00)	2 (1.24)		0 (0.00)	2 (1.38)	
	Other	6 (20.00)	19 (11.80)		9 (19.57)	16 (11.03)	
Marital status	Married	20 (66.67)	121 (75.16)	0.841	32 (69.57)	109 (75.17)	0.817
	Divorced	3 (10.00)	14 (8.70)		4 (8.70)	13 (8.97)	
	Single	3 (10.00)	5 (3.11)		3 (6.52)	5 (3.45)	
	Widow(er)	1 (3.33)	17 (10.56)		2 (4.35)	16 (11.03)	
	Other	3 (10.00)	9 (5.59)		5 (10.87)	7 (4.83)	

Table 5. *significant difference ($p<0.017$). All variables are adjusted for age and sex (except sex itself).
Abbreviations: K&L= Kellgren and Lawrence scale

Discussion

The first aim was to apply the IASP grading system and identify nociplastic pain in KOA patients. Two approaches were used to interpret regional pain: approach 1 included pain at the affected knee and three additional locations, while approach 2 only included two additional locations. Among 197 KOA patients, 15.2% (approach 1) or 23.4% (approach 2) were categorized with 'probable' nociplastic pain. More detailed criteria were proposed to interpret every step of the grading system, except for discrete/regional/multifocal/widespread pain, for which no recommendation for three or four pain locations could be given yet. **The second aim** was to compare biopsychosocial factors between participants with 'possible or no' and 'probable' nociplastic pain. In both approaches the 'probable' group included more woman, had lower age, a higher number of pain locations, higher widespread temporal summation,

higher CSI scores, higher thermal allodynia measured at the medial knee-joint line, and more anxiety and depression compared to 'possible or no' nociplastic pain group. In approach 1, the 'probable' nociplastic pain group also exhibited characteristics such as lower local PPT and higher thermal allodynia measured at lateral knee-joint line, higher local temporal summation and after sensation, and higher widespread heat allodynia. In approach 2, the 'probable' nociplastic pain group also exhibited lower PPT, worse illness perceptions about emotional representations and m. Quadriceps strength, and higher magnification, helplessness and general pain catastrophizing. **The third aim** was to compare the response to TKA treatment between groups. The 'probable' nociplastic pain group had more pain compared to the other group one-year post-TKA. Sensitivity analyses revealed comparable results.

Interpretation of findings and relation to previous research

This study found that the IASP grading system is feasible for identifying and characterizing KOA patients with nociplastic pain. However, challenges emerged in executing its application. First, the use of terms such as 'regional/multifocal/widespread' (which are not necessarily synonyms (63–65)), and information about the specific pain distribution area (which was defined as *"rather cutaneous and regional, multifocal, or widespread in distribution (rather than discrete)"*), lacked clarity (18). While previous research has provided some (unvalidated) thresholds for defining widespread pain in KOA patients (37,38), clear cut-off criteria for regional pain have not been established (65,66). To address this issue, two approaches of having knee pain along with additional locations were used. This additional approach expanded knee pain plus solely one supplementary location, because a significant number KOA patients experience concurrent contralateral KOA pain, which made the inclusion of at least two extra pain locations imperative (39,40). However, body locations were only counted and as such no information about 'more regional' or 'more widespread' pain could be given. Therefore, no recommendation could be made to use 3 or 4 pain locations as adequate to judge this step. More research is needed as this twofold presentation only highlights the need for clearer criteria to judge this step in the future. Secondly, clear guidelines or a grading system to study whether nociceptive pain is entirely responsible for the pain is currently lacking, but necessary for implementing and interpreting the comprehensive patient interview and full physical examination of the patient. Therefore, we had not enough arguments to say that nociceptive pain was entirely responsible for the pain in the participants who reached step 2 (18). Third, an interpretation for 'evoked hypersensitivity' and 'history of comorbidities' was introduced based on previous literature, but further validation is required (30,49,50,52). In terms of comorbidities, a different cut-off as specified in the IASP grading system was chosen (18). Instead of relying solely on patient interviews, the CSI items were used because they covered all comorbidities outlined by the grading system. However, they are formulated with less stringency and are often mentioned as being common. For instance, "I feel tired and unrefreshed" or "getting tired very easily when physically active" are frequently reported among the KOA population given the age or physical condition, but do not necessarily indicate the presence of 'fatigue' (67). Moreover, current study used a cut-off score of ≥ three (often or always present), but discussion remains present whether a score of two (sometimes present) is maybe sufficient to be classified as 'having the comorbidity'. Last, participants presenting with 'possible' or 'no' nociplastic pain were merged to one group, because the

presence of evoked pain hypersensitivity alone ('possible' group) does not automatically classify the pain as predominantly nociplastic pain (68,69). Thereupon, the aim of the current manuscript was to identify participants with a predominant nociplastic pain mechanism (and not with a 'possible' nociplastic pain mechanism).

Previous research provided theoretical guidelines for the grading system in cancer (51) and post-COVID contexts (70) but was based on solely theoretical considerations. No studies, except one preprint in patients with MSK disorders (50) and one study in hemophilia patients (52) applied the IASP grading system to real patient datasets. Foubert et al. (52) found no differences regarding demographic, psychological, functional and quality of life between the 'probable or possible' and 'no' nociplastic pain group. A possible explanation could be the different pathology (hemophilia), but also their group comparison. Due to their small sample size, they decided to merge the 'probable' with the 'possible' nociplastic pain group, while the current study merged the 'possible' with the 'no' nociplastic pain group. The preprint that also tried to apply the grading system (50), categorized only 5% of their osteoarthritis sample as having 'probable' nociplastic pain, but the small sample size (21 participants) and reliance solely on medical imaging to decide if the pain was predominantly nociceptive could explain the discrepancies with our findings. No analyses to study differences between pain mechanism groups and their response to treatment were performed. However, studies have been published comparing KOA patients with a predominant neuropathic-like pain mechanism and a predominant nociceptive pain mechanism (22–24), or comparing TKA patients with a predominant nociceptive, predominant pain sensitization, and mixed pattern (25). The proportions of KOA patients with neuropathic-like pain (30-58% of participants) (22–24) were higher compared to the 'probable' nociplastic pain group in the current study (15-23% of participants), but more similar with the pain sensitization group (25%) in the latter study (25). This is plausible, as the studies comparing neuropathic-like pain with nociceptive pain also indicate that as well individuals with a nociplastic pain mechanism as individuals with a neuropathic pain mechanism were part of this neuropathic-like pain group (22–24). Similar to our findings, KOA patients in the neuropathic-like pain (22–24) or TKA patients in the pain sensitization group (25) experienced more disturbed somatosensory functioning (23–25), higher pain scores and number of pain locations (22,25), or more pain post-TKA (23,24). Similar to participants classified to our approach 2 (3 pain locations), participants in the study of Soni et al. (24) also experienced higher pain catastrophizing. The study of Van Helvoort et al. (22) also found less radiographic damage in the participants with neuropathic-like pain, which could not be detected in our study. Caution is advised for interpreting these comparisons, as KOA patients experiencing neuropathic-like pain were excluded from the current study.

In this KOA-focused study, 30 to 46 participants (15.22 to 23.35%) were categorized as 'probable' nociplastic pain, which is a rather small sample size for our statistical analyses. However, our results are still of value in attempting to gain more insight into the characterization of KOA patients with a predominant 'probable' nociplastic pain mechanism according to the IASP grading system, because of their consistency with the findings of a previous literature review and Delphi consensus expert study (19,26), and the larger sample sizes in each group compared to previous pain mechanism phenotype studies (22–25).

Finally, our study showed that the 'probable' nociplastic pain group had worse TKA outcome compared to the other group. It was indeed expected that TKA would not resolve all the pain complaints, because in a predominant nociplastic pain mechanism, the pain is not (fully) related to tissue damage (KOA) (17). Therefore, it is postulated that other treatment modalities focusing on a more comprehensive modern neuroscience approach are additionally required to further resolve the patient complaints (18,29).

Strengths and limitations of the study

This study possesses several notable strengths. Firstly, it is one of the first studies applying the IASP grading system to a real dataset going beyond mere theoretical descriptions (51), and the first one in KOA patients specifically. Further, it also presents differences in treatment outcome of which the characteristics of both subgroups can be valuable in clinical practice to inform shared decision making about perioperative treatment. Last, it addresses the crucial aspect of defining and providing suggestions for criteria and cut-offs for every step based (except for discrete/regional/multifocal/widespread pain) on reliable measurement methods as indicated by the creators of the IASP grading system (18). However, this paper also has some limitations. Firstly, KOA patients with neuropathic-like pain were excluded, and all patients were awaiting TKA, this makes that our sample is not representative for the general KOA population. Secondly, this was a secondary analysis of another longitudinal prospective study. This makes that an objective measure questioning pain duration, a comprehensive assessment for pathology at other painful sites, and a measurement for dynamic mechanical allodynia were not available in the current dataset. Nevertheless, given that KOA is a chronic disease, all participants were awaiting TKA, and the use of the proposed cut-off of pain or not (34), we argue that there is sufficient rationale to categorize the pain as ≥ three months. In addition, temporal summation was used as alternative for dynamic mechanical allodynia, because this measurement was also performed in the region of pain. Thirdly, the number of pain locations was only counted, without the presentation of a pain drawing (step 2). Therefore, no information about whether the pain location was regional or widespread could be provided. As such, further research is necessary to provide a recommendation for clinical practice. However, the grading system itself does not provide specific criteria for assessing this step, so presenting two approaches for a cut-off was a first suggestion. Fourthly, one patient was planned for revision surgery, suggesting that this missing value was not missing at random regarding the KOOS subscale pain score one-year post-TKA. However, all other missing values were missing at random. Lastly, originally, the test stimulus in the CPM measurement had to be a temperature equal to a pain intensity of 4/10 (71), but only participants reporting 0/10 were excluded in the current analysis. Therefore, it is possible that the stimulus was not noxious enough to elicit a CPM effect in some participants.

Implications for further research and clinical practice

Further research is warranted to validate and further refine the IASP grading system (especially to interpret discrete/regional/multifocal/widespread pain), replicate our interpretation with external validation, and investigate if the proposed IASP grading system is applicable to other MSK patients using our more specific approach. In clinical practice, our approach holds potential value for clinicians in making informed decisions about the presence

of nociplastic pain in KOA patients and shared decision making about the perioperative treatment. As such, clinicians can decide whether these patients require additional or alternative treatments like cognitive behavioral therapy, pain neuroscience education, exposure in vivo, etc. (69).

Conclusion

The current study proposed more refined criteria for the grading system of nociplastic pain (except for discrete/regional/multifocal/widespread pain) and found that a significant portion of participants, ranging from 15.22 to 23.35%, could be categorized as having 'probable' nociplastic pain according to the IASP grading system. Irrelevant of which pain distribution approach was used, the 'probable' nociplastic pain included more woman, participants with a lower age, a higher preoperative number of pain locations, widespread TS, higher CSI scores, higher thermal allodynia measured at medial knee-joint line, anxiety and depression compared to the 'possible or no' nociplastic pain group. In addition, participants in the 'probable' nociplastic pain group experienced more pain one-year after TKA compared to the other group. More research is necessary to validate and to propose suggestions to improve the grading system itself.

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Chapter 4: The evolution of somatosensory processing signs after nociceptive targeted surgery in patients with musculoskeletal disorders: a systematic review

Sophie Vervullens[1,2,3] , Lotte Meert[1,2,3], Mira Meeus[1,3], Isabel Baert[1,3], Christiaan H.W. Heusdens[4], Cleo Caethoven[1], Nina Charpentier[1], Amber Vervliet[1], Rob J.E.M. Smeets[2,3,5]

[1]Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium

[2]Research School CAPHRI, Department of Rehabilitation Medicine, Maastricht University

[3]Pain in Motion International Research Group (PiM), www.paininmotion.be

[4]Department of Orthopedics and Traumatology, University Hospital of Antwerp, Antwerp, Belgium, and Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium

[5]CIR Clinics in Revalidatie, location Eindhoven, The Netherlands

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Abstract

Surgery is often advised when conservative treatment fails in musculoskeletal pain conditions, but a substantial proportion still suffers chronic pain after surgery. Somatosensory processing system (SPS) signs were previously studied as potential predictors for chronic postsurgical pain, but results are inconsistent. Therefore, studying the evolution of SPS signs could be of added value. The aim was to summarize all studies that measured how SPS signs evolved after nociceptive targeted surgery in musculoskeletal disorders, and to find pre-, peri- and postoperative predictors for the evolution of these SPS signs. Data was summarized, and risk of bias and level of evidence and recommendation were determined. Twenty-one studies were included. Five scored a low, three a moderate, and 13 a high risk of bias. In general, no consistent evolution of SPS signs comparing pre- and postoperative values and predictors for this evolution in musculoskeletal disorders could be found. In most cases, static quantitative sensory testing (QST) did not change or conflicting results were found. On the other hand, dynamic QST mostly improved after surgery. Worthfully mentioning is that worsening of SPS signs was only seen at a follow-up of < 3 months after surgery, that conclusions are stronger when evaluating dynamic QST with a follow up of ≥ 3 months after surgery, and that pain improvement postsurgery was an important predictor. Future high quality research should focus on the evolution of SPS signs after nociceptive targeted surgery, accounting for pain improvement groups and focusing on pre, peri- and postoperative predictors of this evolution.

Introduction

Pain is defined as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' (1). Musculoskeletal (MSK) pain is often associated with disorders of the MSK system of the human body, including muscles, joints, tendons, ligaments and other structures (e.g., discs, bursae) (2). When this pain remains present for longer than three months and is associated with an underlying MSK condition, the International Classification of Diseases 11th Revision (ICD-11) defines it as chronic secondary MSK pain (3).

In general, conservative treatment, like medication, injections or physical therapy, is first-choice therapy to target the nociceptive source of MSK pain. However, when this fails and the patient's pain intensity is still significant with a negative impact on functioning, surgery is often advised (4,5). Despite that surgery targets the source of nociception, five up till 85% still experiences chronic postsurgical pain depending on the type of surgery and disorder (6). According to the ICD-11, this postsurgical pain lasts longer than three months or beyond the normal healing process after surgery (3). Different peripheral (e.g., specific factors like malalignment, too much stress on the implant,…) and central (e.g., disturbed somatosensory processing system [SPS]) originated hypotheses for the persistence of this pain have been described (7).

Chronic (postsurgical) pain can, apart from peripheral factors, also be associated with a disturbed SPS in which the central nervous system becomes hypersensitive. Not only local, but also widespread hyperalgesia and allodynia are indicative for this hypersensitivity, and hyperexcitability of the ascending nerve pathways and a less efficient endogenous pain inhibition system are known as underlying mechanisms (8,9). Apart from psychosocial, genetic, metabolic and functional factors, also preoperative disturbed SPS signs are proposed as risk factors for chronic postsurgical pain (6,10).

Quantitative Sensory Testing (QST) can measure and objectify this hypersensitivity, of which pain thresholds, detection thresholds, or dynamic methods -such as the degree of spatial and temporal summation, and conditioned pain modulation (CPM)- are an indispensable part (10). Also questionnaires, such as the Central Sensitization Inventory (CSI) and Pain Sensitivity Questionnaire, could indicate self-reported signs of a disturbed SPS (11).

Recent reviews are contradictory about the predictive value of a preoperative disturbed SPS for chronic postsurgical pain (12,13), but none of them considered the evolution of SPS signs from pre- to postsurgery. The central nervous system is dynamic and it is postulated that disturbed SPS signs can be caused by the peripheral source of nociception (14), defined as chronic secondary pain; or are rather independent of identified peripheral biological contributors, defined as chronic primary pain (3), (15,16).

When the nociceptive source is targeted by surgery, a normalization of SPS signs could be expected (17). Nevertheless, a substantial proportion of patients still reports pain (6). The nociceptive source in combination with disturbed SPS signs (additionally) could be imposed as chronic primary MSK pain, because clear evidence exists that -in a long period of obvious dissociation between the medical causes and chronic pain- other factors determine the

chronic pain condition. Although both primary and secondary pain can involve overlapping nociplastic (from a sensitized nervous system) and nociceptive (from tissue injury) processes, nociplastic pain mechanisms are particularly relevant in chronic primary pain. The underlying disorder may have been treated successfully, but chronic pain remains and becomes the main complaint in its own right (15).

As none of the previous reviews focused on the temporal stability or change of signs of SPS in chronic MSK pain, it remains unclear whether SPS signs improve after a nociceptive targeted surgery or not, and whether pre-, peri- and postoperative predictors can be indicated for the evolution of these signs. Therefore, the first aim of this systematic review is to summarize all studies that measure how SPS signs evolve after nociceptive targeted surgery in MSK disorders. The second aim is to find pre-, peri- and postoperative predictors for an improvement or persistence of disturbed SPS signs after surgery.

Methods

This systematic review is written according to the updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (18).

Eligibility criteria

Studies were eligible if they met all different in- and exclusion criteria based on the Population (P), Intervention (I), Comparison (C), Outcome (O) and Study design (S) model. Studies had to measure evolution in SPS signs (O) before and after nociceptive targeted surgery in patients with MSK pain (P) undergoing nociceptive peripheral (MSK disorder) targeted surgery (I). Eligibility criteria can be found in Table 1.

Information sources and search strategy

Two electronic databases, PubMed (MEDLINE) and Web of Science (WoS), were searched for potentially eligible literature up to 21th, April 2022. A search strategy combined using ‘AND’ and ‘OR’ was set up based on different key words (P, I, O and S) (19). There were no additional search filters added. The search strategy of the two databases can be found in Table 2 and 3. Additionally, reference lists of included studies, which were retrieved from the search strategy, were checked for more relevant articles through hand-search methods.

Selection process

Studies were considered relevant based on a two-phase triple-blind title, abstract and full text screening performed by four reviewers (SV, AV, NC and CC). In the first phase, studies were checked independently for eligibility on title and abstract, and in the second phase on full text both with the help of Rayyan (20). The order of exclusion for the full text screening was as follows: language > study design > population > intervention > outcome. All conflicts during both phases were solved by consensus.

Table 1: Eligibility criteria according to PICOSL

	Inclusion	Exclusion
P	- Human patients with MSK pain disorders	- Animal studies - Patients with neurological disorders, cardiorespiratory disorders, metabolic disorders, or systemic disorders
I	- Peripheral nociceptive targeted (MSK disorder) surgery - Separate statistical analyses for the surgery group	
C	/	/
O	- QST or questionnaires (CSI, PSQ) focusing on afferent somatosensory processing system signs - Measured before and after surgery	- Measured only before or only after surgery
S	- Full text available	- Reviews, Meta-analyses, Abstracts, Letters, Congress proceedings, case reports
L	- Articles written in English, Dutch, German or French	- Articles written in any other language

Abbreviations: P, population; I, intervention; C, comparison; O, outcome; S, study design; L, language; MSK, musculoskeletal; QST, Quantitative Sensory Testing; CSI, Central Sensitization Inventory; PSQ, Pain Sensitivity Questionnaire

Table 2: Search strategy related to Pubmed

Population	Intervention	Outcome	Study design
(("Musculoskeletal Diseases"[Mesh] OR "Musculoskeletal Pain"[Mesh] OR "Arthralgia"[Mesh]) OR musculoskeletal disease* OR musculoskeletal disorder* OR musculoskeletal pain OR orthopedic disorder* OR myalgia OR arthralgia) AND ("Humans"[Mesh] OR "Persons"[Mesh] OR human* OR person* OR people)	("Orthopedics"[Mesh] OR "Orthopedic Procedures"[Mesh] OR "Surgical Procedures, Operative"[Mesh] OR "General Surgery"[Mesh] OR "Arthroplasty"[Mesh]) OR surgery OR orthopedic surgery OR orthopedics OR orthopaedics OR operation OR arthroplasty OR replacement OR orthopedic procedures	("Pain Threshold"[Mesh] OR "Sensory Thresholds"[Mesh] OR "Pain Perception"[Mesh] OR "Central Nervous System Sensitization"[Mesh]) OR Quantitative sensory testing OR QST OR pain threshold OR sensory threshold OR detection threshold OR pain perception OR "central nervous system sensitization" OR algomet* OR temporal summation OR spatial summation OR conditioned pain modulation OR CPM OR endogenous pain inhibition OR "diffuse noxious inhibitory control" OR central sensitization OR central pain processing OR pain sensitivity OR pain modification OR pain facilitation OR wind up OR altered nociception	("Pragmatic Clinical Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Clinical Trial" [Publication Type] OR "Cohort Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Prospective Studies"[Mesh]) OR clinical trial OR randomized controlled trial OR randomised controlled trial OR cohort studies OR prospective studies OR longitudinal studies OR follow-up studies

Table 3: Search strategy related to Web of Science

Population	Intervention	Outcome	Study design
musculoskeletal disease* OR musculoskeletal disorder* OR musculoskeletal pain OR orthopedic disorder* OR myalgia OR arthralgia AND (human* OR person* OR people)	surgery OR orthopedic surgery OR orthopedics OR orthopaedics OR operation OR arthroplasty OR replacement OR orthopedic procedures	Quantitative sensory testing OR QST OR pain threshold OR sensory threshold OR detection threshold OR pain perception OR "central nervous system sensitization" OR algomet* OR temporal summation OR spatial summation OR conditioned pain modulation OR CPM OR endogenous pain inhibition OR "diffuse noxious inhibitory control" OR central sensiti?ation OR central pain processing OR pain sensitivity OR pain modification OR pain facilitation OR wind up OR altered nociception	/

Data collection and items

Data about the evolution of SPS signs of all studies were retrieved and collected. Data about (1) author, year of publication & study design, (2) participants: study sample and characteristics, and eligibility criteria, (3) outcome measurement method and measures of central SPS, (4) measurement locations, (5) type of surgery, (6) follow-up period, (7) chronic pain measurement, and (8) most important results was extracted. The first reviewer (SV) filled in the evidence table, and the second reviewer (LM) checked the table independently. Data about the predictors for SPS change over time or SPS signs-related predictors for surgical outcome were also retrieved and collected. Data about (1) author and year, (2) surgical outcome in relation to SPS sign, (3) follow-up period, (4) method, (5) predictor change in SPS sign, and (6) predictor surgical outcome in relation to SPS sign was extracted.

Risk of bias and level of recommendation of studies

The quality in prognostic studies (QUIPS) checklist (21) was used to assess Risk of bias (RoB) in the individual studies. Six domains, 1) Study Participation, 2) Study Attrition, 3) Prognostic Factor Measurement, 4) Outcome Measurement, 5) Study Confounding, and 6) Statistical Analysis and Reporting, were scored as having either a ‘low’, ‘moderate’ or ‘high’ chance for RoB. The first two reviewers (SV and LM) performed the RoB independently and blinded from each other. In order to create uniform RoB scoring, guidelines for the interpretation of each item were set up based on a previous study (22). The overall RoB judgement of a study was based on all domains; an overall ‘low’ RoB score meant that all domains were scored as ‘low’ or maximum one as ‘moderate’; an overall ‘high’ RoB meant that at least one domain was scored as ‘high’ or ≥ 3 as ‘moderate’; and all other studies were judged as having an overall ‘moderate’ RoB.

Additionally, each study was assigned a level of evidence based on the Oxford Centre for Evidence-Based Medicine (OCEBM) guidelines (23), of which the scoring was based on study design and RoB assessment (23). Table 4 summarizes the levels of evidence and grades of recommendation. Thereafter, results from both reviewers (SV and LM) were compared and discussed until consensus was reached.

To make conclusions, studies were clustered by the first author (SV) and grades of recommendation were assigned according to the OCEBM guidelines. Studies were categorized per SPS sign (threshold measurements also split up into local and widespread threshold measurement), MSK disorder and follow-up period for the first aim. Regarding the second aim, studies were categorized per SPS change and predictor.

Table 4: Level of evidence and strength of recommendation scoring

	Level of evidence		Strength of recommendation
LoE 1a	Systematic review of inception cohort studies or RCTs	A (strong)	Consistent level 1 studies
LoE 1b	Randomized controlled trial or individual inception cohort study with > 80% follow-up	B (moderate)	Consistent level 2 or 3 studies or extrapolations from level 1 studies
LoE 1c	All or none case-series	C (weak)	Level 4 studies or extrapolations from level 2 or 3 studies
LoE 2a	Systematic review of either retrospective cohort studies or untreated control groups in RCT	D (very weak)	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level
LoE 2b	Individual cohort study (including low quality RCT, <80% follow-up)		
LoE 2c	"Outcomes" research		
LoE 3a	Systematic review of case-control studies		
LoE 3b	Individual case-control study		
LoE 4	Case-series		
LoE 5	Expert opinion		

Abbreviations: RCT, Randomized Controlled trial; LoE, Level of Evidence

Results

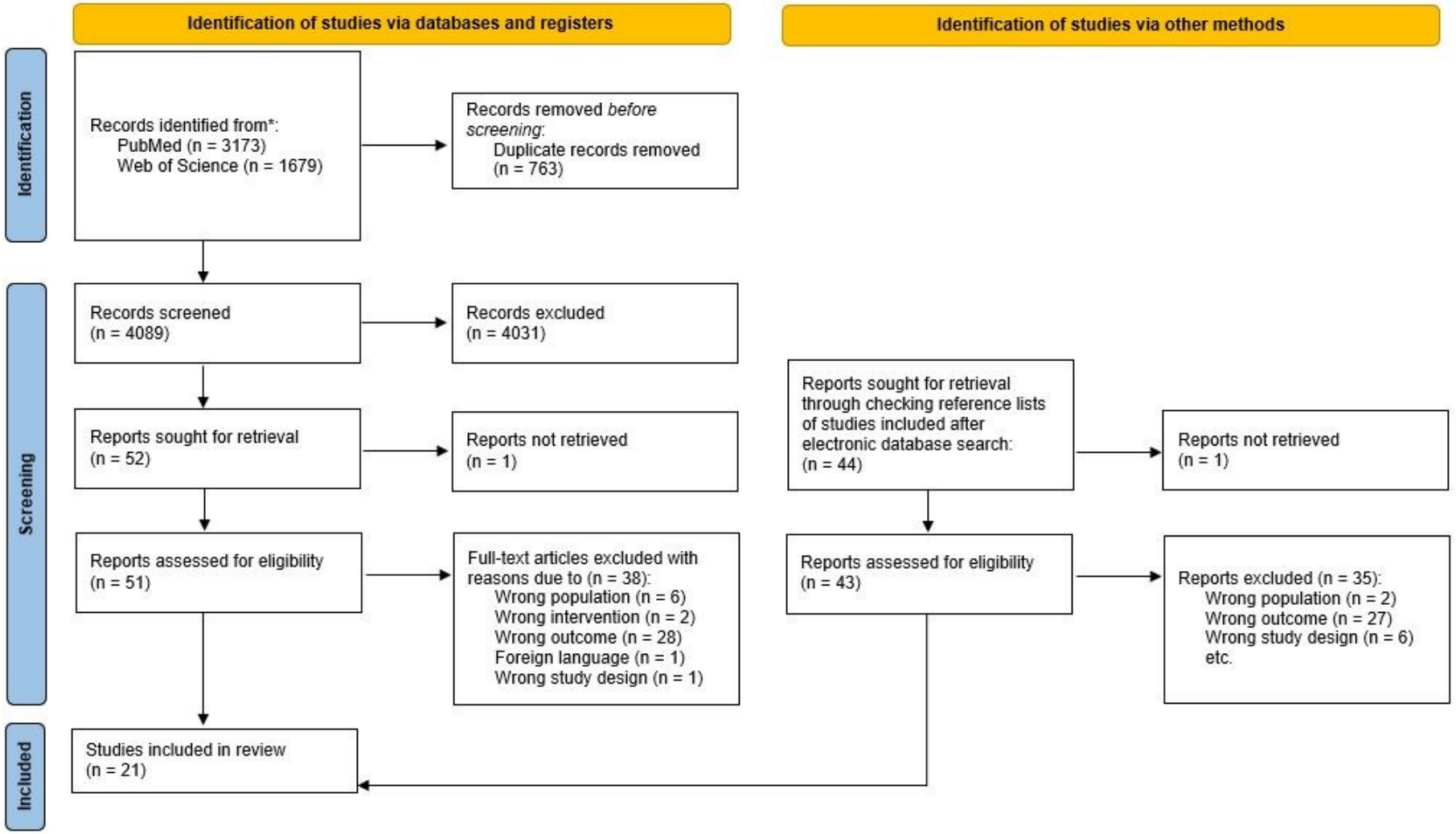
Study selection

The PRISMA flowchart reflects the study selection process (Figure 1). The search strategy yielded 13 eligible studies for inclusion in this review (24–36). After checking their reference lists, eight additional studies were eligible (17,37–43). This resulted in 21 studies, of which 18 prospective cohort studies (17,25,26,28–32,34–43) and three randomized controlled trials (24,27,33). Conflicts in the first (44 studies or 1%) and second (16 studies or 30.7%) screening phase were all solved by consensus. The most prevalent exclusion reasons were 'wrong outcome' and 'wrong population'.

Risk of bias

The two reviewers that scored the RoB (SV and LM) agreed on 75.0% of the domains, and 74.8% of the subdomains. Conflicts were all solved after discussion. The domain 'study attrition' suffered by far the highest RoB, mostly because studies did not report the number and reasons for the losses to follow-up, or the way that they tried to address these losses.

Figure 1: PRISMA flowchart



Study characteristics, population and type of surgery

Five different disorders were targeted in the included studies. Seventeen studies included patients with osteoarthritis (OA): hip OA (25,37–40), knee OA (17,24,27,30–33,36,41,42), shoulder OA (28), and both hip and knee OA (29). All these patients received total joint replacement surgery (17,24,27–33,36–42) or osteotomy (39,40). One study included patients with a closed lock temporomandibular joint who received discectomy (26), and three studies included patients with lumbar disc herniation who received sequestrectomy (34,35,43). In five studies, patients received an additional non-surgical treatment as a prespecified part of the study protocol (postoperative education, exercise, insoles, diet and pain medication (24,33); preoperative pain neuroscience education or biomedical education in combination with mobilization (27); preoperative neuromuscular training (29); or postoperative placebo or fentanyl pain medication (43)). Patients in the other studies underwent standard usual postoperative care rehabilitation (17,25,26,28,30–32,34–42).

Detailed information about the demographics, eligibility criteria, interventions and results can be found in Table 5.

AIM 1: Evolution of SPS signs after nociceptive targeted surgery in MSK disorders

Static QST - Pressure thresholds

Table 6, Supplementary Table 1, Table 7, and Supplementary Table 2 show the results of pain pressure and pain pressure tolerance threshold (PPT and PPTT). In total, 20 studies measured PPT (17,24–26,28–43) and five studies PPTT (25,36,41,43,44) using an algometer or tourniquet cuff. Five studies had a low (25,31,33,37,41), three studies a moderate (29,36,42), and 12 studies a high RoB (17,24,26,28,30,32,34,35,38–40,43). As a result, taking into account the criteria of Table 4, six studies received a level of evidence 1b (29,31,33,36,37,41), and the other 14 received a level 2b (17,24–26,28,30,32,34,35,38–40,42,43).

Follow-up < 3 months

Widespread PPT improved after total knee arthroplasty (TKA) (moderate conclusion) (42,44). Conflicting evidence for a change in PPT was found after total hip arthroplasty (THA) (38), TKA (only local PPT) (31,42,44), and sequestrectomy (34,43). Also for PPTT after sequestrectomy (34,35,43) conflicting evidence was obtained. No change of PPTT values after TKA surgery was seen (44) (weak conclusion).

Follow-up ≥ 3 months

PPT improved after sequestrectomy (34,35) (moderate conclusion), and PPTT after THA (25) (moderate conclusion). Conflicting evidence was found for the change of PPT after THA surgery (25,29,37,39,40), and after TKA (24,33,36,41,42,44). PPT remained unchanged after TKA (36,41,44) (strong conclusion), and after temporomandibular joint discectomy (26) (weak conclusion).

Table 5: Evidence table

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Aranda-Villalobos et al., 2013 (37) Prospective cohort study	Hip OA	N = 20 Age = 65y (41-83y) ♀ = 12 (60%) K&S not reported	-Severe pain (>6/10 on VAS) for >1y	-Previous hip surgery -Presence of other pain syndromes -Presence of physical/psychological limitation preventing testing -Mentally impaired	**O:** PPT **M:** Algometer (Pain Diagnosis and Treatment) **A:** Mean of 3 trials	Bilaterally: -Second metacarpal bone - m. Gluteus medius -m. Vastus medialis & lateralis -m. Tibialis anterior	THA	-3m after surgery -No losses	**Change in SPS signs:** PPT ↑ 3m after surgery on: - all measurement locations ($p<0.01$), except for Vastus Lateralis ($p>0.05$). Changes affected side > unaffected side (p value not given). Covariates age, sex and BMI did not influence the PPT ↑ ($p>0.05$).
Arendt-Nielsen et al., 2018 (24) RCT	Knee OA	N = 50 Age = 65.8y (8.7y) ♀ = 32 (64%) K&S 2: n = 7 K&S 3: n = 21 K&S 4: n = 22	-Referred to orthopaedic surgeon -Eligible for TKA -Diagnosed with knee OA (K&S≥ 1) -≥18y -KOOS ≤75	-Previous ipsilateral TKA -RA -Mean pain (>6/10 VAS) in previous week -Pregnancy -Inability to conform with protocol -Inadequacy in Danish	**O:** PPT **M:** Algometer (Somedic) **A:** Mean of 2 trials + mean of all PPTs on all locations	Bilaterally: -Peripatellar region -m. Tibialis anterior	-TKA -nonsurgical treatment: education, exercise, insoles, diet, and pain medication	-12m -4 losses	**Change in SPS signs:** PPT ↑ 12m after surgery on both locations.

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Bjurström et al., 2022 (25) Prospective cohort study	Disabling OA pain	N= 15 Age = 68.9y (56-77y) ♀ = 9 (60%) K&S not reported	-Age ≥ 18y -Persistent OA-related pain ≥ 12m -Average pain NRS score ≥ 4 and/or movement-related pain score ≥ 4 after 5min walking, spinal anaesthesia during THA	-Acute illness -Malignancy -Immunomodulating treatment -Neurological disorder -Severe psychiatric disorder -Contraindications for lumbar puncture -ASA physical status classification >3 -Substance abuse < 12m -Poor Swedish-language fluency -Inability to provide informed consent	**O1-O2:** PPT & PTT **M:** Digital algometer (SBMEDIC) **A:** Mean of 3 trials **O3-O4:** Punctate pain & temporal summation **M:** Monofilament **A:** O3 pain rating single stimulus, O4 VAS score 10th – 1st stimuli **O5:** CPM **M:** TS PPT, CS occlusion cuff **A:** PPT and cuff PPT during CS - without CS & (PPT with CS – PPT without CS)/PPT without CSx100	-Region of maximal pain around the hip -Corresponding contralateral side -Volar forearm **O5:** CS: cubital fossa	THA	-18m -Not reported	**Change in SPS signs:** -All PPT and PTT ↑ 18m after surgery ($p<0.05$). -Punctuate pain ↓ at the forearm 18m after surgery ($p=0.034$). -TS ↓ in contralateral hip 18m after surgery ($p=0.015$). Other results were non-significant ($p>0.05$).
Feldreich et al., 2017 (26) Prospective cohort study	Unilateral painful chronic closed lock of the TMJ	N = 18 Age: 18-72y ♀ = 18 (100%)	-Age > 18y -Planned for surgical treatment -Diagnosed with unilateral painful chronic closed lock of TMJ	-Generalized joint diseases	**-O1:** PPT **M:** Algometer (Somedic) **A:** Mean of 3 trials **-O2:** EDT & EPT **M:** PainMatcher **A:** Mean of 3 trials	Bilaterally: **O1:** -m. Masseter -Index finger **O2**: -Index finger	Discectomy	-6-24m -7 losses	**Change in SPS signs:** No changes over time for all SPS signs ($p>0.05$).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Graven-Nielsen et al., 2012 (44) Prospective cohort study	Bilateral or unilateral knee OA	N = 20 Age = 68y (48-86y) ♀ = 14 (70%) K&S not reported	-Severe pain (≥4/10 on VAS) >3m	-Other pain problems or sensory dysfunctions -Mentally impaired	**-O1:** PPT **M:** Algometer (Somedic) **A:** Mean of 2 or 3 trials **-O2:** Cuff PPT **M:** Double-chamber tourniquet cuff **A:** Not specified **-O3:** Spatial summation **M:** Double- and single chamber tourniquet cuff **A:** Ratio threshold double-chamber cuff/thresholds from single-chamber cuff **-O4:** CPM **M:** TS = PPT (algometer) and cuff PPT (tourniquet cuff) CS = Ischemic exercise of left arm with tourniquet cuff **A:** PPT and cuff PPT during CS - without CS	Bilaterally: **O1:** -Peripatellar region -m. Extensor carpi radialis longus -m. Tibialis anterior **O2-O3:** -m. Gastrocnemius/ m. Soleus **O4:** -TS: infrapatellar location -CS: ipsilateral upper arm	Knee replacement surgery (not specified total or unicondylar)	-5-28 w (60% reassessed 9-18 w) -Losses not reported	**Change in SPS signs:** -PPT ↑ after surgery ($p<0.04$) on all locations. -Cuff PPT ↑ after surgery in both legs ($p<0.006$) -Spatial summation ratio ↑ only on the affected leg 5-28w after surgery ($p<0.01$). -CPM improved 5-28w after surgery: higher ↑ in PPT values ($p<0.0001$) and cuff PPT values ($p=0.055$) with CS.

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Huysmans et al., 2021 (27) RCT	Chronic knee OA	N= 54 Age PNE group: 67.7y (7.8y) Age control group: 72.8y (5.6y) ♀ PNE group = 15 (68%) ♀ control group = 13 (59%) K&S 2: N= 12 K&S 3: N = 21 K&S 4: N= 11	-Chronic knee OA diagnosed according to the American College of Rheumatology classification criteria -Scheduled for TKA	-Other surgery affected knee < 6m -Chronic widespread pain -Neurological, metabolic or inflammatory comorbidities -Cognitive impairment -Illiteracy -Inability to speak or write Spanish	**O1:** CSI **M:** Questionnaire **A:** The higher the score, the more central sensitization	NA	TKA + preoperative PNE plus knee joint mobilization OR biomedical education plus knee joint mobilization	-Immediate after intervention, 1m, 3m -10 losses	**Change in SPS signs:** The CSI score ↓ after surgery ($p<0.001$, ES: 0.278) (over all 4 time points).
Izumi et al., 2017 (38) Prospective cohort study	Hip OA	N = 40 Age = 65y (45-81y) ♀ = 14 (50%)	-≥3m unilateral hip pain while walking with ≥4/10 on VAS -Bilateral hip OA if one hip was pain free (0/10 on VAS)	-Other ongoing pain problems -Past history of chronic pain condition -Sensory symptomatic dysfunctions -Mental illness	**-O1:** PPT **M:** Algometer (Somedic) **A:** Mean of 3 trials **-O2:** Cuff PPT **M:** Double-chamber tourniquet cuff **A:** Mean of 3 trials **-O3:** Temporal summation **M :** Tourniquet cuff **A:** Mean VAS score 10th stimuli – 1st stimuli	Bilaterally: **O1:** -m. Gluteus medius & maximus -m. Vastus lateralis -M. Tensor fascia latae -m. Tibialis anterior -m. Extensor carpi radialis longus **O2-O4:** -Thigh **O5-O9:** -Lateral hip	THA	-6 w -4 losses	**Change in SPS signs:** -PPT ↑ on all locations 6w after surgery ($p<0.01$). -Temporal summation ↓ in patients with pain relief ($p<0.002$), but not in patients without pain relief ($p>0.05$) 6w after surgery. -Spatial summation ↓ 6w after surgery ($p<0.002$).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Izumi et al., 2017 (38) Prospective cohort study **(continued)**					**-O4:** Spatial summation **M:** Single- and double chamber tourniquet cuff **A:** Ratio threshold double-chamber cuff/thresholds from single-chamber cuff **-O5:** Cutaneous pin-prick pain sensitivity **M:** Pinprick device **A:** 0-10 VAS score **-O6-O9:** CDT, WDT, HPT & CPT **M:** Contact thermode **A: N**ot specified **-O10:** CPM **M:** TS = PPT (algometer) and cuff PPT (tourniquet cuff) CS= tourniquet cuff **A:** PPT and cuff PPT during CS - without CS	**O10:** TS: see O1 and O2 CS: Biceps brachii contralateral arm			Other results were non-significant (p>0.05)

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Kadum et al., 2018 (28) Prospective cohort study	Primary shoulder OA	N = 70 Age = 71y (53-89y) ♀ = 31 (50%) Samilson and Prieto classification: OA grade 4	-Primary shoulder OA	-Secondary OA -Contralateral TSA -Previous fracture -Surgery involving the affected shoulder -Non-Swedish speaker	**O1:** EPT **M:** Pain Matcher unit (Medical) **A:** Mean of 2 trials	Bilaterally: -Hand	Stemless anatomical TSA	-3m and 6m -7 losses	**Change in SPS signs:** -EPT did not change 3 or 6m after surgery (p=0.09).
Kosek et al., 2000a (40) Prospective cohort study	Painful hip OA	N = 14 Age = 53y (29-66y) ♀ = 5 (36%)	-Radiological OA -Severe pain > 1y -Healthy apart from OA -No pain contralateral side	Not reported	**O1:** PPT **M:** Pressure algometer (Somedic) **A:** Mean of 2 trials **O2:** Light-touch DT **M:** Von Frey filaments **A:** Descending order until sensation disappeared **O3-O6:** WDT & CDT & HPT & CPT **M:** Thermode (Thermotest Somedic) **A:** Mean of last two perception levels	Most painful site + corresponding contralateral side: -Greater femoral trochanter (n= 11) -Buttock (n= 1) -Lateral part knee (n= 1) -Lateral part calf (n= 1) -Lateral (n= 7), frontal (n= 3), medial (n= 2), and dorsal (n= 1) part of the thigh -Groin (n= 7) -Dorsolateral part calf (n= 5) -Knee (n= 7) -Ankle (n= 2)	THA (n=10), osteotomy (n=2)	-6-24m (mean was 10m) -2 losses	**Change in SPS signs:** -PPT ↑ on the affected side 6-24m after surgery (p<0.05). -Light-touch DT ↓ on the affected side 6-24m after surgery (p<0.01). -WDT ↓ on the affected side 6-24m after surgery (p<0.05). Other results were non-significant (p>0.05).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Kosek et al., 2000b (39) Prospective cohort study	Painful hip OA	N= 15 Age: 52y (29-66y) ♀ = 6 (40%)	-Radiological OA -Severe pain > 1y -Considered for surgery -Healthy apart from OA	Not reported	**O1:** PPT **M:** Pressure algometer (Somedic) **A:** Mean of 2 trials **O2:** Light-touch DT **M:** Von Frey filaments **A:** Descending order until sensation disappeared **O3-O6:** WDT & CDT & HPT & CPT **M:** Thermode (Thermotest Somedic) **A:** Mean of last two perception levels + all QST reassessed during and after Tourniquet test	Most painful site + corresponding contralateral side: -Greater femoral trochanter (n= 11) -Buttock (n= 1) -Lateral part knee (n= 1) -Lateral part calf (n= 1) -Lateral (n= 7), frontal (n= 3), medial (n= 2), and dorsal (n= 1) part of the thigh -Groin (n= 7) -Dorsolateral part calf (n= 5) -Knee (n= 7) -Ankle (n= 2)	THA (n=11), osteotomy (n=2)	-6-24m (mean was 9m) -2 losses	**Change in SPS signs:** -PPT ↑ 6-24m after surgery ($p<0.001$), location not specified. -Light-touch DT ↓ 6-24m after surgery ($p<0.001$). -CDT ↓ 6-24m after surgery ($p<0.001$). Other results were non-significant ($p>0.05$).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Kosek et al., 2013 (29) Prospective cohort clinical trial study	Knee & hip OA	Total N= 134 Hip OA: N= 51 Knee OA: N= 83 Age hip OA= 67.1y (4.0y) Age knee OA= 68 (4.3y) ♀ = 42 (39%)	Primary OA	-Post-traumatic OA -Rheumatoid arthritis -Psoriatic arthritis -Severe heart failure -Neurological diseases -Congenital hip deformities -Morbitus perthes -THA or TKA in last 12m -Dementia -Non Swedish-speaking -Use of antidepressant, neuroleptics, anticonvulsive drugs or steroids	**O1-O3:** PPT, PP4, PP7 **M:** Pressure algometer (Somedic) **A:** Not reported **O4:** EIA **M:** PPT measured 5s after beginning and 30s during isometric contraction of knee extension (Pressure algometer, Somedic) **A:** Change in PPT during contraction	Bilaterally **O1-O3:** -m. Supraspinatus, -Lateral epicondyle elbow -m. Gluteus -Greater trochanter -Medial knee **O4:** -m. Quadriceps affected side -m. Deltoideus contralateral side	-THA, TKA -Preoperative individualized, goal based neuromuscular training	-3m -21 losses	**Change in SPS signs:** -PPTS (EIA) ↑ during contraction 3m after surgery at m. Quadriceps ($p<0.009$). Other results were non-significant ($p>0.05$).
Kurien et al., 2018 (41) Prospective cohort study	Chronic knee OA	N= 50 Age= 66.4y (8.3y) ♀ = 30 (60%)	Knee OA	-Associated symptomatic hip OA -Psychiatric illness -Active cancer -Sensory dysfunction -Contraindication to MRI -Other chronic pain condition (fibromyalgia, rheumatoid arthritis)	**O1:** PPT **M:** Pressure algometer (Somedic) **A:** Mean of 3 trials **O2-O3:** Cuff PPT & PTT **M:** Single chamber tourniquet cuff **A:** Not reported	**O1:** -Medial, superior and lateral of patella of affected knee -m. Tibialis anterior -m. Extensor carpi radialis longus	TKA	-6m -4 losses	**Change in SPS signs:** -PPT ↑ 6m after surgery at the knee ($p=0.02$). -Temporal summation with cuff and Von Frey ↓ 6m after surgery ($p=0.004$).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Kurien et al., 2018 (41) Prospective cohort study **(continued)**					**O4:** Temporal summation **M:** Single chamber tourniquet cuff **A:** VAS score mean 8th to 10th stimuli – mean 1st to 4th stimuli **O5:** Temporal summation **M:** Von Frey stimulator **A:** VAS score 10th – 1st stimulus **O6:** CPM **M:** TS= cuff PPT affected side, CS= cuff PPT contralateral leg **A:** PPT during CS – PPT without CS	**O2-O4:** -m. Gastrocnemius affected side **O5:** -Affected knee **O6:** -m. Gastrocnemius bilaterally			Other results were non-significant (p>0.05).
Larsen et al., 2021 (30) Prospective cohort study	Knee OA	N= 185 Age= 68.8y (8.92y) ♀ = 103 (56%)	Knee OA	-Use of gabapentinoids, glucocorticoids, opioids, anxiolytics, anti-epileptics, antidepressants -Alcohol abuse -Other pain treatments outside standard care -Malignant conditions -Pregnanc	**O1:** Cuff PPT **M:** Cuff algometer (Cortex Technology) **A:** One trial **O2:** CPM **M:** TS cuff PPT affected side, CS contralateral leg (Tourniquet cuff) **A:** PPT with CS – PPT without CS	**Bilaterally:** -m. Gastrocnemius	Unilateral TKA	-12m -54 losses	**Change in SPS signs:** No change was seen 12m after surgery (p>0.05).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Larsen et al., 2021 (30) Prospective cohort study **(continued)**				-BMI >40kg/m2 -Affected by other peripheral or central-acting disease -Allergy toward chlorzoxazone -Preoperative complications -Liver disease					
Lewis et al., 2018 (31) Prospective cohort study	End-stage knee OA	N= 29 Age= 68y (10y) ♀ = 14 (50%)	-VAS 3/10 on ≥ 3 days per w during past m -Scheduled for TKA during next m	-Contraindications to MRI -Neurological conditions -Inability to communicate in English	**O1:** PPT **M:** Pressure algometer (Somedic) **A:** Not reported **O2:** Temporal summation **M:** Von Frey filament **A:** VAS score 10th – 1st stimulus + TS presentation = difference ≥ 1 **O3:** CPM **M:** TS PPT affected side, CS cold water immersion **A:** PPT with CS – PPT without CS + impaired CPM = increase of PPT during CS < 10%	**O1-O3:** Medial knee **O3** CS: contralateral hand	TKA	-3w, 6m -0 losses	**Change in SPS signs:** -Temporal summation score (p=0.007) and the presence of temporal summation (p<0.001) ↓ 3w and 6m after surgery. -CPM change score ↑ (p=0.033) and presence of impaired CPM (p=0.02) ↓ 3w and 6m after surgery. Other results were non-significant (p>0.05).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Martinez et al., 2007 (32) Prospective cohort study	Knee OA	N= 20 Age= 69y (2y) ♀ = 19 (95%)	-TKA indicated because of knee OA	-Previous surgery/trauma of the knee -Preoperative use of opioids -Mental disorders preventing an accurate understanding of tests	**O1:** Mechanical punctuate stimuli pain threshold **M:** Von Frey hairs (Bioseb) **A:** Not reported **O2-O3:** HPT & CPT **M:** Thermotest (Somedic) **A:** Mean of 3 trals **O3:** Suprathreshold cold & warmth **M:** Thermotest (Somedic) **A:** Not reported **O4:** Dynamic pain **M:** Paintbrush **A:** Painful or not	**O1-O3:** -Patella affected knee -Patella contralateral knee -Right hand **O4:** 5cm above incision affected knee	TKA	-1day, 4 days, 1m and 4m -Not reported	**Change in SPS signs:** -Mechanical and CPT ↓ at affected knee day 1 and 4 after surgery. Other results were non-significant (p>0.05).
Petersen et al., 2015 (42) Prospective cohort study	Severe knee OA	N= 78 Age (group VAS <3): 68y (47y-86y) Age (group VAS≥3) : 72y (56y-86y) ♀ = 46 (59%) K&S: 3 or 4	-Severe knee OA -Scheduled for TKA surgery -OA defined following the American College of Rheumatology classification criteria	-Previously diagnosed rheumatoid arthritis or fibromyalgia -Fractured knee -Presence of other pain problems -Sensory dysfunction -Mental impairment	**O1:** PPT **M:** Pressure algometer **A:** Not reported	Bilaterally: -Peripatellar region -m. Tibialis anterior -m. Extensor Carpi radialis	TKA	-2m, 12m -Not reported	**Change in SPS signs:** PPT ↑ on all locations except for the m. Extensor carpi radialis longus in the low pain group 2 and 12m after surgery (p<0.05).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Petersen et al., 2015 (42) Prospective cohort study **(continued)**									PPT ↑ only at the m. Extensor carpi radialis in the high pain group 2 and 12m after surgery (p=0.049). Other results were non-significant (p>0.05)
Skou et al., 2016 (33) RCT	Radiographic and symptomatic knee OA	N= 50 Age= 65.8y (8.7y) ♀ = 32 (64%) K&S 2: n= 7 K&S 3: n= 21 K&S 4: n = 22	K&S ≥ 2	-Previous TKA on affected side -Need for bilateral simultaneous TKA -Mean knee pain intensity > 60 mm on 100 mm VAS -Recurrent disc herniation	**O:** PPT **M:** Algometer (Somedic) **A:** Mean of 2 trials + mean of all PPTs on all locations	Bilaterally: -Peripatellar region -m. Tibialis anterior	-TKA -Nonsurgical treatment: education, exercise, insoles, diet, and pain medication	-3m -9 losses	**Change in SPS signs:** PPT ↑ 3m after surgery.
Tschugg et al., 2016 (34) Prospective cohort study	Single level lumbar disc herniation	N= 52 Age= 44.3y (10y) ♀ not given	-Single level lumbar disc herniation (MRI) -sensory dysfunction in the corresponding nerve root distribution of L3 to S1	Recurrent disc herniation	**O1:** PPT **M:** Pressure gauge device (Wagner) **A** : Not reported **O2:** MDT **M:** Von Frey hairs **A:** Not reported **O3:** Pinprick pain threshold **M:** Pinprick **A:** Not reported	A test and control side (not specified)	Sequestrectomy	-1w, 6m, 12m -16 losses	**Change in SPS signs:** -PPT ↑ 12m after surgery (p<0.005). -MDT and VDT ↓ 1w after surgery (p<0.001). -MDT ↓ 12m after surgery (p<0.005)

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Tschugg et al., 2016 (34) Prospective cohort study **(continued)**			-Indication for sequestrectomy according guidelines DGNC, DGOOC -No previous back surgery -No metabolic, peripheral nervous system disorders		**O4-O7:** CDT, WDT, CPT & HPT **M:** Sensory Analyser TSA-II (Medoc) **A**: Not reported **O8:** VDT **M:** Rydel-Seifer tuning fork **A:** Not reported				-Pinprick pain threshold ↑ 12m after surgery (p value not given). -CDT ↑ 6m ($p<0.05$) and 12m ($p<0.005$) after surgery.
Tschugg et al., 2017 (35) Prospective cohort study	Single level lumbar disc herniation	N= 52 Age not reported ♀ = 21 (40%)	-Single level lumbar disc herniation (MRI) -sensory dysfunction in the corresponding nerve root distribution of L3 to S1 -Indication for sequestrectomy according guidelines DGNC, DGOOC -No previous back surgery -No metabolic, peripheral nervous system disorders	Recurrent disc herniation	**O1:** PPT **M:** Pressure gauge device (Wagner) **A**: Not reported **O2:** MDT **M:** Von Frey hairs **A:** Not reported **O3:** Pinprick pain threshold **M:** Pinprick **A:** Not reported **O4-O7:** CDT, WDT, CPT & HPT **M:** Sensory Analyser TSA-II (Medoc) **A**: Not reported **O8:** VDT **M:** Rydel-Seifer tuning fork **A:** Not reported	Not reported	Sequestrectomy	-12m -14 losses	**Change in SPS signs:** -PPT and pinprick pain threshold ↑ 12m after surgery ($p<0.005$). -CDT ↑ and MDT ↓ 12m after surgery ($p<0.005$). -PPT, pinprick pain threshold, CDT, MDT and VDT improved in sensory function restoration group ($p<0.05$). -Pinprick pain threshold, MDT and CDT improved in disturbed sensory function group ($p<0.05$).

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Vaegter et al., 2017 (36) Prospective cohort study	Knee OA	N= 15 Age= 66.3y (5.9y) ♀ = 7 (47%)	-Scheduled for unilateral TKA -K&S ≥2 -Able to use a stationary bicycle	-Neurological, psychiatric or cardiovascular disease	**O1:** PPT **M:** Pressure algometry (Somedic) **A:** Mean of 2 trials **O2-O3:** Cuff PPT and PTT **M:** Tourniquet cuff (NociTech) **A:** Not reported **O4:** CPM **M:** CPT **A:** PPT with CS – PPT without CS **O5:** EIH **M:** aerobic bicycling + isometric muscle + measuring PPTs contraction **A:** Change in PPT	**O1:** -m. Quadriceps affected side -m. Quadriceps non-affected side -m. Biceps brachii dominant side -m. Upper trapezius non-dominant side **O2-O3:** Upper leg **O4:** Foot non-affected leg	TKA	-6m -1 loss	**Change in SPS signs:** -PPT ↑ 6m after surgery at m. Quadriceps and m. Biceps brachii of the affected side (p=0.006, ES: 0.29) Other results were non-significant (p>0.05)
Wilder-Smith et al., 1996 (43) Prospective cohort study	Disc herniation	N= 30 Age (fentanyl): 44.1y (27-62y) Age (placebo): 47.8 (24-64y) ♀ = 8 (27%)	Not reported	Not reported	**O1-O3:** Sensation DT, PPT & PTT M: Constant skin current stimulation	Dermatome most affected by disc prolapse (flanks, ipsi- and contralateral of incision) + arm	Elective herniated intervertebral disc surgery + placebo or fentanyl	-1h, 2h, 4h, 6h, 24h, 5 days -Not reported	**Change in SPS signs:** -PTT ↓ at the arm in the placebo group 5 days after surgery (p<0.05). -PTT ↑ contralateral of the incision in the fenatyl group 4h

Table 5 (continued)

Author, year & study design	Participants				Outcome, measurement method and analysis of central SPS sign	Measurement location	Type of surgery + additional treatment in study (if performed)	FU + losses to FU	Results (change in SPS signs after surgery)
	MSK disorder	Study sample and characteristics	Inclusion criteria	Exclusion criteria					
Wilder-Smith et al., 1996 (43) Prospective cohort study **(continued)**									after surgery ($p<0.05$). -PTT ↑ in the dermatome region in both groups 4h after surgery ($p<0.05$) and also in the placebo group 6h after surgery ($p<0.05$).

Abbreviations: MSK, musculoskeletal; SPS, somatosensory processing system; FU, follow-up period; OA, osteoarthritis; N, number; y, years old; K&S, Kellgren & Lawrence scale; VAS, Visual Analogue Scale; O, outcome; M, measurement method; A, analysis; PPT, pressure pain thresholds; m., musculus; RCT, randomised controlled trial; TKA, total knee arthroplasty; KOOS, Knee Osteoarthritis Injury and Outcome Score; RA, rheumatoid arthritis; min, minutes; TMJ, temporomandibular joint; EDT, electrical detection threshold; EPT, electrical pain threshold; CPM, conditioned pain modulation; TS, test stimulus; CS, conditioning stimulus; PTT, pain tolerance threshold; TDT, thermal detection threshold; TPT, thermal pain threshold; THA, total hip arthroplasty; CDT, cold detection threshold; WDT, warmth detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; m, month; DT, detection threshold; PP4, pressure pain threshold corresponding to 4/10; PP7, pressure pain threshold corresponding to 7/10; EIA, exercise induced analgesia; s, seconds; PCS, pain catastrophizing scale; MRI, magnetic resonance imaging; ASA, American Society of Anaesthesiology; CSI, Central Sensitization Inventory; w, weeks; DGNC, German Society of Neurosurgery; DGOOC, German Society of Orthopedics and Orthopedic Surgery; MDT, mechanical detection threshold; VDT, vibration detection threshold; VRS, verbal rating score

Static QST - Thermal thresholds

Table 6, Supplementary Table 3, Table 7, and Supplementary Table 4 show the results of the cold- and warmth detection threshold (CDT and WDT), cold- and heat pain threshold (CPT and HPT), and cold- and warmth suprathreshold. Five studies measured CDT and WDT (34,35,38–40), and six studies HPT and CPT (32,34,35,38–40) by using thermodes of which all studies scored a high RoB and as such a level of evidence 2b (32,34,35,38–40). One study with a high RoB and level of evidence 2b measured warmth and cold suprathreshold by using thermodes (32).

Follow-up < 3 months

No change of all thermal thresholds was seen after THA (38) and sequestrectomy (34). Also HPT, widespread CPT, and warmth- and cold suprathreshold remained unchanged after TKA, but local CPT worsened after TKA (32) (all weak conclusion).

Follow-up ≥ 3 months

A positive change of CDT after sequestrectomy was seen (34,35) (moderate conclusion). Conflicting evidence for CDT and WDT was obtained after THA (39,40). Following SPS signs remained unchanged after surgery: HPT and CPT after THA (39,40) (moderate conclusion); HPT, CPT, warmth- and cold suprathreshold after TKA (weak conclusion); and WDT, HPT, and CPT after sequestrectomy (34,35) (moderate conclusion).

Static QST – Other thresholds

Table 6, Supplementary Table 3, Table 7, and Supplementary Table 5 show the results of the pinprick threshold, electrical detection and pain threshold (EDT and EPT), vibration detection threshold (VDT), and light-touch detection threshold. Pinprick pain threshold was measured in five studies with a pinprick (25,32,34,35,38); EDT was measured in one study (26), and EPT in two studies with a painmatcher (26,28); VDT was measured in two studies with a tuning fork (34,35); and five studies measured the light-touch detection threshold with Von Frey hairs (34,35,39,40,43). Only one study scored a low (25), and all the other studies scored a high RoB (26,28,32,34,35,38–40,43). All studies received a level of evidence 2b (25,26,28,32,34,35,38–40,43).

Follow-up < 3 months. VDT improved after sequestrectomy (34,43) (weak evidence). Conflicting evidence was found for a change of light-touch detection threshold after sequestrectomy (34,43). No change was seen for pinprick pain threshold after THA (38) and sequestrectomy (34,43) and also EPT did not change after total shoulder arthroplasty (TSA) (28) (all weak conclusion). Pinprick pain threshold worsened after TKA (32) (weak conclusion).

Follow-up ≥ 3 months. A positive change for widespread pinprick pain threshold and light-detection threshold was reported after THA (25) and sequestrectomy (34,35) (both moderate conclusion). Conflicting evidence was found for VDT after sequestrectomy (34,35). Finally, following SPS signs remained unchanged: pinprick threshold after TKA (32), local pinprick threshold after THA (25), EDT after temporomandibular joint discectomy (26), EPT after temporomandibular joint discectomy (26) and TSA (28) (all weak conclusion).

Table 6: Quality assessment

Study	1	2	3	4	5	6	Overall RoB	LoE
Aranda-Villalobos et al., 2013 (37)	Low	Low	Low	Low	Low	Moderate	**Low**	1b
Arendt-Nielsen et al., 2018 (24)	Low	High	Low	Low	Low	Low	**High**	2b
Bjurström et al., 2022 (25)	Low	Low	Low	Moderate	N/A	Low	**Low**	2b
Feldreich et al., 2017 (26)	High	High	Moderate	Moderate	N/A	Low	**High**	2b
Graven-Nielsen et al., 2012 (44)	High	High	Low	Moderate	N/A	Moderate	**High**	2b
Huysmans et al., 2021 (27)	Low	High	Low	Low	Low	Low	**High**	2b
Izumi et al., 2017 (38)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Kadum et al., 2018 (28)	Low	High	Low	Moderate	Low	Low	**High**	2b
Kosek et al., 2000a (40)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Kosek et al., 2000b (39)	Moderate	High	Low	Moderate	N/A	Moderate	**High**	2b
Kosek et al., 2013 (29)	Low	Low	Low	Moderate	Low	Moderate	**Moderate**	1b
Kurien et al., 2018 (41)	Low	Moderate	Low	Low	N/A	Low	**Low**	1b
Larsen et al., 2021 (30)	Low	High	Low	Low	High	Low	**High**	2b
Lewis et al., 2018 (31)	Low	Low	Low	Moderate	N/A	Low	**Low**	1b
Martinez et al., 2007 (32)	High	High	Low	Moderate	N/A	Low	**High**	2b
Petersen et al., 2015 (42)	Moderate	Low	Low	Moderate	N/A	Low	**Moderate**	2b
Skou et al., 2016 (33)	Low	Moderate	Low	Low	Low	Low	**Low**	1b
Tschugg et al., 2016 (34)	High	High	Low	Moderate	N/A	Low	**High**	2b
Tschugg et al., 2017 (35)	High	High	Low	Moderate	N/A	Low	**High**	2b
Vaegter et al., 2017 (36)	Moderate	Moderate	Low	Low	N/A	Low	**Moderate**	1b
Wilder-Smith et al., 1996 (43)	High	High	Low	Moderate	N/A	Low	**High**	2b

Bias due to 1 = Study participation, 2 = Study attrition, 3 = Prognostic factor measurement, 4 = Outcome measurement, 5 = Study confounding, 6= Statistical analysis and reporting. Abbreviations: RoB, risk of bias; LoE, level of evidence; N/A, not applicable

Table 7: Overview of evolution of static QST after surgery in MSK disorders

Static QST	Overall level of recommendation (references of studies)									
	Hip OA		Knee OA		Shoulder OA		Closed lock TMJ		Disc herniation	
	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m
PPT ***(positive change means increased PPT)***	Conflicting (38)	Conflicting (25,29,37,39,40)	Local = conflicting (31,42,44) Widespread = moderate for + change (42,44)	Conflicting (24,29–31,33,36,41,42,44)	/	/	/	Weak for no change (26)	Conflicting (34,43)	Moderate for + change (34,35)
PTT	/	Moderate for + change (25)	Weak for no change (44)	Strong for no change (36,41,44)	/	/	/	/	Conflicting (43)	/
CDT	Weak for no change (38)	Conflicting (39,40)	/	/	/	/	/	/	Weak for no change (34)	Moderate for + change (34,35)
WDT	Weak for no change (38)	Conflicting (39,40)	/	/	/	/	/	/	Weak for no change (34)	Moderate for no change (34,35)
HPT	Weak for no change (38)	Moderate for no change (39,40)	Weak for no change (32)	Weak for no change (32)	/	/	/	/	Weak for no change (34)	Moderate for no change (34,35)
CPT	Weak for no change (38)	Moderate for no change (39,40)	Local = weak for – change (32) Widespread = weak for no change (32)	Weak for no change (32)	/	/	/	/	Weak for no change (34)	Moderate for no change (34,35)
Warmth suprathreshold	/	/	Weak for no change (32)	Weak for no change (32)	/	/	/	/	/	/
Cold suprathreshold	/	/	Weak for no change (32)	Weak for no change (32)	/	/	/	/	/	/
Pinprick pain threshold	Weak for no change (38)	Local = moderate for no change (25) Widespread = moderate for + change (25)	Weak for - change (32)	Weak for no change (32)	/	/	/	/	Weak for no change (34)	Moderate for + change (34,35)

Table 7 (continued)

Static QST	Overall level of recommendation (references of studies)									
	Hip OA		Knee OA		Shoulder OA		Closed lock TMJ		Disc herniation	
	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m
EDT	/	/	/	/	/	/	/	Weak for no change (26)	/	/
EPT	/	/	/	/	Weak for no change (28)	Weak for no change (28)	/	Weak for no change (26)	/	/
VDT	/	/	/	/	/	/	/	/	Weak for + change (34)	Conflicting (34,35)
Light-touch detection threshold	/	Moderate for + change (39,40)	/	/	/	/	/	/	Conflicting (34,43)	Moderate for + change (34,35)

Abbreviations: QST, quantitative sensory testing; MSK, musculoskeletal; PPT, pressure pain threshold; PTT, pressure pain tolerance threshold; CDT, cold detection threshold; WDT, warmth detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; OA, osteoarthritis; m, month; OA, osteoarthritis; +, positive (*means improvement of SPS sign*); -, negative (*means worsening of SPS sign*); FU, follow-up. Colors: green = positive change, red = negative change, yellow = conflicting, blue = no change

Dynamic QST

Table 6, Supplementary Table 6, Table 8, and Supplementary Table 7 show the results regarding dynamic QST. Temporal summation was measured in four studies with a tourniquet cuff or monofilament (25,31,38,41); spatial summation in two studies with a tourniquet cuff (38,44); and CPM in seven studies, using a test stimulus including (cuff) PPT (17,25,30,31,36,38,41), and a conditioning stimulus including an occlusion or tourniquet cuff (25,30,36,38,41), ischemic exercise (17), or cold water immersion (31). Three studies scored a low (25,31,41), one study a moderate (36), and three studies a high RoB (30,38,44). As a result, three studies received a level of evidence 1b (31,36,41), and two a level of evidence 2b (25,30,38,44).

Follow-up < 3 months

Temporal and spatial summation improved after THA (38) (weak conclusion) and TKA (31,44) (moderate conclusion for temporal summation, weak for spatial summation). An improvement of CPM was seen after TKA (31,44) (moderate conclusion), but not after THA (38) (weak conclusion).

Follow-up ≥ 3 months

Temporal summation improved after THA (25) (moderate conclusion) and TKA (31,41) (strong conclusion), and also spatial summation improved after TKA (17) (weak conclusion). Conflicting evidence for a change of CPM after TKA was found (30,31,36,41,44), while no change was seen after THA (25) (moderate conclusion).

Other SPS signs

Table 6, Supplementary Table 6, Table 8, and Supplementary Table 8 show the results of the remaining SPS signs. Other signs of SPS were measured via exercise induced analgesia, measured in two studies with a moderate RoB and level of evidence 1b (29,36); tactile allodynia/dynamic pain (whether the stimulus was considered painful or not), measured in one study with a paintbrush, scoring a high RoB and level of evidence 2b (32); and via the CSI (self-reported signs), used in only one study with a high RoB and level of evidence 2b (27).

Follow-up < 3 months

The CSI score improved after TKA (27) (weak conclusion), but dynamic pain remained stable (32) (weak conclusion).

Follow-up ≥ 3 months

CSI score improved after TKA (27) (weak conclusion). In addition, exercise induced analgesia improved after THA (29) (weak conclusion), but conflicting evidence was found after TKA (36). No change was seen in dynamic pain after TKA (32) (weak conclusion).

Table 8: Evolution of dynamic QST and other SPS signs after surgery in MSK disorders

Dynamic QST and other SPS signs	Overall level of recommendation (references of studies)			
	Hip OA		Knee OA	
	FU < 3m	FU ≥ 3m	FU < 3m	FU ≥ 3m
Temporal summation	Weak for + change (38)	Moderate for + change (25)	Moderate for + change (31)	Strong for + change (31,41)
Spatial summation	Weak for + change (38)	/	Weak for + change (44)	Weak for + change (44)
CPM	Weak for no change (38)	Moderate for no change (25)	Moderate for + change (31,44)	Conflicting (30,31,36,41,44)
CSI	/	/	Weak for + change (27)	Weak for + change (27)
EIA	/	Weak for + change (29)	/	Conflicting (29,36)
Dynamic pain	/	/	Weak for no change (32)	Weak for no change (32)

Abbreviations: QST, quantitative sensory testing; SPS, somatosensory processing system; MSK, musculoskeletal; CPM, conditioned pain modulation; CSI, central sensitization index; EIA, exercise induced analgesia; OA, osteoarthritis; m, month; OA, osteoarthritis; +, positive (*means improvement of SPS sign*); -, negative (*means worsening of SPS sign*); FU, follow-up. Colors: green = positive change, red = negative change, yellow = conflicting, blue = no change

AIM 2: Predictors to change in SPS signs over time and SPS signs as predictors for surgical outcome

Detailed results can be found in table 9, table 10 and table 11. Only 10 studies reported any kind of predictors for the normalization or stability over time of the SPS signs in the form of a prediction model (linear regression) (24,25,38), interaction effect (30), correlation (24–26,36,37), or difference between groups (27,41,42) (e.g., a group with high and low preoperative pain, men vs. women, etc.). Only 4 studies reported an SPS change-related predictor for the improvement of pain after surgery in the form of a correlation (25,26,36,37) and will be discussed further on. In 7 other studies, SPS-related predictors for postsurgical outcome were reported, but restricted to pre- or postoperative SPS signs (28,30,32,35,38,41,42). However, results of these studies will not be reported in the text (are only available in table 9), because studies that only report preoperative SPS signs, or only postoperative SPS signs in relation to chronic pain/poor surgery are not included in the review (out of the scope of this review).

Static QST – Pressure thresholds

An improvement of pain-related variables over time (24,26,37) and lower baseline PPT (24) predicted an improvement of PPT over time (moderate and weak conclusion, respectively). Conflicting evidence was found for a change in inflammatory variables over time to predict a change of PPT or PPTT over time (25), and baseline pain-related variables over time did not predict a change of PPT or PPTT over time (24) (weak conclusion).

Static QST – Other thresholds

A change in pain-related variable (26) and in inflammatory factors (25) over time did not predict a change of EPT, EDT (26) and punctuate pain (25) over time (all weak conclusion).

Table 9: Predictors to change in SPS signs over time and SPS signs related predictors for surgical outcome

Author, year	MSK disorder	Surgical outcome in relation to SPS sign	FU period	Method	Predictor change in SPS sign	Predictor surgical outcome (PROM) in relation to SPS sign
Aranda-Villalobos et al., 2013 (37)	Hip OA	VAS pain in rest in relation to PPT	3m	Correlation - Δ VAS to predict Δ PPT - Δ PPT to predict Δ VAS	↓ in VAS = ↑ PPT for: - Second metacarpal bone (r= -0.353, p= 0.028) - m. Gluteus medius (r= -0.351, p= 0.002) - m. Vastus medialis (r= -0.394, p= 0.013) TA not reported	↑ PPT for: - Second metacarpal bone (r= -0.353, p= 0.028) - m. Gluteus medius (r= -0.351, p= 0.002) - m. Vastus medialis (r= -0.394, p= 0.013) = ↓ in VAS TA not reported
Arendt-Nielsen et al., 2018 (24)	Knee OA	VAS pain peak, VAS pain 30min walking, Number of body sites with pain in relation to PPT	12m	Linear regression - Baseline PPT to predict Δ PPT and Δ VAS pain rest and walking	- Averaged lower baseline PPT values = higher ↑ PPT after adjustment for age, sex and BMI (affected side: r^2=0.141, p=0.02; unaffected side: r^2=0.161, p=0.01) ➔ But still lowest 12m PPTs both affected (r= 0.73, p< 0.001) and non-affected side (r= 0.73, p< 0.001).	- Averaged lower baseline PPT = less ↓ VAS after 30min (affected side: r^2= 0.110, p= 0.02; unaffected side: r^2= 0.090, p= 0.04) No predictor for peak pain VAS
				Correlation - Δ VAS pain in rest and walking to predict Δ PPT - Δ PPT to predict Δ VAS pain in rest and walking	- ↓ in VAS peak pain intensity (affected and non-affected side: r= 0.20, p= 0.01) - ↓ VAS after 30min walking (affected side: r= 0.23, p= 0.01; non-affected side: r= 0.17, p= 0.04) - ↓ number of body sites with pain (affected side: r= 0.14, p = 0.09; non-affected side: r= 0.16, p= 0.045) = ↑ PPT affected and non-affected side	↑ PPT affected and non-affected side = - ↓ in VAS peak pain intensity (affected and non-affected side: r= 0.20, p= 0.01) - ↓ VAS after 30min walking (affected side: r= 0.23, p= 0.01; non-affected side: r= 0.17, p= 0.04) - ↓ number of body sites with pain (affected side: r= 0.14, p = 0.09; non-affected side: r= 0.16, p= 0.045)
Bjurström et al., 2022 (25)	Hip OA	/ Only inflammatory factors in relation to PPT, PTT, Punctate pain, Temporal summation, CPM	18m	Linear regression - ΔIL-8, ΔIP-10, ΔFlt, ΔMCP-1 to predict Δ PPT, PTT, Punctate pain, Temporal summation, CPM	- ↓ IL-8 (r^2= 0.38, p= 0.01) and ↑ IP-10 (r^2= 0.46, p= 0.006) = ↑ all PTT - Higher ↑ IP-10 = ↑ arm PPT scores above median (p= 0.028) Other results were non-significant (p> 0.05).	/

Table 9 (continued)

Author, year	MSK disorder	Surgical outcome in relation to SPS sign	FU period	Method	Predictor change in SPS sign	Predictor surgical outcome (PROM) in relation to SPS sign
Bjurström et al., 2022 (25) **(continued)**				Correlation - ΔIL-8, ΔIP-10, ΔFlt, ΔMCP-1 to predict Δ PPT, PTT, Punctate pain, Temporal summation, CPM	- ↓ Flt-1 = ↑ temporal summation most painful area (r= -0.560, p= 0.030) - ↑ IP-10 = improved CPM (r= -0.621, p= 0.013) Other results were non-significant (p> 0.05). -	
Feldreich et al., 2017 (26)	Closed lock TMJ	NRS pain in relation to PPT, EDT, EPT	6-24m	Correlation - ΔNRS to predict ΔPPT, EDT and EPT - ΔPPT, EDT and EPT to predict ΔNRS	- ↓ NRS = ↑ PPT contralateral index finger (r= -0.68, p=0.02). Other results were non-significant (p> 0.05).	- ↑ PPT contralateral index finger = ↓ NRS (r= -0.68, p=0.02). Other results were non-significant (p> 0.05).
Graven-Nielsen et al., 2012 (44)	Knee OA	/ Only evolution in PPT, Cuff PPT, Spatial summation, CPM	5-28w	/	/	/
Huysmans et al., 2021 (27)	Knee OA	/ Only sex in relation to CSI	Immediate, 1m and 3m postop	Linear mixed model - Difference in sex to predict ΔCSI	Sex (being a women) = ↓ CSI (ES of 0.600 in the PNE group, versus 0.074 in the control group (over all 4 time points), p= 0.010) compared to men.	/
Izumi et al., 2017 (38)	Hip OA	VAS pain in rest and after walking in relation to PPT, Cuff PPT, Temporal summation, Spatial summation, Cutaneous pin-prick pain sensitivity, CDT, WDT, HPT, CPT, CPM	6w	Correlation - Baseline QST to predict postoperative VAS pain in rest and walking	/	Examined, but results were non-significant (p> 0.05).
Kadum et al., 2018 (28)	Shoulder OA	QuickDASH in relation to EPT	12m	Correlation & linear regression Baseline EPT to predict postoperative QuickDASH	/	Higher baseline EPT = lower postoperative QuickDASH (affected side: r=-0.80, p< 0.001; r^2= -2.20, p= 0.0001; non-affected side: r= -0.40, p= 0.02; r^2 = non-significant (p>0 .05))

Table 9 (continued)

Author, year	MSK disorder	Surgical outcome in relation to SPS sign	FU period	Method	Predictor change in SPS sign	Predictor surgical outcome (PROM) in relation to SPS sign
Kosek et al., 2000a (40)	Hip OA	/ Only evolution of PPT, Light-touch DT, WDT, CDT, HPT, CPT	6-24m	/	/	/
Kosek et al., 2000b (39)	Hip OA	/ Only evolution of PPT, Light-touch DT, WDT, CDT, HPT, CPT	6-24m	/	/	/
Kosek et al., 2013 (29)	Knee & hip OA	/ Only evolution of PPT, PP4, PP7, EIA	3m	/	/	/
Kurien et al., 2018 (41)	Knee OA	VAS pain in rest in relation to PPT, Cuff PPT & PTT, Temporal summation, CPM	6m	Paired T-test - Difference in high- and low baseline PainDETECT groups to predict Δ in PPT, Cuff PPT & PTT, Temporal summation, CPM	Examined, but results were non-significant (p> 0.05).	/
				Correlation - Baseline PPT, Cuff PPT & PTT, Temporal summation, CPM to predict postoperative VAS	/	- Higher baseline temporal summation = higher postoperative VAS (r= 0.343, p = 0.010) - Other results were non-significant (p>0.05)
Larsen et al., 2021 (30)	Knee OA	VAS pain in rest in relation to CPM	12m	Correlation - Baseline CPM to predict postoperative VAS	/	- Baseline inefficient CPM = higher postoperative VAS (r= -0.18, p= 0.04)
				Linear regression - Baseline CPM to predict postoperative VAS	/	Examined, but baseline CPM was no independent factor for postoperative VAS (p> 0.05)
				Mixed-effects - Baseline CPM to predict ΔVAS - Preoperative PCS to predict ΔCPM	Examined, but results were non-significant (p> 0.05).	Examined, but results were non-significant (p> 0.05).

Table 9 (continued)

Author, year	MSK disorder	Surgical outcome in relation to SPS sign	FU period	Method	Predictor change in SPS sign	Predictor surgical outcome (PROM) in relation to SPS sign
Lewis et al., 2018 (31)	Knee OA	/ Only evolution of PPT, Temporal summation, CPM	3w, 6m	/	/	/
Martinez et al., 2007 (32)	Knee OA	VAS in rest and after walking in relation to Mechanical punctuate stimuli pain threshold, HPT, CPT, Suprathreshold cold & warmth, Dynamic pain	1day, 4 days, 1m and 4m	Correlation - Preoperative QST to predict postoperative pain	/	Examined, but results were non-significant (p> 0.05).
Petersen et al., 2015 (42)	Knee OA	VAS 24h in relation to PPT, Temporal summation, CPM	2m, 12m	Mixed-model ANOVA - Difference between baseline low- and high VAS pain group to predict ΔPPT	Examined, but results were non-significant (p> 0.05).	/
				Correlation - Baseline PPT, temporal summation and CPM to predict postoperative VAS	/	- Higher baseline temporal summation = higher postoperative VAS (r= 0.240, p= 0.037) Other results were non-significant (p> 0.05).
				Logistic regression - Baseline PPT, temporal summation and CPM to predict postoperative VAS	/	Examined, but results were non-significant (p> 0.05).
Skou et al., 2016 (33)	Knee OA	/ Only evolution of PPT	3m	/	/	/
Tschugg et al., 2016 (34)	Lumbar disc herniation	/ Only evolution of PPT, MDT, Pinprick pain threshold, CDT, WDT, CPT, HPT, VDT	1w, 6m, 12m	/	/	/

Table 9 (continued)

Author, year	MSK disorder	Surgical outcome in relation to SPS sign	FU period	Method	Predictor change in SPS sign	Predictor surgical outcome (PROM) in relation to SPS sign
Tschugg et al., 2017 (35)	Lumbar disc herniation	NRS pain in relation to PPT, MDT, Pinprick pain threshold, CDT, WDT, CPT, HPT, VDT	12m	Correlation - Postoperative QST to predict postoperative NRS	/	Examined, but results were non-significant (p> 0.05).
Vaegter et al., 2017 (36)	Knee OA	NRS peak pain in relation to CPM, EIH	6m	Correlation - Baseline EIH to predict ΔNRS - ΔNRS to predict ΔCPM and ΔEIH - ΔCPM and ΔEIH to predict ΔNRS	- ↓NRS = improved CPM (r= 067, p< 0.008) - ↓NRS = improved EIH (r= 068, p< 0.008)	- Baseline better CPM = ↓ NRS (r= 0.57, p< 0.04) - Baseline better EIH = ↓ NRS (r= 0.53, p< 0.05) - Improved CPM = ↓NRS (r= 067, p< 0.008) - Improved EIH = ↓NRS (r= 068, p< 0.008)
Wilder-Smith et al., 1996 (43)	Disc herniation	/ Only evolution of sensation DT, PPT & PTT	-1h, 2h, 4h, 6h, 24h, 5 days	/	/	/

Abbreviations : SPS, somatosensory processing system; FU, follow-up; PROMS, patient reported outcome measure; PPT, pressure pain threshold; VAS, visual analogue scale; min, minutes; m., musculus; TA, m. Tibialis anterior; postoperative; O, outcome; IL-8, interleukin 8; IP-10, interferon gamma-induced protein 10; Flt-1, Fms related tyrosine kinase 1; MCP-1, monocyte chemoattractant protein 1; w, weeks; PTT, pressure pain tolerance threshold; CPM, conditioned pain modulation; EDT, electrical detection threshold; EPT, electrical pain threshold; CSI, central sensitization index; NRS, numeric rating scale; CDT, cold detection threshold; WDT, warmth detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; QuickDASH, quick disabilities of arm, shoulder and hand

Table 10: Level of recommendation table predictors for change of SPS sign

SPS change	Predictor	MSK disorder	Method of predictor	Result	Level of recommendation
Improved PPT	Change pain-related variable	Hip OA Knee OA Closed lock TMJ	↓VAS in rest (37) ↓VAS peak pain (24) ↓VAS after 30min walking (24) ↓number of body sites with pain (24) ↓NRS (26) **(only widespread PPT)**	Influence	**Moderate for influence**
	Baseline pain-related variable	Knee OA	High/low baseline painDETECT (41) High/low baseline VAS (42)	No influence	**Moderate for no influence**
	Baseline PPT	Knee OA	Lower baseline PPT (24)	Influence	**Weak for influence**
	Change inflammatory-related variable	Hip OA	↑IP-10 (25) **(only widespread)** ΔIL-8 (25) ΔFlt (25) ΔMCP-1 (25)	Influence No influence	**Conflicting**
Improved PTT	Change inflammatory-related variable	Hip OA	↑IL-8 (25) ΔIP-10 (25) ΔFlt (25) ΔMCP-1 (25)	Influence No influence	**Conflicting**
	Baseline pain-related variable	Knee OA	High/low baseline painDETECT (41)	No influence	**Weak for no influence**
Change in EPT	Change pain-related variable	Closed lock TMJ	ΔNRS (26)	No influence	**Weak for no influence**
Change in EDT	Change pain-related variable	Closed lock TMJ	ΔNRS (26)	No influence	**Weak for no influence**
Change in punctuate pain	Change inflammatory-related variable	Hip OA	ΔIP-10 (25) ΔIL-8 (25) ΔFlt (25) ΔMCP-1 (25)	No influence	**Weak for no influence**
Improved Temporal summation	Change inflammatory-related variable	Hip OA	↑Flt (25) ΔIP-10 (25) ΔIL -8 (25) ΔMCP-1 (25)	Influence No influence	**Conflicting**
	Baseline pain-related variable	Knee OA	High/low baseline painDETECT (41)	No influence	**Weak for no influence**

Table 10 (continued)

SPS change	Predictor	MSK disorder	Method of predictor	Result	Level of recommendation
Improved CPM	Change pain-related variable	Knee OA	↓ NRS (36)	Influence	**Moderate for influence**
	Change inflammatory-related variable	Hip OA	↑IP-10 (25) ΔIL-8 (25) ΔFlt (25) ΔMCP-1 (25)	Influence No influence	**Conflicting**
	Baseline pain-related variable	Knee OA	High/low baseline painDETECT (41)	No influence	**Weak for no influence**
	Pain catastrophizing	Knee OA	High/low pain catastrophizing (30)	No influence	**Weak for no influence**
Improved EIH	Change pain-related variable	Knee OA	↓ NRS (36)	Influence	**Moderate for influence**
Improved CSI	Sex	Knee OA	Being a woman (27) ↓VAS in rest (37)	Influence	**Weak for influence**

Abbreviations: SPS, somatosensory processing system; PPT, pressure pain threshold; VAS, visual analogue scale; IL-8, interleukin 8; IP-10, interferon gamma-induced protein 10; Flt-1, Fms related tyrosine kinase 1; MCP-1, monocyte chemoattractant protein 1; PTT, pressure pain tolerance threshold; CPM, conditioned pain modulation; CSI, central sensitization index; EIH, exercise induced analgesia; NRS, numeric rating scale

Dynamic QST

An improvement of pain-related variable over time predicted CPM over time (36) (moderate conclusion). Conflicting evidence was found for a change in inflammatory variables to predict a change of temporal summation and CPM over time (25), and a baseline pain-related variable did not predict a change of temporal summation and CPM over time (24) (both weak conclusion). In addition, also a baseline pain catastrophizing score failed to predict a change of CPM over time (weak conclusion) (30).

Other SPS signs

An improvement of pain-related variable over time predicted EIH over time (36) (moderate conclusion) and also being a woman predicted an improvement of CSI score over time (27) (weak conclusion).

SPS change-related predictors for improvement of pain

An improvement in PPT (24,26,37), CPM and EIH (36) over time predicted and improvement in pain-related variables over time (all moderate conclusion).

Table 11: Level of recommendation table SPS change-related predictor for postsurgical outcome

PROM outcome	Method outcome	MSK disorder	SPS-related predictor	Result	Level of recommendation
Improvement of pain-related variables	VAS pain in rest (37) VAS peak pain (24) VAS after 30min walking (24) number of body sites with pain (24) NRS (26) **(only widespread PPT)**	Hip OA (3) Knee OA (8) Closed lock TMJ (19)	↑PPT	Influence	**Moderate for influence**
	NRS (36)	Knee OA	Improved CPM	Influence	**Moderate for influence**
	NRS (36)	Knee OA	Improved EIH	Influence	**Moderate for influence**

Abbreviations: SPS, somatosensory processing system; PPT, pressure pain threshold; CPM, conditioned pain modulation; EIH, exercise induced analgesia; VAS, visual analogue scale; NRS, numeric rating scale

Discussion

The first goal of this systematic review was to summarize all studies that measure how SPS signs evolve after nociceptive targeted surgery in MSK disorders. The second aim was to find pre-, peri- and postoperative predictors for an improvement or persistence of disturbed SPS signs after surgery. Regarding the first aim, results are all very divergent and heterogenous. However, worsening of some SPS signs was only seen at a follow-up of < 3 months after surgery, conclusions are stronger with a follow up of ≥ 3 months after surgery, and in general more positive results are seen regarding dynamic QST. An explanation could be that after 3 months the pain in most patients was resolved. Regarding the second aim, only a change in pain-related variables over time and baseline lower PPT predicted an improved PPT over time, a change in pain-related variables over time predicted an improved CPM and EIH over time, and being a woman predicted an improved CSI score over time. Accordingly (because correlation analyses work in two directions), also a change in PPT, CPM and EIH over time predicted an improvement of pain-related variables over time.

Relation to other research and explanations for findings

There is no consistent pattern in the evolution of SPS signs when comparing results pre- and post-surgery. A possible explanation could be the fact that most included studies did not compare a group in which the pain persisted or pain resolved after surgery. Two studies categorized patients according to more- or less preoperative pain (41,42), but found no differences in SPS signs in the long term between groups. This could be explained by the fact that they did not analyze the groups according to pain improvement (they only focused on the preoperative pain values). It is known that higher preoperative pain scores are a risk factor for developing chronic postsurgical pain, however, not all patients with a high preoperative pain

score will experience chronic postsurgical pain (45,46). Findings of previous systematic reviews are also in line with this theory, because they also mainly focused on preoperative SPS signs and the link with postoperative pain, and found as such no fully consistent conclusions (12,13,47–50). A recent review indicates the importance of performing more studies focusing on the evolution of SPS signs in combination with or without pain improvement (51), and also our review reveals that the improvement of pain-related variables over time is a predictor (according to correlation analyses) for an improvement of PPT, CPM and EIH over time and vice-versa, which also strengthens this theory. It is possible that disturbed SPS signs are present preoperatively, but if they normalize after surgery in combination with pain relief, it is postulated that the driving factor for the disturbed SPS sign was the nociceptive source itself (chronic secondary MSK pain) (8,44). On the other hand, if disturbed SPS signs appear or remain present after surgery in combination with chronic pain, it is postulated that the driving factor is primary chronic MSK pain (15). Phenotyping of patients remains thus highly necessary to make clear predictions of patients experiencing chronic postsurgical pain.

In addition to previous theory, it is also possible that SPS signs were not disturbed before surgery. If these were not disturbed before surgery, it is also obvious that no positive evolution could be found. The same theory applies for a negative or positive evolution of SPS signs, one could expect a positive or negative evolution after surgery if SPS signs were disturbed or not-disturbed before surgery, respectively. However, to date, it is still challenging to decide whether a certain SPS sign is disturbed at a certain time-point, because a clear guideline for normative values is lacking (52).

Stronger conclusions were found at a follow-up ≥ 3 months after surgery, which is logical, because of the MSK population and surgeries of the included studies. Most studies focused on TKA of THA surgeries, and research has shown that most of the pain improvement is seen three to six months after surgery (53–56). Patients are still recovering from the surgery at a follow-up of < 3 months, and as such, very divergent patterns can be assumed. A cut-off of three months after surgery was chosen, based on the definition of chronic postsurgical pain of the ICD-11 (3).

It is also remarkable that stronger and more positive results are seen regarding dynamic QST. The difference with static QST could be the fact that dynamic QST is related to a more centrally driven pain hypersensitivity, while static QST can reflect both a combination of more peripherally (local thresholds) and centrally driven pain hypersensitivity (widespread thresholds) (57,58). However, caution is advised, because this research is limited to THA and TKA surgery. The results are also characterized by stronger conclusions after TKA compared to after THA, because more studies with lower RoB were found in the knee OA population.

Lastly, apart from knee OA, hip OA and spinal pain patients, research about this topic in other MSK pathologies is scarce. Only one study studied shoulder OA and closed lock TMJ pain patients, and only three spinal pain patients. This is remarkable, because persistent pain is present around 20% after shoulder TKA (59,60), and around 15% after TMJ discectomy [2,4], of which a part could be possibly due to disturbed SPS signs based on the presence due to prolonged nociception (explanation see introduction).

Limitations of the included studies

First of all, it is remarkable that more than half of the studies reported a high RoB, which is accounted for in the interpretation of the conclusion (lower evidence and as such weaker conclusions). Many conclusions (level of recommendations) were weak due to the fact that conclusions could only be made based on the findings of solely one study that reported high RoB. So, it is advised to take caution in interpreting these findings. Secondly, only 10 studies did investigate some kind of predictor for the normalization of the SPS sign and were mainly focused on PPT. Of these 10 studies, only 3 did report a real prediction based on regression analyses. Finally, as mentioned earlier, studies focusing on subgroups correcting for the potential change in pain are lacking.

Clinical implications for future research and clinical practice

Future research should focus on the stratification of patient groups, preferably based on pain improvement in which a group of patients with pain normalization or disappearance will be compared with a group with persistent pain after three months or more after surgery, and investigate the evolution of the SPS signs. It is also important for future studies to examine predictors for the (non-) normalization of SPS signs, as this could give us a clearer explanation for the findings. This way, it could be possible to reveal different subgroups based on chronic postsurgical pain (e.g., primary chronic and secondary chronic postsurgical pain), making decisions about whether to perform surgery or first to focus on the disturbed SPS signs is more convenient.

Strengths and limitations of the review

This review has a couple of strengths, as this is the first review to summarize and analyze all studies that investigated the evolution of SPS signs after MSK surgery. Thereupon, the triple-blind screening, the data extraction and the RoB assessment strengthen the power of this paper. In addition, the systematic approach gives the reader a nice overview covering all MSK patients undergoing surgery.

This review also presents with some limitations, so conclusions should be interpreted with caution. Eight studies (1/3rd of total included studies) were retrieved by hand-search methods. A possible explanation could be that in the PICO term, only variation of 'MSK disorders' was used, not specifying which MSK disorders. In addition, our search was restricted to studies including QST or questionnaires to measure SPS signs, future research could go further and add also more invasive SPS measurements (e.g. Magnetic Resonance Imaging, electromyography, etc.). Finally, no meta-analysis was performed, however, this was impossible due to the heterogeneity of the MSK population and SPS signs measured.

Conclusion

In general, no consistent evolution of SPS signs comparing pre- and postoperative values and predictors for this evolution in MSK disorders could be found. In most cases, static QST did not change or conflicting results were found. On the other hand, dynamic QST mostly improved after surgery. Worthfully mentioning is that worsening of some SPS signs was only seen at a follow-up of < 3 months after surgery, that conclusions are stronger when evaluating dynamic

QST with a follow up of ≥ 3 months after surgery, and that pain improvement over time was an important predictor for improvement of SPS signs. Future high-quality research should focus on the evolution of SPS signs after nociceptive targeted surgery, accounting for pain improvement patient groups and focusing on pre, peri- and postoperative predictors of this evolution.

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Chapter 5: Does the change in pain intensity after total knee arthroplasty depend on somatosensory functioning in knee osteoarthritis patients? A prospective cohort study

Sophie Vervullens[1,2,3], Lotte Meert[1,2,3], Rob J.E.M. Smeets[2,3,6], Jonas Verbrugghe[1,4], Peter Verdonk[5], Mira Meeus[1,2]

[1]Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium

[2]Research School CAPHRI, Department of Rehabilitation Medicine, Maastricht University

[3]Pain in Motion International Research Group (PiM), www.paininmotion.be

[4]REVAL-Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Hasselt, Belgium

[5]ORTHOCA, Antwerp, Belgium and ASTARC department, Antwerp University, Belgium

[6]CIR Clinics in Revalidatie, location Eindhoven, The Netherlands

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Abstract

Objective: To determine whether the change in pain intensity over time differs between somatosensory functioning evolution profiles in knee osteoarthritis (KOA) patients undergoing total knee arthroplasty (TKA).

Method: This longitudinal prospective cohort study, conducted between March 2018 and July 2023, included KOA patients undergoing TKA in four hospitals in Belgium and the Netherlands. The evolution of the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale pain over time (baseline, three months- and one-year post-TKA scores) was the outcome variable. The evolution scores of quantitative sensory testing (QST) and Central Sensitization Inventory (CSI) over time (baseline and one-year post-TKA scores) were used to make subgroups. Participants were divided in separate normal, recovered and persistent disturbed somatosensory subgroups based on the CSI, local and widespread pressure pain threshold [PPT] and heat allodynia, temporal summation [TS], and conditioned pain modulation [CPM]. Linear mixed model analyses were performed.

Results: 223 participants were included. The persistent disturbed somatosensory functioning group had less pronounced pain improvement (based on CSI and local heat allodynia) and worse pain scores one-year post-TKA (based on CSI, local PPT and heat allodynia and TS) compared to the to normal somatosensory functioning group. This persistent group also had worse pain scores one-year post-TKA compared to the recovered group (based on CSI).

Conclusions: The study suggests the presence of a 'centrally-driven central sensitization'-subgroup in KOA patients awaiting TKA in four of seven grouping variables, comprising their less pain improvement or worse pain score after TKA. Future research should validate these findings further.

Introduction

Knee osteoarthritis (KOA) is the third most prevalent musculoskeletal disorder in the world (1), causing substantial chronic pain and disability (2). When conservative treatments are ineffective, and patients still continue to experience joint symptoms that significantly impact their quality of life, a total knee arthroplasty (TKA) is advised (3). Despite the high TKA success rate, approximately 20% of patients experiences chronic post-TKA pain (4–6). Various biopsychosocial contributors have shown to be associated with this chronic post-TKA pain (7).

One notable potential biological contributor to chronic post-TKA pain is hypersensitivity of the central nervous system (7–10). This is reflected in the disturbance of somatosensory functioning, leading to hyperexcitability of the facilitatory ascending nerve pathways, along with reduced descending inhibition and changes in brain structures (11,12). Quantitative sensory testing (QST) and the Central Sensitization Inventory (CSI) are often used to measure this central nervous system disturbance (13), and disturbed somatosensory functioning itself has been reported to be associated with chronic post-TKA pain (7,9). KOA pain is currently categorized as 'chronic secondary MSK pain', which means that pain is associated and maintained by the osteoarthritis disease itself (14). Interestingly, one might expect that if all KOA patients suffered 'chronic secondary MSK pain' solely (14), the pain and possible disturbed somatosensory functioning would resolve after effective treatment of KOA (i.e. TKA). This would imply that the disturbed somatosensory functioning is more peripherally-driven (i.e. caused by an ongoing source of nociception and therefore indeed 'chronic secondary MSK pain'). However, as +/- 20% of patients continue experiencing chronic pain after TKA, and considering that the normalization of somatosensory functioning is not consistent in KOA patients after TKA (4,6,12,15), this theory is being challenged.

Hence, it is postulated that in a subgroup of KOA patients, pain and somatosensory disturbances are more centrally-driven, less reliant on peripheral source of nociception (and rather to be classified as 'chronic primary MSK pain', in which pain has become a condition on its own right (14)). Consequently, this subgroup may not experience full amelioration of pain and disturbed somatosensory functioning after surgery. This finding would warrant a broader treatment approach beyond the exclusive focus on the peripheral aspect, such as a more comprehensive modern neuroscience approach, including pain neuroscience education, cognitive behavioral therapy, cognition-targeted exercise therapy etc. (16,17).

In light of these considerations, a previous systematic review showed that unfortunately most studies lacked subgrouping based on somatosensory functioning in KOA patients undergoing TKA, despite the association between improvement in some somatosensory functioning parameters and a pain improvement over time (15). Two studies in the United Kingdom compared KOA patients undergoing TKA based on somatosensory functioning preoperatively, finding higher postoperative pain scores six months post-TKA (18), or a higher proportion of patients with moderate-to-severe one-year post-TKA pain (19) in a neuropathic-like pain group compared to a nociceptive pain group (18). However, their somatosensory functioning categorization was limited to only preoperative neuropathic-pain like symptoms using the painDETECT questionnaire (18–20). Two other studies in Denmark used somatosensory

functioning as outcome variable and compared chronic postoperative pain groups (one after TKA (21) and one after total hip arthroplasty (22)), but only found between-group differences regarding temporal summation. However, none of the previous studies explored differences in post-TKA pain scores or their evolution over time between different somatosensory functioning evolution groups. This approach has the potential to improve our current understanding of pain mechanisms in KOA and post-TKA, as well as to identify possible subgroups of KOA patients.

Consequently, this study aimed to determine whether the change in pain intensity over time and pain intensity scores after TKA differed between somatosensory functioning evolution profiles in KOA patients undergoing TKA. Therefore, three somatosensory evolution profiles were defined and patients were classified accordingly. The hypothesis was that patients who experienced normal somatosensory functioning before and after TKA surgery (i.e. normal somatosensory functioning group or no indices for central sensitization) and patients who experienced disturbed somatosensory functioning before TKA surgery, but normalized somatosensory functioning after TKA (i.e. recovered somatosensory functioning group as an index for peripherally-driven central sensitization) had more pain improvement or better pain scores after TKA compared to patients who experienced disturbed somatosensory functioning before and after TKA (i.e. persistent disturbed somatosensory functioning group as index for centrally-driven central sensitization).

Materials and methods

The Strengthening The Reporting of Observational studies in Epidemiology (STROBE) guidelines for cohort studies were used to conduct this multi-center longitudinal prospective cohort study (23). The protocol is registered at clinicaltrials.gov (NCT05380648).

Setting and participants

KOA patients awaiting TKA were recruited in the University Hospital of Antwerp and AZ Monica in Belgium, and the academic Hospital of Maastricht and St. Jans Gasthuis Weert in the Netherlands between March 2018 and July 2022. The study was approved by the respective ethical committees (BE300201319366 and NL6465408618).

Participants were eligible if diagnosed with KOA, were awaiting TKA and aged ≥ 40 years. They were excluded if they experienced neurological or systemic diseases possibly impacting their pain, and were unable to speak or understand Dutch. After signing informed consent, participants completed a demographic, a somatosensory functioning (grouping variable), and a pain-related questionnaire (outcome variable) on paper or online via Qualtrics (www.qualtrics.com). After a practical skills training, two executive researchers (S.V. or L.M.) conducted the QST measurements (other grouping variables) at the Sensoric Functioning Lab (M2SENS) at the University of Antwerp's campus 'Drie Eiken' (Belgian participants), or at the orthopedic department of the academic Hospital of Maastricht and St. Jans Gasthuis Weert (Dutch participants) with standardized measurement forms. As this was a longitudinal study, data collection occurred between March 2018 and July 2023 at the following time points: four

weeks pre-TKA (baseline), three months, and one-year post-TKA. All participants had to stop first-stage pain medication, coffee, and alcohol 24 hours before the physical measurements.

Outcome variable

The outcome variable 'pain intensity evolution from baseline to three months and one-year post-TKA' was measured with the Knee Injury and Osteoarthritis Outcome score (KOOS) subscale pain. The questionnaire comprises nine questions with a percentage score ranging from zero (worst pain) to 100 (no pain) (24). The KOOS is a reliable and valid questionnaire in KOA patients (25,26).

Group classifications

Indices of somatosensory functioning were assessed at baseline and one-year post-TKA with the Central Sensitization Inventory (CSI) and QST. The CSI, pressure pain thresholds [PPTs], heat allodynia, temporal summation [TS], and conditioned pain modulation [CPM] were used to make group classifications. More details about the measurement methods (27–30) and the decision about 'normal' somatosensory functioning (31–36) can be found in Table 1.

For each somatosensory functioning variable (local PPT, widespread PPT, local heat allodynia, widespread heat allodynia, TS, CPM and CSI) criteria were defined to categorize participants as '**normal somatosensory functioning**', '**recovered somatosensory functioning**' or '**persistent disturbed somatosensory functioning**'. This categorization was done for each single variable, and as such the number of participants in the somatosensory functioning groups differed slightly for each variable. Details about this categorization can be found in Table 2.

Sample size

The sample size calculation of this project was based on the method of Diggle et al. (37). Considering a minimal clinically important difference (MCID) of eight points in the KOOS subscale pain, 16 points as within-group standard deviation after TKA (24,38), three measurement points, a confidence level of 0.05 and power of 0.80, at least 25 subjects per group were necessary (37). Anticipating disturbed somatosensory functioning in 30% of KOA patients (10,39), we hypothesized that 15% would have disturbed somatosensory functioning at baseline and one-year post-TKA. Therefore, at least 223 participants were necessary to recruit to encounter a loss-to-follow-up of 25%.

Table 1: Measurement methods and interpretation for normal somatosensory functioning

	Measurement method and device	Localization and position of participant	Normal somatosensory functioning
PPT	Method: A probe (1cm^2) was placed perpendicular to the test surface and pressure was increased until the subject, in supine position, reported a feeling of discomfort. An average of two measurements, separated by a pause of 30 seconds, was taken for analysis[25]. Device: hand-held pressure algometer (*Wagner FDX 25 Force Gage*, *USA*)	Localization: Medial and lateral knee joint-line of the affected knee **(local PPT – combined)**, the m. ECRL of the non-dominant side, and the forehead **(widespread PPTs - combined)** Position: Supine	Despite the absence of clear cut-off or normative values for PPTs [28], patients were categorized using median scores, where higher scores indicated normal somatosensory functioning (post-hoc determined)
Heat allodynia	Method: A roll-movement was performed for 10 seconds, after which participants scored their pain intensity on a NRS ranging from zero (no pain) to 10 (unbearable pain). Device: Thermal rollers (Rolltemp II Somedic Senselab) at 40°C (hot stimulus)	Localization: Medial and lateral knee joint-line of the affected knee **(local heat allodynia – combined)**, and the m. ECRL of the non-dominant side **(widespread heat allodynia)** Position: Supine	No pain (<1/10 on NRS) was interpreted as normal somatosensory functioning[29] (a priori determined)
Temporal summation	Method: Thirty pinpricks were given at a pace of 1 pinprick/second, of which the first and last pinprick were scored for pain intensity on NRS ranging from zero (no pain) to 10 (unbearable pain). The differences between the NRS scores of the first and last pinprick were calculated and used for analysis[26]. Device: Von Frey monofilament of 60 grams	Localization: Medial knee joint-line and wrist of the affected side **(combined to one variable)** Position: Supine	A difference of < two points on NRS score difference (last - first stimulus) was interpreted as normal somatosensory functioning[30,31] (a priori determined)
CSI	A questionnaire with 25 questions, rates self-reported sensitization-associated symptoms (somatic and emotional symptoms, as well as pain sensitivity-related questions such as morning fatigue, anxiety attacks, poor sleep, light sensitivity, teeth grinding,.. etc.) on a five-point Likert scale[23,24].	/	A score ≥ 40 indicates the presence of self-reported symptoms of central sensitization[27] (a priori determined)

Table 1 (continued)

	Measurement method and device	Localization and position of participant	Normal somatosensory functioning
CPM	Method: First, a temperature corresponding to a pain intensity NRS score of 4/10 (up to a maximum of 46°C) was identified. This identified temperature (or 46°C when the 4/10 on a NRS was not reached) was used as test stimulus. The participant had to score the test stimulus on a NRS 4 times. After a pause of 120 seconds, a conditioning stimulus (with a temperature of 0.5°C more than the test stimulus) was added for 65 seconds and 20 seconds after its initiation, the test stimulus was repeated. Again, the participants had to score their pain for 4 times, but only on the test site. If the NRS at 46°C and the mean of the NRS of test stimulus was equal to zero, the participant was excluded for analysis. The relative CPM scores ((absolute score [NRS score during conditioning stimulus – NRS score during only test stimulus]/NRS score during test stimulus) * 100) were used for analysis[26]. Device: Q-sense CPM device (Medoc, USA)	Localization: Test stimulus: the wrist of the affected side Conditioning stimulus: the wrist of the non-affected side Position: Supine	CPM values were categorized as patients being a facilitator (positive CPM values, indicating a less-efficient CPM), a non-responder (value 0, indicating no CPM response), and an inhibitor (negative CPM values, indication a more-efficient CPM) [32] (a priori determined)

Abbreviations: NRS = numeric rating scale, PPT= pressure pain threshold, CSI= Central Sensitization Inventory, CPM= conditioned pain modulation

Table 2: categorization of somatosensory functioning groups

	Normal somatosensory functioning	Recovered somatosensory functioning	Persistent disturbed somatosensory functioning
Pressure pain threshold	A score of above the group median at baseline and follow-up	A score below the group median at baseline, but above the group median at follow-up	A score below the group median at baseline and follow-up
Heat allodynia	A score <1/10 on NRS (no pain)	A score of ≥ 1/10 on NRS at baseline, but < 1/10 on NRS (no pain) at follow-up	A score of ≥ 1/10 on NRS at baseline and follow-up
Temporal summation	An NRS difference score (last - first stimulus) of < two points	An NRS difference score (last - first stimulus) of < two points at baseline, but a difference of ≥ two points at follow-up	An NRS difference score (last - first stimulus) of ≥ two points at baseline and follow-up
Central sensitization inventory	A score of < 40	A score of ≥ 40 at baseline, but a score of < 40 at follow-up	A score of ≥ 40 at baseline and follow-up
Conditioned pain modulation	Being an inhibitor (negative CPM values, indicating a more-efficient CPM)	Being a facilitator (positive CPM values, indicating a less-efficient CPM) or non-responder (a score of 0, no CPM response) at baseline, but inhibitor at follow-up	Being a facilitator (positive CPM values, indicating a less-efficient CPM) or non-responder (a score of 0, no CPM response) at baseline and follow-up

Abbreviations: NRS = numeric rating scale, CPM= conditioned pain modulation

Statistical analyses

Statistical analyses were conducted using the IBM Statistical Package for Social Sciences Version 29 (SPSS, IBM Corporation, Armonk, NY), and R software (version 4.2.3) for multiple imputation. Boxplots were used to check univariate outliers, which were only deleted if unreasonable. Missing data were handled with multiple imputation (n= 10 imputed datasets) using predictive mean matching with the 'mice' package in R (40). To decrease the amount of grouping variables for defining somatosensory functioning groups, univariate association analyses using Pearson correlation and Wilcoxon rank-sum tests between the different QST variables were performed. When variables were at least moderately correlated (correlation coefficient $r \geq 0.40$), they were merged by taking the average of both values (if they measured the same somatosensory construct), and otherwise, only one variable was chosen for further analyses based on expertise and consistency with previous research. Demographic data was presented as mean and standard deviation (continuous data), and as number and frequency (categorical data). All data was pooled according to Rubin's rules (41).

Thereafter, seven linear mixed model for repeated measures analyses were performed (local and widespread PPT and heat allodynia, TS, CPM and CSI used to make seven normal, resolved and persistent disturbed somatosensory functioning groups). Time, somatosensory functioning group, time x somatosensory functioning group (interaction term) and covariates (age and sex) were used as fixed effects. Subject identification was used as random effect.

Residuals were checked for normality with a histogram and homogeneity of variance with a scatterplot. The median p-value of the interaction of all imputed datasets was calculated (42). Least squares estimated means intervals and 95% confidence intervals were calculated and pooled according to Rubin's rules (41). Within-group, between-group at each timepoint, and interaction results are reported. A Benjamini-Hochberg correction was applied to correct for multiple testing and the significance level was therefore set to $p<0.028$ (43). If results were significant, post-hoc analyses were performed, a Bonferroni correction was applied to the post-hoc p-values and corrected to $p<0.05$.

Results

Participants

The study included 223 KOA participants with a mean age of 66 years old (standard deviation [SD]: 7.66) and 111 (49.8%) being female. Most participants had TKA surgery in AZ Monica (129 or 58% of participants), followed by SJG Weert (51 or 23% of participants, University Hospital of Antwerp (41 or 18% of participants), and University Hospital of Maastricht (2 or 1% of participants). Out of the 223 participants, 166 (75% of participants) had a Kellgren & Lawrence scale 3 or 4 (the higher, the worse structural KOA). Eighteen participants (8% of participants) were tested > four weeks preoperatively due to COVID-19 surgery postponement, however no differences between groups regarding outcome variable and group division were found ($p>0.05$).

Missing data-analysis

The KOOS subscale pain had 5.4% (12 participants) missing data at baseline, 22.0% (49 participants) at three months post-TKA, and 24.7% (55 participants) at post-TKA. Baseline missingness was mainly due to participants who forgot to complete questionnaires before surgery, while missingness at follow-up was due to exclusion of participants (diagnosed with rheumatoid arthritis diagnosis, cancer, or neuropathic pain symptoms in the lower legs due to hernia – 2.3%, 5 participants), and primarily from losses-to-follow-up (unreachable, time constraints, or planned revision – 22.4%, 50 participants). Grouping variables had missing data ranging from 1.3 to 34.1% (3 to 76 participants). The missing data at baseline stemmed from participants absent during the planned physical testing (1.3%, 3 participants), absence of the baseline PPT measured at forehead because of protocol updates at February 2019 for future project purposes (17%, 38 participants), and missing CPM data due to device issues or reported absence of pain during test-stimulus (10.8%, 22 participants). At follow-up, missing data was due to the same reasons as missingness in the KOOS subscale pain.

Details can be found in Supplementary table S1. Because multiple imputation handled missing data, all participants (n= 223) were analyzed.

Group division

To avoid an overload of group classifications and to manage to interpretation of the somatosensory functioning groups correlated QST variables of the same construct were

combined and averaged: (a) PPTs measured at medial and knee joint-line were merged into one local PPT (r=0.711-0.764), (b) PPTs measured at m. Extensor carpi radialis longus and the forehead were merged into one widespread PPT (r=0.650-0.721), (c) heat allodynia measured at medial and lateral knee joint-line was bundled into local heat allodynia (r=0.640-0.702), and (d) TS measured at the medial knee joint-line and medial wrist was also bundled into TS in general (r=0.418-0.501). Regional PPT (measured at m. Tibialis anterior) and cold allodynia were not reported as grouping variables, because of their moderate to high correlation with local (r=0.686-0.805) and widespread PPT variables (r=0.526-0.726), and heat allodynia variables (r=0.561-0.727), respectively (supplementary table S2 and S3).

Regarding the separate somatosensory functioning groups, the number of participants varied depending on QST variables or CSI used for subgrouping: 15.07 to 77.13% (34 to 172 participants) for normal somatosensory functioning, 9.87 to 22.42% (22 to 50 participants) for recovered somatosensory functioning, and 12.11 to 62.33% (27 to 139 participants) for persistent disturbed somatosensory functioning (Table 3).

Table 3: Number and percentage of participants divided by somatosensory functioning group

N (% of total sample)	**Normal somatosensory functioning**	**Recovered somatosensory functioning**	**Persistent disturbed somatosensory functioning**
Local PPT	83 (37.22)	40 (17.94)	100 (44.84)
Widespread PPT	81 (36.32)	43 (19.28)	99 (44.39)
Local THA	142 (63.68)	30 (13.45)	51 (22.87)
Widespread THA	133 (59.64)	22 (9.87)	68 (30.49)
TS	132 (59.19)	44 (19.73)	47 (21.08)
CSI	172 (77.13)	24 (10.76)	27 (12.11)
CPM	34 (15.07)	50 (22.42)	139 (62.33)

Abbreviations: PPT= pressure pain threshold, THA= thermal heat allodynia, TS= temporal summation, CPM= conditioned pain modulation, CSI= Central Sensitization Inventory

Results of change in pain intensity after surgery in different somatosensory evolution groups

Detailed results can be found in Figure 1 and 2, and Table 4.

*Interaction effect (time*group)*

Only differences in changes of the KOOS subscale pain over time were found between the normal, resolved and persistent disturbed somatosensory functioning groups classified according to local heat allodynia (p= 0.011), and CSI (p< 0.001). No differences were found regarding the other somatosensory functioning grouping variables (p>0.028). Regarding these two significant grouping variables, post-hoc analyses showed that the persistent disturbed somatosensory group had less pain-improvement from baseline to one-year post-TKA compared to the normal somatosensory functioning group (p=0.018 and p=0.001, respectively). Other post-hoc analyses were non-significant (p>0.05).

Within-group time-effect

All somatosensory functioning groups classified according to the seven grouping variables experienced an improvement of the KOOS subscale pain score from baseline to three months

and one-year after the TKA (p< 0.001), expect for the persistent disturbed somatosensory group classified according to the CSI, which showed no improvement over time (p=0.213).

Between-group effect at each timepoint

Differences between somatosensory functioning groups classified according to local PPT (p=0.009) and heat allodynia (p=0.003), temporal summation (p=0.027) and CSI (p<0.001) were found at one-year post-TKA. At baseline, also differences between groups classified according to CSI were found (p=0.003). At one-year post-TKA, post-hoc analyses showed that the persistent disturbed somatosensory functioning group had worse pain scores compared to the normal somatosensory group (p= 0.009 for local PPT, p=0.003 for local heat allodynia, p=0.027 for temporal summation, and p<0.001 for CSI), and compared to the recovered somatosensory group (p=0.044 for CSI). At baseline, the recovered somatosensory functioning group had worse pain scores compared to the normal somatosensory functioning group (p=0.003 for CSI). No other post-hoc differences could be found (p> 0.05).

Figure 1: Evolution of KOOS subscale pain over time in the different somatosensory functioning groups for pressure pain threshold and thermal allodynia

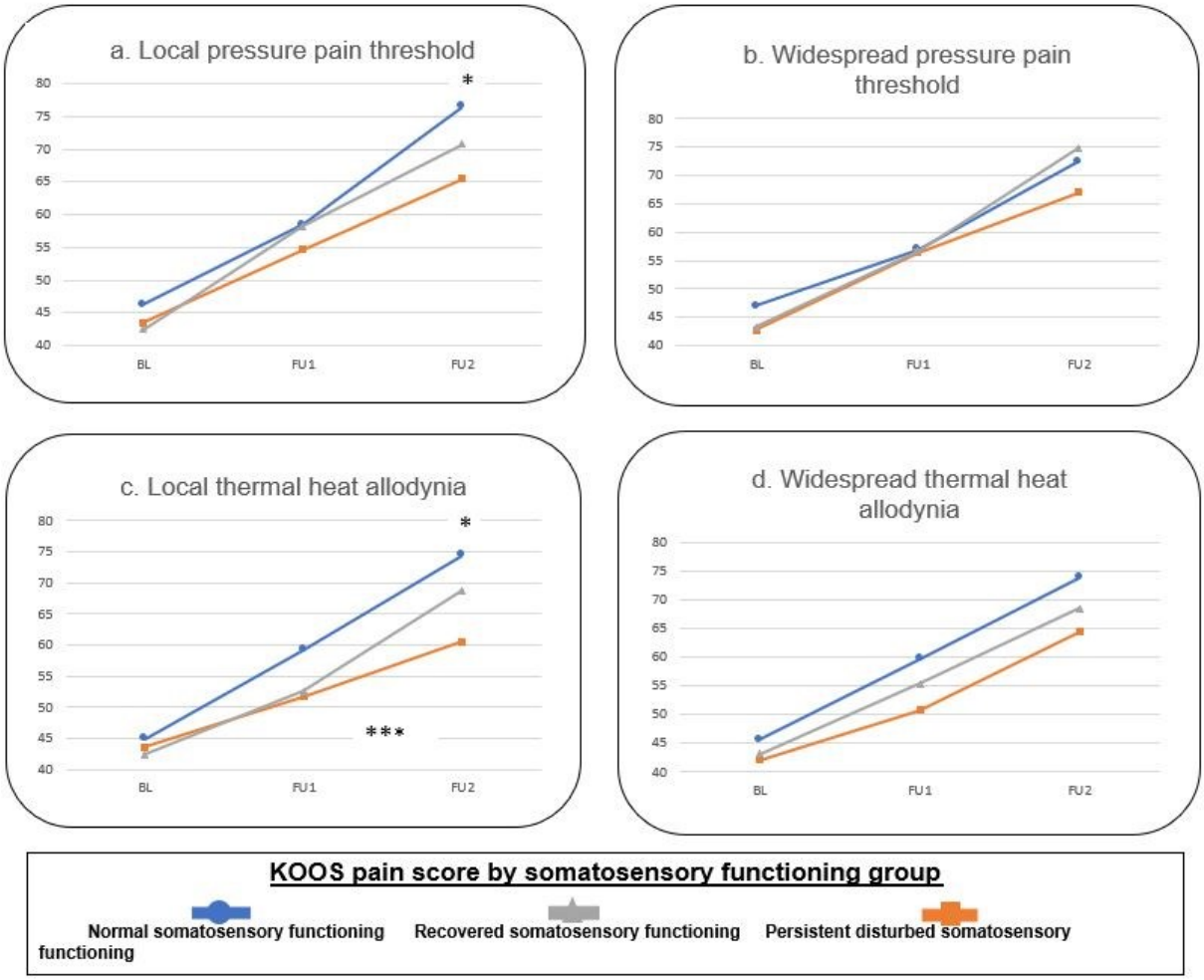

Figure legend: *= significant different between normal and persistent disturbed somatosensory group at one-year postoperative. **= significant different between normal and recovered somatosensory functioning group at baseline. ***= significant interaction effect (time*group). Abbreviations: KOOS= Knee Injury and Osteoarthritis Outcome Score

Figure 2: Evolution of KOOS subscale pain over time in the different somatosensory functioning groups for temporal summation, conditioned pain modulation and the CSI

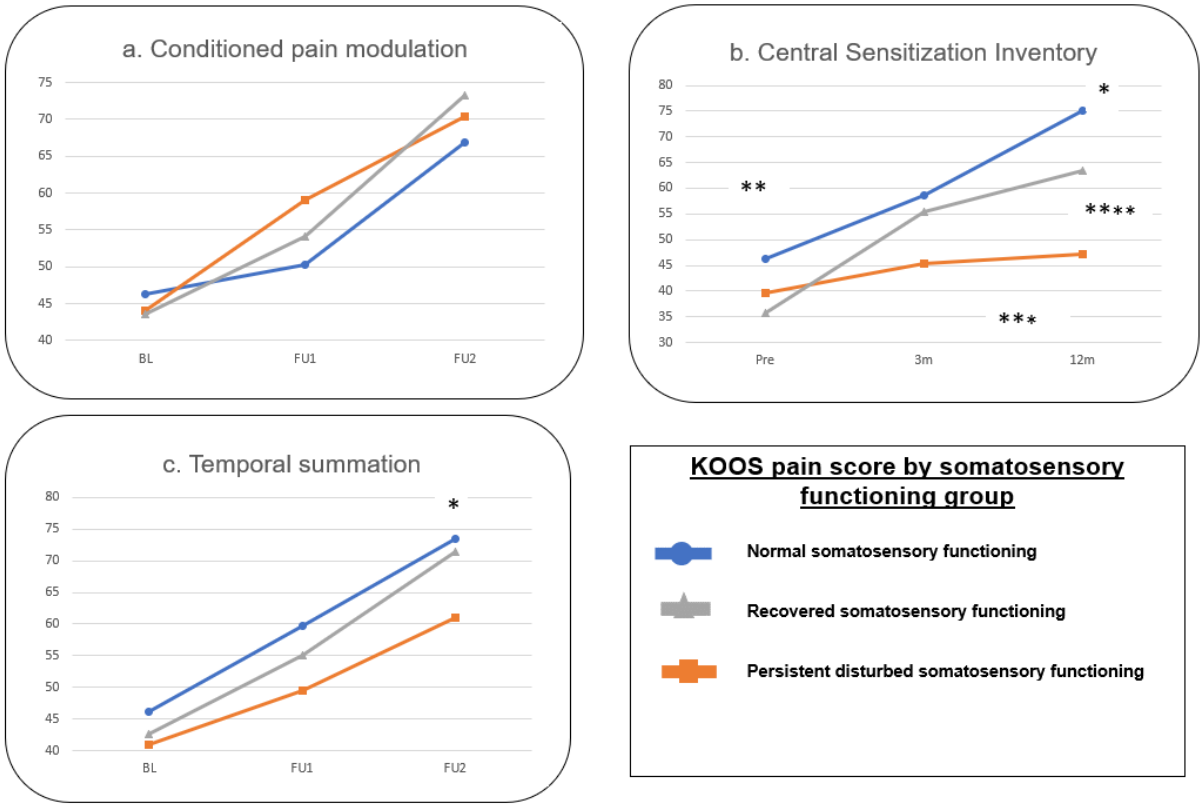

Figure legend: *= significant different between normal and persistent disturbed somatosensory group at one-year postoperative. **= significant different between normal and recovered somatosensory functioning group at baseline. ***= significant interaction effect (time*group). ****= significant different between recovered and persistent group at one-year postoperative. Abbreviations: KOOS= Knee Injury and Osteoarthritis Outcome Score, CSI= Central Sensitization Inventory

Table 4: Evolution of KOOS subscale pain over time in the different somatosensory functioning groups

Grouping variable	Time-point	Normal somatosensory functioning	Persistent disturbed somatosensory functioning	Recovered somatosensory functioning	P-value between groups at each time-point and interaction (time*group)	P-value post-hoc between groups at each time-point and interaction
		Estimated mean (95% CI) of KOOS subscale pain				
Local PPT	**BL**	46.24 (41.03, 51.45)	43.50 (38.56, 48.44)	42.53 (34.72, 50.33)	0.306	
	FU1	58.45 (52.25, 64.66)	54.64 (48.78, 60.50)	58.20 (50.12, 66.28)	0.618	
	FU2	76.53 (70.54, 82.52)	65.50 (59.95, 71.05)	70.82 (59.92, 81.72)	0.009*	Normal vs. persistent: 0.009*
P-value time-effect within-group		<0.001*	<0.001*	<0.001*	Time*group: 0.202	
Widespread PPT	**BL**	46.96 (41.50, 52.42)	42.68 (37.43, 47.94)	43.22 (35.91, 50.54)	0.080	
	FU1	56.95 (51.11, 62.80)	56.42 (50.93, 61.91)	56.71 (49.04, 64.39)	0.862	
	FU2	72.51 (67.07, 77.94)	67.03 (61.01, 73.06)	74.84 (65.68, 84.00)	0.238	
P-value time-effect within-group		<0.001*	<0.001*	<0.001*	Time*group: 0.498	
Local THA	**BL**	44.99 (41.13, 48.85)	43.61 (36.74, 50.48)	42.38 (33.96, 50.81)	0.612	
	FU1	59.30 (55.18, 63.42)	51.68 (43.41, 59.95)	52.60 (40.63, 64.58)	0.221	
	FU2	74.46 (70.51, 78.42)	60.52 (50.18, 70.86)	68.78 (58.31, 78.64)	0.003*	Normal vs. persistent: 0.003*
P-value time-effect within-group		<0.001*	<0.001*	<0.001*	Time*group: 0.027*	Normal vs persistent BL to FU2 : 0.018*
Widespread THA	**BL**	45.62 (41.63, 49.60)	42.12 (36.05, 48.18)	43.23 (33.02, 53.45)	0.359	
	FU1	59.76 (55.64, 63.88)	50.82 (43.17, 58.47)	55.43 (42.78, 58.09)	0.084	
	FU2	73.87 (69.50, 78.23)	64.44 (56.34, 72.54)	68.46 (56.89, 80.03)	0.066	
P-value time-effect within-group		<0.001*	<0.001*	<0.001*	Time*group: 0.519	
Temporal summation	**BL**	46.11 (42.00, 50.23)	40.91 (32.07, 49.75)	42.60 (35.49, 49.71)	0.058	
	FU1	59.69 (55.46, 63.92)	49.55 (39.60, 59.51)	55.06 (47.87, 62.25)	0.067	
	FU2	73.55 (69.17, 77.93)	60.92 (51.67, 70.17)	71.42 (63.96, 78.89)	0.027*	Normal vs. persistent: 0.027*
P-value time-effect within-group		<0.001*	<0.001*	<0.001*	Time*group: 0.344	
CPM	**BL**	46.33 (38.03, 54.64)	44.13 (40.04, 48.21)	43.57 (36.63, 50.50)	0.516	
	FU1	50.33 (40.69, 59.98)	59.10 (54.46, 63.74)	54.10 (44.76, 63.44)	0.156	
	FU2	66.85 (57.29, 76.42)	70.40 (65.82, 74.97)	73.27 (65.65, 80.90)	0.377	
P-value time-effect within-group		<0.001*	<0.001*	<0.001*	Time*group: 0.100	

Table 4 (continued)

	Grouping variable	Time-point	Normal somatosensory functioning	Persistent disturbed somatosensory functioning	Recovered somatosensory functioning	P-value between groups at each time-point and interaction (time*group)
CSI	**BL**	46.26 (42.83, 49.68)	39.73 (30.80, 48.65)	35.65 (25.42, 45.87)	0.003*	Normal vs. recovered: 0.010*
	FU1	58.58 (54.87, 62.30)	45.44 (34.90, 55.98)	55.34 (43.24, 67.44)	0.106	
	FU2	75.07 (70.88, 79.25)	47.08 (35.53, 58.64)	63.48 (53.29, 73.68)	<0.001*	Normal vs. persistent: <0.001*, recovered vs. persistent: 0.044*
P-value time-effect within-group		<0.001*	0.213	<0.001*	Time*group: 0.003*	Normal vs. persistent BL to FU2 : 0.001*

All p-values (within-group, between-group at each time-point and interaction term) < 0.028* (Benjamini-Hochberg correction), all post-hoc p-values underwent a Bonferroni correction and p-value set to <0.05*, all no reported post-hoc p-values > 0.05.

Abbreviations: BL= baseline, FU= follow-up, CI= confidence interval, KOOS= Knee Injury and Osteoarthritis Outcome score, PPT= pressure pain threshold, TA= m. Tibialis anterior, MK= medial knee, LK= lateral knee, ECRL= m. Extensor carpi radialis longus, FH= forehead, TCA= thermal cold allodynia, THA= thermal heat allodynia, TS= temporal summation, CPM= conditioned pain modulation, CSI= Central Sensitization Inventory, KOOS= Knee Injury and Osteoarthritis Outcome Score

Discussion

This study aimed to determine whether the change in pain intensity over time differs between somatosensory functioning evolution profiles in KOA patients undergoing TKA. This study revealed that the three somatosensory functioning subgroups (separately classified according to all seven grouping variables) decreased in pain score (= less pain) from baseline to three months and one-year post-TKA, except for the persistent disturbed somatosensory group classified according to the CSI which had no change in pain-score over time. In addition, the persistent disturbed somatosensory functioning group had less pain-improvement from baseline to one-year post-TKA, and worse pain intensity scores at one-year post-TKA compared to the normal somatosensory group classified according to local heat allodynia and CSI. Moreover, the same subgroup classified according to the CSI also exhibited worse pain intensity scores at one-year post-TKA compared to the recovered somatosensory functioning group. The persistent disturbed somatosensory functioning group classified according to local PPT and TS also presented worse pain intensity scores one-year post-TKA compared to the normal somatosensory functioning group.

Interpretation of findings

Our hypothesis of no or less pain improvement or worse pain scores one-year post-TKA in the persistent disturbed somatosensory functioning group (i.e. indicative of centrally-driven central sensitization) compared to the other groups was only confirmed with the difference in pain improvement over time or pain intensity one-year post-TKA between the normal and persistent disturbed somatosensory group classified according to four of the seven grouping variables. This aligns with the notion that, especially in the persistent disturbed somatosensory functioning group other factors can contribute to persistent post-TKA pain (44), beyond the peripheral source of nociception (KOA), and are often overlooked factors in current rehabilitation (45,46).

No differences between the recovered somatosensory functioning group and the other groups were found, except for the one-year post-TKA pain score between the recovered and persistent disturbed somatosensory functioning groups according to the CSI group classification. The absence of differences in the QST grouping classification variables could suggest the likelihood that chronic post-TKA pain is also associated with various other preoperative variables (including also psychological, sociodemographic and functional factors (7)), beyond specific somatosensory dysfunction. This plausible theory gains support from the highly clinically relevant differences in the CSI grouping variable, which also includes questions about state psychological factors (a dimension not covered by QST). It is possible that delving more into the evolution of psychological variables, commonly associated with primary chronic pain (14) and not limited to somatosensory dysfunction, may reveal additional distinctions. However, future research should confirm or refute this proposition.

Notably, pain intensity values at one-year post-TKA of the recovered somatosensory functioning group are in between the values of the other two groups. Better scores were seen compared to the persistent disturbed somatosensory functioning group, but worse compared

to the normal somatosensory functioning group (except for groups based on CPM or widespread PPT). This might be an indication that chronic pain indeed needs to be approached as a continuum, meaning that overlap between different mechanisms (e.g. no-, peripherally-, or centrally-driven disturbed somatosensory functioning in current study) can be present (47).

Another possible explanation for the absence in differences between the recovered and persistent disturbed somatosensory functioning group is, apart from the cut-off of 40 on the CSI (31), a consensus about the optimal methodology to assess disturbed somatosensory functioning, including normative and cut-off values is lacking. While we adhered to previous literature and theoretical rationale (33–36) in defining persisted disturbed vs. non-disturbed somatosensory functioning groups using QST methods, it should be acknowledged that this is an exploratory effort, emphasizing the need for confirmation in future research.

Relation to previous literature

Two previous studies on somatosensory functioning subgroups in KOA patients undergoing TKA (18) showed that the preoperative disturbed somatosensory functioning group had higher postoperative pain intensity scores six months post-TKA, or a higher proportion of participants with moderate-to-severe one-year post-TKA pain (19) compared to the normal somatosensory functioning group. This aligns with four of our grouping variables, but contrasts with the other three. More specifically, our study revealed that this difference was only seen between the normal and persistent disturbed somatosensory functioning group, and not between the recovered and normal somatosensory group, suggesting that preoperative disturbed somatosensory functioning alone is not as strongly associated with worse post-TKA pain-scores as pre- and postoperative disturbed somatosensory functioning. Importantly, these studies relied on baseline painDETECT scale scores to form subgroups (high neuropathic-like pain symptoms vs. low neuropathic-like pain symptoms), lacking focus on other specific somatosensory functioning variables and longitudinal changes as in the current study.

Two additional studies in osteoarthritis also adopted subgroup analyses instead of focusing on osteoarthritis patients in general, using chronic pain after surgery (NRS pain score at 12 months post TKA ≥ 3 (21), or NRS pain score at 6 weeks post total hip arthroplasty > 0 (22)) or not (NRS pain score at 12 months < 3, or NRS pain score = 0) as grouping variable, and somatosensory functioning as outcome variables. Petersen et al. (21) showed significant improvement of all PPTs after surgery in the no chronic pain group, while the chronic pain group only had significant improvement for widespread PPT. However, no between-group differences were significant. Similarly, Izumi et al. (22) found no differences regarding PPT outcomes. The current study found between-group differences classified according to local PPT for one-year post-TKA pain, which is in contrast to Petersen et al. (21), but no differences between-groups classified according to widespread PPT, aligning with both studies (21,22). Concerning TS, within-group analyses in Izumi et al. (22) revealed improvement in the no pain group after surgery, but not in the pain group. In addition, Petersen et al. (21) also showed worse TS values in the chronic pain subgroup compared to the no chronic pain group at 12 months post-TKA. The current study found that all subgroups classified according to TS improved in pain intensity over time, but between-group differences classified according to

TS were also found at one-year post-TKA. No differences for CPM were found in both studies (21,22), which is also in line with findings of the current study.

Implications for future research and clinical practice

The present study represents an initial effort in subgrouping based on somatosensory profiles. However, future research should further validate these variables and methods to accurately capture somatosensory functioning groups in KOA patients due to the existing variability in QST methods (48), including cut-offs and normative values. In clinical practice, recognizing the potential existence of a 'centrally-driven central sensitization'-subgroup in KOA patients, as indicated by the presence of self-reported central sensitization according to baseline and one-year post-TKA CSI scores in the current study, can be relevant. Healthcare professionals may consider additional therapeutical approaches for this subgroup, such as multidisciplinary pain management programs (49), next to the more peripheral focus of today to achieve comprehensive pain relief (16,17). This could additionally have positive influence on healthcare and society, as lower healthcare and society costs are expected when the disorder and source of pain is more adequately targeted (50,51).

Strengths and limitations of the study

This study presents with several strengths. First, this study has taken the first step to account for differences in somatosensory functioning evolution within the KOA population and whether this is related to the evolution of pain intensity over time. Next, thorough statistical analyses including appropriate missing data analysis in combination with the presentation of a broad spectrum of different somatosensory functioning grouping variables was performed. A limitation of this study is the broad range of sample sizes in the different somatosensory functioning groups. However, the amount of grouping variables was kept to a minimum by bundling local and widespread measurements. The different QST variables were presented separately, because they measure different constructs of (possible) disturbed somatosensory functioning (CPM measures the endogenous pain inhibition system, TS measures the excitability of the ascending pathways, etc..) (12). However, studies that validate the ideal methods to assess somatosensory functioning, cut-offs and normative values are necessary. Last, also the CPM-method, for which patients who had a NRS score of 0/10 on the test-stimulus were excluded, is a possible limitation. It is possible that the noxious stimulus was too low to provoke a CPM effect and resulted in unexpected results**.**

Conclusion

The present study classified KOA patients undergoing TKA in three somatosensory functioning evolution groups (normal, persistent disturbed and recovered) based on seven variables that were considered proxies of somatosensory functioning. The study compared pain intensity evolution from baseline to post-TKA and pain intensity at one-year post-TKA between the groups and found differences between the three groups classified according to four out of seven grouping variables (local PPT, and heat allodynia, TS and CSI). The most important finding was that the persistent disturbed somatosensory functioning group had less pronounced pain improvement (based on CSI and local heat allodynia) and had a worse pain scores one-year post-TKA (based on CSI, local PPT and heat allodynia and TS) compared to the

to normal somatosensory functioning group. The persistent disturbed somatosensory functioning group had also worse pain scores one-year post-TKA compared to the recovered group classified according to the CSI. These are preliminary results suggesting a 'centrally-driven central sensitization'-subgroup in KOA patients awaiting TKA, comprising their less pain improvement and disturbed somatosensory functioning after TKA. Future research should further validate methods, cut-offs and normative values to adequately assess somatosensory functioning, including studies with bigger sample sizes regarding the disturbed somatosensory functioning group.

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PART 2: Predictors of (in)sufficient treatment outcome in individuals with osteoarthritis

Chapter 6: Preoperative glycaemic control, number of pain locations, structural knee damage, self-reported central sensitisation, satisfaction, and personal control are predictive of one-year postoperative pain and change in pain from pre- to one-year post-total knee arthroplasty

Sophie Vervullens[1,2,3*], Lotte Meert[1,2,3*], Rob J.E.M. Smeets[2,3,4], Jonas Verbrugghe[1,8], Peter Verdonk[6], Christiaan H.W. Heusdens[5], Frank Th.G. Rahusen[7], Mira Meeus[1,3]

[1]Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium

[2]Research School CAPHRI, Department of Rehabilitation Medicine, Maastricht University

[3]Pain in Motion International Research Group (PiM), www.paininmotion.be

[4]CIR Clinics in Revalidatie, location Eindhoven, The Netherlands

[5]Department of Orthopedics and Traumatology, University Hospital of Antwerp, Antwerp, Belgium, and Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium

[6]ORTHOCA, Antwerp, Belgium and ASTARC department, Antwerp University, Belgium

[7]Department of Orthopaedics, St Jans Gasthuis Weert, The Netherlands

[8]REVAL-Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Hasselt, BELGIUM.

*= shared first author

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Abstract

Purpose: To identify preoperative predictors for one-year post-total knee arthroplasty (TKA) pain and pre- to post-TKA pain difference in knee osteoarthritis (KOA) patients.

Methods: From March 2018 to July 2023, this prospective longitudinal cohort study enrolled KOA patients awaiting TKA from four hospitals in Belgium and the Netherlands. Different biopsychosocial predictors were assessed preoperatively by questionnaires and physical examinations (input variables). The Knee injury and Osteoarthritis Outcome Score (KOOS) subscale Pain was used to measure pain intensity. The absolute KOOS subscale Pain score one year post-TKA and the difference score (ΔKOOS = one year postoperative - preoperative) were used as primary outcome measures (output variables). Two multivariable linear regression analyses were performed.

Results: 223 participants were included after multiple imputation. Worse absolute KOOS subscale Pain scores one year post-TKA and negative or closer to zero ΔKOOS subscale Pain scores were predicted by self-reported central sensitization, lower KOA grade and preoperative satisfaction, and higher glycated haemoglobin, number of pain locations, and personal control (adjusted R2 = 0.25). Additional predictors of negative or closer to zero ΔKOOS subscale Pain scores were being self-employed, less preoperative pain and better self-reported function (adjusted R2= 0.37).

Conclusion: This study reports different biopsychosocial predictors for both outcomes that have filtered out other potential predictors and provides value for future studies on developing risk assessment tools for the prediction of chronic TKA pain.

Introduction

Despite the generally high success rate of total knee arthroplasty (TKA), approximately 20% of patients experience chronic postoperative pain (1-3). Understanding and identifying factors associated with chronic TKA pain is crucial to identify causal predictors, which could optimize interventions and facilitate stratified care (2, 4).

A recent umbrella review of 18 systematic reviews summarized all potential preoperative predictive factors for chronic postoperative pain after TKA or total hip arthroplasty (5). The factors identified encompassed the entire biopsychosocial model (Table 1). However, as this was an umbrella review, distinguishing findings of multivariable and univariate analyses was not possible (5). Univariate analyses reveal potential predictive factors (i.e. factors associated with a certain outcome) but these should not be confused with definitive predictors or causal factors. To identify the latter, consistent findings from high-quality multivariable regression models are necessary. This enables the real predictive factors to be distinguished by 'filtering out' irrelevant factors (4, 6).

Fortunately, a recent systematic review and meta-analysis of factors associated with post-TKA pain presents a distinction between results of univariate and multivariable analyses (7). Only higher state anxiety and depression had consistent bidirectional univariate associations with persistent post-TKA pain, and higher preoperative pain severity was the only independent predictive factor emerging from all multivariable analyses. The authors emphasize that current findings are from low-quality evidence and based on limited data, warranting more research. Moreover, multicentre prospective studies that comprehensively combine a broad range of possible biopsychosocial predictors into one multivariable analysis are scarce (7), with the study of Edwards et al. (8) predicting being the only one to date.

Despite the significant contribution of Edwards et al. (8), only potential predictors of six-month post-TKA pain were studied, although a recovery period of one year is regarded as essential for complete recuperation after TKA (9). This makes more exhaustive research in this domain necessary to offer potentially valuable insights for future studies to identify causal predictors for chronic post-TKA pain, which in turn could improve the quality of care for TKA care by developing consistent clinical prediction models. It is for instance postulated that prehabilitation may improve post-surgical outcomes by targeting modifiable causal predictive factors for post-TKA pain (4, 10).

Thus, the aim of this prospective, multicentre longitudinal study was to determine preoperative predictors for one-year post-TKA pain and difference in pain from pre- to post-TKA in knee osteoarthritis (KOA) patients. These predictors, encompassing the entire biopsychosocial model, were analysed using two multivariable linear regression models.

Table 1: Prognostic factors of postsurgical pain with confidence in conclusion level according to the umbrella review of Fernández-de-Las-Peñas et al. (5)

Variable	High/ moderate confidence in conclusion for association with worse postop pain	High/ moderate confidence in conclusion for no association with worse postop pain	Low/ very low confidence in conclusion for association with worse postop pain	Low/ very low confidence in conclusion for no association with worse postop pain	Conflicting or not possible to draw a conclusion
Demographic factors	African-American ethnicity				Age, gender
Structural variables			Less radiographic damage, presence of preoperative flexion contracture		
Metabolic variables			Presence of diabetes mellitus		BMI
Functional variables	Poor function			Lower ROM	
Pain-related variables	Pain at other sites, higher pain severity, the presence of neuropathic pain, disturbed somatosensory functioning, opioid use				
Psychological variables	Higher level of pain catastrophizing, anxiety, depression, fear of movement, and worse mental health and coping				Having purpose in life, psychological distress, patient expectations, quality of life, self-efficacy
Social variables	Lower social support				Educational level, socioeconomic status, personality (optimistic or pessimistic)
Comorbidities		Heart and lung disease, stroke, nervous system disorders such as Alzheimer's disease, Parkinson's disease, dementia, and poor blood circulation	Contralateral hip osteoarthritis		Kidney disease, low back pain
Other variables					Length of the waiting list

Abbreviations: ROM= Range of Motion, BMI= body mass index

Methods

The Strengthening The Reporting of Observational studies in Epidemiology (STROBE) guidelines for cohort studies were used to conduct this longitudinal prospective cohort study (11). The protocol is registered at clinicaltrials.gov (NCT05380648).

Setting and participants

This multicentre prospective cohort study was conducted from March 2018 to July 2023 (recruitment period between March 2018 and July 2022, followed by one-year data collection). Patients with KOA awaiting TKA were recruited at the University Hospital of Antwerp and AZ Monica in Belgium, and the Academic Hospital of Maastricht and St Jans Gasthuis Weert in the Netherlands. The ethical committees of both countries approved the study (BE300201319366 and NL6465408618, respectively).

Participants were eligible if diagnosed with KOA, awaiting their first TKA, and aged 40 years or older. Exclusion criteria included neurological or systemic diseases that could potentially impact pain perception or the inability to speak or understand Dutch. After providing informed consent, participants completed demographic, psychological, functional, and symptom-related questionnaires, as described below, either on paper or online via Qualtrics (www.qualtrics.com). Two executive researchers (SV or LM) conducted the physical measurements at the Sensoric Functioning Lab (M2SENS) at the University of Antwerp's campus 'Drie Eiken' for Belgian participants and in the orthopaedic department of the Academic Hospital Maastricht and St Jans Gasthuis Weert for Dutch participants. Both researchers had completed practical skills training and used standardized measurement forms. Data were collected four weeks before TKA surgery (baseline) and one year post-TKA. All individuals were asked to stop early-stage pain medications, coffee, and alcohol 24h before physical evaluations.

Outcome variable

The 'pain' subscale of the Knee injury and Osteoarthritis Outcome Score (KOOS) was used as the primary outcome measure for pain intensity one year after surgery. Scores were converted to percentages, and ranging from zero (extreme pain) to 100 (no pain) (12). The absolute KOOS Pain score one year post-TKA and the difference in KOOS Pain scores pre- and postoperatively (Δ KOOS = postoperative - preoperative) were used as outcome measures. A negative score or a score closer to zero for Δ KOOS subscale pain was interpreted as a less sufficient outcome.

Possible predictors

All potential predictors were prospectively collected four weeks prior to the TKA surgery, except for C-reactive protein (CRP) which was retrospectively extracted from patients' medical records. A list of these possible predictors, along with their respective measurement methods and clinimetric properties, can be found in Table 2.

Table 2: Overview of possible predictors

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Demographic variables		
Age	Date first physical measurement - birth date	-Demographic questionnaire -Continuous variable
Sex	Man or woman	-Demographic questionnaire -Nominal variable
Structural factors		
Grade of KOA	-X-ray images in AP, profile and Rosenberg weight-bearing position(13). -Retrospectively extracted from the participant's record by the general practitioner of the participants or the participants themselves -If one of the images was not available, scoring was based on the available image(s). If no X-ray image was available, MRI in coronal and sagittal position were extracted and MRI grading was transferred to K&L grading. If none of the X-ray or MRI images could be found, this variable was recorded as missing value. -All images were scored by the same orthopedic surgeon (C.H.).	-K&L scale (14) or MRI grading system (15) -Ordinal variable -5-point Likert scale: 0 (no KOA) to 4 (worst grade of KOA) -K&L: Good reliability and validity in KOA (16) MRI grading: Good reliability and responsiveness (17)
Metabolic and inflammatory factors		
BMI	-Length: self-reported -Weight: standing on an electronic scale at the moment of testing	-Length: demographic questionnaire; weight: electronic scale -Continuous variable -Formula: kg/cm^2 -Valid(18)
HbA1c	-Sitting position -Taking a blood sample by pricking into a fingertip	-A1CNow+ system (*PTS Diagnostics, China*) and a fingerprick (19) -Continuous variable -% -Accurate measurement to detect diabetes (20)
Fat mass **Lean mass**	-Supine lying position -Skinfold electrodes on hand and foot connected to the device	-Bioelectrical Impedance Analysis (Bodystat Quadscan 4000) -Continuous variable -% -Accurate measurement to measure body composition (21)
C-reactive protein	-Blood sample before surgery, retrospectively extracted from participant's record by executive researchers	-Blood sample -Continuous variable -mg/L -Reliable method (22)
Functional variables		
Strength m. Quadriceps **Strength m. Hamstrings**	-Sitting position with hip and knee in 90°, upper leg fully supported by the table, and arm crossed over their chest. Isometric strength measurement was assured by using a traction belt. -Perform flexion (Hamstrings) or extension (Quadriceps) of the knee against the device -3 times, highest value used for analysis	-MicroFET 2 hand-held dynamometer (*ProCare, Groningen*) -Continuous variable -Kgf -Reliable and valid (23)

Table 2 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Functional variables (continued)		
Proprioception	-Sitting position with hip and knee in 90°, upper leg fully supported by the table -Repositioning error during a knee joint position sense test (20°, 45° and 70° flexed knee) -Twice assessed, mean of 6 trials used for analysis	-Plurimeter *(Dr. Rippstein, Switzerland)* -Continuous variable -° of knee angle -Reliable (24)
Functional symptoms	-Questionnaire: questions related to stiffness, noises and mobility of the knee	-KOOS subscale symptoms -Continuous variable -5-point Likert scale: 0 (no symptoms) to 4 (always symptoms) for question 1 to 5, 4 (always) to 1 (never) for question 6 and 7. Scores were converted to a 0–100 scale, ranging from zero (extreme knee problems) to 100 (no knee problems) -Valid and reliable (25)
Physical function	-Questionnaire: asking questions related to different activities	-KSSS Functional Score -Continuous variable -Scored 0 (impossible to perform any activities) – 120 (possible to perform any activity); Sum of subscales 'walking and standing', 'standard activities', 'advanced activities' and 'discretionary activities -Valid and reliable (26)
	-Sitting position with arms resting next to the body -Standing up and again sitting down as much as possible without support in 30s	-30 CST -Continuous variable -Number of times to stand up -Reliable (27)
Pain-related variables		
Pain intensity	-Questionnaire: questions related to pain intensity and specific movements during previous months	-KOOS subscale pain -Continuous variable -5-point Likert scale: 0 (no pain) to 4 (unbearable pain); Scores were converted to a 0–100 scale, ranging from zero (extreme pain) to 100 (no pain) -Valid and reliable (25)
Number of pain locations	To draw their pain on a body chart by crossing all body parts that were painful during the last week	-Pain drawings on body chart -Continuous variable -Number of body parts -Valid and reliable (28)

Table 2 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Somatosensory functioning		
Pressure pain thresholds	-A probe (1cm2) was placed perpendicular to the test surface and pressure was increased until the subject reported a feeling of discomfort. Measured at the medial and lateral knee joint-line, and m. Tibialis anterior of the affected knee, the m. Extensor carpi radialis longus (ECRL) of the non-dominant side, and the forehead.	-Hand-held pressure algometer (Wagner FDX 25 Force Gage, USA) -Continuous variable -An average of two measurements, separated by a pause of 30 seconds, was taken for analysis (Newton). -Reliable (29)
Temporal summation and painful after sensations	-Thirty pinpricks were given at a pace of 1 pinprick/second. Measured at the medial knee joint-line and medial wrist of the affected side.	-Von Frey monofilament (60 grams) -Continuous variable -NRS score 0-10. -Reliable (30, 31)
Heat and cold allodynia	-A roll-movement was performed for 10 seconds at the medial and lateral knee joint-line of the affected knee, and the m. Extensor carpi radialis longus of the non-dominant side.	-Thermal rollers (Rolltemp II Somedic Senselab) having a temperature of 25°C (cold stimulus) and 40°C (hot stimulus) -continuous -NRS score 0-10. -reliability unknown
Conditioned pain modulation	-First, a temperature corresponding to a pain intensity NRS score of 4/10 (up to a maximum of 46°C) was identified at the wrist of the affected side. This identified temperature (or 46°C when the 4/10 on a NRS was not reached) was used as test stimulus. The participant had to score the test stimulus on an NRS 4 times. After a pause of 120 seconds, a conditioning stimulus (with a temperature of 0.5°C more than the test stimulus) was added at the wrist of the non-affected side for 65 seconds and 20 seconds after its initiation, the test stimulus was repeated. Again, the participants had to score their pain for 4 times, but only on the test site. If the NRS at 46°C and the mean of the NRS of test stimulus was equal to zero, the participant was excluded for analysis.	-Q-sense CPM (Medoc, USA) -Continuous variable -NRS: 0 (no pain) to 10 (unbearable pain); Percentage change ((absolute score/NRS score during test stimulus)*100) scores were used for analysis -Reliability to better confirmed (31)
Sensitization-associated symptoms	-Questionnaire: assesses self-reported central sensitization signs in 25 questions.	-CSI -Continuous variable -Five-point Likert scale with zero meaning ‘never’ and four meaning ‘always’; Score from 0-100 -reliable (32)

Table 2 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Psychological variables		
Pain catastrophizing	-Questionnaire: questions related to pain catastrophizing -Three subdomains: magnification, rumination and helplessness	-PCS -Continuous variable -5-point Likert scale: 0 (not at all) to 4 (all the time); Total score was used for the analysis -Valid and reliable (33, 34)
Depression Anxiety	-Questionnaire: questions related to depression and anxiety -Two subscales : depression and anxiety	-HADS -Continuous variable -4-point Likert scale: 0 to 3 (variable meaning per item); Scores of two subscales were used for analysis -Valid and reliable (35)
Expectations	-Questionnaire: questions related to surgery result expectation -Subscale 'expectations' was used for analysis	-KSSS -Continuous variable -6-point Likert scale: 0 (no expectation) to 5 (high positive expectations) -Valid and reliable (26)
Satisfaction	-Questionnaire: questions related to satisfaction about knee complaint -Subscale 'satisfaction' was used for analysis	-KSSS -Continuous variable -5 items scored from 0 (no expectation) to 8 (high positive expectations) -Valid and reliable (26)
Consequences	-Questionnaire: questions related to consequences of KOA complaint	
Timeline	-Questionnaire: questions related to timeline of KOA complaint	
Timeline cyclical		
Personal control	-Questionnaire: questions related to personal control over the KOA disease	-IPQR -Continuous variable -6 items scored from 1 (strongly disagree) to 5 (strongly agree), subscale identity scored differently: 9 symptoms related to illness scored 0 (no) or 1 (yes) -Reliable, expect for subscale coherence (36)
Treatment control	-Questionnaire: questions related to treatment control over the KOA treatment	
Emotional representation	-Questionnaire: questions related to emotional representation	
Illness cohorence	-Questionnaire: questions related to illness coherence	
Identity	-Questionnaire: questions related to experienced symptom related (or not) to the disease	

Table 2 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Social variables		
Work	-Questionnaire: questions related to work level including pension, self-employed, white-collar worker, laborer, unemployed, or other	-Demographic questionnaire -Nominal variable -Scored from 1 to 6
Education	-Questionnaire: questions related to educational level going from no degree, primary school degree, technical secondary school degree, higher secondary school degree, high school degree, university degree to other	-Demographic questionnaire -Nominal variable -Scored from 1 to 7
Marital status	-Questionnaire: questions related to marital status including married, divorced, single, widow(er) or other	-Demographic questionnaire -Nominal variable -Scored from 1 to 5

Abbreviations: AP = anterior-posterior; MRI = magnetic resonance images; K&L scale = Kellgren & Lawrence scale; KOA = knee osteoarthritis; N/A = not applicable; BMI = body mass index; HbA1c = glycated haemoglobin; mg/l = milligram/litre, kgf = kilogram force; KOOS = Knee Osteoarthritis Outcome and Index Score; KSSS = Knee Society Scoring System; 30CST = 30s timed chair stand test; ECRL = extensor carpi radialis longus; g = gram; NRS = numerical rating scale; h = hour; SPS = somatosensory processing signs; CPM = conditioned pain modulation; CSI = Central Sensitization Inventory; PCS = Pain Catastrophizing Scale; HADS = Hospital Anxiety and Depression Scale; IPQR = Illness Perception Questionnaire Revised

Statistical analysis

R software (version 4.2.3) (multiple imputation) and the IBM Statistical Package for Social Sciences Version 29 (SPSS, IBM Corporation, Armonk, NY) (all other statistical analyses) were used.

First, univariate outliers were checked using boxplots and only deleted if due to data input mistakes. Thereafter, missing data were checked, and multiple imputations (n= 10 imputed datasets), using predictive mean matching with the 'mice' package in R, were performed for data with <40% missing values (37). Data were presented as mean and standard deviations (continuous demographic data), or number and frequency (categorical demographic data). Rubin's rules were applied to pool all data.

Next, the assumption of multicollinearity was checked with univariate association analyses using Pearson correlation (normal and linear distributed data) and Wilcoxon rank-sum tests (non-normal and non-linear distributed data) between the possible predictors. When variables were highly correlated (correlation coefficient $r \geq 0.70$ or ≤ -0.70), only one was chosen to include for further analyses (choice based on expertise). In addition, the variance inflation factor was checked and, if > 4, the variable was deleted from analysis (38).

Last, a multivariable regression analysis of variance (ANOVA) was performed for each outcome variable. Univariate associations between the two outcomes and the possible predictors were checked using Pearson correlation (normally and linearly distributed data) and Wilcoxon rank-sum tests (non-normally and non-linearly distributed data), and variables with $p < 0.2$ were

included at the start of the multiple regression ANOVA to ensure that the rule of thumb of one predictor per 10 subjects was met (38). If non-linearity with one of the outcome variables was present, this variable was transformed to a categorical variable, a logarithmic value, or a box-cox transformation, to meet this assumption. Also, normality and homogeneity of variance of the residuals were checked using histograms and scatterplots. Backward selection was performed using the median p-values of the 10 imputed datasets (39). If this p-value was < 0.05, the variable was kept in the model. All results were pooled using Rubin's ruleseym, and median p-values for the 10 imputed datasets were reported (39).

Sample size

All eligible candidates between March 2018 and July 2022 were included, based on a priori sample size calculations for another study in this project (40). The rule of a minimum of 10 subjects per predictor was used to decide the number of predictors in the multivariable linear regression models (38).

Results

Participants

A total of 223 participants were analysed after multiple imputation, of which 18 participants were tested less than four weeks preoperatively due to COVID-19 surgery postponement. However, these 18 reported no difference with other participants in ΔKOOS Pain or in the absolute scores at one year post-TKA ($p > 0.05$). Fifty-three (23.7%) participants underwent surgery in the Netherlands (two [1%] in the University Hospital of Maastricht; 51 [23%] in SJG Weert), and 170 (76.3%) in Belgium (41 [18%] in the University Hospital of Antwerp; 129 [58%] in AZ Monica). All demographic, baseline values and outcome scores are presented in Table 3.

Missing data in the outcome variables and potential preoperative predictors

A detailed overview of all missing data with reasons, at baseline and at one-year follow-up, can be found in Figure 1 and Table 3. The variables CRP-value, fat- and lean body mass were not imputed because the missing data exceeded 40% (37). These variables were therefore excluded from the analyses. However, for all other data, multiple imputation was used, and therefore all participants (n= 223) were analysed for all univariate correlation and both multivariable linear regression analyses.

Univariate associations

Correlation between all possible predictors

To meet the assumption of non-multicollinearity, the pressure pain threshold (PPT) measured at the lateral knee-joint line, Tibialis anterior, and on the forehead, and thermal allodynia measured at lateral knee-joint line were excluded from further analyses (high correlations ($r > 0.70$) with other possible predictors, Online Resource 1).

Table 3: Demographics, baseline and outcome scores of participants

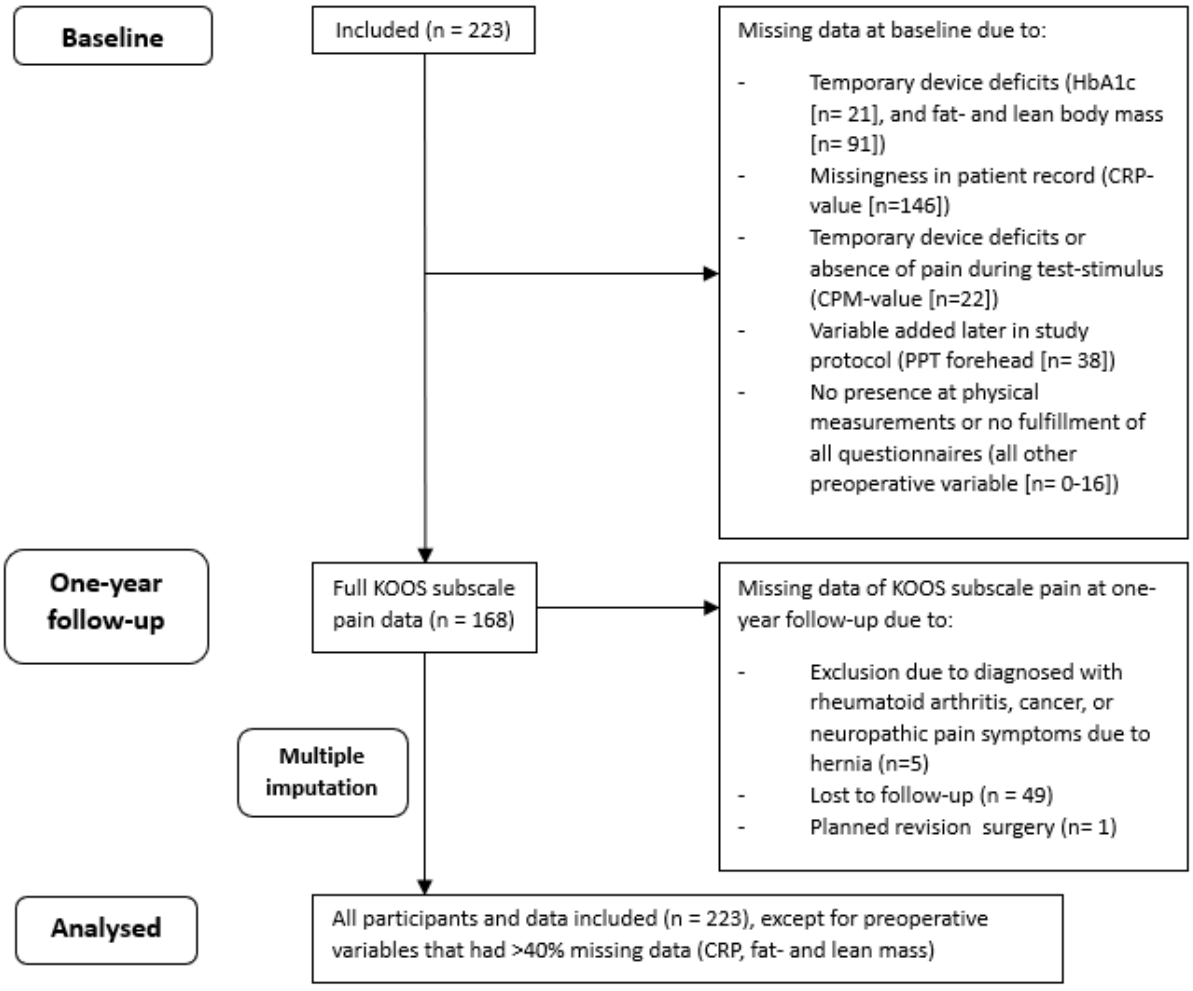
Continuous variables			Categorical variables		
Variable	**Mean (SD)**	**N Missing (%)**	**Variable**	**N (%)**	**N missing (%)**
Demographic variables			**Demographic variables**		
Age (y)	65.52 (7.66)	0 (0)	Sex (n, % F)	111 (49.8)	0 (0)
Metabolic and inflammatory variables			**Structural variables**		
BMI (kg/cm^2)	29.99 (5.25)	3 (1.3)	K&L scale		9 (4)
HbA1c (%)	5.60 (0.60)	21 (9.4)	1	4 (1.8)	
Fat (%)	35.15 (8.88)	91 (40.8)	2	44 (19.7)	
Lean (%)	64.85 (8.88)	91 (40.8)	3	77 (34.5)	
C-reactive protein (mmol/dl)	3.51 (4.83)	146 (65.5)	4	89 (39.9)	
			Social variables		
Functional variables			Marital status		10 (4.5)
Strength m. Quadriceps (kgf)	27.37 (13.04)	3 (1.3)	Married	125 (68.2)	
Strength m. Hamstrings (kgf)	11.73 (5.94)	3 (1.3)	Divorced	20 (9.0)	
Proprioception (°)	4.44 (2.04)	6 (2.7)	Single	8 (3.6)	
KOOS symptoms (0-100)	48.89 (18.06)	12 (5.4)	Widow(er)	19 (8.5)	
30CST (n)	10.66 (3.97)	6 (2.7)	Other	14 (6.3)	
KSSS Functional score (0-100)	43.07 (15.17)	14 (6.3)			
			Work		10 (4.5)
Pain-related variables			Pension	115 (51.6)	
KOOS subscale pain BL (0-100)	44,07 (15.31)	12 (5.4)	Self-employed	15 (6.7)	
Number of pain locations (n)	3.45 (2.24)	16 (7.2)	White-collar worker	29 (13.0)	
PPT m. tibialis anterior (Newton)	50.89 (24.81)	3 (1.3)	Laborer	26 (11.7)	
PPT medial knee (Newton)	42.83 (23.71)	3 (1.3)	Unemployed	2 (0.9)	
PPT lateral knee (Newton)	48.06 (26.58)	3 (1.3)	Other	26 (11.7)	
PPT m. ECRL (Newton)	37.55 (17.24)	3 (1.3)	Education	12 (5.4)	11 (4.9)
PPT forehead (Newton)	30.18 (12.73)	38 (17)	No degree	12 (5.4)	
TS after sensation medial knee (0-10)	0.40 (1.11)	4 (1.8)	Primary	47 (21.1)	
TS medial knee (Difference in NRS)	1.23 (2.02)	3 (1.3)	Technical secondary	1 (0.4)	
TS after sensation medial wrist (0-10)	0.16 (0.59)	4 (1.8)	Higher secondary	50 (22.4)	
TS medial wrist (Difference in NRS)	0.98 (1.56)	4 (1.8)	High school	20 (9.0)	
TCA medial knee (0-10)	0.36 (0.96)	4 (1.8)	University	41 (18.4)	
THA medial knee (0-10)	0.82 (1.46)	4 (1.8)	Other	12 (5.4)	
TCA lateral knee (0-10)	0.27 (0.91)	4 (1.8)			
THA lateral knee (0-10)	0.37 (1.09)	4 (1.8)			
TCA m. ECRL (0-10)	0.19 (0.75)	4 (1.8)			
THA m. ECRL (0-10)	0.45 (1.11)	4 (1.8)			
CPM (%)	9.94 (48.31)	24 (10.8)			
CSI (0-100)	28.06 (13.14)	12 (5.4)			
Psychological variables					
PCS total score (0-52)	16.24 (10.33)	11 (4.9)			
HADS depression (0-21)	5.06 (3.26)	10 (4.5)			
HADS fear (0-21)	5.34 (4.01)	10 (4.5)			
KSSS expectation (3-15)	13.96 (1.63)	13 (5.8)			
KSSS satisfaction (0-40)	15.67 (7.35)	13 (5.8)			
IPQR Timeline (6-30)	17.77 (5.25)	10 (4.5)			
IPQR Consequences (6-30)	19.34 (4.21)	10 (4.5)			
IPQR Timeline cyclical (4-25)	11.97 (3.85)	10 (4.5)			
IPQR personal control (6-30)	19.74 (3.94)	10 (4.5)			
IPQR treatment control (5-25)	18.06 (3.10)	10 (4.5)			
IPQR Emotional representations (6-30)	15.73 (4.63)	10 (4.5)			
IPQR Illness coherence (5-25)	18.74 (2.12)	10 (4.5)			
IPQR Identity (0-14)	2.07 (1.43)	9 (4)			

Table 3 (continued)

Variable	Continuous variables Mean (SD)	N Missing (%)
Outcome variables		
Δ KOOS subscale pain (Diff KOOS FU - BL)	28.66 (26.01)	60 (26.9)
KOOS subscale pain FU (0-100)	73.45 (24.15)	55 (24.7)

Abbreviations: BMI = body mass index; kg/m2 = kilogram/metre squared; PPT = pressure pain threshold; ECRL = extensor carpi radialis longus; TS = temporal summation; THA = thermal heat allodynia; TCA = thermal cold allodynia; CSI = central sensitization inventory; Diff = difference; NRS = numerical rating scale; CPM = conditioned pain modulation; kgf = kilogram force; N = newton; HbA1c = glycated haemoglobin; IPQR = Illness Perceptions Questionnaire Revised; PCS = Pain Catastrophizing Scale; HADS = Hospital Anxiety and Depression Scale; KSSS = Knee Society Scoring System; KOOS = Knee injury and Osteoarthritis Outcome Score; mmol/dl = millimole/decilitre; K&L = Kellgren and Lawrence scale; FU = follow-up one year post-TKA; BL = baseline

Figure 1: Flow diagram of missing data



Abbreviations: n = number of participants; FU = Follow-up; HbA1c = glycated haemoglobin, CRP = creatine phosphate; CPM = conditioned pain modulation; PPT = pressure pain threshold; KOOS = Knee Injury and Osteoarthritis Outcome Score

Table 4: **Results of univariate associations**

Predictors	KOOS subscale pain FU	Δ KOOS subscale pain
	r-value (P-value)	
Demographic variables		
Age	0.138 (0.073)*	0.014 (0.853)
Sex	0.037 (0.600)	0.004 (0.953)
Metabolic and inflammatory variables		
BMI	0.057 (0.432)	0.106 (0.130)*
HbA1c	-0.210 (0.008)*	-0.186 (0.016)*
Functional variables		
Strength m. Quadriceps	0.066 (0.386)	-0.054 (0.488)
Strength m. Hamstrings	0.028 (0.723)	-0.070 (0.389)
Proprioception	0.037 (0.612)	-0.015 (0.835)
KOOS symptoms	-0.022 (0.774)	-0.170 (0.026)*
30CST	0.054 (0.507)	-0.029 (0.719)
KSSS Functional score	0.088 (0.229)	-0.296 (<0.001)*
Pain-related variables		
KOOS subscale pain BL	0.189 (0.011)*	0.397 (<0.001)*
Number of pain locations	-0.270 (<0.001)*	-0.136 (0.075)*
PPT m. tibialis anterior	/	/
PPT medial knee	0.101 (0.198)*	-0.005 (0.951)
PPT lateral knee	/	/
PPT m. ECRL	0.151 (0.049)*	0.017 (0.855)
PPT forehead	/	/
TS after sensation medial knee	-0.079 (0.317)	-0.047 (0.557)
TS medial knee	-0.03 (0.690)	0.028 (0.719)
TS after sensation medial wrist	0.051 (0.470)	0.028 (0.684)
TS medial wrist	-0.026 (0.733)	0.023 (0.768)
TCA medial knee	-0.089 (0.298)	0.020 (0.803)
THA medial knee	-0.147 (0.047)*	-0.082 (0.273)
TCA lateral knee	/	/
THA lateral knee	/	/
TCA m. ECRL	-0.048 (0.541)	0.018 (0.811)
THA m. ECRL	-0.108 (0.174)*	-0.054 (0.487)
CPM	0.077 (0.346)	-0.054 (0.488)
CSI	-0.328 (<0.001)*	-0.172 (0.022*
Psychological variables		
PCS total score	-0.159 (0.035)*	-0.007 (0.920)
HADS depression	-0.054 (0.504)	0.025 (0.744)
HADS anxiety	-0.189 (0.030)*	-0.119 (0.134)*
KSSS expectation	0.121 (0.119)*	0.091 (0.247)
KSSS satisfaction	0.292 (<0.001)*	-0.124 (0.124)*
IPQR Timeline	-0.012 (0.882)	0.030 (0.683)
IPQR Consequences	-0.066 (0.349)	0.084 (0.277)
IPQR Timeline cyclical	-0.074 (0.333)	-0.124 (0.107)*
IPQR personal control	-0.154 (0.052)*	-0.246 (0.002)*
IPQR treatment control	-0.076 (0.284)	-0.161 (0.020)*
IPQR Emotional representations	-0.179 (0.017)*	-0.034 (0.643)
IPQR Illness coherence	0.034 (0.670)	-0.002 (0.976)
IPQR Identity	-0.155 (0.044)*	-0.043 (0.568)
Structural variables		
K&L scale	0.211 (0.010)*	0.108 (0.181)*
Social variables		
Marital status	-0.084 (0.311)	-0.101 (0.230)
Work	-0.004 (0.953)	0.109 (0.140)*
Education	-0.029 (0.720)	-0.032 (0.685)

Table 4 (continued)

Abbreviations: FU = follow-up one year post-TKA; BMI = body mass index; PPT = pressure pain threshold; ECRL = extensor carpi radialis longus; TS = temporal summation; THA = thermal heat allodynia; TCA = thermal cold allodynia; CSI = Central Sensitization Inventory; Diff = difference; NRS = numerical rating scale; CPM = conditioned pain modulation; HbA1c = glycated haemoglobin; IPQR = Illness Perceptions Questionnaire Revised; PCS = Pain Catastrophizing Scale; HADS = Hospital Anxiety and Depression Scale; KSSS = Knee Society Scoring System; KOOS = Knee injury and Osteoarthritis Outcome Score; K&L = Kellgren and Lawrence scale; BL = baseline; *= $p < 0.2$

Correlation between each possible predictor and absolute KOOS subscale pain scores one-year post-TKA on the one hand, and ΔKOOS subscale pain on the other hand

Seventeen variables were associated with the KOOS Pain score one year post-TKA, and 14 variables with the ΔKOOS Pain, each with a $p < 0.2$. These were consequently included at the start of the multivariable regression model (Table 4).

Multivariable regression models

Data preparation

The variance inflation factor indicated no multicollinearity. The linearity assumption was not met for PPT measured at medial knee-joint line, the Knee Society Scoring System (KSSS) subscale Expectation, and the Illness Perceptions Questionnaire Revised (IPQR) subscale Treatment Control, and heat allodynia measured at m. Extensor carpi radialis longus (ECRL). Therefore, these variables were transformed into their logarithmic forms, except for heat allodynia, for which a box-cox transformation was used. In addition, the linearity assumption was not met for the Central Sensitization Inventory (CSI) and BMI, so these were treated as categorical variables (CSI: 1 = CSI score ≥ 40 and 0 = CSI score < 40 (41); BMI: 0 = < 25 kg/cm2, 1= 25-29.9 kg/cm2, 2 = ≥30 kg/cm2 (42)) because other transformations did not fulfil the linearity assumption.

Multivariable regression models

The final multivariable regression models of KOOS Pain score one year post-TKA and the ΔKOOS Pain had adjusted R^2 values of 0.25 and 0.37, respectively.

Higher HbA1c values, higher number of pain locations, higher IPQR subscale Personal Control scores, a lower KSSS subscale Satisfaction scores, KOA grade (K&L scale grade two), and a score of ≥ 40 on the CSI were significant predictors for lower scores on the KOOS Pain one year after surgery, after backwards selection (Table 5).

The *same variables* were significant predictors for negative or closer to zero ΔKOOS Pain scores**;** however, *K&L scale grade 1* (instead of K&L scale grade 2) was a significant predictor. Moreover, also a *higher KSSS subscale Functional Score, higher KOOS Pain score at baseline, and work status* (being self-employed) were also significant predictors, after backward selection (Table 6).

No other variables were significant predictors for either both outcomes ($p > 0.05$). To ensure adequate interpretation of Table 5 and 6, a real-life example is presented in Table 7 to illustrate prediction of both outcomes.

Table 5: Multiple linear regression model for KOOS subscale pain one-year after surgery

Full multiple linear regression model		
Predictor	**Exp(B) (95%CI)**	**P-value**
(Constant)	142.26 (84.90, 199.62)	<0.001*
Age	0.06 (-0.43, 0.55)	0.688
Hba1c	-6.36 (-12.14, -0.58)	0.021*
KOOS subscale pain baseline	-0.09 (-0.43, 0.25)	0.603
Number of pain locations	-1.69 (-3.42, 0.05)	0.025*
PPT medial knee	-4.63 (-12.31, 3.05)	0.188
PPT m. ECRL	0.13 (-0.18, 0.43)	0.352
THA medial knee	-2.08 (-5.61, 1.46)	0.224
THA m. ECRL	0.84 (-5.62, 7.30)	0.674
CSI ≥ 40	-11.02 (-22.09, 0.05)	0.035*
PCS	0.01 (-0.38, 0.39)	0.838
HADS subscale anxiety	0.23 (-1.10, 1.56)	0.593
KSSS subscale satisfaction	0.77 (0.05, 1.48)	0.008*
KSSS subscale expectations	-9.75 (-22.15, 2.65)	0.104
IPQR subscale identity	-0.36 (-2.92, 2.21)	0.579
IPQR subscale personal control	-0.97 (-1.82, -0.11)	0.016*
IPQR Emotional representations	-0.10 (-1.09, 0.89)	0.648
KLscale= grade 1	-17.87 (-48.44, 12.69)	0.094
KLscale= grade 2	-9.21 (-18.95, 0.52)	0.030*
KLscale= grade 3	-0.42 (-8.27, 7.44)	0.814
R-squared = 0.31 and adjusted R-squared = 0.25		
Final multiple linear regression model after backward selection		
Predictor	**Exp(B) (95%CI)**	**P-value**
(Constant)	126.46 (92.25, 160.67)	<0.001*
Hba1c	-5.62 (-11.08, -0.16)	0.029*
Number of pain locations	-1.61 (-3.28, 0.05)	0.025*
CSI≥ 40	-10.91 (-20.93, -0.89)	0.011*
KSSS subscale satisfaction	0.69 (0.21, 1.16)	0.002*
IPQR subscale personal control	-1.13 (-1.97, -0.30)	0.002*
K&L scale= grade 1	-20.47 (-50.28, 9.33)	0.060
K&L scale= grade 2	-9.60 (-19.02, -0.17)	0.018*
K&L scale= grade 3	-1.11 (-9.07, 6.85)	0.656
R-squared = 0.27 and adjusted R-squared = 0.25		

K&L scale = grade 4 and CSI < 40 are reference categories.
Abbreviations: KOOS = Knee injury and Osteoarthritis Outcome Score; Exp (B) = regression coefficient; CI = confidence interval; HbA1c = glycated haemoglobin; PPT = pressure pain threshold; ECRL = extensor carpi radialis longus; THA = thermal heat allodynia; PCS = Pain Catastrophizing Scale; HADS = Hospital Anxiety and Depression Scale; KSSS = Knee Society Scoring System; IPQR = Illness Perceptions Questionnaire Revised; K&L = Kellgren and Lawrence scale; CSI = Central Sensitization Inventory; BL = baseline; *= $p < 0.05$

Table 6: Multiple linear regression model for ΔKOOS subscale pain

Full multiple linear regression model		
Predictor	**Exp (B) (95%CI)**	**P-value**
(Constant)	168.83 (108.82, 228.84)	<0.001*
BMI= 25-29.9 kg/m2	2.61 (-6.77, 11.99)	0.577
BMI= ≥30 kg/m2	6.89 (-2.35, 16.13)	0.116
Hba1c	-6.40 (-11.98, -0.83)	0.010*
KOOS subscale symptoms	-0.18 (-0.37, 0.02)	0.042*
KSSS subscale functional score	-0.20 (-0.53, 0.12)	0.164
KOOS subscale pain baseline	-0.94 (-1.28, -0.60)	<0.001*
Number of pain locations	-1.81 (-3.50, -0.11)	0.011*
CSI ≥40	-12.98 (-23.94, -2.03)	0.006*
HADS subscale anxiety	0.19 (-0.86, 1.24)	0.591
KSSS subscale satisfaction	0.96 (0.24, 1.69)	0.002*
IPQR subscale treatment control	-8.21 (-25.90, 9.48)	0.270
IPQR subscale personal control	-0.91 (-1.79, -0.04)	0.021*
IPQR subscale timeline cyclical	-0.49 (-1.38, 0.40)	0.278
K&L scale= grade 1	-21.44 (-50.41, 7.53)	0.045*
K&L scale= grade 2	-7.73 (-17.35, 1.88)	0.074
K&L scale= grade 3	-1.08 (-8.78, 6.61)	0.623
Work= pension	-6.98 (-18.14, 4.17)	0.180
Work= self-employed	-17.22 (-33.81, -0.62)	0.010*
Work= white-collar worker	-4.03 (-18.82, 10.76)	0.586
Work= laborer	-12.67 (-26.59, 1.24)	0.042*
Work= unemployed	-14.30 (-59.01, 30.42)	0.358
R-squared = 0.44 and adjusted R-squared = 0.37		
Final multiple linear regression model after backward selection		
Predictor	**Exp (B) (95%CI)**	**P-value**
(Constant)	139.95 (104.58, 175.32)	<0.001*
Hba1c	-5.83 (-11.19, -0.47)	0.018*
KSSS subscale functional score	-0.29 (-0.60, 0.02)	0.022*
KOOS subscale pain baseline	-0.93 (-1.27, -0.59)	<0.001*
Number of pain locations	-1.71 (-3.37, -0.05)	0.014*
CSI≥ 40	-11.71 (-21.91, -1.52)	0.006*
KSSS subscale satisfaction	0.91 (0.20, 1.63)	0.005*
IPQR subscale personal control	-1.06 (-1.92, -0.21)	0.009*
K&L scale= grade 1	-23.29 (-52.55, 5.98)	0.033*
K&L scale= grade 2	-7.93 (-17.32, 1.47)	0.052
K&L scale= grade 3	-0.81 (-8.68, 7.07)	0.732
Work= pension	-8.78 (-19.71, 2.15)	0.057
Work= self-employed	-16.89 (-33.58, -0.19)	0.012*

Table 6 (continued)

Final multiple linear regression model after backward selection (continued)		
Predictor	**Exp (B) (95%CI)**	**P-value**
Work= white-collar worker	-4.23 (-18.78, 10.31)	0.649
Work= laborer	-11.41 (-25.25, 2.43)	0.077
Work= unemployed	-11.75 (-55.62, 32.12)	0.436
R-squared = 0.41 and adjusted R-squared = 0.37		

K&L scale = grade 4, CSI < 40, BMI < 25 kg/m2, and work = 'other category' are the reference categories. Abbreviations: KOOS = Knee injury and Osteoarthritis Outcome Score; Exp (B) = regression coefficient; CI = confidence interval; BMI = body mass index; HbA1c = glycated haemoglobin; HADS = Hospital Anxiety and Depression Scale; KSSS = Knee Society Scoring System; IPQR = Illness Perceptions Questionnaire Revised; K&L = Kellgren and Lawrence scale; CSI = Central Sensitization Inventory; BL = baseline; *= p < 0.05

Table 7: example for the prediction of the KOOS subscale pain score one-year postoperative, and ΔKOOS subscale pain score (after backward selection)

KOOS subscale pain score one-year postoperative	
Data of patient (example): - HbA1c-value: 5.7 - Number of pain locations: 3 - CSI≥ 40: yes - KSSS subscale satisfaction score: 10 - IPQR subscale personal control score: 16 - K&L scale: 2	**KOOS subscale pain score one-year postoperative =** 126.46 – (5.62*5.7) – (1.61*3) – (10.91*1) + (0.69*10) –(1.13*16) – (20.47*0) – (9.60*1) – (1.11*0)= 57.91
ΔKOOS subscale pain score	
Data of patient (example): - Hba1c: 5.7 - KSSS subscale functional score: 30 - KOOS subscale pain baseline score: 55 - Number of pain locations: 3 - CSI≥ 40: yes - KSSS subscale satisfaction: 10 - IPQR subscale personal control: 16 - K&L scale: 2 - Work: unemployed	**ΔKOOS subscale pain score =** 139.95 – (5.83*5.7) – (0.29*30) – (0.93*55) – (1.71*3) - (11.71*1) + (0.91*10) –(1.06*16) – (23.29*0) – (7.93*1) – (0.81*0) – (8.78*0) – (16.89*0) – (4.23*0) – (11.41*0) – (11.75*1)= 2.49

Abbreviations: Abbreviations: KOOS = Knee injury and Osteoarthritis Outcome Score; HbA1c = glycated haemoglobin; KSSS = Knee Society Scoring System; IPQR = Illness Perceptions Questionnaire Revised; K&L = Kellgren and Lawrence scale; CSI = Central Sensitization Inventory; BL = baseline

Discussion

The most important findings of the current study were the following: Higher HbA1c values and number of pain locations, lower preoperative satisfaction, KOA grade and personal control, and self-reported symptoms of central sensitization were consistent preoperative predictors for both more pain and pain deterioration or lower pain improvement one year post-TKA. In addition, also being self-employed, less preoperative pain and better self-reported function also appeared to be predictors for pain deterioration or lower pain improvement one year post-TKA. The multivariable regression model for one year post-TKA pain and pain deterioration or lower pain improvement one year post-TKA had an adjusted R2 values of 0.25 and 0.37 after backward selection, respectively.

Interpretation for results and relation to previous literature

HbA1c is a measure for glycaemic control (20). Previous research has been inconclusive about the role of diabetes in chronic post-TKA pain (43-46). However, these studies only measured self-reported presence of diabetes, overlooking the nuanced assessment provided by HbA1c concentration (which goes broader than the simple presence of diabetes). Our study emphasizes the importance of HbA1c levels in their potential predictive role for one-year post-TKA pain when higher values (= less adequate blood sugar control in people with or without diabetes (20)) are present.

Furthermore, both widespread pain (high number of pain locations) and self-reported symptoms of central sensitization may be indicative of disturbed somatosensory functioning (41, 47), which has been previously found to be predictive of chronic postoperative pain (5, 7, 8, 48). Nevertheless, the current study shows that quantitative sensory testing (QST) is not predictive for post-TKA pain. As reported in the systematic review of Paredes et al. (49), the predicted roles of QST parameters also remain unclear in previous research, mainly due to the heterogeneous methodologies used in different studies.

To the best of our knowledge, preoperative satisfaction about knee pain during various functional activities was not previously examined as possible predictor of poor TKA-outcome. The current study shows that low preoperative satisfaction was an important predictor for more pain at one year post-TKA, while the baseline pain intensity score was not. Satisfaction about pain during functional activities is not only influenced by pain intensity itself, but also by other factors (expectations, psychological factors, etc. (50)). Previous research indicated no consistent association between pain intensity and satisfaction (51), emphasizing the importance of measuring satisfaction as well as pain intensity.

Minimal structural knee damage being a predictor of post-TKA pain aligns with findings of previous systematic reviews (52, 53). This could be explained by the weak associations found between structural and clinical features (54), which is also typical for KOA patients presenting with disturbed somatosensory functioning (55), and can be indicative of chronic primary musculoskeletal pain (i.e. in which pain is or has become a condition in its own right, no longer related to the musculoskeletal condition anymore (56)). These findings suggest consideration

of delaying surgical interventions and prioritizing alternative treatment strategies when low structural damage is present.

Despite another study showing no association between self-efficacy and chronic TKA-pain (57), our study showed that better personal control to be predictive of worse post-TKA pain, contrary to our expectations (5, 58). However, an explanation could be that individuals with low 'personal control' had actually no 'personal control' option to improve pain intensity other than a TKA. This is the first study to include the IPQR as a possible predictor of chronic post-TKA pain, which makes comparison with other studies difficult.

Interestingly, less pain intensity at baseline and better function were also predictors (of pain deterioration or lower pain improvement). This could be attributed to a ceiling effect, implying that individuals with only mild symptoms have a narrower margin for pain intensity improvement, while those with more severe symptoms have a wider margin for improvement (59). No correction for participants scoring more extreme scores was made in this study, indicating the need for further research into this factor's contribution to post-TKA pain scores.

Lastly, being self-employed was also predictive for pain deterioration or lower pain improvement. This is the only predictive social factor, while marital status or education level were not. Being self-employed often also means no or less income while on 'sick leave', which can be associated with more stress, in turn interrelated with chronic pain (60). Additionally, self-employed individuals may return to work sooner and may not be able to devote sufficient attention to comprehensive rehabilitation (60). Remarkably, Edwards et al. found that higher education and not employment status was predictive of pain intensity six months post-TKA in the final multivariable model (8).

Notably, baseline pain intensity score was not predictive for pain one year post-TKA, and anxiety and pain catastrophizing were not predictive for either outcomes, contrasting with previous research findings (5, 7, 8). An explanation could be that better preoperative satisfaction filtered out the baseline pain intensity (tending to strongly correlation: Supplementary Table S2), and that self-reported symptoms of central sensitization filtered out pain catastrophizing and anxiety (moderately correlated: Supplementary Table S2). The CSI also measures several psychological constructs and previous research even found strong correlation with pain catastrophizing and anxiety (61). In the current study, only variables having a variance inflation factor of > 4 or correlated > 0.7 with another possible predictor were excluded at the start of the multivariable regression model.

All multivariable models showed an (adjusted) R^2 of 0.26 or higher, indicative of an acceptable effect (62). This suggests that a significant portion of the variance in pain one year post-TKA and pain deterioration or lower pain improvement post-TKA is explained by the predictors in these models. These findings align with those reported by Edwards et al., whose methodology was similar to ours and demonstrated an R^2 of 0.34 (8). However, a significant portion of the variance (69% vs. 56%) remains unexplained, highlighting the importance of further research.

Implications for future research and clinical practice

This study provides valuable information for future studies to select the most important potential predictors of the presence of chronic post-TKA pain or of 'treatment success' (decided based on absolute post-TKA pain score or on reaching the minimal clinical important change when valid cut-off points have been identified). However, more studies are needed that incorporate as many potential predictors of chronic TKA pain as possible in one linear multivariable regression model to identify the consistent and most important predictors, and should focus on replicable and easy-to-use measures in clinical practice. This can ultimately lead to an internally and externally validated clinical risk assessment tool. Future prehabilitation research should then investigate if positively changing the modifiable factors identified (e.g., self-reported symptoms of central sensitization, higher HbA1c, lower preoperative satisfaction, higher number of pain locations, and better personal control in the current study) with stratified treatment modalities would result in better postoperative outcomes (10). For clinical practice, making the patients aware of possible negative predictors can provide valuable insights for shared decision-making between the caregivers and the patient about the focus of treatment and their realistic expectations of TKA. This approach can increase patients' engagement in the treatment, but also assist caregivers in offering more tailored and effective treatment (63).

Strengths and limitations

This was the first multicentre study to evaluate different possible predictors covering the entire biopsychosocial model using multivariable regression models with a follow-up period of one year post-TKA. Its value is enhanced on the one hand by the presentation of both one year post-TKA pain, with pain deterioration or lower pain improvement, and on the other by the magnitude of the effect of the predictors (acceptable R2) (62). However, the limitations of the study also need to be addressed. First, no a priori sample size calculation was performed, but full power (at least 10 subjects for each possible predictor (38)) was preserved by first selecting possible predictors using univariate associations. Second, linear regression to predict post-TKA pain scores was used, instead of logistic regression. As such, only absolute pain scores (higher or lower) or difference in pain scores (pain deterioration or lower pain improvement) could be predicted, and not the presence of chronic pain or not. However, this approach was chosen because no valid cut-off points for the presence of chronic TKA pain or for the minimal clinically important change of the KOOS Pain have been identified (12), and because dichotomizing continuous variables carries the risk of losing (possible) important information. Therefore, fewer potential predictors are allowed in logistic regression due to its dependence on the sample size of the smallest subgroup (i.e. +/- 20% are estimated to report chronic TKA pain (1-3)) (38). Third, some participants rated the maximum temperature of the test stimulus for the CPM measurement (46°Celsius) lower than the originally cut-off of 4/10. Only participants scoring 0/10 were excluded from the analyses. It is possible that the test-stimulus was not noxious enough for all participants, obscuring the real CPM effect. Fourth, missing data for fat- and lean mass, and for CRP, were very low (device deficits or not registered in medical record), so these could not be analysed. Lastly, while our primary focus was on identifying preoperative predictors, it is important to note that peri- and postoperative factors, not considered here, might also significantly influence postoperative outcomes (64).

Conclusion

The study found that self-reported symptoms of central sensitization, higher HbA1c, satisfaction, less structural damage, higher number of pain locations, and better personal control were consistent preoperative predictors both of more pain one year post-TKA, and of pain deterioration or lower pain improvement post-TKA. In addition, being self-employment, more pain at baseline, and better function were significant preoperative predictors for pain deterioration or lower pain improvement post-TKA. Current results may be valuable for future studies that want to develop risk assessment tools for the prediction of chronic post-TKA pain.

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Chapter 7: Clinical prediction model for interdisciplinary biopsychosocial rehabilitation in osteoarthritis patients

Sophie Vervullens [1,2,3], Lissa Breugelmans [2,4], Laura Beckers [2], Sander M.J. Van Kuijk [5], Miranda Van Hooff [6,7], Bjorn Winkens [8], Rob J.E.M. Smeets [2,3,9]

[1]Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium

[2]Research School CAPHRI, Department of Rehabilitation Medicine, Maastricht University

[3]Pain in Motion International Research Group (PiM), www.paininmotion.be, Antwerp

[4]Biodiversity informatics, Department Collections and Library, Meise Botanical Garden, Meise, Belgium

[5]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, Netherlands

[6]Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands

[7]Department of Orthopaedic surgery, Radboud university medical center, Nijmegen, The Netherlands

[8]Department of Methodology and Statistics, Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands;

[9]CIR Clinics in Revalidatie, location Eindhoven, The Netherlands

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Abstract

Background: Osteoarthritis (OA) is a heterogenous condition, in which different subgroups are present. Individualized interdisciplinary multimodal pain treatments (IMPT) based on the biopsychosocial model have resulted in positive improvement of pain, health and disability in OA patients. Moreover, predictive factors for treatment success of IMPT in different musculoskeletal pain populations have been examined, but a clinical prediction model which informs whether a OA patient is expected to benefit or not from IMPT is currently lacking.

Aim: The aim was to develop and internally validate a clinical prediction model to inform patient-tailored care based on identified predictors for positive or negative outcomes of IMPT in patients with OA

Design: Longitudinal prospective cohort study

Setting: Center for Integral Rehabilitation at six locations in the Netherlands

Population: Chronic OA patients

Methods: Data in this study were collected during January 2019 until January 2022. Participants underwent a 10-week IMPT program based on the biopsychosocial model. Treatment success was defined by a minimal decrease from baseline of 9 points on the Pain Disability Index (PDI). Candidate predictors were selected by experts in IMPT and literature review. Backward logistic regression analysis was performed to develop the clinical predication model and bootstrap validation was performed for internal validation.

Results: 599 OA patients were included, of which 324 experienced treatment success. Thirty-four variables were identified as possible predictors for good IMPT outcome. Age, gender, number of pain locations, PDI baseline score, maximal pain severity, use of pain medication and alcohol, smoking, work ability, brief illness perceptions questionnaire subscales timeline, consequences, identity and treatment control, pain catastrophizing scale- and self-efficacy questionnaire score were found as predictors for treatment success. The internally validated model has an acceptable discriminative power of 0.71.

Conclusions: This study reports a specific clinical prediction model for good outcome of IMPT in patients with OA. The internally validated model has an acceptable discriminative power of 0.71.

Clinical rehabilitation impact: After external validation, this model could be used to develop a clinically useful decision tool.

Introduction

Osteoarthritis (OA) is one of the most common and rising chronic diseases in the elderly (1) and known as a frequent cause of pain, disability and loss of quality of life (2). It is a heterogeneous condition, in which different subgroups (i.e., phenotypes) are present; several studies identified a subgroup of OA patients experiencing disturbed somatosensory processing with disturbed psychological features, a subgroup with mainly inflammatory features, a subgroup with minimal joint disease, etc. (3,4). Challenging this condition is highly important, because OA patients still experience more disability days, medication costs and health-care consultations compared to age- and sex-matched people without OA (5). In recent years, various studies have indicated positive effects of a conservative biopsychosocial oriented approach in OA treatment (6,7). Despite the recommendation of this treatment in OA, effect sizes of conservative treatment remain only small or at best moderate (7). A possible explanation for this relative lack of treatment success could be related to suboptimal patient selection (8,9). The European League Against Rheumatism (EULAR) recommends different treatment steps related to a combination of biopsychosocial factors that are present and need attention in each patient, but still holds on to a stepped-care approach (i.e., giving the patient the next treatment only when they do not react sufficiently on the treatment provided in the first or previous step) (10).

However, because of the heterogeneity in OA it is postulated that individuals will benefit more from individualized treatment (11,12). Individualized interdisciplinary multimodal pain treatments (IMPT) have resulted in positive improvement of several patient-reported and clinician measured outcomes regarding pain, disability and psychological factors in patients experiencing different chronic primary musculoskeletal pain disorders (13), but also for self-reported pain, health and clinically observed disability in OA patients specifically (6). This sort of treatment usually targets different components of the biopsychosocial model that contribute to the maintenance of chronic pain and/ or disability, requires active participation of the patients, and is given by a team of different health professionals (e.g. physiotherapist, psychologist, physiatrist, social worker, etc.) who work interdisciplinary (6,14). Moreover, predictive factors for IMPT treatment success in different musculoskeletal pain populations (baseline lower levels of negative psychological factors and disability, and higher levels of physical functioning), and some specific in OA populations (younger age, baseline lower BMI and having knee OA) are reported (15–17). However, a clinical prediction model which informs whether an OA patient is expected to benefit or not from IMPT is currently lacking. This clinical prediction model would fit within the personalized medicine approach and could provide the patient and clinician with a more accurate prediction of treatment success before the start of the IMPT for more optimal use of resources and time and energy. Presenting the patient this specific treatment success percentage could facilitate shared decision- making whether other treatments before IMPT should be started first in order to increase treatment expectancy and hence the chance for a successful IMPT (16) (e.g., integrating motivational interviewing in pain neuroscience education (18), acceptance and commitment therapy, graded activity, exposure in vivo and emotional awareness and expression therapy (19)). Ultimately, this could lead to a higher efficiency in the healthcare system.

Therefore, the aim of this study was to develop a clinical prediction model for predicting good or negative outcome of IMPT in patients with OA an to internally validate this prediction model.

Materials and methods

The Medical Research Ethics Committee (MREC) Isala Zwolle in the Netherlands has approved this study (reference number: 200510). This prospective cohort study was written according to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines and registered at clinicaltrials.gov (NCT05661760). All participants received and signed informed consent before inclusion.

Setting and treatment

Data in this study were collected during routine clinical practice of Clinics in revalidatie (CIR), which is an independent secondary care treatment center specialized in chronic musculoskeletal pain interdisciplinary rehabilitation and provides outpatient IMPT at six locations across the Netherlands (i.e., Alkmaar, Amsterdam, Arnhem, Eindhoven, Zeist, and Zwolle). Data were collected in the electronic patient file developed by Asterisque during a three-year period (January 2019 - January 2022). All participants underwent an average 10-week IMPT program including a combination of physical and psychosocial treatment: emotional awareness and expression therapy, pain neuroscience education, acceptance and commitment therapy, graded activity, exposure in vivo and experiential learning through physical training. An individual program based on an extensive screening of completed self-reported questionnaires by a psychologist, a physical medicine and rehabilitation physician, and physiotherapist at the start of the treatment was developed. The treatment was divided over three phases: a start- (week 1), an education- (week 2-3) and a skills learning phase (week 4-10). Both individual (physical and mental coaching) and group sessions (education, movement and behavior therapy) were organized. Participants were treated twice a week during two to four sessions (three to four hours) per treatment day by physiotherapists, psychologists and a physiatrist. Detailed information about the IMPT treatment program can be found in a previous publication (19). The Template for Intervention Description and Replication (TIDieR) Checklist (20) is also provided, with a column based on current study and the study containing the detailed information about the IMPT (19) (Supplementary Digital Material 5).

Participants

Participants were included if they were aged ≥ 18 years, experienced chronic musculoskeletal pain (>3 months) and were diagnosed with and referred because of OA based on clinical and/or radiological examination by a medical doctor.

This study was part of a greater prospective longitudinal study including all people who underwent IMPT, but it was planned to also develop a clinical prediction model solely for OA-patients. Given that the primary referral diagnosis for IMPT was readily available in the electronic patient file, it was decided to examine inclusion criteria related to OA-diagnosis

after the ending of the data collection of the study. Therefore, the electronic patient file was searched after data collection ended based on OA-related key terms (Supplementary Digital Material 1 (Supplementary Text File 1)). Participants were eligible if the diagnosis 'OA' was reported in either the referral letter of the general practitioner, medical specialist or occupation doctor. In case no diagnosis was present, participants were still included if OA was mentioned as a diagnosis contributing to the pain problem by the physiatrist who was involved in the screening for eligibility for the IMPT program. In addition, participants had to experience personal and social participation problems with an interplay of biological, social and psychological factors maintaining pain and/or disability. Participants were excluded if they were unable to actively participate in treatment (insufficient motivation based on the estimate of the treatment team, limited Dutch language skills, environmental factors, or other pending treatments), if they had severe personality or other psychiatric disorders, if a disagreement was present between patient and care providers on content of treatment, or if pending legal procedures hindered full cooperation.

Outcome variable

The outcome variable was treatment success measured by the evolution of the Pain Disability Index (PDI) over time (from baseline to right after the 10-week IMPT program). The PDI is a patient reported questionnaire to measure the influence of average pain complaints on their daily life activities. It consists of seven subitems: 1) family/home responsibilities; 2) recreation; 3) social activity; 4) occupation; 5) sexual behavior; 6) self-care; and 7) life support activity. Each subitem is scored with a numeric rating scale from 0 ("no disability") to 10 ("maximum disability"), with a maximum score of 70 where higher scores indicate higher degrees of disability. The PDI was dichotomized based on the minimal clinically important change (MCIC): a change from baseline smaller than the MCIC (decrease of ≤ 8 points, 'no change' or increase in points) was interpreted as no treatment success (non-response), whereas a change equal to or larger than the MCIC (decrease of ≥ 9 points) was interpreted as treatment success (response) (21). The baseline PDI baseline score was also added as predictor in the model to correct for PDI baseline scores (22).

Construct validity of the Dutch language version of the PDI is confirmed and test-retest reliability is good in patients with chronic pain (21,23). The PDI was chosen based on generalizability and implementation of the model that was developed, because this outcome is included as the primary outcome in the coreset Dutch Dataset Pain Rehabilitation (DDPR) and internationally used (24).

Candidate predictors

Candidate predictors were carefully selected by opinions of experts in the field (six medical researchers, physiatrist, physiotherapist/IMPT trajectory coordinator and two patients with chronic musculoskeletal pain and OA), in combination with an explorative literature review of individual papers and meta-analyses on predictive factors of IMPT (16,25–28). A digital consensus meeting was set up to decide which predictors should be included in the model. All experts were allowed to brainstorm about which factors they assumed important for treatment success of IMPT based on their experience. Again, to ensure generalizability and

implementation of the model that was developed, all predictors needed to be quantitative variables and part of the DDPR (both the compulsory and optional part) as standard measured at intake at CIR of each participant. This means that results of both the brainstorm session and the explorative literature review were compared to the list of measured variables of the DDPR. In Supplementary Digital Material 2 (Supplementary Table I) detailed information is shown about the variables quoted in the brainstorm session and the list of measured variables of the DDPR, including the measurement scales.

Sample size

The required sample size was dependent on the number of candidate predictors and the number of patients who underwent treatment and who provided data at start and end of treatment. Since the candidate predictors were established during this project, the final sample size could not be determined beforehand. However, knowing that roughly 300-400 chronic pain patients with OA are admitted to the IMPT within CIR per year and accounting for an event rate of about 50% responders (29), even 60-80 predictors could be used in the model using the rule of thumb of at least 5 events-per-variable as a criterion for enough power in a logistic regression model with binary outcome (30).

Statistical analysis

Statistical analysis was performed in the IBM Statistical Package for Social Sciences Version 25 (SPSS, IBM Corporation, Armonk, NY) and R version 4.0.2.

Data preprocessing

Multiple imputation with fully conditional specification (n=5 imputations) was used to impute incomplete records (predictor variables as well as outcome variable). Predictive mean matching was used for the imputation model for the continuous variables.

Second, multicollinearity of predictor variables was assessed using collinearity diagnostics (variance inflation factor > 4 was seen as evidence of multicollinearity (31)). Third, the assumption of linearity between predictor variables and the log odds of the outcome variable (PDI) was explored by using the Box-Tidwell test and visual inspection. In case the linearity assumption was violated for a variable, quadratic (and cubic) terms of this variable were added to the regression model to examine the best fit.

Final model development

Logistic regression analysis was performed to estimate model coefficients. In order to reduce the number of predictors with the goal of building a model that is simple enough to be used in clinical practice, a backwards selection method was used on the imputed datasets based on the significance levels of the likelihood-ratio criterion (cut-off for removal p=0.2 according to regression and prediction modelling guidelines (32)). Variables that were part of at least two out of five final step models were included in a final model through the forced entry method, and the results over imputations were combined using Rubin's rules (33). The discriminative ability, which is most relevant at the group level, was visualized by a receiver operating characteristic curve (ROC) and estimated by the area under the curve (AUC). The latter was

interpreted as acceptable if the AUC ≥ 0.7, and as excellent if the AUC ≥ 0.8(34). Probability distributions were displayed in a histogram, using different cut-off points (Youden Index (35), 0.2, 0.3 and 0.5) to show the prediction quality (sensitivity analysis) and to see when specificity and sensitivity was the highest. In addition, the Hosmer and Lemeshow Goodness-of-fit was applied to test the goodness of fit of the model (p>0.05). Calibration was visualized by a calibration plot of the predicted probabilities versus observed frequencies.

Internal validation

Finally, the internal validity of all five imputed models was evaluated using bootstrap validation (package rms in R with 1000 iterations) to estimate a shrinkage factor to penalize model coefficients, and to estimate optimism-corrected performance (AUC and Nagelkerke R2). The results of all imputed models were again combined using Rubin's rules (33). The regression coefficients of the original model were multiplied by the shrinkage factor, and the model intercept was subsequently re-estimated.

The logistic regression equation is presented as follows: first, the 'linear predictor' (LP of treatment success) part was computed as 'B0 + B1*X1 + B2*X2 + ⋯ + Bn * Xn' based on the regression coefficients from the model. Then, the predicted probability was calculated as: 1/(1 + EXP-(LP(treatment success))).

Results

Participants and descriptive data

Data of 599 chronic pain patients with referral diagnosis of OA that underwent IMPT could be retrospectively retrieved out of the patient's file. Demographics and baseline values of participants are presented in Table I. Of the 599 participants, 553 completed the IMPT program (92.4%). The primary outcome variable had 12.9% missing values because patients either stopped treatment prematurely (n= 46) or did not complete the questionnaires pre- (n= 6) or posttreatment (n= 25). Reasons to stop treatment were too large time investment (n= 5), going into a new medical diagnostic or interventional trajectory (n= 8), insufficient fit between patient and CIR team regarding treatment goals (n= 11), or other (n= 22). However, all missing data was imputed and as such, data of every participant was described and analysed. The IMPT treatment was a success (≥ 9 points decrease of PDI) in 324 participants and no success in 275 participants.

Table I: demographics and baseline values of 599 included participants (possible predictors)

Numerical variables		Mean (SD)	N Missing (%)
Age (y)		52.63 (10.40)	0 (0.00)
BMI (kg/m^2)		28.80 (5.57)	38 (4.67)
Number of pain locations		4.79 (2.50)	23 (4.84)
PDI at baseline (0-70)		38.68 (11.82)	22 (3.67)
Pain severity (average, 0-10)		6.63 (1.74)	23 (3.84)
Pain severity (worst, 0-10)		7.74 (1.61)	23 (3.84)
CIS (20-140)		94.88 (22.52)	19 (3.17)
Self-rated work capacity (0-10)		3.09 (2.65)	24 (4.01)
HADS subscale anxiety (0-21)		8.68 (4.16)	25 (4.17)
HADS subscale depression (0-21)		8.21 (4.23)	25 (4.17)
IPQK subscale consequenses (0-10)		8.01 (1.85)	26 (4.34)
IPQK subscale timeline (0-10)		8.33 (2.05)	26 (4.34)
IPQK subscale personal control (0-10)		3.35 (2.47)	26 (4.34)
IPQK subscale treatment control (0-10)		6.40 (2.12)	26 (4.34)
IPQK subscale identity (0-10)		7.75 (1.62)	26 (4.34)
IPQK subscale illness concern (0-10)		7.33 (2.43)	26 (4.34)
IPQK subscale coherence (0-10)		5.35 (2.76)	26 (4.34)
IPQK subscale emotional representation (0-10)		7.29 (2.25)	26 (4.34)
PCS (0-56)		21.58 (10.89)	27 (4.34)
PIPS subscale avoidance (10-70)		34.74 (8.73)	82 (13.69)
PIPS subscale cognitive fusion (6-42)		22.73 (3.50)	21 (3.51)
PSEQ (0-60)		30.56 (11.47)	23 (3.84)
SCL90 subscale hostility (0-30)		8.85 (2.89)	22 (3.67)
SF12 mental component (0-50)		38.34 (9.95)	29 (4.84)
SF12 physical component (0-50)		29.80 (6.41)	29 (4.84)
Categorical variables		**N (%)**	
Sex	Male	174 (29)	0 (0.00)
	Female	425 (71)	
Pain duration	0-2 y ago	156 (27)	23 (3.80)
	2-5 y ago	153 (27)	
	>5y ago	267 (46)	
Pain medication	No	168 (29)	24 (4.00)
	Yes	407 (71)	
Education level	Low	126 (22)	24 (4.00)
	Medium	334 (58)	
	High	115 (20)	
Alcohol use	No	304 (53)	24 (4.00)
	Yes	271 (47)	
Smoking	No	454 (79)	24 (4.00)
	Yes	121 (21)	
Drugs	No	561 (98)	24 (4.00)
	Yes	14 (2)	

Abbreviations: kg/m2= kilograms/square meter, PDI= pain disability index, CIS= Checklist individual strength, HADS= hospital anxiety and depression scale, IPQK= illness perceptions questionnaire-short version, PCS= pain catastrophizing scale, PIPS= psychological inflexibility pain scale, PSEQ= pain self-efficacy questionnaire, SCL90= symptom checklist – 90 items, SF12= short-form 12

Pooling possible predictors from the consensus meeting and literature review yielded a definite list of 34 possible predictor variables (32 variables, of which two were categorical with three categories and therefore counted as two extra) before the start of the backward selection logistic regression analysis, which are presented in Supplementary Digital Material 3 (Supplementary Table II). A mix of demographic (age and sex), pain-related (number of pain locations, duration, severity-average, severity-worst, and use of pain medication), social (education and work capacity), psychological (anxiety, depression, pain catastrophizing, avoidance, cognitive fusion, self-efficacy, hostility, mental health, fatigue and illness perceptions), functional (disability/physical function, and physical health), and other (body mass index, alcohol use, smoking, and drugs) variables were included.

Candidate predictors

Missing value analysis showed that 30 out of 32 predictor variables had missing values (all < 6.3%). The avoidance scale of the Psychological Inflexibility Pain Scale (PIPS) had 13.7% missing values. One question of the PIPS appeared to not have been included by the software developer in Asterisque, and was added halfway through the study period. Patients who completed the first version of the scale were given a missing value allocated to that question, in order to ensure recorded values were comparable.

Multicollinearity and assumption testing

Collinearity diagnostics revealed no evidence for multicollinearity (range variance inflation factor: 1.06-3.38), as such all possible predictor variables were used for model development. Regarding the linearity assumption, the Box-Tidwell test indicated non-linearity for the relationship between the log odds of the outcome on the one hand, and the PDI score at baseline (p=0.012) and number of pain locations (p=0.031) on the other hand. After visually inspecting the relationship between the log odds of the outcome and the frequency of successful outcome for deciles of these two variables, the quadratic and cubic terms were added to the regression model. The Wald test indicated that cubic terms of the two variables did not improve the model significantly and were therefore not implemented in the final model.

Model development

The backward selection method reduced the number of predictors to 18. One out of these 18 variables was withheld in only one of the five final step models. The removal of this one variable did not lead to a significant decrease in log-likelihood for all imputed sets, and therefore these variables were removed from the model. Our remaining model thus resulted in 17 predictors and an intercept (including variables of at least two of five final step models). The (pooled) results from this model can be found in Table II. Performance measures for the model for five imputed datasets can be found in Supplementary Digital Material 4 (Supplementary Table III).

Table II: Estimated parameters of final model and internally validated model

Variables included	Exp(B) (95%CI)	B	Shrunk B*
Constant (B_0)	NA	-4.478	-3.552
Age (yr)	0.98 (0.96 - 1.00)	-0.017	-0.014
Sex	1.39 (0.88 - 2.19)	0.330	0.277
Number of pain locations	0.59 (0.41 - 0.83)	-0.535	-0.449
Number of pain locations (quadratic term)	1.05 (1.01 - 1.09)	0.048	0.0403
PDI baseline	1.27 (1.14 - 1.40)	0.236	0.198
PDI baseline (quadratic term)	1.00 (1.00 - 1.00)	-0.002	-0.002
Pain severity (worst)	0.92 (0.80 - 1.06)	-0.083	-0.070
Use of pain medication	0.55 (0.34 - 0.91)	-0.591	-0.496
Self-rated work capacity	1.13 (1.03 - 1.24)	0.124	0.104
Alcohol use	1.37 (0.92 - 2.03)	0.312	0.262
Smoking	1.41 (0.85 - 2.32)	0.342	0.287
IPQK consequences	1.11 (0.96 - 1.29)	0.105	0.088
IPQK timeline	0.93 (0.84 - 1.04)	-0.069	-0.058
IPQK treatment control	1.13 (1.02 - 1.25)	0.121	0.102
IPQK identity	0.88 (0.74 - 1.04)	-0.133	-0.112
PCS	1.02 (1.00 - 1.05)	0.023	0.019
PSEQ	1.02 (1.00 - 1.05)	0.022	0.018

Abbreviations: B= regression coefficient. SE= standard error. Exp(B)= Odds ratio. CI= confidence interval. PDI= pain disability index. HADS= hospital anxiety and depression scale. IPQK= illness perceptions questionnaire-short version. PCS= pain catastrophizing scale. PSEQ= pain self-efficacy questionnaire. *= intercept estimated again (not multiplied by shrunk factor)

Calibration

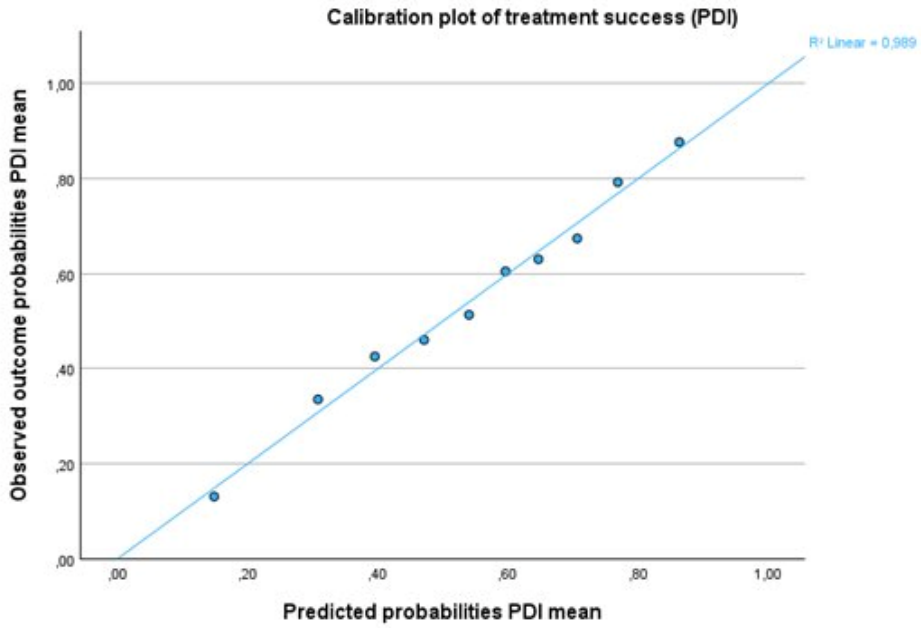
The Hosmer and Lemeshow goodness-of-fit test implied no evidence that the model was not well calibrated (p-value varied from 0.07 to 0.33 for the five imputed datasets). The calibration plot can be seen in Figure 1. The model seems to predict well over the whole range of probabilities, meaning all points in the calibration plot are positioned close to the 45° midline and no obvious under- or overestimation in part of the range.

Discrimination

The ROC-curve for the pooled model of all imputed datasets can be found in Figure 2. The AUC for this pooled model was ‘acceptable’ (0.74 with 95% confidence interval [CI] 0.70-0.79).

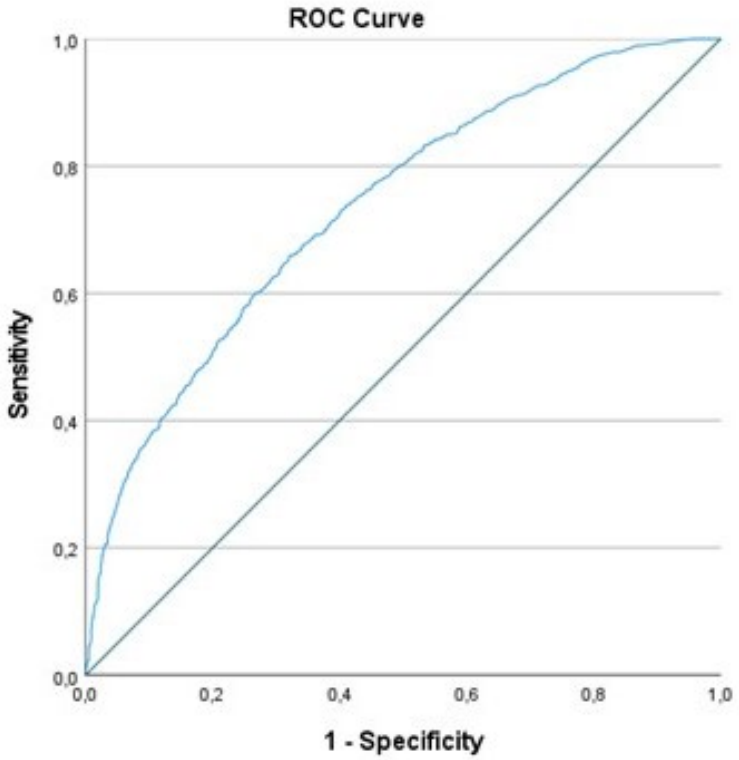
Figure 3 shows a histogram of the predicted probabilities for the treatment responders (PDI score= 1) and non-responders (PDI score= 0). There is a large amount of overlap between the probability distributions, indicating that there is no clear separation of the two groups. Taking a cut-off point of 0.532 for the model, resulted in the highest sensitivity (71%) and specificity (64%), i.e. Youden’s index value(35). Also other cut-off points (0.2, 0.3 and 0.5) of the model are tabulated, together with their sensitivity, specificity, positive and negative predictive value in Table III.

Figure 1: Calibration plot



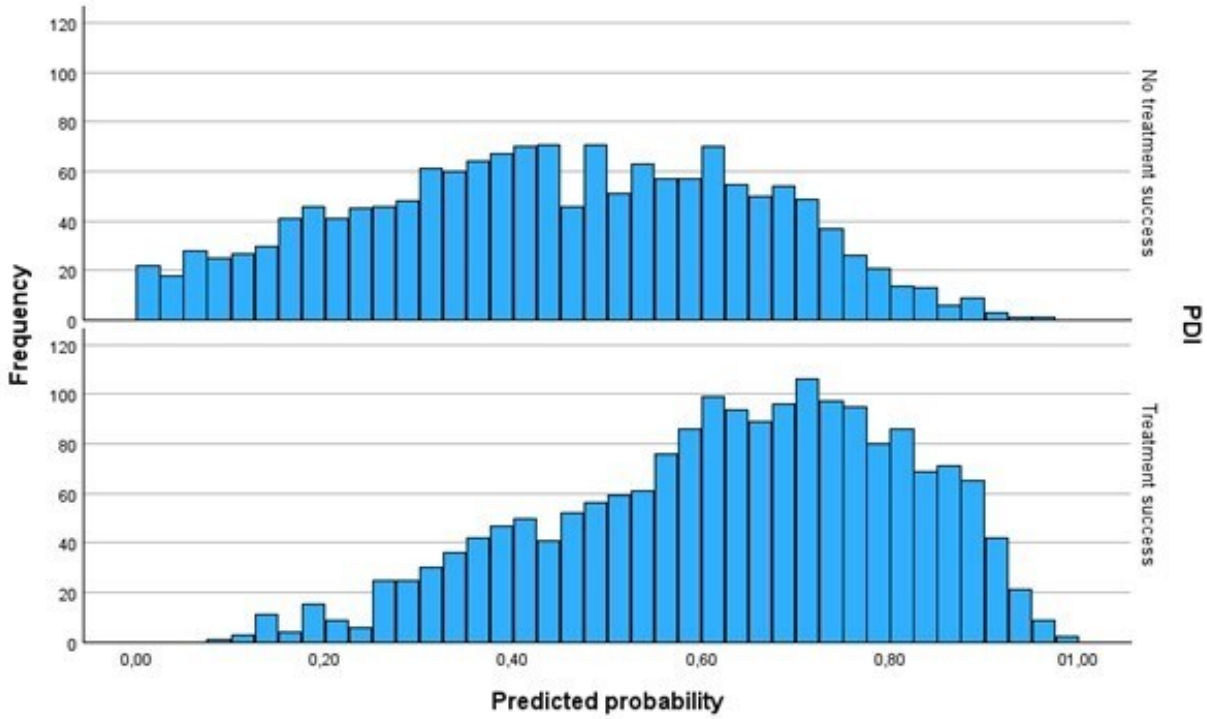
Abbreviations: PDI = pain disability index

Figure 2: Receiver Operating Characteristics curve



Abbreviations: ROC= receiver operating characteristics

Figure 3: Histogram of predicted probabilities stratified by event status



Abbreviations: PDI= pain disability index

Table III: Cross-tabulated predicted versus observed 'cases' for Youden's index, and cut-off points 0.2, 0.3 and 0.5 accompanied with sensitivity, specificity, positive predictive and negative predictive values

		PDI		Total		
		0	1		Sensitivity	0.71
Youden Cut-off point 0.532	0	176	93	269	Specificity	0.64
	1	101	230	330	Positive predictive value	0.69
Total		276	323	599	Negative predictive value	0.65
		0	1		Sensitivity	0.75
Cut-off point 0.5	0	164	80	244	Specificity	0.59
	1	112	243	355	Positive predictive value	0.68
Total		276	323	599	Negative predictive value	0.67
		0	1		Sensitivity	0.95
Cut-off point 0.3	0	74	17	91	Specificity	0.27
	1	203	306	508	Positive predictive value	0.60
Total		276	323	599	Negative predictive value	0.81
		0	1		Sensitivity	0.98
Cut-off point 0.2	0	41	6	47	Specificity	0.15
	1	235	317	552	Positive predictive value	0.57
Total		276	323	599	Negative predictive value	0.87

Abbreviations: PDI= pain disability index, 0 = no treatment responder, 1= treatment responder

Internal validation

The bootstrap and shrinkage technique resulted in a pooled optimism-corrected AUC value of 0.71 and a pooled optimism-corrected Nagelkerke R2 value of 0.18. The pooled shrinkage factor was 0.84. The internally validated model with adjusted intercept (B0) and regression coefficients (B) can be found in Table II. In order to acquire a clear idea of the actual chance of treatment success based on these results, the logistic regression equation is presented according to an example, which can be found in Table IV.

Table IV: example for treatment success calculation

Data of patient (example): - 58 years old - Man - 4 pain locations - PDI score: 41 - Pain severity (worst): 8 - Use of pain medication - Ability to work: 4/10 - No alcohol use - Smoking yes - IPQK consequences score: 4 - IPQK timeline score: 7 - IPQK treatment control score: 6 - IPQK identity: 5 - PCS score: 38 - PSEQ score: 32	**LP for treatment success=** -3.552 - (0.014*58) + (0.277*1) – (0.449*4) + (0.040*4^2) + (0.198*41) – (0.002*41^2) – (0.070*8) – (0.496*1) + (0.104*4) + (0.262*0) + (0.287*1) + (0.088*4) – (0.058*7) + (0.102*6) – (0.112*5) + (0.019*38) + (0.018*32)= 0.456 **Chance for treatment success= 1/(1 + e $^{-(-0.456)}$) = 0.61 = 61%**

Abbreviations: PDI= pain disability index, HADS= hospital anxiety and depression scale, IPQK= illness perceptions questionnaire-short version, PCS= pain catastrophizing scale, PSEQ= pain self-efficacy questionnaire

Discussion

This prospective cohort study intended to develop a clinical prediction model based on different predictors for good or negative outcome of IMPT to facilitate patient-tailored interdisciplinary care in patients with OA and to internally validate this model. A clinical prediction model is reported, including a specific regression equation (with lower age, being female, fewer number of pain locations, higher disability, lower pain severity at worst, no use of pain medication, higher self-rated work capacity, alcohol use, smoking, lower negative illness perceptions regarding timeline and identity and higher regarding consequences of condition, higher positive illness perceptions regarding treatment control, higher pain catastrophizing and higher pain self-efficacy as predictors) for good outcome of IMPT. The internally validated model has an acceptable discriminative power (AUC= 0.71), which is only a small decrease compared to the value of 0.74 of the original model.

Interpretation of findings and relation to previous studies

Our goal was to develop a clinical prediction model based on current available data standard measured at intake at CIR, which can be directly used in clinical practice (after external validation). Different cut-off points for treatment success are presented (Youden's index, 20-50%), because we advise not to use any cut-off scores as the 'gold standard' to in- or exclude

the patient in the IMPT program. Each cut-off point has his own specific performance values, which helps the treatment team decide whether higher sensitivity (higher value means lower chance for an incorrect fault negative prediction of 'treatment success') or specificity (higher value means lower chance for an incorrect fault positive prediction of 'treatment success') is the most important element for in- or exclusion in the IMPT program. In other words, this calculated chance for treatment success should be used to start and facilitate the discussion between the treatment team and patient whether to join the IMPT program or not, whether other treatment goals (not improving disability as measured with PDI, but improving other relevant factors for the patient) for the patient are relevant, or whether other treatment modalities should be started first (e.g., to improve certain predictive factors for treatment success of IMPT). Another option could be to start with a short try-out treatment and evaluate with the patient after a few weeks whether the treatment is suitable and changes on modifiable predictive factors have been achieved. Besides, presenting patients a certain percentage for treatment success can increase their motivation and as such improve their active involvement in the therapy (36). This in turn can lead to higher treatment and healthcare system efficiency.

The findings of the current study are in line with some findings of previous studies in different musculoskeletal populations, which also indicated lower pain severity levels (37), lower number of pain locations (26), lower age (15,16,37), high levels of protective cognitive behavioral factors (e.g., higher self-efficacy, positive illness perceptions regarding treatment control), and low levels of cognitive behavioral risk factors (e.g., negative illness perceptions regarding timeline and identity) (16,26,27,37,38) as important predictive factors for good outcome after IMPT, while pain duration (26,37) and education level (37) were not. Remarkably, a recent meta-analysis in OA patients found that higher pain severity was a moderator for better function post-treatment (39), contrasting our and another IMPT study's findings (37). This difference may arise because this meta-analysis' solely focused on exercise therapy, and not IMPT. Moreover, it focused on other disability measures (e.g., Western Ontario and McMaster Universities Osteoarthritis Index vs. PDI in our study) (39).

Higher scores on the subscale consequences of the IPQ-K and pain catastrophizing can be seen as 'cognitive behavioral risk factors', but according to our model, a higher score predicted better chance of treatment success. This is in contrast with a previous meta-analysis, which included 4068 patients but pooled various cognitive and behavioral factors together (did not only focus on illness perception) (16). Also, our study found that higher levels of disability predicted good treatment outcome, while the other studies showed the opposite (16,38). In addition, other studies indicated that lower BMI (15), lower emotional stress (16,37), lower pain acceptance, higher psychological inflexibility (40) were relevant predictive factors for good treatment outcome, and that pain severity (16,37) and sex (15,37) were not. In this study, we also investigated whether emotional stress (anxiety and depression), BMI and psychological inflexibility were important factors to set-up our regression equation to predict treatment success, but these did not add significantly to the prediction of treatment success when other predictors are taken into account. On the other hand, pain severity at worst and sex were found to be relevant to include in our final regression equation model.

The main reason for above mentioned differences might be explained by the use of a different p-value cut-off for predictor exclusion in the model (p=0.2 in our study versus p=0.05 in the other studies) (26,27,37,38,40). However, the best model is postulated to be the most complete model, in which choosing a p-value of 0.05 would be too strict to define whether a variable is a predictor or not (32). Moreover, the model of current study was created to easily use in clinical practice in a later phase; and all chosen variables are part of the DDPR, which is standardly measured at intake at CIR and other (Dutch) pain rehabilitation centers for every participant. As such, it would be a waste not to use all the (relevant) information that is available. Other possible reasons for differences in findings compared to other studies are the development of a clinical prediction model in this study instead of just looking at possible influencing factors for treatment outcome in other studies (15,40), the different multidisciplinary treatment content in another study (e.g., treatment team did not include a psychiatrist, education had a biomedical approach instead of a pain neuroscience-directed approach, or a dietician was involved in the treatment (15)), the different outcome measurements to calculate treatment success, or the focus on other chronic pain populations, not specifically diagnosed with OA (16,26,27,37,40).

Interestingly, also the use of pain medication and alcohol, smoking and work capacity appeared important for calculating treatment success, but were not examined as possible predictive factors in the previous studies (15,16,26,27,37,40). However, as this is the first study to explicitly present a clinical prediction model for IMPT in OA patients, direct comparison with other studies is not possible.

Strengths and limitations of the study

The main strength of this article is the state of the art and detailed statistical analysis (multiple imputation for missing data, large enough sample for the number of predictors, calibration testing, etc.) and the fact that this is the first study to actually present and internally validate a clinical prediction model (with an example) to facilitate shared decision making for implementing IMPT in patients with chronic musculoskeletal pain and OA. Other strengths of this article include the way of selecting potential predictor variables for treatment success (literature review and consensus meeting); and the inclusion of predictor variables that are part of the DDPR (both the compulsory and optional part) as standard measured at intake at CIR of each participant (24). This requires no need for extra measurements (which take extra time and resources) to predict an acceptable realistic chance for treatment success after IMPT. A first limitation of the study could be the fact that the OA diagnosis was retrospectively searched in existing medical patient files without knowing that the OA complaint is the main responsible factor for their chronic pain (despite it was the referral diagnosis of the medical doctor for IMPT). A second limitation can be the choice of using the MCIC in PDI to calculate treatment success. Previous research in other patient reported outcomes found that OA patients with only mild symptoms require less improvement than the provided MCIC to experience treatment success (22). However, because >76.5% of the included participants reported a relatively high baseline PDI score of 30 or higher (max score = 70), we believe this limitation is kept to a minimum in our study. Another remark is that this MCIC calculation was based on chronic low back pain patients. However, a MCIC for PDI change for OA patients

specifically is not yet available, and that is why in our opinion using a value in another chronic musculoskeletal population was the best option.

Clinical and research implications

First, we recommend to externally validate the model as developed in this study before it can be used as a clinically useful decision tool in clinical practice (41). After external validation, this model can be used as a guideline for clinical practitioners next to the inclusion criteria mentioned in the method section. By developing a prediction model, we aimed to facilitate shared decision-making about inclusion in the IMPT program, and the focus of the content of the IMPT program (based on scores of the identified predictors), and whether other treatment goals (not improving disability as measured with PDI, but improving other relevant factors for the patient) are relevant, or whether other treatments before IMPT should be started first in order to increase expectance and hence the chance for a successful IMPT. The predictive profile could be of help for choosing the right treatments in clinical rehabilitation settings based on the identified predictor scores, which could include motivational interviewing (18), pain medication withdrawal(42), etc.

Conclusions

This study reports a specific clinical prediction model including lower age, being female, fewer number of pain locations, higher disability, lower pain severity at the worst, no use of pain medication, higher ability to work, alcohol use, lower negative illness perceptions regarding timeline and identity and higher regarding consequences of condition, higher positive illness perceptions regarding treatment control, higher pain catastrophizing and higher pain self-efficacy as predictors for good outcome of IMPT in patients with OA. The internally validated model has an acceptable discriminative power of 0.71. We recommend to externally validate this model before using it as a useful decision tool in daily clinical practice.

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PART 3: An overview of stratified and non-stratified prehabilitation care in knee osteoarthritis patients undergoing total knee arthroplasty

Chapter 8: Prehabilitation before total knee arthroplasty: A systematic review on the use and efficacy of stratified care

Sophie Vervullens[1,2,6]; Lotte Meert[1,2,6]; Isabel Baert[1,6]; Rob J.E.M. Smeets[2,3,6]; Peter Verdonk[4]; Frank Rahusen[5]; Mira Meeus[1,7]

[1]Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium

[2]Research School CAPHRI, Department of Rehabilitation Medicine, Maastricht University

[3]CIR Clinic in Revalidatie, location Eindhoven, The Netherlands

[4]ORTHOCA, Antwerp, Belgium and ASTARC department, Antwerp University, Belgium

[5]Department of Orthopaedics, St Jans Gasthuis Weert, The Netherlands

[6]Pain in Motion International Research Group (PiM), www.paininmotion.be

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Abstract

Background: Preoperative rehabilitation (hereafter called “prehabilitation”) has been proposed as a potentially effective treatment to target preoperative risk factors in order to prevent insufficient outcome after total knee arthroplasty (TKA).

Purpose: We aimed to assess whether previous clinical trials of non-surgical, non-pharmacological prehabilitation in individuals with knee osteoarthritis (KOA) awaiting TKA focused on specific clinical phenotypes or specific individual characteristics and whether the content of the prehabilitation was stratified accordingly. Second, we aimed to summarize and compare the long-term effects of stratified and non-stratified care on pain, satisfaction, function and quality of life.

Methods: A systematic literature search of PubMed, Web of Science, Scopus and Embase was performed. All relevant articles published up to April 19, 2021 reporting “(randomized controlled) clinical trials or prospective cohort studies” (S) related to the key words “total knee arthroplasty” (P), “preoperative conservative interventions” (I), “pain, function, quality of life and/or satisfaction” (O) were included.

Results: After screening 3498 potentially eligible records, 18 studies were assessed for risk of bias. Twelve studies had low, 2 moderate, 3 serious, and one high risk of bias. The latter study was excluded, resulting in 17 included studies. Five studies investigated a “stratified prehabilitation care” and 12 “non-stratified prehabilitation care”. Stratified prehabilitation in 4 studies meant that the study sample was chosen considering a predefined intervention, and in the fifth study, the prehabilitation was stratified to individuals’ needs. No direct comparison between the 2 approaches was possible. We found weak evidence for a positive effect of biopsychosocial prehabilitation compared to no prehabilitation on function (stratified studies) and pain neuroscience education prehabilitation compared to biomedical education on satisfaction (non-stratified studies) at 6 months post-TKA. We found strong evidence for positive effects of exercise prehabilitation compared to no prehabilitation on pain at 6 months and on function at 12 months post-TKA (non-stratified studies).

Conclusion: More research is needed of stratified prehabilitation care focusing on individual characteristics in people with KOA awaiting TKA.

Introduction

Knee osteoarthritis (KOA) is one of the most common forms of osteoarthritis (1), representing a degenerative joint disease known as a frequent cause of pain, disability and loss of quality of life (2,3). KOA has a huge impact on an individual's personal life but also on society, especially given the high costs related to total knee arthroplasty (TKA) (4). Although TKA appears to be an effective treatment in most people with end-stage KOA (5), 20% to 40% of individuals remain dissatisfied and experience chronic postoperative pain (6–8).

Given the expected increase in TKA surgeries due to the ageing of population and the increasing prevalence of obesity, the outcomes and satisfaction rates after TKA must be optimized (4). Physiotherapy is traditionally delivered as rehabilitation after surgery to improve the timeline and extent of recovery. However, various preoperative functional, metabolic, as well as psychosocial risk factors and abnormal sensory processing signs for chronic postoperative pain and dissatisfaction have been described (6,9–11). Therefore, preoperative rehabilitation (hereafter called "prehabilitation") has also been proposed as a potentially effective treatment to target these preoperative risk factors and to prevent insufficient outcome after TKA (12,13).

Results of previous systematic reviews and meta-analyses are contradictory and in general indicate no or only little positive effect of various forms of prehabilitation on postoperative outcomes (12–17). This observation might be explained by the fact that KOA is a heterogeneous pathology: individuals can present different aetiological backgrounds, prognoses and/or clinical presentations and may respond differently to specific treatment contents (18,19).

Considering the heterogeneous nature of the KOA population, subgroups of individuals may exist (19–23). In the context of intervention studies, the identification of phenotypes based on clinical signs are assumed necessary for more efficacious and personalized treatments (24). Therefore, Dell'Isola et al. (most recent review on clinical phenotypes) tried to classify these into 5 clinical phenotypes: chronic pain, inflammatory KOA, metabolic syndrome, bone and cartilage metabolisms, mechanical overload and minimal joint disease (19). Recognizing relevant clinical phenotypes and adapting the intervention to these phenotypes (stratified care) is considered fundamental to offer individuals the best matching and most effective treatment (24–26). For example, if treatment focusses on losing weight, likely little or no therapeutic effect will be achieved when everyone with KOA, regardless of their body mass index (BMI), receives this treatment.

To date, we do not know whether previous experimental clinical trials on the effect of prehabilitation identified these clinical phenotypes in people with KOA, gave stratified prehabilitation related to these characteristics, and as a consequence reported different long-term results as compared with studies not accounting for these subgroups. None of the previous systematic reviews studied whether a stratified approach is more effective than a "one-size-fits-all" approach (non-stratified care) (15) (Appendix S1). Hence, more evidence in this field is highly necessary (27). According to research of people with KOA (28,29) and back pain (30,31), outcomes might be better when clinical phenotypes are taken into account and

prehabilitation is adapted to these phenotypes. The non-stratified approach may have attenuated treatment effects because of the varying number of potential responders and non-responders in this heterogenous population (27).

Therefore, the first aim of this systematic review was to investigate whether prehabilitation in previous clinical trials focused on specific clinical phenotypes (or other more specific individual characteristics beyond the KOA diagnosis) in people with KOA scheduled for TKA and whether the content of the prehabilitation was stratified accordingly. The second aim was to synthesise and compare the long-term results on postoperative pain, satisfaction, function and/or quality of life of the clinical trials with a more tailored approach (stratified care) in relation to clinical trials with a "one-size-fits-all" approach (non-stratified care).

Methods

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines (32), and the protocol was prospectively registered on PROSPERO (CRD42021221098; March 22, 2021). The Participant, Intervention, Comparison, Outcomes and Study (PICOS) design was used to define the eligibility criteria and key words of search strategy (33).

Eligibility criteria

To be included in this systematic review, articles had to describe results of studies that evaluated the effect of preoperative conservative (non-pharmacological, non-surgical) interventions (prehabilitation) (I) on postoperative pain, satisfaction (main outcomes), function or quality of life (additional outcomes) (O) in individuals diagnosed with KOA scheduled for TKA (P). Only (randomized controlled) clinical trials, single-case experimental designs and prospective cohort studies were allowed (S). The search results had to be in accordance with the criteria presented in Table 1.

Information sources and search strategy

Two reviewers (SV, LM) searched 4 electronic databases, including PubMed (MELDINE) (34), Web Of Science (35), Embase (36) and Scopus (37), up to April 19, 2021. Four groups of key words were used, related to "Total Knee Arthroplasty" (P), "Preoperative conservative Interventions" (I), "Pain, Satisfaction, Function, and Quality of life" (O) and "randomized controlled trials (RCTs), clinical trials or prospective cohort studies" (S). More details can be found in Table 2, Table S1 and Table S2.

Table 1: Eligibility criteria

	Inclusion	Exclusion
P	- Human adults diagnosed with KOA scheduled for TKA - > 18 years of age	- Scheduled for partial, unicompartimental or revision knee arthroplasty - Statistical analyses of mixed population (e.g. KOA participants plus other indications for TKA, or TKA and THA participants)
I	- Prehabilitation includes preoperative conservative (non-pharmacological and non-surgical) intervention - A follow-up period of at least 6 months after TKA	
C	/	
O	- Pain (primary) - Participant satisfaction (primary) - Function, e.g., muscle strength; functional ability, range of motion etc. (secondary) - Quality of life (secondary)	- Other outcomes
S	- Articles written in English, Dutch or French - Experimental designs or prospective cohort studies	- Other languages - Other study designs

KOA, knee osteoarthritis; THA, total hip arthroplasty; TKA, total knee arthroplasty

Study selection

Results of the searches were imported into Endnote and duplicates were removed (38). Eligibility criteria were checked by 2 reviewers (SV, LM) using the Rayyan screening tool (39). The first screening was conducted on the title and abstract, and if the study was considered potentially relevant, the full text was retrieved. A second selection was based on the full text, and after both screening phases, all disagreements on inclusion or exclusion were discussed and resolved by consensus.

Table 2: Search query (PubMed)

	Key words
Group 1 (P)	(('Knee Prosthesis'[Mesh]) OR 'Arthroplasty, Replacement, Knee'[Mesh]) OR (knee arthroplasty OR knee prosthesis OR knee replacement OR knee surgery)
Group 2 (I)	(('Preoperative Period'[Mesh] OR 'Preoperative Care'[Mesh]) OR (preoperative OR pre-operative OR presurgical OR pre-surgical OR pre-surgery OR preadmission)) AND ((((((('Physical Therapy Specialty'[Mesh] OR 'Physical Therapy Modalities'[Mesh] OR 'Cognitive Behavioral Therapy'[Mesh] OR 'Acupuncture Therapy'[Mesh] OR 'Exercise Therapy'[Mesh] OR 'Behavior Therapy'[Mesh] OR 'Cryotherapy'[Mesh] OR 'Therapy, Soft Tissue'[Mesh] OR 'Acceptance and Commitment Therapy'[Mesh]) OR ('Exercise Movement Techniques'[Mesh] OR 'Resistance Training'[Mesh] OR 'Exercise'[Mesh])) OR ('Rehabilitation'[Mesh] OR 'rehabilitation' [Subheading] OR 'Telerehabilitation'[Mesh])) OR ('Manipulation, Orthopedic'[Mesh] OR 'Musculoskeletal Manipulations'[Mesh])) OR 'Dry Needling'[Mesh]) OR (physical therapy OR physiotherapy OR cognitive behavioral therapy OR cognitive therapy OR acupuncture OR exercise therapy OR manual therapy OR mobilization OR mobilisation OR behavior therapy OR behaviour therapy OR cryotherapy OR soft tissue therapy OR 'acceptance and commitment' OR resistance training OR strength training OR conservative therapy OR graded activity OR graded exposure OR graded exercise OR pain education OR participant education))
Group 3 (O)	(((((('Pain'[Mesh] OR 'Musculoskeletal Pain'[Mesh] OR 'Chronic Pain'[Mesh]) OR 'Disability Evaluation'[Mesh]) OR 'Activities of Daily Living'[Mesh]) OR 'Quality of Life'[Mesh]) OR ('Personal Satisfaction'[Mesh] OR 'Participant Satisfaction'[Mesh])) OR (pain OR functioning OR 'activities of daily living' OR activities OR participation OR quality of life OR satisfaction OR disability)
Group 4 (S)	(('Pragmatic Clinical Trial' [Publication Type] OR 'Controlled Clinical Trial' [Publication Type] OR 'Randomized Controlled Trial' [Publication Type] OR 'Clinical Trial' [Publication Type] OR 'Cross-Over Studies'[Mesh]) OR ('Cross-Sectional Studies'[Mesh] OR 'Cohort Studies'[Mesh] OR 'Longitudinal Studies'[Mesh] OR 'Follow-Up Studies'[Mesh] OR 'Case-Control Studies'[Mesh] OR 'Prospective Studies'[Mesh])) OR (clinical trial OR randomized controlled trial OR randomised controlled trial OR cohort studies OR prospective studies OR longitudinal studies OR follow-up studies OR case-control studies OR cross-sectional studies)

Data items and collection

Relevant information from every included article was extracted and reported in an evidence table (Table 3). The following data (if available) were extracted from every article: 1) author and year of publication, 2) study design and setting, 3) participant characteristics (sample size, age, number of women, inclusion and exclusion criteria, study criteria related to clinical phenotype according to Dell'Isola et al. (19)), 4) prehabilitation (content, modalities and provider in intervention and control groups and whether the intervention was related to phenotype or study criteria of the study), 5) continuation in the postoperative period (yes/no + content), 6) follow-up times (6-month minimum), 7) lost to follow-up, 8) outcome measure, and 9) results (mean difference [increase or decrease] + effect size). The evidence table was completed by the first author (SV) and independently checked by the second author (LM).

Risk of bias in individual studies

The risk of bias (RoB) within the different articles was assessed by using the international Cochrane Risk of Bias checklist (ROB-II) for RCTs (40) and non-RCTs (ROBINS-I) (41). The ROB-

II checklist contains 5 domains, which can be rated as high, moderate or low RoB. The 7 domains of the ROBINS-I checklist can be rated as critical, serious, moderate or low RoB. Studies were considered to have an overall high RoB if one domain was judged as high or serious RoB and as having an overall moderate RoB if one domain was considered moderate; all others were rated as low RoB. Only when all domains were judged as low RoB was the overall RoB of the study considered low (Table 4). Interpretation of the guidelines regarding the scoring items was harmonised beforehand to improve consensus. We excluded studies with an overall RoB score of high or critical in order to guarantee conclusions of a bundle of high-quality research.

The Evidence-Based Guideline Development (EBRO) was used to evaluate the overall level of evidence per study. In accordance with the methodology, a classification of the selected studies was based on following criteria: A2, a double-blind RCT of good quality and substantial size and B, a controlled trial not satisfying the conditions of A2 (Table 4). In addition, the EBRO method was used to determine the level of conclusions per outcome. A level-one conclusion was based on at least two A2 studies and converted into strong evidence. A level-two conclusion was determine if one A2 study or at least two B studies agreed on the results, called moderate evidence. A level-three conclusion was based on one B study and converted to weak evidence. Finally, the term “conflicting evidence” was used if results were contradictory. Conclusions were established per outcome measure and targeted approach (Table 5 and Table 6) (42).

Two reviewers (SV, LM) assessed the RoB independently and with blinding to each other’s assessment. Results were compared and in case of disagreement, the article was analysed again. Conflicts were resolved by consensus.

Results

Study selection and characteristics

Figure 1 provides an overview of the study selection process. A first literature search was conducted on November 9, 2020 and updated on April 19, 2021. After removing duplicates, the search strategies led to 3578 studies based on previous described inclusion and exclusion criteria. After the first screening phase, 65 studies were considered eligible for the second screening phase, which resulted in 18 studies to score for RoB (43–60). The main reasons for exclusion were wrong timing (e.g., follow-up less than 6 months or no postoperative outcomes described) or wrong population (e.g., no separate data reports for people with KOA undergoing TKA). With a high RoB, the study of Jahic et al. (51) was additionally excluded. This resulted in 17 eligible studies. Conflicts in the first (1.37%) and second (15.38%) screening phase were resolved by consensus of the 2 reviewers (SV, LM). Fourteen studies (45–50,52,54–60) were RCTs and 3 (43,44,53) were non-RCTs. Details and characteristics of the included studies are in Table 3.

Figure 1: Flowchart of study selection

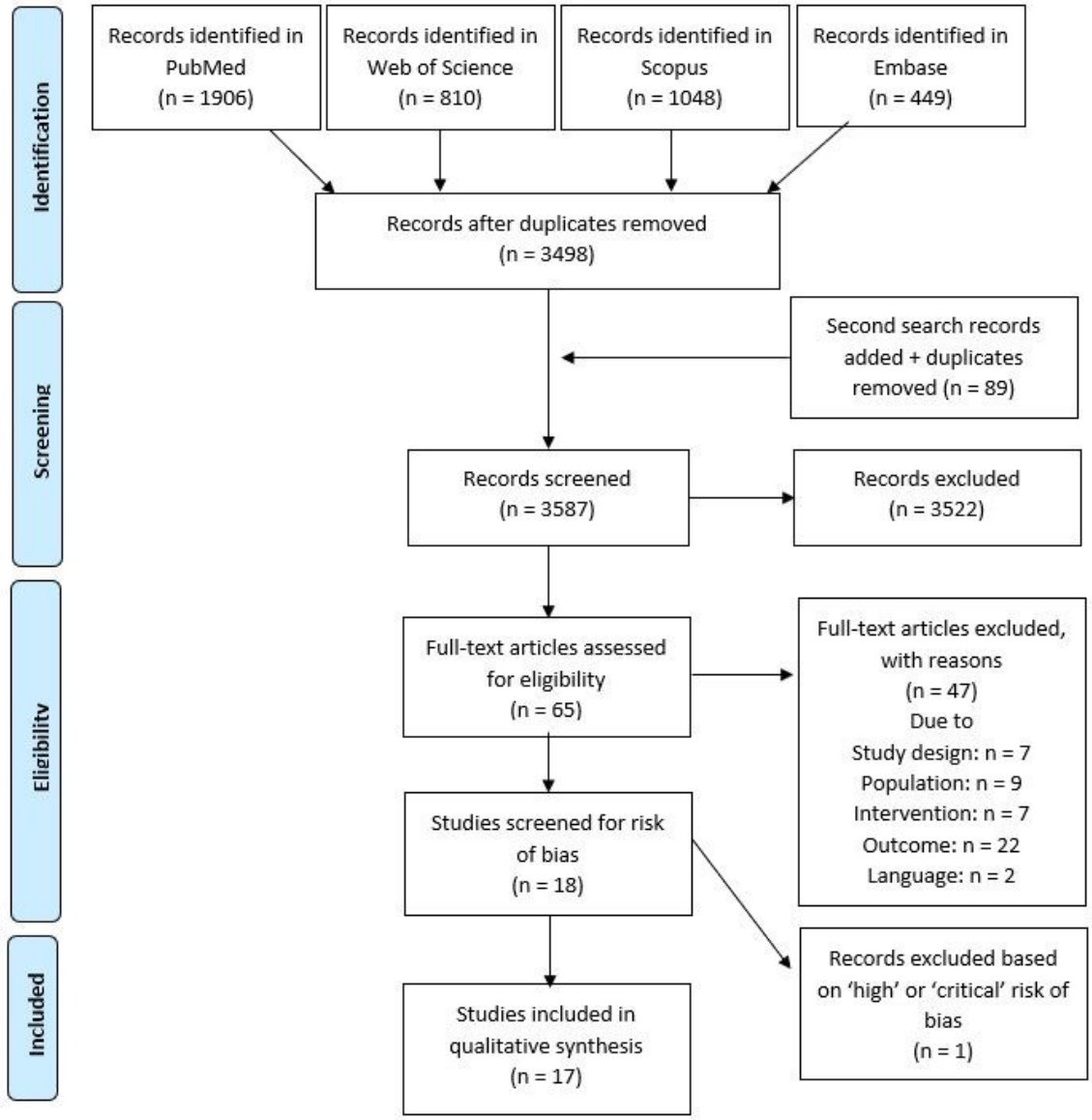

Table 3a: Evidence table part 1

Author and year	-Study design -Setting -Aim	Subject characteristics Sample size Age, mean (SD) Number of ♀ K-L scale	Inclusion and exclusion criteria	Suggested clinical phenotype	Prehabilitation Intervention group (IG) -Content -Modalities -Provider	Control group (CG) -Content -Modalities -Provider (if mentioned)	Intervention related to phenotype or specific study criteria
Aytekin et al. (2019)(43)	-Prospective non-randomized controlled study -Home-based -To detect difference in IG and CG in improving pain and functional ability	Total: n = 44 IG: n = 21, 68y (6) ♀ 18 K-L scale 3 : n = 8 K-L scale 4: n= 13 CG: n = 23, 70y (6) ♀ 18 K-L scale 3 : n = 12 K-L scale 4: n= 11	Inclusion: -Severe KOA with pain not responsive to conservative treatment scheduled for TKA Exclusion: -Inflammatory arthritis -Dermatological conditions affecting the thigh -Neurological disorders -Implanted pacemakers -History of uncontrolled angina -Severe cardiomyopathy -Contraindications for exercise -Revision surgery	/	-Training program: Exercise (mobility, strength and stretching of lower extremity) and education (general, joint protection, home safety and TKA + manual booklet) -12w before surgery, 5x/w, 60 sessions -Physiatrist	No information given	No
Barral et al. (2020)(44)	-Prospective non-randomized controlled study -Setting not given - To detect difference in IG and CG in improving pain and opioid consumption	Total: n = 81 IG: n = 41, 74y (8) ♀ 23 CG: n = 40, 75y (7) ♀ 24 K-L scale not reported	Inclusion: -KOA scheduled for primary TKA Exclusion: -History of surgery on the operated knee -Bilateral TKA in same operation -Participant refusal	/	-Osteopathic manipulative therapy (rhythmic mobilization and myofascial relaxation) -3w and 1w before surgery, 2 sessions -Osteopath	Traditional preoperative management	No
Beaupre et al. (2004)(45)	-RCT -Community physical therapy clinic - To detect difference in IG and CG in improving functional recovery, QoL, health service utilization and costs	Total: n = 131 IG: n = 65, 67y (7) ♀ 39 CG: n = 66, 67y (6) ♀ 33 K-L scale not reported	Inclusion: -Non-inflammatory arthritis -Scheduled for primary TKA -Between 40 and 75y -Willing to take intervention and follow-up visits -Understand English or have a translator	/	-Education (crutch walking, mobility and transfers, postop ROM routine) + exercise (mobility and strength exercises of lower extremity) -4w before surgery, 3x/w, 12 sessions -Not specified who	Usual care: same treatment routinely received (as if they not entered the study)	No

Table 3a (continued)

Author and year	-Study design -Setting -Aim	Subject characteristics Sample size Age, mean (SD) Number of ♀ K-L scale	Inclusion and exclusion criteria	Suggested clinical phenotype	Prehabilitation Intervention group (IG) -Content -Modalities -Provider	Control group (CG) -Content -Modalities -Provider (if mentioned)	Intervention related to phenotype or specific study criteria
Birch et al. (2020)(46)	-RCT -Setting not given - To detect difference in IG and CG in improving pain coping, physical function, QoL, self-efficacy and pain catastrophizing	Total: n = 67 IG: n = 31, 66y (9) ♀ 22 CG: n = 29, 66y (10) ♀ 18 K-L scale not reported	Inclusion: -Primary KOA scheduled for primary TKA -Age ≥ 18y **- >22 on the PCS** -Proficiency in written and spoken Danish -Informed consent Exclusion: **-Severe depression diagnosed with Major Depression Inventory** -Contralateral TKA within 1y postop	Chronic pain	-CG intervention + education based on CBT -2w before surgery, 3 (or 2) sessions -2 physiotherapists	Usual care: multidisciplinary information meeting	Yes: phenotype
Culliton et al. (2018)(47)	-RCT -Home - To detect difference in IG and CG in fulfilling expectations and improving satisfaction	Total: n = 345 IG: n = 167, 64y (8) ♀ 98 CG: n = 178, 63y (9) ♀ 123 K-L scale not reported	Inclusion: -KOA scheduled for elective primary TKA - >20y -Cognitive capacity to give consent Exclusion: -Revision TKA -Patellar resurfacing -Hemi- or unicondylar TKA -High tibial osteotomy -Knee surgery to address a tumour	/	-CG intervention + an online e-learning tool (TKA animation, expectations about pain, function, limitations; demonstrations of participants after TKA) -Before surgery, 1 session -Videos of therapists, surgeons and previous TKA recipients	Hard copy of 'my guide to TKA'	No

Table 3a (continued)

Author and year	-Study design -Setting -Aim	Subject characteristics Sample size Age, mean (SD) Number of ♀ K-L scale	Inclusion and exclusion criteria	Suggested clinical phenotype	Prehabilitation Intervention group (IG) -Content -Modalities -Provider	Control group (CG) -Content -Modalities -Provider (if mentioned)	Intervention related to phenotype or specific study criteria
das Nair et al. (2018)(48)	-RCT -Home or hospital (as preferred by participants) - To detect difference in IG and CG in improving pain, function and mood	Total: n = 50 IG: n = 25, >18y ♀ 14 CG: n = 25, >18y ♀ 9 K-L scale not reported	Inclusion: -KOA scheduled for TKA - >18y **- >7 on either Hospital Anxiety and Depression subscale** Exclusion: -Severe psychiatric conditions -Inflammatory arthritis -Currently receiving any psychological interventions	Chronic pain	-Psychological intervention based on CBT for anxiety depression and pain management -18w before surgery, 10 sessions -Psychologists	Usual care: standard care delivered by each clinical service (no focus on participants' psychological state)	Yes: phenotype
Domínguez-Navarro et al. (2021)(49)	-RCT -Setting not given - To detect difference in IG and CG in improving balance and functional outcomes	Total: n = 82 IG1: n = 20, 70y (6) ♀ 13 IG2: n = 24, 71y (5) ♀ 14 CG: n = 21, 70y (6) ♀ 14 K-L scale > 3	Inclusion: -Idiopathic KOA with >3 on K-L scale scheduled for TKA -Scheduled sufficient time until surgery (5-8 weeks) Exclusion: -Contraindications physical activity - < 21 in the Berg Balance Scale - < 20 Mini-Mental State test -Systemic illness	/	IG1: -Strength training, balance- and proprioception training of lower extremity -4w before surgery, 3x/w, 12 sessions IG2: -Strength training of lower extremity -4w before surgery, 3x/w, 12 sessions -Not specified who	No experimental preoperative intervention	No
Huber et al. (2015)(50)	-RCT -Setting not given - To detect difference in IG and CG in improving lower extremity function	Total: n = 45 IG: n = 22, 69y (8) ♀ 11 CG: n = 23, 72y (8) ♀ 10 K-L scale not reported	Inclusion: -KOA scheduled for primary TKA -Aged between 55y and 90y -Scheduled sufficient time until surgery (to take 8 sessions) -Understood German Exclusion: -Revision surgery -Inflammatory arthritis -Cognitive impairments -inability to walk at least 3m	/	-CG intervention + neuromuscular and biomechanical training (stability, functional alignment, strength of lower extremity and functional exercises) -4 to 12w before surgery, 4-12 sessions -Physiotherapist	-Knee school (information on anatomy, activities, post-operative pain management and rehabilitation) -4w before surgery, 1x/w, 3 sessions -Physiotherapist	No

Table 3a (continued)

Author and year	-Study design -Setting -Aim	Subject characteristics Sample size Age, mean (SD) Number of ♀ K-L scale	Inclusion and exclusion criteria	Suggested clinical phenotype	Prehabilitation Intervention group (IG) -Content -Modalities -Provider	Control group (CG) -Content -Modalities -Provider (if mentioned)	Intervention related to phenotype or specific study criteria
Liljensoe et al. (2021)(52)	-RCT -Home - To detect difference in IG and CG in improving QoL, function, mobility and body composition	Total: n = 76 IG: n = 38, 65y (46-81) ♀ 27 CG: n = 38, 65y (46-85) ♀ 27 K-L scale not reported	Inclusion: -KOA scheduled for primary TKA **- BMI ≥30** -Motivated for weight loss Exclusion: -Rheumatoid arthritis -Planned bariatric surgery	Metabolic syndrome or mechanical overload	-Low-energy liquid diet (810kcal/day) and nutritional education -61.6 to 8w before surgery, 1x/w -Dietitian	-Standard care with no benefit of losing weight before TKA	Yes: phenotype
Louw et al. (2019)(53)	-Prospective controlled clinical trial -Hospital - To detect difference in IG and CG in improving function, pain, pain medication use, fear, catastrophizing and satisfaction	Total : n = 103 IG : n = 49, 74y (10) ♀ 32 CG : n = 54, 70y (11) ♀ 28 K-L scale not reported	Inclusion: -KOA scheduled for TKA and standard preoperative TKA education program -Willingness to participate -Ability to read and understand English Exclusion: -Previous or bilateral TKA	/	-CG intervention + pain neuroscience education - 2 to 12 days before surgery, one session - Physiotherapist	-Preoperative TKA education class (anatomy, expectations, information surgery, pain medication and rehabilitation) - 2 to 12 days before surgery, one session - Not specified who	/
Matassi et al. (2012)(54)	-RCT -Home - To detect difference in IG and CG in improving ROM and functional recovery	Total : n = 122 IG : n = 61, 66y (7) ♀ 33 CG : n = 61, 67y (8) ♀ 26 K-L scale not reported	Inclusion: -Non-inflammatory OA scheduled for unilateral TKA -Moderate to severe knee pain -Aged between 18y and 90y -Willing to participate -Stable health Exclusion: **-BMI >35 + physical activity needs less than moderate** -TKA or THA or knee physiotherapy in last 6m -Failed TKA or unicondylar KA or high tibial osteotomy	/	-Exercises for lower extremity muscle strength and flexibility (individual explanation + written information) - 6w before surgery, 5x/w, 30 sessions - Individual explanation by physiotherapist	-To continue with regular activities	Yes: exclusion criteria (BMI, physical activity, joint motion)

Table 3a (continued)

Author and year	-Study design -Setting -Aim	Subject characteristics Sample size Age, mean (SD) Number of ♀ K-L scale	Inclusion and exclusion criteria	Suggested clinical phenotype	Prehabilitation Intervention group (IG) -Content -Modalities -Provider	Control group (CG) -Content -Modalities -Provider (if mentioned)	Intervention related to phenotype or specific study criteria
Matassi et al. (2012)(54) **(continued)**			-Active local/systemic infection or contraindicated conditions -Grade 3 collateral ligament insufficiency **- < 80° knee flexion, >20° fixed flexion deformity, >10° varus/valgus** -Immunosuppressive disorder or therapy, auto-immune disease or pregnancy -Recent fracture (3m) or steroid infiltration (6weeks) -Inability to understand the study				
Mayoral et al. (2013)(55)	-RCT -Hospital - To detect difference in IG and CG in improving pain	Total : n = 40, ♀ 29 IG : n = 20, 72y (6) CG : n = 20, 73y (8) K-L scale not reported	Inclusion: -KOA scheduled for TKA -Presence of active or latent MTrPs in at least one muscle Exclusion: -Any other condition that could cause myofascial or neuropathic pain in lower limb -Any condition considered a perpetuating factor of MTrPs	/	-Dry needling -Right before surgery during anaesthesia, one session -Physical therapist	-No needling (simulated needling without any application)	Yes: in- and exclusion criteria (MTrPs)
Rooks et al. (2006)(56)	-RCT -Setting not given - To detect difference in IG and CG in improving functional status, pain and muscle strength	Total: n = 45 IG: n = 22, 65y (8) ♀ 11 CG: n = 23, 69y (8) ♀ 13 K-L scale not reported	Inclusion: -Advanced KOA scheduled for THA or TKA -Ability to answer in English -Scheduled sufficient time until surgery (8-12 weeks) Exclusion: -Inflammatory arthritis -Parkinson's disease -Exercise contraindicated	/	-Water and land-based exercise (mobility, strength, flexibility and cardiovascular exercises of total body) -6w before surgery, 3x/w, 18 sessions -Physical therapist	-Education in accessibility, reduce falling and injury and preparing for surgery -6w before surgery, 1x/w, 4 sessions -Mail and telephone, not specified who	No

Table 3a (continued)

Author and year	-Study design -Setting -Aim	Subject characteristics Sample size Age, mean (SD) Number of ♀ K-L scale	Inclusion and exclusion criteria	Suggested clinical phenotype	Prehabilitation Intervention group (IG) -Content -Modalities -Provider	Control group (CG) -Content -Modalities -Provider (if mentioned)	Intervention related to phenotype or specific study criteria
Skoffer et al. (2020)(57)	-RCT -University Hospital - To detect difference in IG and CG in improving functional performance, muscle strength, pain, function and QoL	Total : n = 59 IG : n = 30, 71y (7) ♀ 19 CG : n = 29, 70y (6) ♀ 17 K-L scale not reported	Inclusion: -KOA scheduled for primary unilateral TKA -Residents in the Aarhus municipality -Able to transport themselves Exclusion: -Aged <18y -Heart disease or uncontrolled hypertension -Neuromuscular or neurodegenerative disorders -Unable to comprehend the protocol instructions	/	-Exercises for lower extremity muscle strength and flexibility -4w before surgery, 3x/w, 12 sessions -Physiotherapist	Usual care (live as usual)	No
Sun et al. (2020)(58)	-RCT -Outparticipant clinic - To detect difference in IG and CG in improving pain, function, QoL and pain catastrophizing	Total: n = 80 IG: n = 42, 58y (9) ♀ 19 K-L scale 2: n = 22 K-L scale 3: n= 17 K-L scale 4: n= 3 CG: n = 38, 60y (8) ♀ 21 K-L scale 2: n = 18 K-L scale 3: n= 16 K-L scale 4: n= 4	Inclusion: -Understand/speak Chinese -Primary KOA scheduled for primary TKA -Aged > 18y -Provide informed consent Exclusion: -Cognitive disorders -Trigeminal neuralgia, neuritis, migraine, and other similar reasons for pain -Long-term use of sleeping pills or addiction to opioids -Renal insufficiency -History of knee ligament, meniscus injury, or surgery	/	-CG intervention + education based on CBT -2w before surgery, 3 sessions -Physiotherapist	-Usual care (nursing procedure and education, meeting about operation method, risk and postop rehabilitation) -Nurses, orthopaedists, physiotherapists and anaesthesiologists	No

Table 3a (continued)

Author and year	-Study design -Setting -Aim	Subject characteristics Sample size Age, mean (SD) Number of ♀ K-L scale	Inclusion and exclusion criteria	Suggested clinical phenotype	Prehabilitation Intervention group (IG) -Content -Modalities -Provider	Control group (CG) -Content -Modalities -Provider (if mentioned)	Intervention related to phenotype or specific study criteria
Tolk et al. (2021)(60)	-RCT -Setting not given - To detect difference in IG and CG in fulfilling expectations and improving satisfaction	Total: n = 204 IG: n = 101, 68y (9) ♀ 60 CG: n = 103, 69y (10) ♀ 62 K-L scale not reported	Inclusion: -Symptomatic KOA scheduled for primary TKA Exclusion: -Medical illness that results in life expectancy shorter than 1y -Previous contralateral TKA -Unicompartmental KA -Staged or bilateral TKA -Insufficient command of the Dutch language	/	-CG intervention + 30-min joint-specific educational module aimed at achieving realistic expectations on long-term recovery after TKA -Before surgery, 1 session -Not specified who	-Standard 90-min multidisciplinary education program (what to expect from perioperative period) -Before surgery, 1 session -Not specified who	No
Tungtrongjit et al. (2012)(59)	-RCT -Home - To detect difference in IG and CG in improving pain, ROM, quadriceps strength and QoL	Total: n = 60 IG: n = 30, 63y (8) ♀ 26 K-L scale 2: n = 1 K-L scale 3: n= 5 K-L scale 4: n= 24 CG: n = 30, 66y (7) ♀ 24 K-L scale 3: n= 10 K-L scale 4: n= 20	Inclusion: -Idiopathic/secondary KOA grade ≥2 on K-L scale scheduled for primary TKA - ≥50y Exclusion: -History of old cerebrovascular accident -Knee joint or postop wound infection, dehiscent or trauma	/	-Quadriceps exercises -3w before surgery, daily sessions -Not specified who	-Usual care (to continue normal activities)	No

CBT, Cognitive Behavioural Therapy; CG, control group; CPM, continuous passive motion; K-L, Kellgren and Lawrence; m, month; RCT,a randomized controlled trial; TKA, total knee arthroplasty; x/w, times weekly; y, year

Table 3b: Evidence table part 2

Author and year	Continuation in post-op period	Post-op follow-up time (≥6m)	Lost to follow-up + ITT or PPA analysis	Outcome measurements at all follow-up times	Results (compared to baseline) Effect size (if mentioned)
Aytekin et al. (2019)(43)	/	6m	IG: n = 10 CG: n = 0 ITT	-Pain intensity: VASrest & during activities KOOSpain -Function KOOStotal, stiffness, daily living activities & sports -QoL KOOSQoL	No interaction effect (p>0.05) Within-group scores: All results decreased in both groups (p<0.01)
Barral et al. (2020)(44)	/	6m 12m	Total 6m: n = 19 (IKS) n = 33 (WOMAC) Total 12m: n = 45 (IKS & WOMAC) PPA	-Pain intensity WOMACpain -Funtion: IKSknee & function WOMACstiffness & function	No between-group differences at 6 and 12m (p>0.05) (results of both groups compared at 6 and 12m, not compared to baseline)
Aytekin et al. (2019)(43)	/	6m	IG: n = 10 CG: n = 0 ITT	-Pain intensity: VASrest & during activities KOOSpain -Function KOOStotal, stiffness, daily living activities & sports -QoL KOOSQoL	No interaction effect (p>0.05) Within-group scores: All results decreased in both groups (p<0.01)
Birch et al. (2020)(46)	IG: -education based on CBT -until 3m after surgery, 4 sessions CG: /	12m	IG: n = 4 CG: n = 3 ITT	-Pain intensity VASrest & during activities OKS KOOSpain -Function OKS 6min walk test Sit to stand -QoL EQ-5D	No interaction effect (p>0.05). Within-group scores: -Pain intensity: VASduring activities decreased and OKS increased in both groups(p<0.05) -Function: OKS increased in both groups (p<0.05) -No significant results for all the other outcomes (p>0.05)

Table 3b (continued)

Author and year	Continuation in post-op period	Post-op follow-up time (≥6m)	Lost to follow-up + ITT or PPA analysis	Outcome measurements at all follow-up times	Results (compared to baseline) Effect size (if mentioned)
Culliton et al. (2018)(47)	IG: Online e-learning tool -6w, 3 m and 1y after surgery, 3 sessions CG: /	12m	IG: n = 13 CG: n = 13 ITT	-Pain intensity KOOSpain -Satisfaction KSSsatisfaction PASS -Function KSSsymptoms, functional activities, activities of daily living & sports -Quality of life KOOSquality of life	Between-group differences: -Function: KSSSsymptoms and functional was higher in CG (p=0.04) -No significant results for all the other outcomes (p>0.05) (results of both groups compared at 12m, not compared to baseline) Interaction effects and within-group scores not given
das Nair et al. (2018)(48)	/	6m	IG: n = 12 CG: n= 13 ITT	-Pain intensity IPOC WOMACpain -Function WOMACstiffness & physical function -QoL EQ-5D	Between-group differences: -Function: WOMACphysical function was higher in IG (p=0.009, ES= 1.16) - No significant results for all the other outcomes (p>0.05) (results of both groups compared at 12m, not compared to baseline) Interaction effects and within-group scores not given.
Domínguez-Navarro et al. (2021)(49)	/	12m	IG1: n = 5 IG2: n = 5 CG: n = 5 ITT	-Pain intensity KOOSpain -Function Berg Balance Scale KOOS-ADL ROM flexion & extension Strength Quadriceps TUG Functional reach test Single leg standing -QoL KOOSQoL	Interaction effect: -Function: Single leg standing increased in favour of IG1 and IG2 compared to CG (p=0.043) - No significant results for all the other outcomes (p>0.05) Within-group scores not given

Table 3b (continued)

Author and year	Continuation in post-op period	Post-op follow-up time (≥6m)	Lost to follow-up + ITT or PPA analysis	Outcome measurements at all follow-up times	Results (compared to baseline) Effect size (if mentioned)
Huber et al. (2015)(50)	/	12m	IG: n = 5 CG: n = 4 ITT	-Pain intensity KOOSpain SF36pain EQ-5Dpain & VAS -Function KOOSfunction, symptoms & sports SF- function & role physical -QoL KOOSQoL EQ-5Dmobility & activities	No interaction effect (p>0.05). Within-group scores: -Pain intensity: KOOSpain increased in both groups (p≤0.001) SF36pain increased in IG (p≤0.05) -No significant results for all the other outcomes (p>0.05) (all results are compared to three months after surgery)
Liljensoe et al. (2021)(52)	IG: Low-energy liquid diet + nutritional education -until 1y postop, 1x/w -Dietitian	12m	IG: n = 0 CG: n = 0 ITT and PPA (focus on ITT)	-Pain intensity KOOSpain -Function SF36 PCS KOOSsymptoms, activities of daily living & sports 6min walk test -QoL KOOSQoL	ITT: No interaction effects (p>0.05). Within-group differences: -Function: SF36 PCS improved in all participants (CI: 5 to 10) KOOSsymptoms improved in all participants (CI : 16.0 to 25.0) 6min walk test improved in all participants (CI: 56 to 100) -QoL: KOOSQoL improved in all participants (CI: 26.4 to 37.7) No significant results for pain intensity (p>0.05)
Louw et al. (2019)(53)	/	6m	IG: n = 18 CG: n = 18 ITT and PPA (focus on PPA)	-Pain intensity NPRS -Satisfaction Statement: 'the surgery met my expectations' -Function WOMACfunction	PPA: Interaction effects: -Satisfaction: The 'met expectations statement' improved in favour of IG (p=0.03) Within-group differences: -Pain intensity and function: NPRS and WOMACfunction improved over time for all participants (p<0.001) (compared to 3m postop)
Matassi et al. (2012)(54)	/	6m 12m	IG: n = 0 CG: n = 0 ITT	-Function ROM active, passive knee flexion & knee extension Knee Society Clinical Rating System - Knee & function score	Between-group differences (within not given): -Function: The evolution (baseline to 12m postop) of the extension was different between groups (p = 0.032), but not the absolute score (as in other studies) -No significant results for all the other outcomes (p>0.05)

Table 3b (continued)

Author and year	Continuation in post-op period	Post-op follow-up time (≥6m)	Lost to follow-up + ITT or PPA analysis	Outcome measurements at all follow-up times	Results (compared to baseline) Effect size (if mentioned)
Mayoral et al. (2013)(55)	/	6m	IG: n = 4 CG: n = 5 ITT	-Pain intensity VAS WOMACpain -Function WOMACstiffness & function ROM Strength Quadriceps & Hamstrings	-No between- and within-group significant results for all the outcomes (p>0.05)
Rooks et al. (2006)(56)	/	6m	IG: n = 8 CG: n = 8 ITT	-Pain intensity: WOMACpain SF-36bodily pain -Function: WOMACfunction SF-36function &role physical 1RM leg press test Functional reach test TUG	Interaction effect: -Pain intensity: decrease in SF-bodily pain (p<0,05) in favour of IG -No significant results for all the other outcomes (p>0.05) Within-group scores not given.
Skoffer et al. (2020)(57)	IG: -Exercises for lower extremity muscle strength and flexibility -4 w after surgery, 3x/w, 12 sessions -Physiotherapist	12m	IG: n = 6 CG: n = 9 ITT	-Pain intensity KOOSpain Current, worst & average pain score -Function KOOSsymptoms, activities of daily living & sports 30s time chair stand test TUG 10min & 6min walk test Strength Quadriceps & Hamstrings (both legs) ROM active and passive flexion & extension -QoL KOOSQoL Health-related QOL	Interaction effect: -Function: Strength of the Quadriceps (p=0.002) and Hamstrings (p=0.042) of the operated leg increased in favour of IG. -No significant results for all the other outcomes (p>0.05) Within-group scores not given.

Table 3b (continued)

Author and year	Continuation in post-op period	Post-op follow-up time (≥6m)	Lost to follow-up + ITT or PPA analysis	Outcome measurements at all follow-up times	Results (compared to baseline) Effect size (if mentioned)
Sun et al. (2020)(58)	IG: -Usual care + education based on CBT -2w after surgery, 3 sessions Physiotherapist CG: - Active exercise and CPM exercise	12m	IG : n = 8 CG : n = 12 PPA	-Pain intensity VASrest & during activities -Function Knee ROM OKS HSS Knee rating scale -QoL EQ-5D	No interaction effects (p>0.05) Within-group differences: -Pain intensity and Function: Knee ROM, EQ-5D and HSS increased over time, while OKS and VAS scores decreased over time in both groups (p<0.001) -No significant results for all the other outcomes (p>0.05)
Tolk et al. (2021)(60)	/	12m	IG: n = 8 CG: n = 9 ITT and PPA (focus on ITT)	-Pain intensity NRS pain -Satisfaction NRS satisfaction, HSS-KRES -Function KOOSfunction -QoL EQ-5D	Interaction effect: ITT: No interaction effects (p>0.05), PPA: Higher NRS satisfaction in favour of IG 12m postop (p= 0.012) Within-group differences: -Satisfaction: Subscale kneel (p=<0.001), squat (p=0.015) and walk long distance (p=0.006) more fulfilled in IG 12m -No significant results for all the other outcomes (p>0.05) (Within-group differences at 12m, not to baseline)
Tungtrongjit et al. (2012)(59)	/	6m	Total: n = 4 PPA	-Pain intensity VAS WOMACpain -Function Total WOMAC WOMACstiffness & function Strength Quadriceps ROM flexion, extension & total	Interaction effect: -Pain intensity: WOMACpain score decreased in favour of IG (p=0.029) -No significant results for all the other outcomes (p>0.05) Within-group differences not given

1RM, one repetition maximum; CPM, continuous passive motion; EQ-5D, Euro Quality of Life – 5D; EQ-5Dmobility, EQ-5D – subscale mobility; EQ-5Dpain, EQ-5D – subscale pain; EQ-5Dusualactivities, EQ-5D – subscale usual activities; EQ-5DVAS, EQ-5D – subscale visual analog scale; HSS-KRES, Hospital for Special Surgery Knee Replacement Expectations Survey; IG, intervention group; IKSfunction, International Knee Society – subscale function; IKSknee, IKS – subscale knee; ITT, intention to treat analysis; KOOSdaily living activities, KOOS – subscale daily living activities; KOOSpain, Knee Injury and Osteoarthritis Outcome Score – subscale pain; KOOSquality of life, KOOS – subscale quality of life; KOOSsports, KOOS – subscale sports; KOOSstiffness, KOOS – subscale stiffness; KOOStotal, KOOS total; KSSfunctional activies, KSS – subscale functional activities; KSS-satisfaction, KSS – subscale satisfaction; KSSsymptoms, Knee Society Score System – subscale symptoms; NPRS, numeric rating scale for pain; OKS, Oxford Knee Score; PASS, Participant Acceptable Symptom State; PCS, Pain Catastrophizing Scale; PPA, per protocol analysis; QoL, quality of life; ROM, range of motion; SF PCS, SF – subscale physical component score; SF- role physical, SF – subscale role physical; SF-bodily pain, 36-item Short Form Survey – subscale bodily pain; SF-physical function, SF- subscale physical function; TUG, Timed Up and Go; VASduring activities, VAS during activities; VASrest, visual analogue scale at rest; w, week; WOMACfunction, WOMAC – subscale function; WOMACpain, Western Ontario and McMaster Universities Osteoarthritis Index – subscale pain

Table 4: Risk of bias

Study	Study-design	RoB tool	1	2	3	4	5	6	7	Overall	LoE
Aytekin et al. (43)	Non-RCT	ROBINS-I	Serious	Low	Low	Moderate	Serious	Low	Low	**Serious**	B
Barral et al. (44)	Non-RCT	ROBINS-I	Serious	Low	Low	Low	Moderate	Low	Low	**Serious**	B
Beaupre et al. (45)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Birch et al. (46)	RCT	ROB-II	Low	Some concerns	Low	Low	Low			**Some concerns**	B
Culliton et al. (47)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
das Naïr et al. (48)	RCT	ROB-II	Low	Some concerns	Some concerns	Low	Low			**Some concerns**	B
Dominquez-Navarro et al. (49)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Huber et al. (50)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Jahic et al. (51)	RCT	ROB-II	Some concerns	Low	Low	High	Some concerns			**High**	N/A
Liljensoe et al. (52)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Louw et al. (53)	Non-RCT	ROBINS-I	Serious	Low	Low	Low	Moderate	Low	Low	**Serious**	B
Matassi et al. (54)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Mayoral et al. (55)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Rooks et al. (56)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Skoffer et al. (57)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Sun et al. (58)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Tolk et al. (60)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2
Tungtrongjit et al. (59)	RCT	ROB-II	Low	Low	Low	Low	Low			**Low**	A2

LoE, level of evidence; N/A, not applicable due to exclusion; RCT, randomized controlled trial; ROB-II, Revised Cochrane Risk of Bias tool for randomized trials; ROBINS-I, Risk of Bias In Non-randomized Studies of Interventions. Articles scored with ROBINS-I: bias due to 1 = confounding, 2 = selection of participants in the study, 3 = classification of interventions, 4 = deviations from intended interventions, 5 = missing data, 6 = measurement of outcomes. Articles scored with ROB-II: bias due to 1 = randomization process, 2 = deviations from intended interventions, 3 = missing outcome data, 4 = measurement of outcome, 5 = selection of the reported result.

Risk of bias

The RoB assessment and levels of evidence results are presented in Table 4. Almost excellent agreement of 94.22% and 98.48% was achieved between both assessors, before consensus, for the ROB-II and ROBINS-I, respectively. Twelve studies had low (45,47,49,50,52,54–60), 2 moderate (46,48), 3 serious (43,44,53), and one high RoB (51). RoB due to confounding or missing data was the main reason for increased RoB. The study with the highest RoB (51) was excluded from this systematic review. Because all studies were comparative, the 12 studies with an overall low RoB score received a level of evidence of A2 (good evidence) (45,47,49,50,52,54–60) and the other 5 studies a level of evidence of B (moderate evidence).

Study population and intervention

Study population

None of the studies described subgroups or focused on a specific clinical phenotype explicitly. However, the study population in 3 studies could be classified as a specific KOA phenotype. Birch et al. (46) and das Naïr et al. (48) focused on KOA individuals with specific psychological features, consistent with the chronic pain phenotype, and Liljensoe et al. (52) on KOA individuals with increased BMI, consistent with the metabolic syndrome or mechanical overload phenotype. Two other studies described more specific inclusion and exclusion criteria than only KOA diagnosis but could not be classified as a specific clinical phenotype (54,55). Matassi et al. (54) excluded OA individuals with high BMI, less than moderate physical needs and limited joint motion, and Mayoral et al. (55) included KOA individuals with myofascial trigger points. In 4 of 5 studies (46,52,54,55), a predefined prehabilitation was set up, and only participants with a certain matching phenotype or more specific inclusion and exclusion criteria were included. Only in the das Naïr et al. (48) study was the intervention stratified to the individuals' needs. The other 12 studies (43–45,47,49,50,53,56–59) used a "one-size-fits-all" approach and described general inclusion criteria such as signs related to KOA diagnosis.

When a study used more stringent eligibility criteria than the KOA diagnosis itself and when the intervention was tailored to these criteria (or vice versa, e.g., if individuals were chosen according to a predefined intervention), studies were classified as the stratified care approach. Otherwise, studies were classified as the non-stratified care approach.

The sample size ranged from 40 (55) to 122 (54) individuals for the stratified care approach studies, and 44 (43) to 345 (47) for the non-stratified care approach studies.

All details are presented in Table 3.

Intervention and control groups

All studies were comparative experimental designs consisting of 14 RCTs and 3 controlled clinical trials and had at least one intervention group and one control group. As mentioned, the phenotype (46,48,52) or specific individual characteristics (54,55) of almost all the stratified care studies were chosen to match the intervention (except for das Naïr et al. (48)). The interventions could be divided into 4 domains: interventions based on a more

biopsychosocial approach for individuals with the chronic pain phenotype (46,48); weight loss intervention for individuals with the metabolic syndrome or mechanical overload phenotype (52); exercise (lower limb strength and flexibility) for individuals with lower BMI, more than moderate physical needs and normal joint motion (54); and dry needling for individuals with myofascial trigger points (55). The biopsychosocial approach of the das Naïr et al. study was based on cognitive behavioural therapy (CBT) focusing on anxiety, depression and pain management, and was tailored to each individual's needs (48). The biopsychosocial approach of Birch et al. was also based on CBT but focused on standardized pain education, pain coping skills training and ways to apply these skills into real life and as such, less tailored to individuals' needs (46). Nevertheless, the study was still considered stratified because more stringent inclusion criteria (related to the chronic pain phenotype) were used.

Interventions in other studies were given to a general group of people with KOA and could be divided into 5 domains: exercise (strength, balance, neuromuscular or cardiovascular) (49,56,57,59), biomedical education alone (47), exercise + biomedical education (43,45,50), osteopathic manipulative interventions (44) and interventions based on a more biopsychosocial approach (53,58,60). As biopsychosocial interventions, a standardized pain neuroscience education was used in Louw et al. (53) and a realistic expectation program in Tolk et al. (60). The same CBT program as in Birch et al. (46) was used in Sun et al. as a biopsychosocial intervention (58).

Most control groups received no specific prehabilitation intervention and were asked to continue their activities as if they had not entered the study (43–46,48,49,52,54,55,57,59). Individuals in the control group of 6 studies received a preoperative biomedical-oriented education (47,50,53,56,58,60). None of the studies compared a non-stratified care approach with a stratified care approach to prehabilitation but only compared the approaches with a control intervention.

The mean starting time before surgery ranged from 61 weeks before surgery (52) to the day of surgery (55). The prehabilitation interventions ended before surgery, except for in 5 studies (46,47,52,57,58) in which the content of the prehabilitation continued in the postoperative phase. As such, the intervention phase of the study continued postoperatively (ranging from 3 weeks to 1 year post-TKA). All other studies involved standard postoperative rehabilitation (as if participants had not entered the study).

All details about follow-up time, loss to follow-up, content, modalities and provider of intervention are in Table 3.

Long-term outcome after a stratified care approach (Table 5)

The effects of the studies of Birch et al. (46) and Liljensoe et al. (52) are presented as interaction effects (group x time), and the effects of das Naïr et al. (48), Matassi et al. (54) and Mayoral et al. (55) are only presented as between-group differences at a given time (no interaction effect).

Pain. Four of 5 studies investigated the effect on pain. Dry needling in individuals with myofascial trigger points (55) and a biopsychological approach (based on tailored CBT) in

individuals with the chronic pain phenotype (48) as prehabilitation resulted in no improvement at 6 months after TKA as compared with no prehabilitation ($p>0.05$). In addition, no effect was found for a biopsychological approach (based on standardized CBT) in individuals with the chronic pain phenotype (46) or weight loss intervention in individuals with the metabolic syndrome or mechanical overload phenotype (52) at 12 months after TKA as compared with no prehabilitation ($p>0.05$).

Function. All 5 studies investigated the effect on several aspects of function. Only das Naïr et al., in which a biopsychosocial prehabilitation (stratified CBT) in individuals with the chronic pain phenotype was performed (48), reported a significant effect on function at 6 months post-TKA as compared with no prehabilitation ($p=0.009$). Dry needling in participants with myofascial trigger points (55) and exercise in individuals with specific criteria related to BMI, physical function and joint motion (54) resulted in no difference after 6 months as compared with no prehablitation ($p>0.05$). In addition, a biopsychosocial prehabilitation approach (standardized CBT) in individuals with the chronic pain phenotype resulted in no significant improvement at 12 months post-TKA as compared with no prehabilitation ($p>0.05$) (46). Also, the weight loss intervention in individuals with the metabolic syndrome or mechanical overload phenotype conferred no significant improvement at 12 months post-TKA as compared with no prehabilitation ($p>0.05$) (52).

Quality of life. Quality of life was assessed in 3 studies. Despite the phenotype or specific study criteria-tailored prehabilitation in the studies, no differences over time were found for the biopsychosocial approaches in individuals with chronic pain phenotype at 6 months (48) and 12 months post-TKA (46) and a weight loss intervention in individuals with the metabolic syndrome or mechanical overload phenotype (52) at 12 months post-TKA as compared with no prehabilitation ($p>0.05$).

Satisfaction. This outcome measure was not used in the studies with a stratified care approach. Details can be found in Table 3 and Table 5.

Table 5: Level of conclusion of the "stratified care" approach: interaction effects and between-group differences

Outcome measure	Intervention	Effect	Studies	Follow-up time	Level of evidence	RoB	Level of conclusion
Pain	Biopsychosocial approach	-	Das Naïr et al. (48)	6m	B	Some concerns	Weak
		-	Birch et al. (46)	12m	B	Some concerns	Weak
	Weight loss intervention	-	Liljensoe et al. (52)	12m	A2	Low	Moderate
	Dry needling	-	Mayoral et al. (55)	6m	A2	Low	Moderate
Function	Biopsychosocial approach	+	Das Naïr et al. (48)	6m	B	Some concerns	Weak
		-	Birch et al. (46)	12m	B	Some concerns	Weak
	Weight loss intervention	-	Liljensoe et al. (52)	12m	A2	Low	Moderate
	Dry needling	-	Mayoral et al. (55)	6m	A2	Low	Moderate
	Exercise	-	Matassi et al. (54)	6m/12m	A2	Low	Moderate
QoL	Biopsychosocial approach	-	Das Naïr et al. (48)	6m	B	Some concerns	Weak
	Weight loss intervention	-	Birch et al. (46)	12m	B	Some concerns	Weak
		-	Liljensoe et al. (52)	12m	A2	Low	Moderate

m, months; QoL, quality of life; RoB, risk of bias

Long-term outcome after a non-stratified care approach (Table 6)

All effects are presented as interaction effects (group x time), except for the studies of Barral et al. (44) and Cullliton et al. (47), in which only the between-group differences at one given time (baseline and postoperative) are described (no interaction effects).

Pain. All 12 studies used pain as an outcome measure. None of the prehabilitation intervention types had an effect on pain at 6 or 12 months after TKA as compared with no or biomedical education prehabilitation, except for the studies of Rooks et al. (56) and Tungtrongjit et al. (59). These studies found a significant improvement at 6 months after TKA in favour of their intervention groups receiving exercise ($p<0.05$ and $p=0.029$, respectively) as compared with biomedical education prehabilitation and no prehabilitation, respectively.

Satisfaction. Three studies investigated the effect of prehabilitation on satisfaction; only Louw et al. (53) reported a significant positive effect of a biopsychosocial prehabilitation (standardized pain neuroscience education) approach at 6 months after TKA as compared with biomedical education prehabilitation ($p=0.03$). However, Tolk et al. (60) found no significant improvement in satisfaction at 12 months after TKA for the biopsychosocial prehabilitation (realistic expectations program) approach as compared with the biomedical education prehabilitation using an intention-to-treat analysis ($p>0.05$). The authors also performed a per protocol analysis for this outcome, which did reveal a significant positive effect of the intervention on satisfaction at 12 months post-TKA ($p= 0.012$). However, the intention-to-treat analysis was dominant according to their methodology. Additionally, an online e-learning tool of biomedical education prehabilitation resulted in non-significant improvements at 12 months after TKA as compared with a biomedical education given on a hard copy ($p>0.05$) (47).

Function. All 12 studies investigated the effect on function. None of the interventions had an effect on postoperative function as compared with no prehabilitation or biomedical education prehabilitation, again except for exercise (49,57). Despite no significant effect found at 6 months post-TKA ($p>0.05$), exercise did result in a significant increase in single leg standing time [$p=0.043$] (49) and increase in strength of quadriceps ($p=0.002$) and hamstrings ($p=0.042$) (57) at 12 months post-TKA as compared with no prehabilitation.

Quality of life. Exercise, exercise + biomedical education, a biopsychosocial approach or biomedical education alone as prehabilitation resulted in no significant effects regarding quality of life at 6 months (43) or 12 months (47,49,50,57,60) post-TKA ($p>0.05$) as compared with no or biomedical education prehabilitation. Details can be found in Table 3 and Table 6.

Table 6: Level of conclusion of "non-stratified care" approach: interaction effects and between-group differences

Outcome measure	Intervention	Effect	Studies	Follow-up time	Level of evidence	RoB	Level of conclusion
Pain	Exercise	+	Rooks et al. (56)	6m	A2	Low	Strong
		+	Tungtrongjit et al. (59)	6m	A2	Low	
		-	Domínguez-Navarro et al. (49)	12m	A2	Low	Strong
		-	Skoffer et al. (57)	12m	A2	Low	
	Exercise + biomedical education	-	Aytekin et al. (43)	6m	B	Serious	Moderate
		-	Beaupre et al. (45)	6m	A2	Low	
		-	Beaupre et al. (45)	12m	A2	Low	Moderate
		-	Huber et al. (50)	12m	A2	Low	
	Biopsychosocial approach	-	Louw et al. (53)	6m	B	Serious	Weak
		-	Sun et al. (58)	12m	A2	Low	Strong
		-	Tolk et al. (60)	12m	A2	Low	
	Biomedical education	-	Culliton et al. (47)	12m	A2	Low	Moderate
	Osteopathic manipulation	-	Barral et al. (44)	6m/12m	B	Serious	Weak
Satisfaction	Biopsychosocial approach	+	Louw et al. (53)	6m	B	Serious	Weak
		-	Tolk et al. (60)	12m	A2	Low	Moderate
	Biomedical education	-	Culliton et al. (47)	12m	A2	Low	Moderate
Function	Exercise	-	Tungtrongjit et al. (59)	6m	A2	Low	Moderate
		+	Domínguez-Navarro et al. (49)	12m	A2	Low	Strong
		+	Skoffer et al. (57)	12m	A2	Low	
	Exercise + biomedical education	-	Aytekin et al. (43)	6m	B	Serious	Moderate
		-	Beaupre et al. (45)	6m	A2	Low	
		-	Beaupre et al. (45)	12m	A2	Low	Strong
		-	Huber et al. (50)	12m	A2	Low	
	Biopsychosocial approach	-	Louw et al. (53)	6m	B	Serious	Weak
		-	Sun et al. (58)	12m	A2	Low	Strong
		-	Tolk et al. (60)	12m	A2	Low	
	Biomedical education	-	Culliton et al. (47)	12m	A2	Low	Moderate
	Osteopathic manipulation	-	Barral et al. (44)	6m/12m	B	Low	Weak
QoL	Exercise	-	Domínguez-Navarro et al. (49)	12m	A2	Low	Strong
		-	Skoffer et al. (57)	12m	A2	Low	
		-	Aytekin et al. (43)	6m	B	Serious	Weak

Table 6 (continued)

Outcome measure	Intervention	Effect	Studies	Follow-up time	Level of evidence	RoB	Level of conclusion
	Exercise + biomedical education	-	Huber et al. (50)	12m	A2	Low	Moderate
	Biopsychosocial approach	-	Tolk et al.(60)	12m	A2	Low	Moderate
	Biomedical education	-	Culliton et al. (47)	12m	A2	Low	Moderate

m, months; QoL, quality of life; RoB, risk of bias

Discussion

The first aim of this systematic review was to investigate whether previous prehabilitation studies of people with KOA awaiting TKA included phenotypes or specific individual characteristics as study inclusion or exclusion criteria and whether the content of the prehabilitation was stratified accordingly. The second aim was to synthesise and compare the long-term outcomes after TKA regarding pain, satisfaction, function or quality of life of the studies with non-stratified prehabilitation care in relation to studies with stratified prehabilitation care.

For the first aim, our systematic review found that none of the previous prehabilitation clinical trials explicitly mentioned clinical phenotypes in their study inclusion criteria. The study inclusion criteria of 3 studies (46,48,52) could be related to a specific phenotype, and 2 others (54,55) described more specific criteria beyond the KOA diagnosis. The study inclusion and exclusion criteria of 4 studies (46,52,54,55) were adapted to the intervention accordingly; only in the das Naïr et al. (48) study was the intervention adapted to individuals' needs.

Regarding the second aim, none of the studies compared a non-stratified care approach with a stratified care approach to prehabilitation. Our systematic review found that all studies compared their prehabilitation with a control group, and as such, could only provide a comparison of stratified care versus control and non-stratified care versus control prehabilitation. Evidence was weak for a positive effect of the stratified care approach: biopsychosocial prehabilitation (stratified CBT) resulted in a positive effect at 6 months after TKA on function as compared with no prehabilitation. Accordingly, evidence was weak for a positive effect of the non-stratified care approach of a standardized pain neuroscience education program compared to a biomedical education program but not on satisfaction at 6 months post-TKA. However, evidence was strong for a positive effect of exercise prehabilitation on pain at 6 months after TK and on function at 12 months after TKA in the non-stratified care approach as compared with no prehabilitation. We could not establish other significant results on any outcome and follow-up time regarding other prehabilitation interventions compared to control groups. Details about all levels of conclusions are presented in Table 5 and Table 6.

Despite the acknowledged importance of subgrouping and stratified care in heterogenous diseases such as KOA (61), most of the literature including prehabilitation before TKA completely lacked this approach. In people with back pain, Foster et al. (26) identified 3 approaches for stratified care: stratification based on risk profile, mechanisms and treatment respondents. The third approach was used in 4 stratified studies included in this review (46,52,54,55). The interventions of these studies already existed, and individuals were selected on the basis of criteria matched to the factors the intervention were thought to address (26). However, this strategy seemed not ideal. For example, in the study of Mayoral et al. (55) (one of stratified care studies), people with KOA were screened for myofascial trigger points to match their predefined intervention; regardless, every individual screened by the authors fulfilled the criteria and therefore none could be excluded. As such, this seemed no argument for a subgroup of people with KOA. Only the das Naïr et al. study (48) (one of the stratified care studies) implemented biopsychosocial prehabilitation care stratified to individuals' needs, instead of visa versa (such as the other 4 studies). Remarkably, this is also the only stratified care study that showed a significant positive effect. As such, this study probably used a more effective way of stratification.

The treatment-respondents approach is in fact not the most ideal way of individual centered care in research and clinical practice. Current Osteoarthritis Research Society International guidelines still recommend a "stepped care" approach in KOA intervention studies; that is, all people with KOA receive the same intervention, and treatments are modified only if an individual–does not benefit sufficiently. Exercise and education are the core elements. However, these guidelines focus on non-surgical management, and clear guidelines for prehabilitation are lacking (62).

All the prehabilitation interventions of the included studies had the aim to improve certain postoperative outcomes more than control interventions. Nevertheless, the goal of prehabilitation itself is to focus on improving risk factors for insufficient postoperative outcome (13). None of the non-stratified studies explicitly targeted this, and hence, the aim of prehabilitation was probably missed. More ideally, the most suitable prehabilitation intervention is to probably tailor the intervention based on the phenotype or specific individual's characteristics (including risk factors for insufficient postoperative outcome). This situation creates a sub-clustering of people with KOA in which the intervention needs to be adapted to the modifiable prognostic characteristics of the individual (63,64).

In terms of research, single-case experimental designs or pragmatic trials, with the possibility to stratify the intervention, are a great option to test the hypothesis that stratified rather than non-stratified prehabilitation is more effective (65). This will be the only way to finally find evidence about whether to use a stratified approach or not and if so, to draw conclusions about the best matched stratified approach. A recent review also indicated the importance of a direct comparison of effective stratified versus non-stratified care because this kind of research in musculoskeletal diseases is extremely lacking (63).

In addition, previous research of people with KOA suggested the importance of identifying a clinical phenotypes based on modifiable factors first, to guarantee optimal individual stratified treatment (24–26). Hence, the phenotypes chosen in the Dell'Isola et al. study (19) were based

on people with KOA not awaiting TKA and therefore not specifically chosen for prehabilitation purposes. More studies building further on clinical phenotypes are necessary, to find the optimal division of clinical phenotypes that can be used in people with KOA awaiting TKA and to test the prognostic value of identified phenotypes.

In general, we found the strongest evidence for the effect of exercise prehabilitation on pain at 6 months and on function at 12 months post-TKA in the non-stratified care approach as compared with no prehabilitation. This finding is in line with studies focusing on the effect of exercise as treatment in people with KOA or as rehabilitation in individuals with TKA (62). Exercise therapy seems to have a positive effect on pain and function in many populations; however, most of the time, the positive effects of exercise therapy have been rather small to moderate (66,67). The extent of the positive effect of exercise in the included studies is unclear because none reported effect sizes. As suggested above, effective matched stratified prehabilitation care might result in even better effects (18,63,64). This hypothesis is strengthened because in a recent study, a stratified exercise approach in people with KOA (not awaiting TKA) revealed higher improvements regarding pain and functional activity as compared with previous stepped care research (29). Therefore, ineffective stratified care (matching the individuals to the intervention instead of visa versa) could have resulted in non-significant positive effects of exercise prehabilitation in the stratified care studies of this review.

Another important observation is that none of the studies included a process evaluation of the given prehabilitation, except for Birch et al. (46), in which physiotherapists regularly met to align their given treatment. Only in Beaupre et al. (45) and Matassi et al. (54) were individuals instructed to complete a log book to have an idea about their therapy compliance, which was in both studies about 80%. No other control factor to guarantee the quality of the intervention was mentioned in these and other studies.

The lack of effect of other prehabilitation strategies, apart from exercise, is in line with a recent systematic review and meta-analysis of Dennis et al. (15), which found low to moderate evidence that prehabilitation before TKA resulted in no benefit on long-term pain outcomes, and also other recent systematic reviews reported only a benefit on short-term outcomes (68,69). This situation might be related to the aforementioned theories of effective stratified care (29). Likely, the included studies in the reviews did not perform personalized stratified care, or none of the reviews intended to compare studies with a stratified care approach to studies with a non-stratified care approach.

Moreover, in 2 studies of the non-stratified care approach as well as in more than the half of the studies using the stratified care approach (44,47,48,54,55), statistical analyses did not measure interaction effects. Therefore, the difference in results was only measured and compared at a specific time and so the analyses were cross-sectional. This situation may have resulted in indecisive changes over time. Additionally, 2 stratified care studies exhibited only medium RoB; therefore, conclusions could only be made with moderate or weak evidence (46,48). Both reasons again might not have revealed potentially positive results of prehabilitation.

In general, to date, there are not enough high-quality studies to draw hard conclusions. Scientific research is the basis for our education and clinical practice, so this field of research must be brought to a higher level. First, an adequate assessment of the individual taking into account all modifiable risk factors for insufficient postoperative outcome with the prognostic value is necessary for sub-clustering individuals in scientific research and clinical practice. Second, an individual-characteristics stratified intervention with a sufficient process evaluation including all qualitative (adherence to intervention protocol, control whether the changes are as expected) and quantitative (number of sessions, frequency per week etc.) elements, including the clear aim of the prehabilitation must follow.

Strengths and limitations of the review

A huge strength of this systematic review is that this is the first review of people with KOA that tried to investigate the difference in effectiveness between studies with a stratified care approach and those with a non-stratified care approach. We were not able to make a direct comparison, but the comparison of stratified care versus control and non-stratified care versus control was possible to a certain level.

A limitation is that studies that used a follow-up period of < 6 months were excluded. Perhaps if other studies with a shorter follow-up were included, the short-term differences could also be investigated. One of the 2 approaches could have resulted in better outcomes sooner as compared with the other approach, but the difference in treatment effect faded away at a longer follow-up. This study could also be interesting, because in this population, apart from the influence of other factors, the sooner individuals get better, the fewer treatment sessions they might need. However, our focus, and thus main outcomes, were persistent pain and satisfaction. Because previous research on the effect of TKA in people with KOA has shown that most of the improvement was seen at 3 to 6 months after surgery (a normal expected healing process) (70–73), this strengthened our decision to opt for a minimum follow-up time of 6 months.

A second limitation Is that we used the clinical phenotypes described by Dell-Isola et al. (19). We do not know whether all study characteristics included in the different phenotypes were modifiable factors with a sufficient prognostic value as the studies, on which the division of Dell-Isola et al. was based, were cross-sectional. The characteristics of the described phenotypes have never been tested in an intervention study, and therefore, no definite conclusion about the “modifiability” and “prognostic value” can be drawn. Nevertheless, this is the first review that described such clinical division, and in a later study, Dell-Isola et al. found that 84% of their 600 participants with KOA could be divided into these phenotypes (74). This finding strengthens our choice to analyse the included studies based on their identified phenotypes, as this is currently the only available “more clinically based stratification”. More research on stratifying and its treatment efficacy is certainly warranted.

Conclusion

To date, only 5 existing clinical prehabilitation intervention trials in people with KOA awaiting TKA focused on a specific sample, which was based on a KOA phenotype or more stringent inclusion or exclusion study criteria and thus used a kind of stratified prehabilitation care. However, in 4 of the 5 studies, this stratification was not that efficient because the intervention was set up first and the study participants were matched to the intervention instead of visa versa. This systematic review found strong evidence for a positive effect of exercise prehabilitation versus no prehabilitation on pain at 6 months post-TKA and function at 12 months post-TKA and weak evidence for a positive effect of a pain neuroscience education prehabilitation versus biomedical education on satisfaction at 6 months post-TKA regarding the non-stratified care studies. Evidence was weak for a positive effect of a biopsychosocial approach prehabilitation on function at 6 months after TKA as compared with no intervention regarding the stratified care studies. This was also the only study that used stratification based on individual characteristics instead of visa versa. No direct comparison of stratified compared to non-stratified studies was possible. More matched stratified care studies using a pragmatic trial or single-case experimental design in people with KOA are highly needed.

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Chapter 9: General discussion (with impact paragraph)

The heterogeneity present in (knee) osteoarthritis remains a challenge to understand in current research and clinical practice (1), resulting in suboptimal conservative (2,3) and surgical (4–6) treatment outcomes. A 'whole person' approach embedded in a biopsychosocial framework is considered necessary to unravel the mechanisms behind and the clinical manifestations of this heterogeneity in individuals with (knee) osteoarthritis (7,8). Focusing on an individual's pain experience is particularly important, as also pain needs to be approached from a biopsychosocial perspective and is the main symptom and reason for seeking medical help in this population (9).

This dissertation was initiated to gain better insight into the heterogeneity in individuals with knee osteoarthritis (KOA), especially those awaiting total knee arthroplasty (TKA) and its impact on outcome from a biopsychosocial perspective. To achieve this main goal, three sub-aims were identified:

1. The **first aim** was to identify and characterize subgroups based on different biopsychosocial variables, pain mechanisms and somatosensory functioning within a KOA population awaiting TKA and compare their long-term treatment response. **(Chapters 2-5)**
2. The **second aim** was to identify predictors of (in)sufficient treatment outcome in individuals with KOA undergoing TKA and individuals with osteoarthritis (not restricted to KOA) admitted to an interdisciplinary multimodal pain treatment (IMPT). **(Chapters 6-7)**
3. The **third aim** was to provide an overview of all previous stratified and non-stratified prehabilitation studies in KOA patients awaiting TKA and their differences in long-term outcomes after TKA. **(Chapter 8)**

The general discussion is organised around these three sub-aims, each of which includes different chapters. First, a comprehensive overview of the results of the different chapters is provided, followed by a critical review of the results. Thereafter, methodological considerations are discussed, as well as the valorisation and clinical implications (impact paragraph) and suggestions for future research. Finally, a general conclusion summarizes the whole dissertation.

1. Overview of main findings

Part 1: KOA phenotypes and their long-term treatment response to TKA

Four studies **(Chapters 2-5)** were conducted to gain better insight in the heterogeneity of individuals with KOA by identifying phenotypes and their long-term treatment response to TKA. **Chapters 2, 3 and 5** used data of the large multicentre prospective cohort study conducted in Belgium and the Netherlands, in which 223 individuals with KOA awaiting TKA were included (*prospective cohort study 1*).

Chapter 2 describes a secondary analysis of *prospective cohort study 1* that aimed to identify phenotypes in individuals with KOA awaiting TKA based on various preoperative biopsychosocial-related variables, including structural, metabolic, pain-related, psychologic, and social variables, using a data-driven approach. In addition, concurrent validity and differences in pain intensity one-year post-TKA were tested between the identified phenotypes. After excluding multivariate outliers, 217 participants were included in the phenotype-construct. Twenty-one variables were used in the final phenotype-construct, which resulted in two phenotypes that significantly differed in 14 of the 21 included variables. Phenotype 1 encompassed 156 participants (72%) who had higher BMI, higher m. Quadriceps strength, better physical function, lower number of pain locations, lower local and widespread pressure pain thresholds (PPT), higher temporal summation (TS), more self-reported symptoms of central sensitisation (CS), higher pain catastrophizing, more anxiety and depression, and more structural knee damage compared to phenotype 2, which included 61 participants (28%). Concurrent validity was confirmed, and phenotype 2 had worse one-year post-TKA pain intensity scores compared to phenotype 1.

Chapter 3 includes another secondary analysis of *prospective cohort study 1* that applied the International Association for the Study of Pain (IASP) grading system to identify individuals with KOA awaiting TKA with a predominant 'no', 'possible' or 'probable' nociplastic pain mechanism and aimed to propose more refined criteria to improve the grading system itself (10). In addition, preoperative biopsychosocial-related variables and pain intensity scores one-year post-TKA were compared between the identified subgroups. Out of 223 participants, data of 197 participants could be used to run through the grading system (complete data was necessary). The current study proposed two approaches for step two of the grading system: more regional/multifocal/widespread pain was interpreted as four pain locations (affected knee + three additional – approach 1) or three pain locations (affected knee + two additional – approach 2). Therefore, a predominant 'probable' nociplastic pain mechanism was identified in 30 (15% - approach 1) and 46 (23% - approach 2) participants. Irrespective of the pain location approach, the 'probable' nociplastic pain group included more women, participants with a lower age, a higher preoperative number of pain locations, widespread TS, self-reported symptoms of CS, higher thermal allodynia measured at the medial knee joint-line, anxiety and depression, and higher one-year post-TKA pain intensity scores compared to the 'possible or no' nociplastic pain group. However, there were also differences between approach 1 and 2 when comparing the 'probable' and 'possible or no' nociplastic pain groups. Following approach 1, participants in the 'probable' nociplastic pain group exhibited lower local PPTs, higher thermal allodynia measured at the lateral knee-joint line, higher TS, higher painful after sensations, and higher widespread heat allodynia, whereas following approach 2, participants in the 'probable' nociplastic pain group exhibited lower PPT, worse illness perceptions about emotional representations, lower m. Quadriceps strength, and higher magnification, helplessness and general pain catastrophizing, compared to the 'possible or no' nociplastic pain group, respectively.

Chapter 4 was a preparatory step for **Chapter 5** and describes the *systematic review 1* which summarised 21 studies investigating the evolution of somatosensory functioning from pre- to postoperative in individuals with musculoskeletal disorders undergoing nociceptive-targeted

surgery (11). Results were in general inconsistent for all musculoskeletal disorder. However, as the scope of the current dissertation is mainly focused on KOA awaiting TKA and their long-term outcome, findings specifically for this condition for an evolution from baseline to a follow-up of more than three months post-TKA will be summarised in this paragraph (11 studies). A weak conclusion was made for no change of thermal and pinprick pain (supra)threshold and a positive change in spatial summation and self-reported CS, and a strong conclusion for no change in pressure tolerance threshold and a positive change in TS after TKA. A conflicting conclusion was found for PPT, conditioned pain modulation (CPM) and exercise induced analgesia (EIA). Finally, a moderate conclusion was found for an association between positive improved PPT, CPM and EIA after TKA on the one hand, and positive improved pain after TKA on the other hand.

Based on the findings of the previous chapter, the last chapter of part 1, **Chapter 5** (the primary analysis of *prospective cohort study 1*) was set up to examine the difference of the change in pain intensity over time (baseline to three months- to one-year post-TKA) and at one-year post-TKA between different subgroups of individuals with KOA undergoing TKA of the cohort study (12). Subgroups were formed based on pre- and one-year post-TKA somatosensory functioning. For each outcome related to somatosensory functioning, participants were classified in a normal, recovered and persistent disturbed somatosensory functioning group. Apart from the persistent disturbed somatosensory group classified according to self-reported symptoms of CS, all three somatosensory functioning groups improved in pain score from baseline to three months and one-year post-TKA. The persistent disturbed somatosensory functioning group classified according to local heat allodynia and self-reported symptoms of CS had less pain improvement from baseline to one-year post-TKA compared to the normal somatosensory functioning group. More pain at one-year post-TKA was present in the persistent disturbed somatosensory functioning group compared to the normal somatosensory group classified according to local PPT and thermal allodynia, TS and self-reported symptoms of CS. Last, the persistent disturbed somatosensory functioning group classified according to self-reported symptoms of CS also experienced more one-year post-TKA pain compared to the recovered somatosensory functioning group.

Part 2: Predictors of (in)sufficient treatment outcome in individuals with osteoarthritis

Part 2 encompasses two studies **(Chapters 6 and 7)** of two different projects to identify predictors of (in)sufficient treatment outcome in individuals with osteoarthritis. **Chapter 6** includes the same data of the 223 participants of the multicentre prospective cohort study conducted in Belgium and the Netherlands used in **Chapters 2, 3 and 5** (*prospective cohort study 1*). **Chapter 7** presents data of the multicentre prospective cohort study conducted over six different clinics in rehabilitation centres in the Netherlands, including 599 osteoarthritis patients (not restricted to KOA) undergoing an IMPT (*prospective cohort study 2*).

Chapter 6 contains a last secondary analysis of *prospective cohort study 1* which aimed to identify preoperative biopsychosocial-related predictors for one-year post-TKA pain intensity on the one hand, and for difference in pain intensity from pre- to one-year post-TKA on the other hand in individuals with KOA undergoing TKA using multivariable linear regression analyses (13). Higher glycated haemoglobin and number of pain locations, lower preoperative

satisfaction and structural damage, and better personal control were consistent predictors for higher pain intensity one-year post-TKA and for pain deterioration or less pain improvement from pre- to one-year post-TKA. In the final (after backward selection) prediction model of pain deterioration or less pain improvement after TKA, also less preoperative pain intensity and better function, and being self-employed appeared as a predictor.

In **Chapter 7**, a clinical prediction model was developed and internally validated to predict the chance for treatment success immediately after IMPT (i.e. reaching minimal clinically important change [MCIC] of pain disability from pre-to post-treatment) in individuals with osteoarthritis. In this *prospective cohort study 2*, participants received an individual IMPT program of 10 weeks, which included mainly individual, but also group sessions of various physical and psychosocial treatment modalities (14). Candidate predictors were decided based on literature review and a consensus meeting of experts and patients in the field. These candidate predictors included patient-reported outcome measures (PROMS) which are currently standard measured in the clinics and rehabilitation centres. Lower age, being female, lower number of pain locations, pain severity at worst, and negative illness perceptions regarding timeline and identity, higher pain disability, self-rated work capacity, pain catastrophizing, pain self-efficacy, negative illness perceptions regarding consequences of condition, and positive illness perceptions regarding treatment control, the use of pain medication and alcohol, and being a smoker were predictors for higher chances of treatment success after IMPT.

Part 3: Stratified and non-stratified prehabilitation care in individuals with KOA undergoing TKA

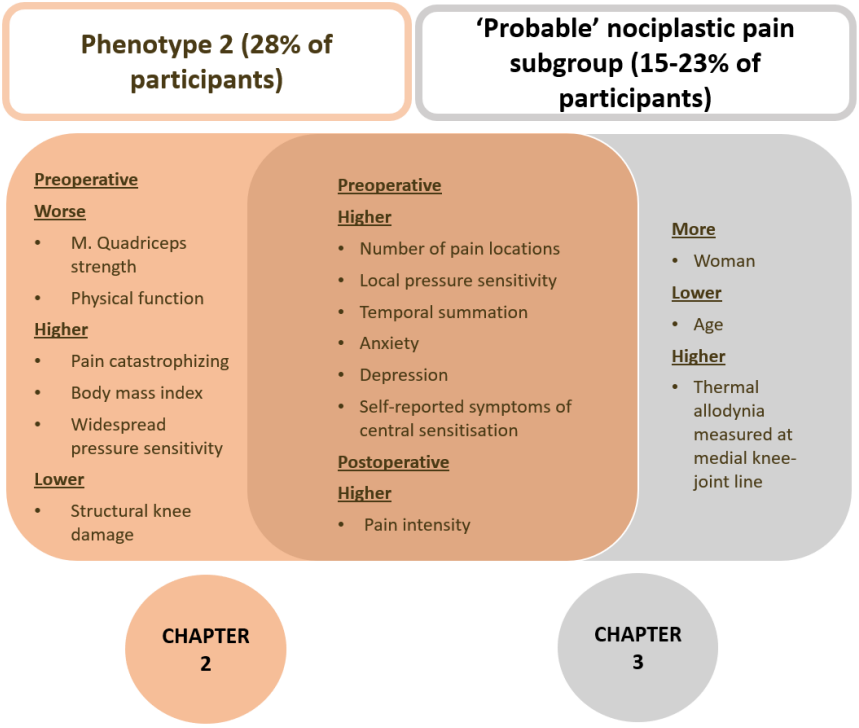
In **chapter 8**, *systematic review 2*, was used to provide an overview of prehabilitation care studies in individuals with KOA undergoing TKA (15). This study investigated if previous prehabilitation research in this population focused on specifical clinical phenotypes (or more specific individual characteristics) beyond the more general KOA diagnosis, and if differences were present in long-term pain, function, quality of life and satisfaction between studies with a more stratified approach compared to studies with non-stratified approach. Seventeen studies were included, of which five focused on more specific eligibility characteristics beyond the KOA itself. All stratified and non-stratified studies compared their intervention with a control group. As such, a direct comparison of stratified versus non-stratified prehabilitation care was impossible. Weak evidence showed a positive effect on function six months post-TKA of a more stratified care cognitive behavioural therapy prehabilitation compared to no prehablitation. Other findings of the stratified-care studies showed no evidence in favour of the intervention group compared to control groups receiving no prehabilitation. Strong evidence was found for positive effects on pain six months post-TKA, and on function 12 months post-TKA of non-stratified exercise prehabilitation compared to no prehabilitation. Weak evidence also showed positive effects on satisfaction six months post-TKA of a non-stratified pain science education prehabilitation compared to no prehabilitation. Other findings of the non-stratified care studies showed no evidence in favour of the intervention group compared to control groups receiving no prehabilitation or biomedical education.

2. Critical review of the main findings

Part 1: KOA phenotypes and their long-term treatment response to TKA

Combining the results of **Chapters 2 and 3**, it appears that phenotype 2 in **Chapter 2** (28% of participants) shares similar pre- and post-TKA characteristics to the 'probable' nociplastic pain mechanism group in **Chapter 3** (15-23% of participants). Both subgroups were characterized preoperatively by a higher number of pain locations, higher local pressure sensitivity, higher TS, more anxiety, more depression, and self-reported symptoms of CS, and one-year postoperatively by worse pain intensity compared to phenotype 1 in **Chapter 2** and the 'no or possible nociplastic pain' subgroup in **Chapter 3**, respectively. The greatest overlap was present between phenotype 2 from **Chapter 2** and the 'probable' nociplastic pain mechanism group using approach 2 (knee + two additional pain locations) from **Chapter 3** (Figure 1). Apart from these similarities, participants of these subgroups preoperatively had additional preoperative lower m. Quadriceps strength and higher levels of pain catastrophizing compared to phenotype 1 in **Chapter 2**, and the 'no or possible nociplastic pain' subgroup in **Chapter 3**, respectively.

Figure 1: Overlap of characteristics phenotype 2 (Chapter 2) and 'probable' nociplastic pain subgroup (Chapter 3)



Although most phenotype studies have not included factors related to the whole biopsychosocial model into one phenotype construct (16), three previous phenotype studies have attempted to do so. The studies of Pan et al. (17) and Carlesso et al. (18) included different factors covering all the three domains (bio-, psycho-, and social domain), while Kittelson et al. (19) also included a wide range of different biological and psychological factors, but without including social factors. Therefore, despite some differences in measurement methods, variables included, and the population being a general KOA population, the studies

of Pan et al. (17), Carlesso et al. (18) and Kittelson et al. (19) covered phenotype methods and variables to determine phenotype membership like **Chapter 2**. **Chapter 3** had a non-data-driven approach, as the IASP grading system for nociplastic pain was used. Identical to our findings, these three studies found that their largest phenotype was characterized by having less psychological distress, less somatosensory dysfunction and better function-related variables compared to the other phenotype(s) (17–19). Only the finding on structural knee damage in **Chapter 2** was different for this phenotype in different studies. Pan et al. (17) and Kittelson et al. (19) indicated less structural knee damage in this largest phenotype, whereas Carlesso et al. (18) found no differences in structural knee damage. The latter is comparable to **Chapter 3**, but both contrast with **Chapter 2**, which found a lower likelihood of less structural knee damage in the largest phenotype. The difference in population (individuals with KOA awaiting TKA in the current dissertation versus individuals with KOA in general in the studies of Carlesso et al. (18), Pan et al. (17) and Kittelson et al. (19)) could be a logical explanation for this contradiction.

The size and characteristics of phenotype 2 from **Chapter 2** (28% of participants) and of the 'probable' nociplastic pain group using approach 2 (knee pain + two additional pain locations – 23% of participants) from **Chapter 3** are consistent with a 'chronic pain phenotype' (16,17,20–22). This phenotype is characterized by pain sensitisation and/ or psychological distress in studies investigating pain phenotypes in individuals with KOA on a data-driven and non-data-driven basis (16-38% of participants in these studies) (16,17,20–22). However, a further subdivision of this phenotype is seen in the studies of Carlesso et al. (18) and Kittelson et al. (19), with the smallest phenotype of this subdivision representing participants with the most pain sensitised or psychologically distressed characteristics (11% and 10% of participants, respectively) compared to the other phenotypes. The percentage of the 'probable' nociplastic pain group using approach 1 (knee pain + three additional pain locations - 15% of participants) from **Chapter 3** is more in line with this smallest phenotype. Interestingly, both the 'chronic pain phenotype' and 'most pain sensitised or psychologically distressed phenotype', as found in previous literature (17–22) and **Chapter 2**, resemble nociplastic pain-related characteristics comparable to the identified 'probable' nociplastic pain group in **Chapter 3**, and are compatible with the findings of a previous systematic review and Delphi expert consensus on methods to distinguish nociplastic pain from other pain mechanisms (23,24).

In addition to confirming the findings of previous research, the results of **Chapters 2 and 3** also make a significant contribution to current knowledge, as these studies specifically included individuals with KOA awaiting TKA and used prescriptive phenotyping which showed that the nociplastic pain-like phenotypes had less treatment success (more pain one-year post-TKA). Moreover, **Chapter 3** was the first study (apart from a study in haemophilia patients (25) and an unpublished preprint in chronic musculoskeletal pain patients (26)) to apply the IASP grading system to a dataset of individuals with KOA going beyond mere theoretical descriptions (27). Additionally, we have provided suggestions for validation of the grading system for nociplastic pain (10), including two approaches for interpreting regional/multifocal/widespread pain (step 2 of the grading system) and suggestions for interpreting evoked hypersensitivity (step 5 of the grading system) and history of

comorbidities (step 6 of the grading system). Previous studies have been published that tried to phenotype individuals with KOA according to pain mechanisms but were restricted to a neuropathic-like pain mechanism (which also included individuals with a nociplastic pain mechanism according to their theoretical rationale (28–30)) and nociceptive pain mechanism, or did focus on a 'pain sensitisation' mechanism and 'mixed-pain' mechanism (not explicitly the nociplastic pain mechanism) (31). Similarities were found with our nociplastic pain mechanism group: KOA patients in the neuropathic-like pain (28–30) or TKA patients in the pain sensitisation group (30) experienced more disturbed somatosensory functioning (29–31), higher pain scores and number of pain locations (31,32), or more post-TKA pain (29,30). However, caution is advised because participants with neuropathic-like pain were excluded in *prospective cohort study 1*.

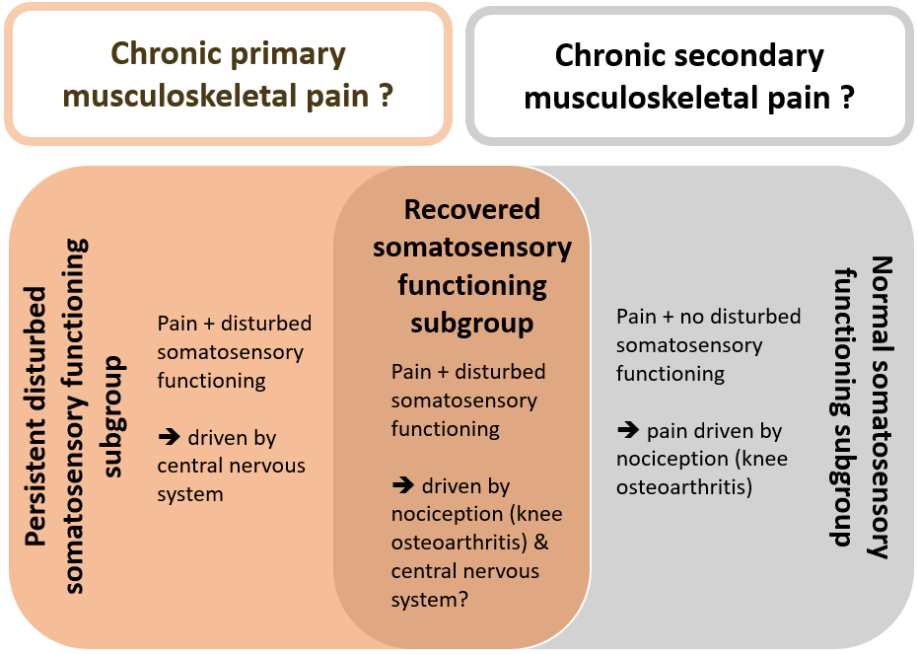
For clarification, both peripheral and central sensitisation (both disturbed somatosensory functioning) can be classified as nociplastic pain (33). These terms should not be confused with the proposed terms peripherally driven (driven by the KOA itself and possibly related to chronic secondary musculoskeletal pain (34)) and centrally driven disturbed somatosensory functioning (driven by the central nervous system and possibly related to chronic primary musculoskeletal pain (35)) used in **Chapters 4 and 5**.

The conclusions presented in **Chapter 4** regarding whether positive, negative or no change in somatosensory functioning was observed from pre- to long-term postoperative were weak or inconsistent (except for TS). An update of the review on 1st of March 2024 specifically focusing on individuals with KOA undergoing TKA revealed one extra study examining the evolution of local PPT from baseline to one-year post-TKA (36), but conclusions remained unchanged. These weak conclusions or inconsistencies have been attributed to the fact that most studies did not categorize participants into subgroups based on the evolution of pain intensity over time or chronic postoperative pain, and that somatosensory functioning may not have been disturbed preoperatively in all participants. This assumption was further explored in **Chapter 5** by creating normal (normal somatosensory functioning), resolved (hypothesis: more peripherally driven disturbed somatosensory functioning) and persistent disturbed somatosensory functioning groups (hypothesis: more centrally driven disturbed somatosensory functioning) and examining differences in the evolution of pain intensity from pre- to post-TKA and post-TKA pain itself (13).

The distinction between peripherally and centrally driven disturbed somatosensory functioning could only be confirmed by somatosensory functioning groups classified according to self-reported symptoms of CS (**Chapter 5)**. The persistent disturbed somatosensory group showed characteristics of centrally driven disturbed somatosensory functioning with the presence of self-reported symptoms of CS pre- and one-year post-TKA, no pain improvement from pre- to one-year post-TKA, and worse one-year post-TKA pain intensity scores compared to the normal and recovered somatosensory functioning group. Although **Chapter 4** showed an association between a positive evolution of different QST measures and a positive evolution of pain intensity after surgery (11), significant differences in pain one-year post-TKA were only found between the normal and persistent disturbed somatosensory functioning groups classified according to local PPT and heat allodynia, and TS (QST measures). There were

no differences between the normal and recovered somatosensory functioning group according to the classification based on all QST variables. This means that subdivision of individuals with KOA into different somatosensory functioning groups still leads to several inconsistencies in the evolution of pain over time and that more research is needed in this area, as is also concluded in **Chapter 4** (11). Two previous studies categorized individuals with KOA undergoing TKA based on somatosensory functioning and also found that participants in the disturbed somatosensory group reported more pain six or one-year post-TKA. However, their subgrouping was only based on preoperative values and neuropathic-like pain (29,30). Other studies focused on postoperative pain subgroups (37,38), but have not yet examined the evolution of self-reported symptoms of CS and thermal allodynia in this population. Nevertheless, the results of these two studies focusing on the evolution of CPM and TS in postoperative pain subgroups were similar compared to the findings in **Chapter 5**: no difference was found for CPM, and TS was found to be impaired in the postoperative pain group compared to the no postoperative pain group (37,38). Conflicting results have been found for PPT in these previous studies (37,38), while more pain at one-year post-TKA was present in the persistent disturbed somatosensory functioning group compared to the normal somatosensory group classified according to local PPT in **Chapter 5**.

Figure 2: Hypothesis of 'recovered somatosensory functioning subgroup' being a mix of chronic primary and secondary pain (Chapter 5)



Despite some inconsistencies found in **Chapters 4, 5** and in previous research (29,37,38), the one-year post-TKA pain intensity scores of the recovered somatosensory functioning group in **Chapter 5** fall in between the scores of the other two groups (although not statistically significant). Worse scores were seen compared to the normal somatosensory functioning group, and better scores compared to the persistent disturbed somatosensory functioning group (except for the groups categorized by CPM or widespread PPT). Nowadays, pain in combination with centrally driven disturbed somatosensory functioning (driven by central nervous system) is categorized under chronic primary musculoskeletal pain, while pain in

combination with peripherally driven disturbed somatosensory functioning (driven by nociception, i.e. knee osteoarthritis) or normal somatosensory functioning is categorized under chronic secondary musculoskeletal pain (34,35). The results of the recovered somatosensory functioning group may indicate that this group represents a kind of continuum, comparable to the dynamic characteristics and mechanisms behind chronic pain (39), with overlap between characteristics of chronic primary and chronic secondary musculoskeletal pain (Figure 2).

Another possibility for the lack of clear and consistent findings could be the lack of uniformity in the measurement of QST, including cut-offs to define disturbed somatosensory functioning (21,40), and the to be further confirmed validity and reliability of thermal allodynia and CPM method used (41). Furthermore, chronic postoperative pain can also be associated with several other preoperative factors (42). For example, there is currently strong evidence that preoperative disturbed psychological factors, such as higher pain catastrophizing and anxiety, are also associated with chronic post-TKA pain (42). This was also confirmed by the highly clinically relevant differences when somatosensory functioning groups were classified according to self-reported symptoms of CS**,** as measured by the Central Sensitisation Inventory (CSI) in **Chapter 5**. **Chapter 5** was the first study to examine and subdivide participants according to the evolution of self-reported symptoms of CS related to pain after TKA. It is important to note that the CSI also covers questions related to psychological factors and is rather an instrument to indirectly measure central somatosensory functioning (i.e. CS) (43,44). A recent systematic review and meta-analysis even found that strong associations were present between psychological constructs (anxiety, depression, pain catastrophizing, etc.) and the CSI, and that associations between CSI and QST measurements were rather weak or not present (43). Additional results may have been found if phenotypes based on the evolution of a combination of different preoperative factors (somatosensory functioning, psychological variables, and other risk factors for chronic TKA-pain (42,45)) were created and examined. However, this theory should be investigated in further research.

Part 2: Predictors of (in)sufficient treatment outcome in individuals with osteoarthritis

After examining pre-treatment factors that may be associated with treatment outcome, multivariable regression model analyses are necessary to provide information about the most important and consistent pre-treatment predictors. This results in the minimum number of predictors necessary to predict as much variance in treatment outcome as possible (46). Both **Chapters 6 and 7** examine a different population, treatment, treatment outcome and follow-up period, namely individuals with KOA awaiting TKA versus individuals with osteoarthritis in general, a TKA surgery versus a 10-week IMPT program, pain intensity measured by the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale pain versus disability measured with Pain Disability Index (PDI), and one-year post-TKA versus immediately after the 10-week IMPT. Therefore, these chapters are critically reviewed separately.

Univariate association analyses between all potential preoperative predictors and one-year post-TKA pain (absolute and pre-post difference scores) were first performed in **Chapter 6** to decide which factors to include at the start of the multivariable linear regression. The results of the univariate analyses showed that several metabolic variables (glycated haemoglobin),

functional variables (self-reported function), pain-related variables (pain intensity, number of pain locations, widespread pressure sensitivity, local heat allodynia, and self-reported symptoms of CS), psychological variables (pain catastrophizing, anxiety, satisfaction about pain, and illness perceptions about personal and treatment control, emotional representations and identity), and structural variables (KOA grade) were associated ($p<0.05$) with at least one of the two outcome variables. With the exception of depression, these findings are fully consistent with those of a previous umbrella review of prognostic factors for chronic pain after TKA or total hip arthroplasty (42). Depression was not found to be associated with either outcome in **Chapter 6**, whereas previous research found an association. This could be explained by differences in the measurement of depression: the systematic review of Ghoshal et al. (45) also showed an association only for preoperative depression measured by the Beck Depression Inventory (21 items for depression), but not for depression measured by the Hospital Anxiety and Depression Scale (7 items for depression, as used in the current dissertation). Illness perceptions and glycated haemoglobin were not examined as possible predictors in previous studies.

Despite the fact univariate association analyses provide information about potential predictors with chronic-TKA pain, multivariable analyses are more valuable to identify the independent predictors that may 'filter out' other potential predictors (46). As a maximum of 22 potential preoperative predictors were possible in the multivariable linear regression analyses (rule-of-thumb of minimum 10 subjects per predictor (47)), the cut-off for the p-value of the univariate association analyses was raised to 0.2. Therefore, also age, body mass index (BMI), local pressure sensitivity, widespread heat allodynia, expectations, and illness perceptions about timeline cyclical were added at the start of the multivariable regression model. After backward selection, higher glycated haemoglobin, number of pain locations, self-reported symptoms of CS, lower preoperative satisfaction, less structural damage, and better personal control were common predictors of both more pain one-year post-TKA and pain deterioration or less pain improvement from pre- to post-TKA. The most interesting findings are discussed below.

Interestingly, a higher number of pain locations and self-reported symptoms of CS were found to be independent predictors, while these two variables were also identified as variables that differed between phenotypes in the previous **Chapters 2, 3 and 5**, being characteristics for nociplastic pain (23,24). On the other hand, our multivariable regression model showed that other psychological factors, that have been found to be associated with chronic post-TKA pain in previous studies (42), may have been filtered out by the inclusion of self-reported symptoms of CS. As highlighted in the last paragraph of the critical review of the main findings of PART 1, the CSI seems to measure a psychologically based construct (44) and is highly relevant to include (apart from the number of pain locations, glycated haemoglobin, grade of KOA, personal control, and pre-operative satisfaction) as a predictive factor in clinical prediction models in future research.

Another interesting and innovative finding is that glycated haemoglobin was an independent predictor of both outcomes, whereas only low confidence for the presence of diabetes being associated with chronic postoperative pain was indicated in the previous umbrella review (42).

This low confidence may be explained by the fact that previous studies measured diabetes as a self-reported dichotomous variable (scored as 'yes or no'). Glycated haemoglobin is a measure of the continuum of glycaemic control that does not only provide information for diagnosing diabetes. Higher levels of glycated haemoglobin indicate poor glycaemic control, which may be observed in individuals with prediabetes or poorly controlled diabetes (48). Therefore, results of **Chapter 6** may indicate that individuals with diabetes who have good glycaemic control may have normal (not too high) glycated haemoglobin levels and as such may have less pain one-year post-TKA than individuals (with or without diabetes) who have poor glycaemic control.

As only one systematic review (49) in the umbrella review examined the association between chronic postoperative pain and structural joint damage, only low evidence of a negative association was found (42). However, **Chapter 6** and another recent study also found that a lower degree of structural knee damage predicted more pain post-TKA in a multivariable regression model (50), making the evidence stronger. To date, structural knee damage is still a non-modifiable predictor (51). Therefore, it would be interesting to examine the factors that differentiate between individuals with KOA awaiting TKA, with minor structural damage compared to those with more advanced structural damage. Preliminary results using the consistent predictors of one-year post-TKA pain identified in **Chapter 6** showed that KOA individuals with less structural knee damage (K&L scale 1 or 2) preoperatively had higher glycated haemoglobin values (p=0.049), lower satisfaction about the pain (p=0.003) and more self-reported symptoms of CS (p=0.001) compared to those with more structural knee damage (K&L scale 3 or 4). Future research could investigate this further and examine whether improving the associated factors with low KOA grade and one-year post-TKA pain results in better TKA outcome or could even support the decision to delay surgery or use alternative treatments apart from surgery to target these associated factors in individuals with less structural knee damage**.**

Chapter 6 explored possible predictors for one-year post-TKA pain intensity with a multivariable linear regression model (12), but not the chance of having chronic pain 'yes or no' explicitly, which would have involved a multivariable logistic regression model. This choice was made because a consensus for cut-offs for the MCIC, the presence of chronic TKA-pain, or patient acceptable state after TKA based on the KOOS subscale pain are currently lacking (52), and dichotomizing continuous variables results in losing (possible) important information (53). Therefore, Moreover, the maximum number of possible predictors to include in a multivariable logistic regression depends on the smallest subgroup to maintain full power (minimum 5 subjects per predictor) (54), which would have been +/- 20% of the participants (4–6). In multivariable linear regression, the number of possible predictors to include in the model depends on the total number of participants (minimum 10 subjects per predictor) (47), which resulted in adding more potential predictors to maintain full power compared to multivariable logistic regression. Thereupon, the main aim of **Chapter 6** was to identify the most important biopsychosocial-related predictors that 'filter out' other potential predictors to assist future research in developing consistent risk assessment tools for chronic-TKA pain when valid cut-off points are identified, and therefore, no further internal validation analysis was performed in this chapter.

A large sample size of 599 participants and an estimation of 50% as treatment responders, made it possible to run a multivariable logistic regression model in **Chapter 7** with all identified potential predictors (14). As all identified potential predictors are measured as part of the standard clinical care for each participant in an IMPT program in clinics in rehabilitation, the aim was to immediately identify and internally validate a clinical prediction model to predict the chance of treatment success, and to implement this model in clinical practice after external validation. The clinical prediction model had an acceptable discriminative power of 71% and different cut-off points with different sensitivity and specificity values were presented (14). The presentation of different performance values can help the treatment team to decide whether higher sensitivity (the higher the value, the lower the chance of a false negative prediction of 'treatment success), or higher specificity (the higher the value, the lower the chance of a false positive prediction of 'treatment success') is important. Consequently, the percentages and cut-offs should not be used as a 'gold standard' for starting or not starting the IMPT treatment. Rather, they should be used to set realistic treatment expectations by discussing the results with the participant, which in turn can improve patient motivation and active participation (55). In addition, they can help shared decision making in deciding about whether other treatment goals, or improvements in other modifiable negative predictors are needed before starting the IMPT treatment.

In line with previous research, the clinical prediction model showed that a lower number of pain locations (56), lower age (57–59), higher levels of protective cognitive behavioural factors (self-efficacy and treatment control), and lower levels of cognitive behavioural risk factors (negative illness perceptions about timeline and treatment control) (56,57,59–61) predicted higher chances of treatment success. Other studies also showed that emotional distress (57,59), lower BMI (58) and higher psychological inflexibility (62) were predictors of treatment success, whereas sex (57,58) was not a predictor, in contrast to the findings in **Chapter 7** (14). In addition, a previous meta-analysis showed that pain intensity was not a predictor of treatment success (59), whereas **Chapter 7** (14) and a recent study of Tseli et al. (57) identified its predictive value. Interestingly, our study also showed that higher levels of disability, pain catastrophizing and illness perceptions about consequences (which could also be categorized as 'cognitive behavioural risk factors' (59)) were predictive of a higher chance of treatment success, whereas previous research also showed their predictive value, but in the opposite direction (59,61). Differences with previous research could be attributed to, for example, differences in the definition of 'treatment success' (e.g. composite scores, general or disease-specific physical functioning or pain disability questionnaires), the inclusion of a different set of possible predictors at the start of the multivariable regression model, the different cut-offs to keep variables in the model ($p<0.05$ versus $p<0.20$), the content of the IMPT program, or differences in the population (more general chronic pain population versus the exclusive focus on individuals with osteoarthritis) (56–62). Therefore, direct comparison with previous research is difficult and should be interpreted with caution.

In **Chapter 7**, a less stringent p-value cut-off for predictors to remain in the model was chosen than in previous research (56–62) because all of the potential predictors included were based on literature review and a consensus meeting of experts in the field and are currently measured as standard at clinics in rehabilitation. As such, chances for missing potentially

important variables were avoided with this approach (14). In addition, a cut-off of 0.05 is currently considered too strict for clinical prediction model building, as the most complete model is still considered the best model, as the risk of excluding potentially relevant predictors reduces (63). Remarkably, smoking and alcohol use were also predictive of higher chances of treatment success. However, it must be emphasised that these variables were treated as dichotomous variables (scored as 'yes' or 'no'). As a result, people who drank only one glass of alcohol or smoked only one cigarette per week were also scored as 'yes' for these variables. The current clinical prediction model does not provide any information about the relationship between higher or lower levels of alcohol use or smoking and the chances of treatment success. In addition, higher pain catastrophizing and worse illness perceptions about consequences were predictive of higher chances of treatment success. One explanation may be that people with worse scores on these predictors had a greater margin for perceived improvement in these predictors (64). Interestingly, previous research has shown associations between positive changes in these variables and positive changes in disability in individuals with osteoarthritis (65,66). It is possible that the IMPT targeted specific illness perceptions and pain catastrophizing (67), which in turn may have led to higher chances of treatment success. However, this has not been investigated yet and future research should confirm this hypothesis.

Part 3: Stratified and non-stratified prehabilitation care in individuals with KOA undergoing TKA

The last search of the systematic review included in **Chapter 8** dated from 19th of April 2021. An update of the literature was therefore carried out up to the 1st of March 2024, which identified five additional studies that met the eligibility criteria (68–72). Three studies again used a non-stratified approach (68,69,72), but two other studies (70,71) used a stratified approach, focusing on individuals with KOA with similar characteristics to the 'chronic pain phenotype' presented in the review of Dell'Isola et al. (16). The two stratified studies and one non-stratified study used prehabilitation focusing on a biopsychosocial approach (cognitive behavioural therapy (71), realistic biopsychosocial-related expectation program (70) and a multidisciplinary treatment (69)) compared with usual care (standard preoperative education (69–71)). The other two non-stratified studies used exercise prehabilitation compared to a usual care (standard preoperative education) (68,72). The outcome satisfaction was not measured in the stratified studies included in **Chapter 8** (15), but both stratified studies of the updated search showed a positive effect on satisfaction in favour of the intervention group at six-months (71), one-year (70) and two-year (71) post-TKA. However, no differences were found between intervention and control groups for function one-year post-TKA (70). Conclusions regarding the other outcomes used in the stratified approach studies were similar to those presented in **Chapter 8** (15). For the non-stratified studies, the conclusion of a positive effect of exercise on pain six months post-TKA in favour of the intervention group changed from strong (two studies that showed positive effect) in **Chapter 8** (15) to conflicting (an additional study that showed no effect) with the updated search. Conclusions about other outcomes used in the non-stratified approach studies remained similar to those presented in **Chapter 8** (15).

Although current research emphasises the need to move towards stratified care to optimize treatment outcomes (73,74), only the minority of prehabilitation studies in individuals with KOA undergoing TKA that examined long-term TKA outcomes used some form of 'stratified care' (15). Thereupon, none of the studies directly compared stratified to non-stratified prehabilitation care, and therefore, only conclusions regarding stratified prehabilitation compared to a control group or non-stratified prehabilitation compared to a control group were possible. Participants in the control group received no prehabilitation or only biomedical-oriented preoperative education. As the follow-up time, prehabilitation content and outcome measures were heterogenous for the stratified studies, only weak to moderate conclusions could be drawn comparing stratified prehabilitation with no prehabilitation. Focusing on the non-stratified care studies in general, no long-term effect was found in favour of prehabilitation studies compared to a control group, expect for prehabilitation with a biopsychosocial focus and its effect on six-months post-TKA satisfaction (weak conclusion), and for exercise prehabilitation and its positive effect on one-year post-TKA function (strong conclusion, but mostly restricted to lower limb strength) compared with a control group (no prehabilitation or biomedical-oriented education).

Interestingly, none of the studies that used a stratified approach focused on specific phenotypes of individuals with KOA explicitly, but rather mentioned more specific eligibility criteria beyond the KOA diagnosis itself. However, characteristics of the 'chronic pain phenotype' as identified by the review of Dell'Isola et al. (16), or of the 'more nociplastic pain-like phenotypes' as identified in **Chapters 2 and 3**, were most commonly present in their stratified population. This again emphasises the importance of this subgroup in the KOA population. All but one of the stratified studies used 'a treatment-respondents focus', which means that a predefined and standardized prehabilitation was set up with participants hypothesized to be 'treatment responders' matched to this intervention (e.g. diet intervention only in those who had a BMI>30) (74). Only in the study of das Nair et al. (75) was the intervention adapted to the specific needs of the participants, rather than vice versa. The latter showed positive effects on function six-months post-TKA (weak evidence) and tends to favour matched care, a more individualized approach, which has been postulated as the optimal goal for future clinical trial research and practice (73,76).

The main aim of prehabilitation should be to improve preoperative risk factors for insufficient treatment outcomes (77). However, the non-stratified care studies probably missed this goal because these studies did not assess the presence of preoperative risk factors in their included population. This is also important for the implementation of prehabilitation in clinical practice, which may be a waste of time and recourses if it is given as standard to everyone undergoing TKA surgery, without assessing preoperative risk factors for insufficient treatment outcome. The lack of results for most long-term outcomes is also consistent with the results of previous systematic reviews (78–80). For example, the review of Gränicher et al. (79) mentions decreasing effects of prehabilitation over time, with only moderate to large effects on function up to 3 months post-TKA. Another meta-analysis of Su et al. (80) even found no effect on pain in the short-term. Apart from the non-stratification method in most studies, a possible explanation could be the higher chance for loss to follow-up in the long term post-TKA and the fact that most prehabilitation protocols were not continued in the postoperative period.

This discontinuation may have led to the loss of the gained short-term effect on long-term follow-up outcomes (79).

3. Methodological considerations

The specific methodological considerations for each chapter, including strengths and limitations, are discussed in the respective studies. However, some more general methodological considerations related to the dissertation and included projects are addressed below.

Strengths

The main strength of this dissertation is the multicentre and pragmatic nature of all original included studies. Different stakeholders (e.g. eight orthopaedic surgeons, four hospitals, six clinics in rehabilitation centres) were involved in the project, and eligibility criteria were not too strict, resembling clinical practice. This enhanced external validity of the results and allowed for a larger and successful patient recruitment. In addition, all the original included studies had a prospective longitudinal design, which limited recall and selection bias, and made it possible to examine treatment outcome. Furthermore, **Chapter 2, 3, 5 and 6** had an adequate follow-up period of one-year post-TKA, which ensured a complete recuperation period after TKA (81). Next, an extensive overview of various biopsychosocial variables was considered, including a mix of PROMS, physical and imaging measures. This allowed the 'whole person' focus approach throughout the whole dissertation. Thereupon, a variety of powerful statistical analysis techniques (multiple imputation, latent profile analysis, linear mixed model analyses, multivariable linear and logistic regression, etc.) and phenotype approaches (data-driven versus non-data-driven) were applied to address the general research questions as broadly as possible. Additionally, the secondary analyses studies included a lot of problem-solving orientated solutions for clinical relevant issues, e.g. a real-word data application was performed by applying the more theoretical IASP grading system for nociplastic pain. Finally, for **Chapter 7**, a clinical prediction tool was developed and internally validated including PROMS that are standardly measured at intake of an IMPT program. After external validation, this clinical prediction model could be used directly in the clinical care setting of IMPT treatment in individuals with osteoarthritis.

Limitations

Although participants were recruited from two countries and four hospitals, including more countries would have increased the generalizability of the results. Moreover, despite that the phenotype studies (**Chapters 2, 3 and 5**) are highly innovative and make a significant contribution to the current scientific knowledge, their results must be interpreted with caution due to their secondary and/ or exploratory nature. Although an estimated sample size of 200-250 participants is acceptable for latent profile analysis (fulfilled in **Chapter 2**) (82–84), and despite the rule of thumb of having at least 30 participants per group to compare differences between groups (fulfilled in **Chapter 3**) (85), no a priori sample size calculation was performed. In addition, as the IASP grading system for nociplastic pain has not yet been validated (10), more specific criteria, cut-offs and discussion points have been suggested, but

it cannot be guaranteed that all individuals categorized as having a predominant 'probable' nociplastic mechanism have a 'true' predominant nociplastic pain mechanism. The exploratory nature of **Chapter 5** lies in its group classification. In addition to the CSI, which measures symptoms related to disturbed somatosensory functioning, quantitative sensory testing (QST) was used to define the presence of disturbed somatosensory functioning. Different suggested cut-offs were used for each QST measure separately, but despite following previous literature and theoretical rationale (86–89), these suggestions are still exploratory in nature and should be confirmed in future research.

In addition, the reliability and validity of CPM, which was used to measure endogenous pain inhibition, and the thermal rollers, which was used to measure thermal allodynia, needs to be confirmed in future research (41). Remarkably, no significant results were found for CPM throughout the whole dissertation. A possible explanation could be that only +/- 50% of participants rated the maximum temperature of the test stimulus as 4 out of 10 on a numeric pain rating scale. It was decided to exclude only participants who scored 0 out of 10 in order to be able to analyse this variable (otherwise it could not be included in the multiple imputation procedure (90)). However, this decision may have confounded the CPM results. Therefore, caution is advised when interpretating these results. Moreover, although the term 'treatment success' was used in all chapters related to *prospective study 1*, a clear definition could not be provided. This is due to the lack of consensus in the current literature regarding the MCIC, the patient acceptable state, or the cut-off for significant chronic postoperative pain related to the KOOS subscale pain.

Next, there was a large amount of missing data for C-reactive protein (CRP) and fat- and lean mass (>40%), due to CRP values being collected retrospectively from the medical records, and due to a deficiency in the Biostat Quadscan device, respectively. Fat- and lean mass were stored on this device during data collection, and every six months, the data were extracted and uploaded to the dissertation's database. Unfortunately, on two occasions when attempting to upload the data, the data were unexpectedly deleted, and the cause remains unknown. As multivariable analyses and multiple imputation were used throughout the whole dissertation, these variables could not be analysed as these variables had over 40% of missing data (90).

Furthermore, although the current dissertation includes an extensive overview of factors related to the biopsychosocial model, more factors could have been added to make it even more comprehensive. For example, other biological factors (e.g. [objective] measures of physical activity, sleep, pain duration), other psychological factors (e.g. perceived injustice, fear of movement), treatment-related factors (e.g. perioperative treatment, adjuvant postoperative rehabilitation), but mainly other social factors (e.g. socio-economic status, social support, religion) because this part of the biopsychosocial model was rather limited, could have been added (42,91). Unfortunately, power of the statistical analyses is not unlimited, and therefore the decision about which factors related to the biopsychosocial model to include in the current dissertation remains very pragmatic in nature.

Finally, although **Chapter 7** has a prospective cohort study design, the initial population outlined in the ethical approval document was broader (not limited to individuals with

osteoarthritis). However, approximately six months into commencing recruitment, the strategic decision was made to develop more specific prediction models, including one focused solely on osteoarthritis patients. As the primary referral diagnosis for IMPT was available in the medical records, it was most convenient to create subgroups of individuals with osteoarthritis after data collection had been completed. A medical doctor screened the medical and physiotherapists record and decided whether osteoarthritis was contributing to the chronic pain symptoms of the participants. As such, this increased the risk of selection bias slightly.

4. Valorisation and clinical implications (impact paragraph)

The main aim of the current dissertation was to provide more insight into the heterogeneity of individuals with KOA, mainly those undergoing TKA, and its impact on treatment outcome from a biopsychosocial perspective.

Based on the results of **Chapters 2 and 3**, it was clear that a small subgroup of individuals with KOA awaiting TKA preoperatively presented with nociplastic pain- related characteristics (15-28%), being disturbed somatosensory functioning (more widespread pain, self-reported symptoms of CS, pressure hypersensitivity and TS) and psychological distress (anxiety, depression, and pain catastrophizing) (23). This smallest subgroup was also less likely to receive sufficient TKA outcome compared to individuals without these characteristics. These findings represent a first step in the identification of nociplastic pain in individuals with KOA awaiting TKA based on a real dataset. In addition to the proposed criteria obtained from a Delphi consensus study (23), the current findings may help healthcare professionals to recognize a predominant nociplastic pain mechanism in this population based on the identified factors. This is particularly important as the management approach for nociplastic pain goes beyond focusing solely on the KOA itself (92,93), which could be implemented in e.g. prehabilitation for KOA patients planned for TKA.

In **Chapters 4 and 5**, the focus was more on somatosensory functioning itself, and **Chapter 5** draws particular attention to individuals who present with self-reported symptoms of CS pre- and one-year post-TKA, as these participants did not even experience any improvement in pain from pre- to one-year post-TKA. This subgroup also presented with worse pain scores compared to groups without symptoms of CS at one-year post-TKA. This indicates the importance for healthcare professionals for recognizing a potential centrally driven disturbed somatosensory functioning subgroup in this population. Some of the findings of **Chapters 2-5** were confirmed by the findings in **Chapter 6**: a higher number of pain locations and self-reported symptoms of CS were also identified as independent predictors of chronic post-TKA pain. Subsequently, glycated haemoglobin, personal control, pain satisfaction and grade of KOA were also consistent independent predictors in **Chapter 6**.

Despite the fact that **Chapters 2, 3, 5 and 6** (i.e. all the studies focusing on the multicentre *prospective cohort study 1*) need further validation and replication, summarizing the findings warrants special attention of healthcare professionals in clinical practice for individuals with KOA awaiting TKA who are characterized by more widespread pain and self-reported symptoms of CS, as these factors were consistently found to be important for a less sufficient

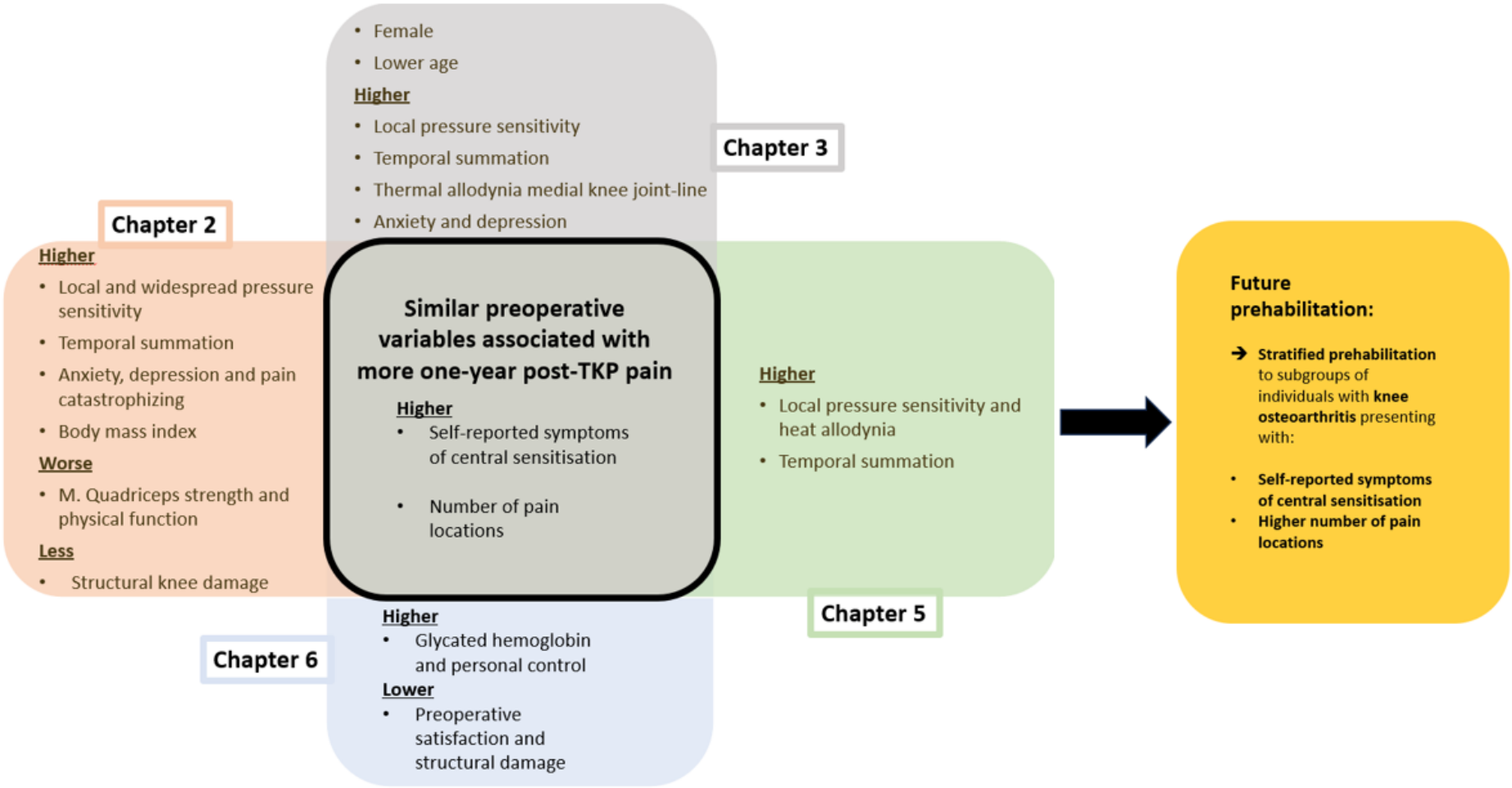
TKA outcome. These findings may be useful in improving shared decision making between healthcare professionals and potential candidates for TKA. Candidates presenting with these characteristics could be made aware of their potential for a less sufficient TKA outcome, resulting in more realistic treatment expectations for the candidate. Additional pre-, peri- and/ or postoperative management strategies or even alternative treatments apart from surgery that go beyond a purely peripheral focus (10,92) could also be considered to potentially achieve treatment success. Furthermore, realistic expectations may improve the candidate's engagement and motivation to the chosen treatment and increases the chance for better treatment outcomes (55). All these things could additionally have positive influence on healthcare and society, as lower healthcare and society costs are expected when the disorder and source of pain is more adequately targeted (94,95).

Apart from summarizing the findings of **Chapters 2-6** and their potential social impact, the real social impact of the findings in **Chapter 7** is not so far away if external validation leads to similar results. A clinical prediction model has been built in **Chapter 7**, as the various potential predictors are standard PROMS filled out by every participant starting the IMPT program. Currently, these findings can already help healthcare professionals working in clinics in rehabilitation in the Netherlands to improve participants with osteoarthritis' treatment expectations and thus their treatment motivation (55), and/ or support shared decision making about whether to start the IMPT program, whether other treatment goals should be identified, or whether modifiable predictors should be changed first. However, findings of this prediction model would be stronger if confirmed with external validation.

Unfortunately, no robust recommendations could be made for clinical practice regarding the long-term effects after TKA of stratified or non-stratified prehabilitation care in individuals with KOA undergoing TKA, because none of the studies in **Chapter 8** and the update directly compared stratified versus non-stratified prehabilitation care. Apart from a strong conclusion for better lower limb strength one-year post-TKA after non-stratified exercise prehabilitation compared with usual care, other conclusions were weak or indicated no effect in favour of prehabilitation for all other long-term outcomes (pain, satisfaction, quality of life and other functional outcomes apart from lower limb strength). However, as prehabilitation is currently performed in some clinical practices and hospitals before TKA in Belgium and the Netherlands, it is important to emphasise that the implementation of prehabilitation as standard before TKA without assessing the presence of potential risk factors for chronic TKA-pain may be a waste of time and recourses for long-term pain, satisfaction and quality of life outcomes (apart from improving long-term lower limb strength) based on the findings of current dissertation. As stated in the previous paragraphs, the results of the current dissertation showed that participants with characteristics such as preoperative a higher number of pain locations and self-reported symptoms of CS consistently presented with less sufficient TKA outcome. Therefore, it could be recommended that investment in prehabilitation may be valuable in this subgroup of individuals with KOA by targeting these modifiable risk factors with e.g. an additional IMPT program including cognitive behavioural therapy, pain science education, etc. (Figure 3).

Finally, the findings of this dissertation also emphasise again the importance of the biopsychosocial nature of (knee) osteoarthritis pain and chronic-TKA pain, which should be translated and applied in current clinical practice. However, to date, the knowledge of pain as 'a biopsychosocial-related term' is often too limited and therefore not adequately applied in clinical practice by healthcare professionals (96,97). This may also be due to the limited time spend on pain management teaching in current medical school curricula (98). A recent study showed that only physiotherapy students improved their knowledge of pain as 'a biopsychosocial-related term' comparing their knowledge in the fourth versus the first year of their education (99). This highlights the need for better and more pain management related curricula in medical schools.

Figure 3: Hypothesis for future stratified prehabilitation in individuals undergoing TKP



5. Implications for further research

The results of the different chapters included in the current dissertation identified several directions for future research.

First, **Chapter 2** was the first study to exploratively phenotype individuals with KOA awaiting TKA based on various biopsychosocial-related variables and to include their treatment response using a data-driven approach. However, due to its exploratory nature, more studies with larger sample sizes (and a priori sample size calculations) are needed in this research area. There is also a need to phenotype individuals with KOA in general and to explore their treatment response to conservative treatments (100).

Second, **Chapter 3** presents the first study to apply the grading system for nociplastic in individuals with KOA awaiting TKA, but further validation is needed. This validation should include other patient populations with chronic pain and the application of our suggestions regarding the interpretation of widespread/regional/multifocal pain, and the assessment of history of hypersensitivity and comorbidities. Thereupon, there is a lack of clear guidelines and/ or the creation of a grading system for nociceptive pain in musculoskeletal populations to interpret step three of the grading system, which involves assessing whether nociceptive pain is entirely responsible for the pain experience. A combination of a comprehensive interview, physical and imaging assessments is currently proposed (23,101), but this still relies on the clinical judgement of the investigator, so more objective guidelines are needed to interpret this step correctly.

Third, future studies should focus on the ideal methods to assess somatosensory functioning, including the presentation of cut-offs or normative data by validating the interpretation proposed in **Chapter 5**. In addition, future research could focus on a data-driven phenotype method to define a disturbed somatosensory functioning group versus no disturbed somatosensory group pre- and postoperatively using a combined set of variables (QST, CSI, and other psychological questionnaires, as impaired factors of these variables are associated with chronic primary pain (35), i.e. more centrally driven disturbed somatosensory functioning) to further confirm the existence of a peripherally and centrally driven disturbed somatosensory functioning group in individuals with KOA.

Fourth, **Chapter 6** confirms previous research that found an association between various preoperative biopsychosocial-related factors and one-year post-TKA pain (42), but also identifies independent predictors of one-year post-TKA pain. One of the identified factors was non-modifiable (less structural knee damage), and future research could investigate associations with other modifiable predictors further to evaluate whether improving the associated factors with both lower KOA grade and one-year TKA pain results in better TKA outcome. However, further studies with larger sample sizes are needed to identify the most consistent independent causal predictors. Studies could also include multivariable logistic regression when valid cut-off points for chronic TKA-pain and MCIC of the KOOS subscale pain have been identified to predict the likelihood of having chronic post-TKA pain or 'treatment success'. However, dichotomizing continuous variables always results in losing (possible) important information (53), and larger sample sizes are required for this statistical technique,

as the number of potential predictors that can be included depends on the size of the smallest subgroup (54). Another possibility is to implement structural equation models, which is also a multivariable data-analysis, but can correct for (possible) measurement errors, and can examine very complex associations (several directions of associations, multiple regression equations in one model, and the handling of unobserved latent variables) (102).

When different studies and analyses show consistent independent predictors, a final comprehensive but concise risk assessment tool should be identified using the most feasible and easy-to-use measurement methods in clinical practice and this tool should be validated internally and externally. To ensure full power and rapid recruitment required for external validation, it may be useful to implement the measurement of the identified predictors in current dissertation as standard in clinical practice and to store these values in a general medical record database. As the predictors identified in **Chapter 7** are already measured and stored in the medical record database as standard at clinics in rehabilitation, the external validation could be carried out in the future and then, the results can be compared with those found in **Chapter 7.** At a later stage, research could investigate whether changing modifiable risk factors prior to IMPT treatment or TKA could improve treatment outcomes. The set-up for this research should be more pragmatic, for which a single-case experimental design (SCED) would be a good option because the treatment can be matched to the individual, and only a small number of participants is necessary to draw firm conclusions (103).

Fifth, studies directly comparing stratified versus non-stratified prehabilitation and their differences in long-term outcome are warranted. As mentioned in the previous paragraph and in **Chapter 8**, more pragmatic randomized controlled trials or even better SCEDs are needed, in which the intervention can be adapted to the individual and not vice versa.

Finally, future research could look more closely at other social factors (e.g. social support, religion, etc.), as the current dissertation was restricted to the inclusion of only three social factors (work, education level and marital status), and at the association between inflammatory biomarkers and chronic pain. These latter variables (C-reactive protein, fat- and lean mass) had too much missing data to include them in the analyses.

6. Conclusion

The current dissertation provides further insight into the clinical presentation and treatment response heterogeneity of individuals with (knee) osteoarthritis based on the biopsychosocial model. Phenotypes representing with centrally driven disturbed somatosensory functioning, as measured by the evolution of self-reported symptoms of CS over time, and phenotypes with nociplastic pain-like characteristics, experienced more pain intensity one-year post-TKA. Thereupon, preoperative glycated haemoglobin, satisfaction about pain, number of pain locations, personal control, self-reported symptoms of CS and structural knee damage were independent predictors of chronic post-TKA pain. The current dissertation also developed an internally validated prediction model to predict treatment success in individuals with osteoarthritis undergoing IMPT. In addition, it was shown that research into stratified prehabilitation in individuals with KOA undergoing TKA is rare and that stratified prehabilitation has never been directly compared to non-stratified prehabilitation in studies

investigating long-term TKA outcomes. Only to improve long-term muscle strength, prehabilitation can be preferred over no prehabilitation, as evidence for other TKA outcomes was absent or weak. As such, more research in the field of stratified prehabilitation is needed. By presenting these findings, the current dissertation makes another step forward in unravelling and contributing to the puzzle of the heterogeneity present in individuals with KOA and their treatment outcomes.

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English summary

Knee osteoarthritis (KOA) is considered one of the most important chronic musculoskeletal pain conditions in the world, due to its common prevalence and its expected increase in numbers attributed to the global trends in ageing and obesity rates. In previous decades, KOA has transitioned from a 'cartilage focused' to a 'whole-joint focused' condition, but recent evidence confirms that even a broader 'whole person focused' approach is needed to understand the complexity of KOA. Indeed, the development and cause of KOA are multifactorial and heterogenous, resulting in very divergent clinical presentations and treatment responses of individuals with KOA. Therefore, this 'whole person' approach is currently recommended for the assessment and treatment of individuals with KOA, integrating all aspects of the entire biopsychosocial model. In addition, it is particularly crucial to focus on the individual's pain experience, as this is the primary symptom of KOA and must also be addressed from a biopsychosocial perspective. Consequently, the main aim of this dissertation was to gain better insight in the heterogeneity in individuals with KOA, especially those awaiting total knee arthroplasty (TKA), and to investigate its impact on treatment outcome from a biopsychosocial perspective.

To contribute to this knowledge, the dissertation was divided into three parts. **Part 1** comprises **Chapters 2, 3, and 5** on data of 223 individuals with KOA undergoing TKA from a large multicentre prospective cohort study in four hospitals in Belgium and the Netherlands, and **Chapter 4**, a systematic review on the evolution of somatosensory functioning after nociceptive targeted surgery in individuals with musculoskeletal disorders. **Part 2** includes **Chapter 6** on data of the same large multicentre prospective cohort study in four hospitals in Belgium and the Netherlands, and **Chapter 7** on data of 599 individuals with osteoarthritis (not restricted to KOA) undergoing interdisciplinary multimodal pain treatment (IMPT) from another large multicentre prospective longitudinal cohort study in six clinics in rehabilitation centres in the Netherlands. Finally, **Part 3** comprises **Chapters 8**, a systematic review on stratified versus non-stratified prehabilitation and their long-term treatment effects in individuals with KOA undergoing TKA.

PART 1: KOA phenotypes and their long-term treatment response to TKA

A data-driven phenotype-analysis (i.e. subgroup-analysis) based on various preoperative variables encompassing the entire biopsychosocial model was used in **Chapter 2.** The results showed that two preoperative phenotypes were present in individuals with KOA awaiting TKA. Participants in the smallest phenotype (28% of participants) had more nociplastic pain-like characteristics combined with less structural knee damage, higher body mass index, lower m. Quadriceps strength, and better physical function compared to those in the largest phenotype (72% of participants). In addition, participants in phenotype 1 had more pain one-year post-TKA compared to participants in the other phenotype. As expected, because pain is the primary symptom of KOA, many pain-related variables were significantly different between phenotypes found in **Chapter 2**. Therefore, the subgrouping focus of **Chapters 3 - 5** was particularly based on pain and somatosensory functioning. In **Chapter 3**, the International Association for the Study of Pain (IASP) grading system was applied to individuals with KOA

awaiting TKA to identify a predominant nociplastic pain mechanism in this population, and suggestions for more refined criteria were proposed. Dependent on the interpretation of the step 'regional/multifocal/widespread pain', 15% (four pain locations – approach 1) or 23% (three pain locations – approach 2) of the participants were classified in the predominant 'probable' nociplastic pain subgroup. Irrespective of the interpretation of pain location, participants in the 'probable' nociplastic pain subgroup (**Chapter 3**) had similar characteristics to those in phenotype 2 (**Chapter 2**). These included preoperative higher number of pain locations, higher local pressure sensitivity, higher temporal summation (TS), higher thermal allodynia measured at medial-knee joint line, more anxiety, more depression, and more self-reported symptoms of central sensitisation (CS), and one-year postoperative worse pain intensity compared to those in the 'possible or no' nociplastic pain subgroup (**Chapter 3**), and phenotype 1 (**Chapter 2**), respectively.

Chapter 4, together with a recent update on the 1st of March 2024, reviewed all studies investigating the evolution of somatosensory functioning from pre- to postoperative in individuals with musculoskeletal disorders undergoing nociceptive-targeted surgery. Specifically for individuals with KOA undergoing TKA, a strong conclusion could be made regarding no long-term change in pressure tolerance threshold and a positive long-term change in TS, but other conclusions regarding long-term changes were weak or conflicting. A moderate conclusion showed a positive association between pain improvement after TKA and improved pressure pain threshold (PPT), conditioned pain modulation (CPM), and exercise-induced analgesia. The lack of clear, consistent findings has been attributed to the lack of subgroups based on pain evolution, postoperative pain or somatosensory functioning in the previous studies. Therefore, **Chapter 5** was designed to investigate whether the evolution of pain intensity and one-year postoperative pain intensity differed between a group with normal somatosensory functioning (normal pre- and one-year post-TKA), a group with recovered somatosensory functioning (disturbed pre-, but normal one-year post-TKA, hypothesized peripherally driven disturbed somatosensory functioning), and a group with persistent disturbed somatosensory functioning (disturbed pre- and one-year post-TKA, hypothesized centrally driven disturbed somatosensory functioning) in individuals with KOA undergoing TKA. A centrally driven disturbed somatosensory functioning group was discovered when groups were classified according to self-reported symptoms of CS. This persistent disturbed somatosensory functioning group showed no pain improvement after TKA and had more pain compared to the other two groups. In addition, the persistent disturbed somatosensory functioning group classified by local heat allodynia and self-reported symptoms of CS had less pain improvement from baseline to one-year post-TKA compared to the normal somatosensory functioning group, and the persistent disturbed somatosensory functioning group classified by local PPT and thermal allodynia, and TS had more pain one-year post-TKA compared to the normal somatosensory functioning group.

PART 2: Predictors of (in)sufficient treatment outcome in individuals with osteoarthritis

Preoperative variables encompassing the entire biopsychosocial model were tested as potential predictors for one-year post-TKA pain intensity in individuals with KOA based on multivariable linear regression analyses in **Chapter 6**. More pain one-year post-TKA and a pain

deterioration or less pain improvement from pre- to one-year post-TKA could be predicted by higher glycated haemoglobin, higher number of pain locations, lower satisfaction about pain, less structural knee damage, self-reported symptoms of CS, and better personal control. In addition, lower preoperative pain intensity, better function, and being self-employed were independent predictors of a pain deterioration or less pain improvement from pre- to one-year post-TKA. Interestingly, both 'number of pain locations' and 'self-reported symptoms of CS' were consistently important factors associated with one-year post-TKA pain in **Chapters 2, 3, 5 and 6**. A clinical prediction model was developed and internally validated in **Chapter 7** to predict the likelihood of treatment success (having pain disability improvement from pre- to post-treatment) following a 10-week IMPT program in individuals with osteoarthritis (not restricted to KOA). Potential predictors were decided based on a literature review and expert consensus meeting. These potential predictors spanned the entire biopsychosocial model and are measured as standard part of care for all participants starting the IMPT program. Variables that predicted a higher chance of treatment success were being female, younger age, lower number of pain locations, lower pain severity at worst, lower negative illness perceptions regarding timeline and identity, higher pain disability, higher self-rated work capacity, higher level of pain catastrophizing, higher self-efficacy, higher negative illness perceptions regarding consequences of condition, higher positive illness perceptions regarding treatment control, the use of pain medication and alcohol, and being a smoker. The internally validated clinical prediction model had an acceptable discriminative power of 71% and should be used to improve shared decision making in IMPT.

PART 3: Stratified and non-stratified prehabilitation care in individuals with KOA undergoing TKA

Finally, **Chapter 8**, together with a recent update on the 1st of March 2024, summarized all studies that focused on prehabilitation and its long-term outcomes in individuals with KOA undergoing TKA. Seven of 22 studies used a more stratified prehabilitation approach, which meant that more specific eligibility criteria were used that the prehabilitation intervention was expected to target or vice versa. All studies compared their (non-)stratified prehabilitation care with a control group but did not compare stratified and non-stratified prehabilitation care directly. For the effect on long-term post-TKA pain, satisfaction, quality of life and functional factors (other than lower limb strength), conclusions were weak or indicated no effect of the prehabilitation. Only a strong conclusion could be drawn for a positive effect on lower limb strength one-year post-TKA after a non-stratified exercise prehabilitation.

In conclusion, the current dissertation provides further insight into the clinical presentation and treatment response heterogeneity of individuals with KOA undergoing TKA, through the identification of phenotypes and their difference in treatment response. Specific independent biopsychosocial predictive factors of treatment outcome (TKA or IMPT) were also identified. However, given the exploratory nature of some of these studies, future research is needed to confirm the present findings. In addition, more research on stratified prehabilitation care and its long-term outcomes is needed to make robust recommendations for clinical practice.

Nederlandse samenvatting

Vanwege de veelvoorkomende prevalentie en stijgende incidentie, door de globale opwaartse trend in leeftijd en personen met obesitas, wordt knie artrose (KA) gezien als één van de belangrijkste chronische musculoskeletale pijn-aandoeningen ter wereld. De afgelopen decennia is KA getransformeerd van een 'kraakbeen-gerichte' naar een 'gehele gewrichts-gerichte' aandoening, maar recentere evidentie bevestigt dat een bredere 'gehele persoons-gerichte' aanpak nodig is om de complexiteit van KA te begrijpen. De oorsprong en oorzaak van KA zijn multifactorieel en heterogeen, wat leidt tot een gevarieerde klinische presentatie en reactie op behandeling. Daarom wordt tegenwoordig een 'gehele persoons-gerichte' aanpak voor het onderzoeken en behandelen van personen met KA aangeraden, waarbij alle aspecten van het biopsychosociale model worden in acht genomen. Bovendien is het van bijzonder belang om te focussen op de pijnervaring van een persoon met KA, aangezien pijn het hoofdsymptoom is van KA en ook benaderd moet worden vanuit een biospsychosociaal perspectief. Als gevolg hiervan is het hoofddoel van dit proefschrift beter inzicht te krijgen in de aanwezige heterogeniteit bij personen met KA, met een specifieke focus op degenen die een totale knie prothese (TKP) ondergaan, en te onderzoeken hoe dit invloed heeft op de behandelingsuitkomst vanuit een biopsychosociaal perspectief.

Om een bijdrage te leveren aan deze kennis was dit proefschrift ingedeeld in drie delen die verschillende hoofdstukken omvatten. **Deel 1** omvat **Hoofdstukken 2, 3 en 5** met data van een grote multicenter prospectieve cohortstudie uitgevoerd in vier Belgische en Nederlandse ziekenhuizen waarin 223 personen met KA een TKP operatie ondergingen, en **Hoofdstuk 4**, een systematische review over de evolutie van het somatosensorisch functioneren na nociceptief-gerichte chirurgie bij personen met musculoskeletale aandoeningen. **Deel 2** omvat **Hoofdstuk 6** met data van dezelfde grote multicenter prospectieve cohortstudie in vier Belgische en Nederlandse ziekenhuizen, en **Hoofdstuk 7** met data van een andere grote multicenter prospectieve cohortstudie in zes 'clinics in revalidatie' centra in Nederland waarin 599 personen met artrose (niet beperkt tot KA) een interdisciplinaire multimodale pijnbehandeling (IMP) ondergingen. Tenslotte, **deel 3** omvat **Hoofdstuk 8**, een systematische review over gestratificeerde en niet-gestratificeerde prehabilitatie en de lange termijn behandelingseffecten bij personen met KA die een TKP ondergingen.

DEEL 1: KA fenotypes en hun lange termijn behandelingsrespons na een TKP

Een data-gedreven fenotype-analyse (d.w.z. subgroep-analyse) gebaseerd op verschillende preoperatieve variabelen die het volledige biopsychosociale model omvatte, werd gebruikt in **Hoofdstuk 2**. De resultaten toonden twee preoperatieve fenotypes aan bij personen met KA die in afwachting waren van een TKP. Deelnemers in het kleinste fenotype (28% van de deelnemers) vertoonden meer nociplastisch-achtige kenmerken, gecombineerd met minder structurele knieschade, een hogere body mass index, lagere m. Quadricepskracht, en betere fysieke functie vergeleken met de deelnemers in het grootste fenotype (72% van de deelnemers). Bovendien hadden deelnemers in fenotype 1 meer pijn één jaar na TKP vergeleken met deelnemers in het andere fenotype. Zoals verwacht, gezien pijn het belangrijkste symptoom is van KA, verschilden veel pijn-gerelateerde variabelen significant

tussen de gevonden fenotypes in **Hoofdstuk 2**. Dit is ook de reden waarom **Hoofdstukken 3 tot 5** voornamelijk gericht zijn op pijn en somatosensorisch functioneren. In **Hoofdstuk 3** werd het klinisch beoordelingssysteem van de 'International Association 288ort he Study of Pain (IASP)' toegepast om predominante nociplastiche pijn te identificeren bij personen met KA in afwachting van TKP. Daarnaast werden er ook suggesties voorgesteld om de criteria te verfijnen. Afhankelijk van de interpretatie van de stap 'regionale/multifocale/wijdverspreide pijn', werd 15% (vier pijnlocaties – aanpak 1) of 23% (drie pijnlocaties – aanpak 2) van de deelnemers geclassificeerd in de predominante 'waarschijnlijk' nociplastische pijn subgroep. Ongeacht de interpretatie van de pijnlocatie, vertoonden deelnemers in de 'waarschijnlijk' nociplastische pijn subgroep (**Hoofdstuk 3**) vergelijkbare kenmerken als deelnemers in fenotype 2 (**Hoofdstuk 2**). Dit omvatte preoperatief meer pijn locaties, hogere lokale druksensitiviteit, hogere temporele summatie (TS), hogere thermale allodynia gemeten aan de mediale gewrichtslijn van de knie, meer angst, meer depressie, meer zelf-gerapporteerde symptomen van centrale sensitisatie (CS), en één jaar postoperatief meer pijn in vergelijking met de personen in de 'mogelijke of geen' nociplastische pijn subgroep (**Hoofdstuk 3**), en personen in fenotype 1 (**Hoofdstuk 2**), respectievelijk.

Hoofdstuk 4, samen met een meer recentere update van 1 maart 2024, omvatte alle studies die de evolutie van het somatosensorisch functioneren van pre- tot postoperatief onderzochten bij personen met musculoskeletale aandoeningen die een nociceptief-gerichte chirurgie ondergingen. Specifiek voor personen met KA die een TKP ondergingen, kon er een sterke conclusie worden getrokken over geen lange termijn verandering van de druk tolereerbaarheidsdrempel en over een positieve lange termijn verandering in TS. Andere conclusies over lange termijnveranderingen waren zwak of geconflicteerd in deze populatie. Een gemiddelde conclusie toonde een positieve associatie aan van pijnverbetering en een verbetering in drukpijndrempel (DPD), geconditioneerde pijnmodulatie (CPM) en oefentherapie-geïnduceerde analgesie na TKP. De afwezigheid van duidelijke en consistente bevindingen werd toegeschreven aan het ontbreken van subgroepen op basis van pijnevolutie, postoperatieve pijn of somatosensorisch functioneren in de geïncludeerde studies. **Hoofdstuk 5** werd opgezet om te onderzoeken of de evolutie van pijnintensiteit anders was tussen een groep met normaal somatosensorisch functioneren (normaal pre- en één jaar post-TKP), een groep met hersteld somatosensorisch functioneren (verstoord pre-, maar normaal één jaar post-TKP, hypothese voor perifeer aangedreven verstoord somatosensorisch functioneren), en een groep met een aanhoudend verstoord somatosensorisch functioneren (verstoord pre- en één jaar post-TKP, hypothese voor centraal aangedreven verstoord somatosensorisch functioneren) van personen met KA die een TKP ondergingen. Het bestaan van een centraal aangedreven verstoord somatosensorisch functioneren groep kon worden bevestigd wanneer de groepen werden geclassificeerd op basis van zelf-gerapporteerde symptomen van CS. De groep met aanhoudend verstoord somatosensorisch functioneren vertoonde geen verbetering van pijn na TKP en had ook meer pijn vergeleken met de andere twee groepen. Bovendien vertoonde de groep met aanhoudend verstoord somatosensorisch functioneren, geclassificeerd op basis van lokale warmte-allodynie en zelf-gerapporteerde symptomen van CS, minder verbetering van pijn van pre- tot één jaar post-TKP in vergelijking met de groep met normaal somatosensorisch

functioneren, en vertoonde de groep met aanhoudend verstoord somatosensorisch functioneren, geclassificeerd op basis van lokale DPD en warmte allodynie, en TS, meer pijn één jaar na TKP in vergelijking met de groep met normaal somatosensorisch functioneren.

DEEL 2: Voorspellende factoren voor (in)effectieve behandelingsuitkomsten bij personen met artrose

In **Hoofdstuk 6** werden preoperatieve variabelen die het volledige biopsychosociale model omvatten, getest als potentieel voorspellende factoren voor pijnintensiteit één jaar na TKP bij personen met KA, gebaseerd op multivariabele lineaire regressieanalyses. Meer pijn één jaar na TKP en een verslechtering van pijn of kleinere verbetering van voor tot één jaar na TKP werden voorspeld door hogere geglyceerde hemoglobine waardes, meer pijnlocaties, lagere tevredenheid over pijn, minder structurele knieschade, zelf-gerapporteerde symptomen van CS en betere persoonlijke controle. Lagere preoperatieve pijnintensiteit, betere functionaliteit en het uitvoeren van een zelfstandig beroep waren aanvullende voorspellende factoren voor een verslechtering van de pijn of kleinere verbetering van voor tot één jaar na TKP. Het is interessant op te merken dat het 'aantal pijnlocaties' en 'zelf-gerapporteerde symptomen van CS' consistente belangrijke factoren waren die geassocieerd waren met pijn één jaar na TKP in **Hoofdstukken 2, 3, 5 en 6**. In **Hoofdstuk 7** werd een klinisch predictiemodel ontwikkeld en intern gevalideerd om de kans op een succesvolle behandeling te voorspellen, wat inhield dat er een positieve evolutie van beperkingen door pijn was van voor tot na de behandeling, na een 10-weken IMP-programma bij personen met artrose (niet beperkt tot KA). Potentieel voorspellende factoren werden gekozen op basis van literatuurreview en een consensusbijeenkomst van experten. Deze factoren omvatten het volledige biopsychosociale model en worden standaard gemeten bij personen die een IMP-programma starten. Variabelen die voorspellend waren voor een succesvolle behandeling, waren een vrouw zijn, minder pijnlocaties, lagere pijnintensiteit op zijn ergst, lagere negatieve ziektepercepties over de tijdslijn en identiteit, hogere pijnbeperking, betere zelf-gerapporteerde werkcapaciteit, meer pijncatastroferen, betere zelfeffectiviteit, hogere negatieve ziekstepercepties over de gevolgen van de aandoening, hogere positieve ziektepercepties over behandelingscontrole, het gebruik van pijnmedicatie en alcohol, en roken. Het intern gevalideerde model vertoonde een acceptabel discriminerend vermogen van 71% en kan worden gebruikt voor het nemen van gedeelde beslissingen met betrekking tot IMP.

DEEL 3: Gestratificeerde en niet-gestratificeerde prehabilitatie bij personen met KA die een TKP ondergaan

Tenslotte vatte **Hoofdstuk 8**, samen met een meer recentere update op 1 maart 2024, alle studies samen die gericht waren op prehabilitatie en hun lange termijnuitkomsten bij personen met KA die een TKP ondergingen. Zeven van de 22 studies pastten een meer gestratificeerde prehabilitatie toe, wat betekende dat ze specifiekere in- en exclusiecriteria gebruikten waarvan werd verwacht dat prehabilitatie effect op zou hebben of andersom. Alle studies vergeleken hun (niet-)gestratificeerde prehabilitatie met een controle groep, maar maakten geen directe vergelijking tussen gestratificeerd en niet-gestratificeerde prehabilitatie. Alleen zwakke conclusies, of conclusies waaruit bleek dat prehabilitatie geen lange termijn effect had na TKP op pijn, tevredenheid, levenskwaliteit of functie (los van kracht

van de onderste ledematen) konden worden getrokken. Alleen een sterke conclusie kon worden getrokken over het positieve effect van een niet-gestratificeerde prehabilitatie gericht op oefentherapie op kracht van de onderste ledematen één jaar na TKP.

In conclusie kunnen we stellen dat dit proefschrift verdere inzichten biedt in de heterogeniteit van de klinische presentatie en behandelingrespons bij personen met KA die een TKP ondergingen, door het identificeren van fenotypes en hun verschil in behandelingsrespons. Specifieke biopsychosociale onafhankelijke voorspellende factors voor behandelingseffect (TKP or IMP) werden ook geïdentificeerd. Echter, vanwege het exploratieve karakter van sommige studies, is verder onderzoek noodzakelijk om de huidige bevindingen te bevestigen. Daarnaast is verder onderzoek naar gestratificeerde prehabilitatie en de lange termijnuitkomsten ook noodzamelijk om robuuste aanbevelingen voor de klinische praktijk te kunnen geven.

Appendices

Supplementary material Chapter 2

Table S1: Demographics, absolute and missing values of all possible variables and TKA response before all analyses

Continuous variables			Categorical variables		
Variable	**Mean (SD)**	**N Missing (%)**	**Variable**	**median (Q1; Q3)**	**N missing (%)**
Demographic variables			**Demographic variables**		
Age (y)	65.5 (7.7)	0 (0)	Sex (n, % F)	111 (50)	0 (0)
Metabolic and inflammatory variables			**Structural variables**		
BMI (kg/m^2)	29.99 (5.25)	3 (1)	K&L scale	3 (3; 4)	9 (4)
HbA1c (%)	6 (1)	21 (9)	**Social variables**		
Fat (%)	35 (9)	91 (41)	Marital status	1 (1; 2)	10 (5)
Lean (%)	65 (9)	91 (41)	Work	1 (1; 4)	10 (5)
C-reactive protein (mmol/dl)	3.51 (4.83)	146 (66)	Education	5 (3; 6)	11 (5)
Functional variables					
Strength m. Quadriceps (kgf)	27.37 (13.04)	3 (1)			
Strength m. Hamstrings (kgf)	11.73 (5.94)	3 (1)			
Proprioception (°)	4.44 (2.04)	6 (3)			
KOOS symptoms (0-100)	48.89 (18.06)	12 (5)			
30CST (n)	10.66 (3.97)	6 (3)			
KSSS Functional score (0-100)	43.07 (15.17)	14 (6)			
Pain-related variables					
KOOS subscale pain BL (0-100)	44.07 (15.31)	12 (5)			
Number of pain locations (n)	3.45 (2.24)	16 (7)			
PPT m. tibialis anterior (Newton)	50.89 (24.81)	3 (1)			
PPT medial knee (Newton)	42.83 (23.71)	3 (1)			
PPT lateral knee (Newton)	48.06 (26.58)	3 (1)			
PPT m. ECRL (Newton)	37.55 (17.24)	3 (1)			
PPT forehead (Newton)	30.18 (12.73)	38 (17)			
TS after sensation medial knee (0-10)	0.40 (1.11)	4 (2)			
TS medial knee (Difference in NRS)	1.23 (2.02)	3 (1)			
TS after sensation medial wrist (0-10)	0.16 (0.59)	4 (2)			
TS medial wrist (Difference in NRS)	0.98 (1.56)	4 (2)			
TCA medial knee (0-10)	0.36 (0.96)	4 (2)			
THA medial knee (0-10)	0.82 (1.46)	4 (2)			
TCA lateral knee (0-10)	0.27 (0.91)	4 (2)			
THA lateral knee (0-10)	0.37 (1.09)	4 (2)			
TCA m. ECRL (0-10)	0.19 (0.75)	4 (2)			
THA m. ECRL (0-10)	0.45 (1.11)	4 (2)			
CPM (%)	10 (48)	24 (11)			
CSI (0-100)	28.06 (13.14)	12 (5)			
Psychological variables					
PCS total score (0-52)	16.24 (10.33)	11 (5)			
HADS depression (0-21)	5.06 (3.26)	10 (5)			
HADS fear (0-21)	5.34 (4.01)	10 (5)			
KSSS expectation (3-15)	13.96 (1.63)	13 (6)			
KSSS satisfaction (0-40)	15.67 (7.35)	13 (6)			
IPQR Timeline (6-30)	17.77 (5.25)	10 (5)			
IPQR Consequences (6-30)	19.34 (4.21)	10 (5)			
IPQR Timeline cyclical (4-25)	11.97 (3.85)	10 (5)			
IPQR personal control (6-30)	19.74 (3.94)	10 (5)			
IPQR treatment control (5-25)	18.06 (3.10)	10 (5)			
IPQR Emotional representations (6-30)	15.73 (4.63)	10 (5)			
IPQR Illness coherence (5-25)	18.74 (2.12)	10 (5)			

Table S1 (continued)

Continuous variables		
Variable	**Mean (SD)**	**N Missing (%)**
Psychological variables (continued)		
IPQR Identity (0-14)	2.07 (1.43)	9 (4)
Outcome variable		
KOOS subscale pain FU2 (0-100)	73.45 (24.15)	55 (25)

Abbreviations: BMI = body mass index, CPM = conditioned pain modulation, CSI = central sensitization inventory, Diff = difference, ECRL = extensor carpi radialis longus, HADS = hospitality anxiety and depression scale, Hb1ac = glycated hemoglobin, IPQR = illness perceptions questionnaire revised, K&L = Kellgren and Lawrence scale, kgf = kilograms force, kg/m2 = kilograms/squared meter, KOOS = knee injury and osteoarthritis outcome scale, KSSS = knee society scoring system, NRS = numeric rating scale, PCS = pain catastrophizing scale, PPT = pressure pain threshold, TCA = thermal cold allodynia, THA = thermal heat allodynia, TS = temporal summation, dl = deciliter, Mmol = 292ensitiza.

Table S2a: Correlation analyses part 1

Variable	BMI	HbA1c	Strength m. Quadriceps	Strength m. Hamstrings	Proprio-ception	30s CST	KSSS functional score	KOOSpain	CSI	Bodychart	PPT mk	PPT lk	PPT m. TA	PPT m. ECRL
BMI	1	0,181**	0,096	0,102	-0,031	-0,199**	-0,229**	0,087	0,115	0,066	-0,062	-0,058	-0,113	0,048
HbA1c	0,181**	1	-0,010	0,004	-0,029	-0,030	-0,081	0,030	0,135*	0,032	-0,137*	-0,034	-0,075	-0,063
Strength m. Quadriceps	0,096	-0,010	1	0,698**	-0,034	0,466**	0,258**	-0,217**	-0,207**	-0,225**	0,343**	0,412**	0,344**	0,355**
Strength m. Hamstrings	0,102	0,004	0,698**	1	-0,122	0,372**	0,239**	-0,175*	-0,209**	-0,195**	0,315**	0,405**	0,329**	0,357**
Proprioception	-0,031	-0,029	-0,034	-0,122	1	-0,041	0,084	-0,064	-0,056	-0,077	-0,022	-0,016	-0,035	-0,028
30CST	-0,199**	-0,030	0,466**	0,372**	-0,041	1	0,305**	-0,165*	-0,191**	-0,161*	0,303**	0,226**	0,208**	0,167*
KSSS functional score	-0,229**	-0,081	0,258**	0,239**	0,084	0,305**	1	-0,653**	-0,312**	-0,211**	0,211**	0,240**	0,177*	0,190**
KOOSpain	0,087	0,030	-0,217**	-0,175*	-0,064	-0,165*	-0,653**	1	0,237**	0,253**	-0,185**	-0,187**	-0,153*	-0,220**
CSI	0,115	0,135*	-0,207**	-0,209**	-0,056	-0,191**	-0,312**	0,237**	1	0,415**	-0,269**	-0,201**	-0,248**	-0,235**
Bodychart	0,066	0,032	-0,225**	-0,195**	-0,077	-0,161*	-0,211**	0,253**	0,415**	1	-0,222**	-0,174**	-0,221**	-0,204**
PPT mk	-0,062	-0,137*	0,343**	0,315**	-0,022	0,303**	0,211**	-0,185**	-0,269**	-0,222**	1	0,770**	0,797**	0,635**
PPT lk	-0,058	-0,034	0,412**	0,405**	-0,016	0,226**	0,240**	-0,187**	-0,201**	-0,174**	0,770**	1	0,804**	0,696**
PPT m. TA	-0,113	-0,075	0,344**	0,329**	-0,035	0,208**	0,177*	-0,153*	-0,248**	-0,221**	0,797**	0,804**	1	0,717**
PPT m. ECRL	0,048	-0,063	0,355**	0,357**	-0,028	0,167*	0,190**	-0,220**	-0,235**	-0,204**	0,635**	0,696**	0,717**	1
TS mk	0,059	0,049	-0,164*	-0,217**	0,054	-0,079	-0,172*	0,092	0,199**	0,166*	-0,306**	-0,316**	-0,350**	-0,319**
TS mw	-0,053	0,025	-0,206**	-0,212**	-0,018	-0,138*	-0,122	0,081	0,158*	0,128	-0,176**	-0,281**	-0,227**	-0,283**
TS after sens mk	-0,017	-0,011	-0,227**	-0,289**	0,033	-0,129	-0,028	-0,095	0,101	0,111	-0,217**	-0,270**	-0,239**	-0,221**
TS after sens mw	-0,119	-0,109	-0,085	-0,183**	0,018	-0,053	0,128	0,062	0,004	0,018	-0,028	-0,145*	-0,065	-0,138*
CPM	0,043	-0,004	-0,053	-0,025	-0,078	-0,075	-0,068	0,013	-0,051	0,125	-0,010	0,033	-0,035	-0,005
PCS	0,193**	0,088	-0,073	-0,148*	0,018	-0,131	-0,325**	0,256**	0,428**	0,218**	-0,108	-0,078	-0,107	-0,067

Table S2a (continued)

Variable	BMI	HbA1c	Strength m. Quadriceps	Strength m. Hamstrings	Proprio-ception	30s CST	KSSS functional score	KOOSpain	CSI	Bodychart	PPT mk	PPT lk	PPT m. TA	PPT m. ECRL
HADS depression	0,124	0,010	-0,018	-0,107	-0,025	-0,218**	-0,260**	0,137*	0,500**	0,264**	-0,028	0,043	-0,042	0,057
HADS anxiety	0,074	0,003	-0,170*	-0,194**	0,032	-0,211**	-0,157*	0,100	0,589**	0,291**	-0,150*	-0,170*	-0,225**	-0,109
KSSS expectations	0,026	0,040	0,066	0,085	0,090	0,100	0,106	-0,081	-0,170*	-0,041	-0,010	0,025	0,030	0,009
KSSS satisfaction	-0,154*	-0,014	0,186**	0,164*	0,067	0,105	0,558**	-0,703**	-0,279**	-0,283**	0,129	0,181**	0,178*	0,166*
KSSS symptoms	-0,082	0,036	0,127	0,051	0,033	0,123	0,457**	-0,550**	-0,185**	-0,162*	0,041	0,049	0,082	0,062
KOOS symptoms	-0,055	-0,005	-0,095	-0,159*	-0,138*	-0,074	-0,187**	0,267**	0,149*	0,135*	-0,016	-0,057	-0,040	-0,069
NRS pain score rest	0,120	-0,083	-0,174*	-0,134	-0,005	-0,106	-0,388**	0,514**	0,101	0,159*	-0,039	-0,114	-0,085	-0,121
PPT forehead	-0,095	0,066	0,298**	0,445**	-0,110	0,266**	0,158*	-0,142*	-0,238**	-0,153*	0,565**	0,592**	0,578**	0,697**
TH cold mk	-0,047	-0,040	-0,157*	-0,202**	0,006	-0,136*	-0,094	0,119	0,122	0,139*	-0,216**	-0,238**	-0,166*	-0,195**
TH heat mk	0,026	-0,091	-0,110	-0,185**	-0,024	-0,086	-0,139*	0,095	0,225**	0,130	-0,220**	-0,267**	-0,202**	-0,217**
TH cold lk	-0,059	-0,057	-0,150*	-0,176**	0,018	-0,123	-0,117	0,143*	0,110	0,147*	-0,170*	-0,232**	-0,180**	-0,219**
TH heat lk	0,045	-0,074	-0,092	-0,189**	-0,040	-0,178**	-0,158*	0,139*	0,239**	0,230**	-0,171*	-0,232**	-0,199**	-0,224**
TH cold m. ECRL	-0,113	-0,102	-0,093	-0,146*	-0,015	-0,118	-0,048	0,042	0,100	0,077	-0,082	-0,180**	-0,137*	-0,171*
TH heat m. ECRL	-0,077	-0,077	-0,079	-0,187**	0,009	-0,125	-0,089	0,067	0,131	0,128	-0,124	-0,178**	-0,121	-0,195**
IPQR Identity	0,153*	0,043	-0,258**	-0,13	-0,147*	-0,073	-0,214**	-0,190**	0,302**	0,108	-0,152*	-0,178*	-0,094	-0,113
IPQR Timeline	-0,063	-0,115	0,060	0,012	-0,070	-0,059	-0,025	0,075	0,162*	0,072	-0,005	0,028	0,051	-0,053
IPQR consequences	0,111	-0,070	0,001	-0,081	-0,051	-0,139*	-0,329**	0,256**	0,252**	0,072	-0,058	-0,014	-0,015	0,035
IPQR personal control	0,044	-0,028	0,160*	0,079	0,062	0,140*	0,192**	-0,187**	0,078	-0,010	0,095	0,021	0,056	0,026
IPQR treatment control	-0,150*	-0,042	0,029	0,048	0,164*	0,103	0,277**	-0,166*	-0,160*	-0,080	0,025	-0,040	0,019	-0,026

Table S2a (continued)

Variable	BMI	HbA1c	Strength m. Quadriceps	Strength m. Hamstrings	Proprio-ception	30s CST	KSSS functional score	KOOSpain	CSI	Bodychart	PPT mk	PPT lk	PPT m. TA	PPT m. ECRL
IPQR illness coherence	-0,045	-0,019	0,107	0,091	0,020	0,182**	0,063	-0,064	-0,066	-0,034	-0,098	-0,013	-0,070	-0,121
IPQ timeline cyclical	-0,036	-0,087	-0,008	-0,067	0,101	0,005	0,092	-0,107	0,087	0,102	0,054	-0,020	0,025	0,013
IPQR emotional representations	0,250**	0,027	-0,151*	-0,155*	-0,073	-0,197**	-0,326**	0,228**	0,463**	0,247**	-0,152*	-0,155*	-0,129	0,023
K-L scale	0,006	-0,031	0,215**	0,169*	-0,066	0,213**	0,171*	0,161*	-0,184**	-0,039	0,201**	0,211**	0,133	0,162*
Work	-0,034	-0,064	-0,091	-0,142*	0,04	-0,01	-0,097	0,056	0,069	0,042	-0,078	-0,068	-0,115	-0,138*
Marital status	0,189**	-0,042	0,06	0	-0,074	-0,026	-0,073	-0,234**	0,142*	0,173*	-0,094	-0,094	-0,123	-0,066
Education	0,051	0,064	-0,031	-0,06	-0,205**	0,148*	-0,012	0,023	0,053	-0,062	-0,103	-0,079	-0,073	-0,042

Abbreviations: 30CST = 30 seconds chair stand test, BMI = body mass index, CPM = conditioned pain modulation, CSI = Central Sensitization Index, ECRL = m. Extensor Carpi Radialis Longus, HADS = Hospital Anxiety and Depression Scale, Hb1Ac = glycated hemoglobin, IPQR = illness perceptions questionnaire revised, KSSS = Knee Society Scoring System, KOOS = Knee Injury and Osteoarthritis Outcome Score, lk = lateral knee, mk = medial knee, mw = medial wrist, m. = musculus, NRS = numeric rating scale, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold, TA = m. Tibialis Anterior, TH = thermal hypersensitivity, TS = temporal summation

**p<0.001, *p<0.05

Table S2b: Correlation analyses part 2

Variable	TS mk	TS mw	TS after sens mk	TS after sens mw	CPM	PCS	HADS depression	HADS anxiety	KSSS expectations	**KSSS satisfaction**	KSS symptoms	KOOS symptoms	NRS pain score rest	**PPT forehead**	**TH cold mk**
BMI	0,059	-0,053	-0,017	-0,119	0,043	0,193**	0,124	0,074	0,049	-0,154*	-0,082	-0,055	0,120	-0,095	-0,069
HbA1c	0,049	0,025	-0,011	-0,109	-0,004	0,088	0,010	0,003	-0,068	-0,014	0,036	-0,005	-0,083	0,066	0,008
Strength m. Quadriceps	-0,164*	-0,206**	-0,227**	-0,085	-0,053	-0,073	-0,018	-0,170*	0,034	0,186**	0,127	-0,095	-0,174*	0,298**	-0,150*
Strength m. Hamstrings	-0,217**	-0,212**	-0,289**	-0,183**	-0,025	-0,148*	-0,107	-0,194**	-0,038	0,164*	0,051	-0,159*	-0,134	0,445**	-0,227**
Proprioception	0,054	-0,018	0,033	0,018	-0,078	0,018	-0,025	0,032	0,107	0,067	0,033	-0,138*	-0,005	-0,110	0,06
30s CST	-0,079	-0,138*	-0,129	-0,053	-0,075	-0,131	-0,218**	-0,211**	0,021	0,105	0,123	-0,074	-0,106	0,266**	-0,092
KSSS functional score	-0,172*	-0,122	-0,028	0,128	-0,068	-0,325**	-0,260**	-0,157*	-0,025	0,558**	0,457**	-0,187**	-0,388**	0,158*	-0,04
KOOSpain	0,092	0,081	-0,095	0,062	0,013	0,256**	0,137*	0,100	-0,012	-0,703**	-0,550**	0,267**	0,514**	-0,142*	-0,137
CSI	0,199**	0,158*	0,101	0,004	-0,051	0,428**	0,500**	0,589**	-0,129	-0,279**	-0,185**	0,149*	0,101	-0,238**	0,114
Bodychart	0,166*	0,128	0,111	0,018	0,125	0,218**	0,264**	0,291**	-0,066	-0,283**	-0,162*	0,135*	0,159*	-0,153*	0,127
PPT mk	-0,306**	-0,176**	-0,217**	-0,028	-0,010	-0,108	-0,028	-0,150*	-0,023	0,129	0,041	-0,016	-0,039	0,565**	-0,255**
PPT lk	-0,316**	-0,281**	-0,270**	-0,145*	0,033	-0,078	0,043	-0,170*	-0,021	0,181**	0,049	-0,057	-0,114	0,592**	-0,267**
PPT m. TA	-0,350**	-0,227**	-0,239**	-0,065	-0,035	-0,107	-0,042	-0,225**	-0,006	0,178*	0,082	-0,040	-0,085	0,578**	-0,165*
PPT m. ECRL	-0,319**	-0,283**	-0,221**	-0,138*	-0,005	-0,067	0,057	-0,109	-0,048	0,166*	0,062	-0,069	-0,121	0,697**	-0,196**

Table S2b (continued)

Variable	TS mk	TS mw	TS after sens mk	TS after sens mw	CPM	PCS	HADS depression	HADS anxiety	KSSS expectations	**KSSS satisfaction**	KSS symptoms	KOOS symptoms	NRS pain score rest	**PPT forehead**	**TH cold mk**
TS mk	1	0,427**	0,359**	0,161*	0,056	0,114	0,053	0,101	-0,04	-0,087	-0,036	0,089	0,155*	-0,294**	0,144*
TS medial wrist	0,427**	1	0,148*	0,274**	-0,050	0,137*	0,044	0,131	0,006	-0,028	-0,012	0,135	0,076	-0,253**	0,071
TS after sens mk	0,359**	0,148*	1	0,391**	-0,063	-0,001	0,005	0,122	0,009	-0,149*	-0,123	0,116	-0,243**	-0,107	0,405**
TS after sens mw	0,161*	0,274**	0,391**	1	-0,052	0,015	-0,158*	0,011	-0,029	0,021	-0,098	-0,015	-0,170*	0,076	0,192**
CPM	0,056	-0,050	-0,063	-0,052	1	0,029	0,036	0,025	-0,015	-0,061	-0,161*	-0,015	0,045	0,073	-0,008
PCS	0,114	0,137*	-0,001	0,015	0,029	1	0,510**	0,580**	0,024	-0,182**	-0,209**	0,047	0,223**	-0,058	0,159*
HADS depression	0,053	0,044	0,005	-0,158*	0,036	0,510**	1	0,618**	-0,105	-0,151*	-0,138*	0,058	0,143*	0,014	0,051
HADS anxiety	0,101	0,131	0,122	0,011	0,025	0,580**	0,618**	1	-0,102	-0,146*	-0,140*	0,085	0,053	-0,098	0,168*
KSSS expectations	-0,042	-0,081	0,009	-0,029	-0,008	-0,106	-0,203**	-0,247**	1	0,084	0,089	-0,069	-0,168*	-0,047	-0,032
KSSS satisfaction	-0,087	-0,028	-0,107	0,076	-0,061	-0,182**	-0,151*	-0,146*	0,029	1	0,619**	-0,216**	-0,552**	0,076	-0,121
KSS symptoms	-0,036	-0,012	-0,149*	0,021	-0,161*	-0,209**	-0,138*	-0,140*	0,042	0,619**	1	-0,239**	-0,541**	-0,043	-0,084
KOOS symptoms	0,089	0,135	-0,123	-0,098	-0,015	0,047	0,058	0,085	-0,025	-0,216**	-0,239**	1	0,187**	-0,035	-0,064
NRS pain score rest	0,155*	0,076	0,116	-0,015	0,045	0,223**	0,143*	0,053	-0,11	-0,552**	-0,541**	0,187**	1	-0,053	0,043
PPT forehead	-0,294**	-0,253**	-0,243**	-0,170*	0,073	-0,058	0,014	-0,098	-0,188*	0,076	-0,043	-0,035	-0,053	1	-0,265**
TH cold mk	0,114	0,266**	0,405**	0,192**	-0,039	0,211**	0,112	0,176*	-0,032	-0,097	-0,056	0,031	0,050	-0,227**	1

Table S2b (continued)

Variable	TS mk	TS mw	TS after sens mk	TS after sens mw	CPM	PCS	HADS depression	HADS anxiety	KSSS expectations	**KSSS satisfaction**	KSS symptoms	KOOS symptoms	NRS pain score rest	**PPT forehead**	**TH cold mk**
TH heat mk	0,163*	0,187**	0,197**	0,133	-0,058	0,221**	0,175*	0,217**	-0,098	-0,110	-0,052	-0,006	0,125	-0,256**	0,499**
TH cold lk	0,119	0,306**	0,282**	0,151*	-0,106	0,175*	0,106	0,161*	0,018	-0,114	-0,046	0,054	0,070	-0,258**	0,682**
TH heat lk	0,186**	0,291**	0,206**	0,203**	-0,048	0,300**	0,213**	0,270**	0,01	-0,105	-0,058	0,062	0,115	-0,267**	0,432**
TH cold m. ECRL	0,099	0,241**	0,178**	0,272**	-0,090	0,147*	0,099	0,153*	-0,046	-0,066	0,010	0,058	0,037	-0,223**	0,573**
TH heat m. ECRL	0,087	0,228**	0,157*	0,151*	-0,097	0,145*	0,167*	0,172*	-0,109	-0,081	0,012	0,039	0,031	-0,261**	0,335**
IPQR Identity	0,058	0,139*	0,183**	0,034	-0,126	0,170*	0,146*	0,177*	-0,057	-0,249**	-0,212**	-0,193**	0,168*	-0,057	0,122
IPQR timeline	0,113	0,051	0,091	0,088	-0,028	0,119	0,147*	0,137*	-0,268**	0,023	-0,046	0,137*	-0,010	-0,064	0,061
IPQR consequences	0,021	0,052	0,117	0,022	-0,070	0,301**	0,324**	0,243**	0,061	-0,264**	-0,263**	0,132	0,141*	0,015	0,09
IPQR personal control	-0,125	-0,007	0,014	0,062	-0,124	0,017	-0,036	0,057	-0,043	0,066	0,079	-0,035	-0,184**	0,021	0,098
IPQR treatment control	-0,090	0,057	0,065	0,119	-0,058	-0,155*	-0,201**	-0,056	0,122	0,094	0,104	-0,015	-0,103	0,027	0,118
IPQR illness coherence	0,037	0,043	-0,017	-0,07	-0,108	-0,139*	-0,143*	-0,159*	0,095	0,057	0,034	-0,034	-0,138*	-0,037	0,073
IPQ timeline cyclical	-0,062	-0,108	-0,003	0,053	-0,070	0,078	0,157*	0,191**	-0,142*	0,077	0,154*	0,017	-0,113	-0,047	0,113
IPQR emotional representations	0,095	0,077	0,057	0,021	0,007	0,560**	0,471**	0,622**	0,012	-0,258**	-0,206**	0,145*	0,107	-0,029	0,098
K-L scale	-0,116	0,056	-0,121	0,012	-0,012	-0,081	-0,056	-0,144*	0,029	0,160*	0,041	0,173*	-0,129	0,128	-0,112
Work	0,094	0,08	0,162*	0,069	0,025	0,036	0,028	0,049	0,004	0,011	-0,05	-0,067	-0,022	-0,168*	0,099
Marital status	-0,016	-0,004	0,082	0,055	0,021	0,044	0,056	-0,004	0,03	-0,151*	-0,208**	-0,129	0,104	-0,169*	0,136
Education	-0,06	-0,008	0,02	-0,029	-0,114	-0,169*	-0,086	-0,118	-0,111	-0,048	0,047	0,049	-0,099	-0,059	-0,034

Abbreviations: 30CST = 30 seconds chair stand test, BMI = body mass index, CPM = conditioned pain modulation, CSI = Central Sensitization Index, ECRL = m. Extensor Carpi Radialis Longus, HADS = Hospital Anxiety and Depression Scale, Hb1Ac = glycated hemoglobin, IPQR = illness perceptions questionnaire revised, KSSS = Knee Society Scoring System, KOOS = Knee Injury and Osteoarthritis Outcome Score, lk = lateral knee, mk = medial knee, mw = medial wrist, m. = musculus, NRS = numeric rating scale, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold, TA = m. Tibialis Anterior, TH = thermal hypersensitivity, TS = temporal summation

**p<0.001, *p<0.05

Table S2c: Correlation analyses part 3

Variable	TH heat mk	TH cold lk	TH heat lk	TH cold m. ECRL	TH heat m. ECRL	IPQR Identity	IPQR timeline	IPQR consequences	IPQR personal control	IPQR treatment control	IPQR illness coherence	IPQ timeline cyclical	IPQR emotional representations	K-L scale	Work	Marital status	Education
BMI	-0,044	-0,013	0,021	-0,086	-0,077	0,153*	-0,063	0,111	0,044	-0,150*	-0,045	-0,036	0,250**	0,006	-0,034	0,189**	0,051
HbA1c	0,003	-0,025	-0,021	-0,083	-0,027	0,043	-0,115	-0,070	-0,028	-0,042	-0,019	-0,087	0,027	-0,031	-0,064	-0,042	0,064
Strength m. Quadriceps	-0,094	-0,139*	-0,058	-0,028	-0,015	-0,258**	0,060	0,001	0,160*	0,029	0,107	-0,008	-0,151*	0,215**	-0,091	0,06	-0,031
Strength m. Hamstrings	-0,158*	-0,180**	-0,202**	-0,094	-0,154*	-0,13	0,012	-0,081	0,079	0,048	0,091	-0,067	-0,155*	0,169*	-0,142*	0	-0,06
Proprioception	-0,04	0,008	-0,098	0,011	0,015	-0,147*	-0,070	-0,051	0,062	0,164*	0,020	0,101	-0,073	-0,066	0,04	-0,074	-0,205**
30s CST	-0,036	-0,083	-0,082	-0,031	0,025	-0,073	-0,059	-0,139*	0,140*	0,103	0,182**	0,005	-0,197**	0,213**	-0,01	-0,026	0,148*
KSSS functional score	-0,067	-0,111	-0,084	0,021	-0,008	-0,214**	-0,025	-0,329**	0,192**	0,277**	0,063	0,092	-0,326**	0,171*	-0,097	-0,073	-0,012
KOOSpain	-0,079	-0,229**	-0,126	-0,058	-0,036	-0,190**	0,075	0,256**	-0,187**	-0,166*	-0,064	-0,107	0,228**	0,161*	0,056	-0,234**	0,023
CSI	0,122	0,093	0,194**	0,091	0,078	0,302**	0,162*	0,252**	0,078	-0,160*	-0,066	0,087	0,463**	-0,184**	0,069	0,142*	0,053
Bodychart	0,025	0,126	0,077	0,061	-0,016	0,108	0,072	0,072	-0,010	-0,080	-0,034	0,102	0,247**	-0,039	0,042	0,173*	-0,062
PPT mk	-0,213**	-0,227**	-0,245**	-0,163*	-0,104	-0,152*	-0,005	-0,058	0,095	0,025	-0,098	0,054	-0,152*	0,201**	-0,078	-0,094	-0,103
PPT lk	-0,252**	-0,263**	-0,294**	-0,221**	-0,150*	-0,178*	0,028	-0,014	0,021	-0,040	-0,013	-0,020	-0,155*	0,211**	-0,068	-0,094	-0,079

Table S2c (continued)

Variable	TH heat mk	TH cold lk	TH heat lk	TH cold m. ECRL	TH heat m. ECRL	IPQR Identity	IPQR timeline	IPQR consequences	IPQR personal control	IPQR treatment control	IPQR illness coherence	IPQ timeline cyclical	IPQR emotional representations	K-L scale	Work	Marital status	Education
PPT m. TA	-0,164*	-0,207**	-0,226**	-0,132	-0,074	-0,094	0,051	-0,015	0,056	0,019	-0,070	0,025	-0,129	0,133	-0,115	-0,123	-0,073
PPT m. ECRL	-0,167*	-0,247**	-0,251**	-0,199**	-0,161*	-0,113	-0,053	0,035	0,026	-0,026	-0,121	0,013	0,023	0,162*	-0,138*	-0,066	-0,042
TS mk	0,088	0,182**	0,138*	0,083	0,061	0,058	0,113	0,021	-0,125	-0,090	0,037	-0,062	0,095	-0,116	0,094	-0,016	-0,06
TS m. ECRL	0,09	0,160*	0,128	0,098	0,064	0,139*	0,051	0,052	-0,007	0,057	0,043	-0,108	0,077	0,056	0,08	-0,004	-0,008
TS after sens mk	0,197**	0,282**	0,206**	0,178**	0,157*	-0,017	-0,003	0,057	0,183**	0,091	0,117	0,014	0,065	-0,121	0,162*	0,082	0,02
TS after sens mw	0,133	0,151*	0,203**	0,272**	0,151*	-0,07	0,053	0,021	0,034	0,088	0,022	0,062	0,119	0,012	0,069	0,055	-0,029
CPM	-0,058	-0,098	-0,04	-0,163*	-0,160*	-0,126	-0,028	-0,070	-0,124	-0,058	-0,108	-0,070	0,007	-0,012	0,025	0,021	-0,114
PCS	0,108	0,131	0,173*	0,054	0,02	0,170*	0,119	0,301**	0,017	-0,155*	-0,139*	0,078	0,560**	-0,081	0,036	0,044	-0,169*
HADS depression	0,118	0,054	0,09	0,008	0,095	0,146*	0,147*	0,324**	-0,036	-0,201**	-0,143*	0,157*	0,471**	-0,056	0,028	0,056	-0,086
HADS anxiety	0,136	0,083	0,141*	0,074	0,026	0,177*	0,137*	0,243**	0,057	-0,056	-0,159*	0,191**	0,622**	-0,144*	0,049	-0,004	-0,118
KSSS expectations	-0,098	0,018	0,01	-0,046	-0,109	-0,057	-0,242**	-0,003	-0,001	0,146*	0,050	-0,189**	-0,152*	0,029	0,004	0,03	-0,111
KSSS satisfaction	-0,086	-0,138	-0,096	-0,055	-0,056	-0,249**	0,023	-0,264**	0,066	0,094	0,057	0,077	-0,258**	0,160*	0,011	-0,151*	-0,048
KSS symptoms	0,01	-0,06	0,049	0,06	0,036	-0,212**	-0,046	-0,263**	0,079	0,104	0,034	0,154*	-0,206**	0,041	-0,05	-0,208**	0,047

Table S2c (continued)

Variable	TH heat mk	TH cold lk	TH heat lk	TH cold m. ECRL	TH heat m. ECRL	IPQR Identity	IPQR timeline	IPQR consequences	IPQR personal control	IPQR treatment control	IPQR illness coherence	IPQ timeline cyclical	IPQR emotional representations	K-L scale	Work	Marital status	Education
KOOS symptoms	0,005	-0,057	-0,049	-0,039	-0,016	-0,193**	0,137*	0,132	-0,035	-0,015	-0,034	0,017	0,145*	0,173*	-0,067	-0,129	0,049
NRS pain score rest	0,089	0,059	0,017	-0,001	0,003	0,168*	-0,010	0,141*	-0,184**	-0,103	-0,138*	-0,113	0,107	-0,129	-0,022	0,104	-0,099
PPT forehead	-0,198**	-0,328**	-0,271**	-0,313**	-0,252**	-0,057	-0,064	0,015	0,021	0,027	-0,037	-0,047	-0,029	0,128	-0,168*	-0,169*	-0,059
TH cold mk	0,499**	0,682**	0,432**	0,573**	0,335**	0,122	0,071	0,055	0,072	0,108	0,050	0,071	0,123	-0,112	0,099	0,136	-0,034
TH heat mk	1	0,365**	0,695**	0,380**	0,664**	0,093	0,089	0,174*	0,092	0,023	-0,015	-0,030	0,176*	-0,122	0,026	-0,002	-0,034
TH cold lk	0,365**	1	0,447**	0,673**	0,336**	0,105	0,045	-0,017	0,015	0,085	0,051	0,036	0,044	-0,052	0,095	0,196**	-0,047
TH heat lk	0,695**	0,447**	1	0,387**	0,619**	0,111	0,053	0,180**	0,006	-0,047	-0,066	0,004	0,212**	-0,146*	0,122	0,033	-0,079
TH cold m. ECRL	0,380**	0,673**	0,387**	1	0,456**	0,08	0,061	0,010	-0,039	0,038	-0,024	0,046	0,060	-0,075	0,067	0,06	-0,001
TH heat m. ECRL	0,664**	0,336**	0,619**	0,456**	1	0,046	0,070	0,060	0,001	0,006	-0,020	0,018	0,088	-0,096	0,07	-0,073	-0,059
IPQR identity	0,093	0,105	0,111	0,08	0,046	1	0,016	0,271**	0,065	-0,131	0,018	-0,069	0,295**	-0,063	0,036	0,038	0,065
IPQR timeline	0,071	-0,004	0,053	0,051	0,063	0,016	1	0,234**	-0,151*	-0,336**	-0,012	-0,002	0,146*	0,022	-0,079	-0,039	-0,015
IPQR consequences	0,155*	0,081	0,188**	0,087	0,07	0,271**	0,234**	1	-0,041	-0,168*	-0,050	-0,047	0,490**	-0,023	-0,042	0,185**	-0,089
IPQR personal control	0,104	0,042	0,062	0,025	0,019	0,065	-0,151*	-0,041	1	0,301**	0,103	0,242**	0,011	0,052	0,042	0,002	-0,018

Table S2c (continued)

Variable	TH heat mk	TH cold lk	TH heat lk	TH cold m. ECRL	TH heat m. ECRL	IPQR Identity	IPQR timeline	IPQR consequences	IPQR personal control	IPQR treatment control	IPQR illness coherence	IPQ timeline cyclical	IPQR emotional representations	K-L scale	Work	Marital status	Education
IPQR treatment control	0,045	0,085	-0,019	0,051	0,009	-0,131	-0,336**	-0,168*	0,301**	1	0,154*	0,050	-0,232**	-0,178*	0,023	-0,096	-0,057
IPQR illness coherence	0,062	0,078	-0,01	0,05	0,074	0,018	-0,012	-0,050	0,103	0,154*	1	-0,222**	-0,156*	0,022	0,099	-0,011	0,022
IPQ timeline cyclical	-0,034	0,065	-0,013	0,084	0,001	-0,069	-0,002	-0,047	0,242**	0,050	-0,222**	1	0,101	0,001	-0,092	-0,190**	-0,016
IPQR emotional representations	0,091	0,012	0,171*	0,041	0,029	0,295**	0,146*	0,490**	0,011	-0,232**	-0,156*	0,101	1	-0,143*	-0,032	0,118	-0,049
K-L scale	-0,122	-0,052	-0,146*	-0,075	-0,096	-0,063	0,022	-0,023	0,052	-0,178*	0,022	0,001	-0,143*	1	-0,079	0,07	-0,031
Work	0,026	0,095	0,122	0,067	0,07	0,036	-0,079	-0,042	0,042	0,023	0,099	-0,092	-0,032	-0,079	1	0,065	-0,061
Marital status	-0,002	0,196**	0,033	0,06	-0,073	0,038	-0,039	0,185**	0,002	-0,096	-0,011	-0,190**	0,118	0,07	0,065	1	0,016
Education	-0,034	-0,047	-0,079	-0,001	-0,059	0,065	-0,015	-0,089	-0,018	-0,057	0,022	-0,016	-0,049	-0,031	-0,061	0,016	1

Abbreviations: 30CST = 30 seconds chair stand test, BMI = body mass index, CPM = conditioned pain modulation, CSI = Central Sensitization Index, ECRL = m. Extensor Carpi Radialis Longus, HADS = Hospital Anxiety and Depression Scale, Hb1Ac = glycated hemoglobin, IPQR = illness perceptions questionnaire revised, KSSS = Knee Society Scoring System, KOOS = Knee Injury and Osteoarthritis Outcome Score, lk = lateral knee, mk = medial knee, m. = musculus, NRS = numeric rating scale, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold, TA = m. Tibialis Anterior, TH = thermal hypersensitivity, TS = temporal summation

**p<0.001, *p<0.05

Table S3: Model development of latent profile analysis

Model	N of classes	BIC	aBIC	Class sizes (%)	VLMR p-value
A	1	25129.54	24971.10	100	NA
	2	**24949.95**	**24686.94**	**72/28**	**0.0062**
	3	24952.56	24584.97	58/18/25	0.7830
	4	24996.40	24524.24	33/12/43/12	0.7696
	5	25071.73	24495.00	34/11/39/5/11	0.6724
B	1	25129.54	24971.10	100	NA
	2	24740.51	24420.45	47/53	0.1909
	3	24740.02	24258.35	29/47/24	0.8282
	4	24822.85	24179.57	25/24/31/20	NA
	5	25077.51	24272.61	18/10/32/19/21	NA

Abbreviations: aBIC = adjusted Bayesian information criterion, BIC = Bayesian information criterion, N = number, NA = not applicable, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test

Table S4: Continuous variables in phenotype construct presented as categorical data (if possible)

	Phenotype 1 N (%)	Phenotype 2 N (%)	P-value
BMI (76)			0.011[C]*
Normal (18.5-24.9 kg/m^2)	32 (21)	3 (5)	
Overweight (25-29.9 kg/m^2)	52 (34)	21 (35)	
Obese (>30kg/m^2)	67 (44)	36 (60)	
Hb1Ac (57)			0.301[A]
Normal (<6.5)	133 (96)	51 (91)	
Not well controlled (≥6.5)	6 (4)	5 (9)	
TS mk (82)			<0.001[A]*
Normal excitability (<2)	131 (85)	36 (61)	
Hyperexcitability (≥2)	24 (16)	23 (39)	
TS mw (82)			0.002[A]*
Normal excitability (<2)	119 (77)	32 (54)	
Hyperexcitability (≥2)	36 (23)	27 (46)	
CPM (83)			0.052[B]
Non-responder (0)	29 (20)	6 (11)	
Inhibitor (<0)	60 (42)	19 (33)	
Facilitator (>0)	55 (38)	56.1 (43)	
CSI (43)			<0.001[A]*
No central sensitization (<40)	145 (97)	23 (41)	
Central sensitization (≥40)	4 (3)	33 (59)	
PCS (44)			<0.001[A]*
Low/no catastrophizing (≤21)	144 (97)	44 (77)	
Catastrophizing (>21)	5 (3)	13 (23)	
HADS fear (45)			<0.001[A]*
No fear (≤7)	137 (91)	17 (30)	
Fear (>7)	13 (9)	40 (70)	
HADS depression (45)			<0.001[A]*
No depression (≤7)	137 (91)	30 (53)	
Depression (<7)	13 (9)	27 (47)	

P associated with [A]Fisher's exact test, [B]Pearson chi-square test, or [C]Mann-Whitney-U test
Abbreviations: BMI = body mass index, CPM = conditioned pain modulation, CSI = Central Sensitization Index, HADS = Hospital Anxiety and Depression Scale, Hb1Ac = glycated hemoglobin, kg = kilograms, m2 = squared meter, N = number, PCS = Pain Catastrophizing Scale, TS = temporal summation

Supplementary Table S5: Concurrent validity

	Odds ratios using reference category 'phenotype 2' compared to 'phenotype 1'	
Variable	**Odds estimate**	**95%CI**
Age	-0.046	0.041; -1.104
Sex	1.208	0.781; 1.546
Strength m. Hamstrings	1.281*	1.006; 1.632
NRS pain in rest	0.750	0.549; 1.024
PPT lateral knee	1.093*	1.022; 1.168
IPQ-R subscale emotional representations	0.549*	0.403; 0.748

*= significant difference between phenotypes (1 not included in 95%CI).

Abbreviations: CI = confidence interval, IPQ-R = illness perceptions questionnaire-revised, NRS = numeric rating scale, PPT = pressure pain threshold

Supplementary material Chapter 3

Table S1: included variables for AIM 2 + references of the table

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Demographic factors		
Age	Birth date until first physical measurement	-Demographic questionnaire -Continuous variable -/
Sex	Man or woman	-Demographic questionnaire -Nominal variable
Structural factors		
Grade of KOA	-X-ray images in AP, profile and Rosenberg weight-bearing position (1). -Retrospectively extracted from the participant's record by the general practitioner of the participants or the participants themselves -If one of the images was not available, scoring was based on the available image(s). If no X-ray image was available, MRI in coronal and sagittal position were extracted. If none of the X-ray or MRI images could be found, this variable was recorded as missing value.	-K&L scale (2) or MRI grading system (3) -Ordinal variable -5-point Likert scale: 0 (no KOA) to 4 (worst grade of KOA) -K&L: Good reliability and validity in KOA (4) MRI grading: Good reliability and responsiveness (5)
Metabolic and inflammatory factors		
BMI	-Length: demographic questionnaire -Weight: standing on an electronic scale at the moment of testing	-Formula: Weight/(length in cm)^2 -Continuous variable -kg/cm^2 -N/A
Hb1Ac	-Sitting position -Taking a blood sample by pricking into a fingertip	-A1Cnow+ system (*PTS Diagnostics, China*) and a fingerstick (6) -Continuous variable -% -Accurate measurement to detect diabetes (7)
Fat mass **Lean mass**	-Supine lying position -Skinfold electrodes on hand and foot connected to the device	-Bioelectrical Impedance Analysis (Bodystat Quadscan 4000) -Continuous variable -N/A -Accurate measurement to measure body composition (8)
C-reactive protein	-Blood sample before surgery, retrospectively extracted from participant's record by executive researchers	-Blood sample -Continuous variable -mg/L -Reliable method (9)

Table S1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Functional variables		
Strength m. Quadriceps **Strength m. Hamstrings**	-Sitting position with hip and knee in 90°, upper leg fully supported by the table, and arm crossed over their chest. Isometric strength measurement was assured by using a traction belt. -Perform flexion (Hamstrings) or extension (Quadriceps) of the knee against the device -3 times, highest value used for analysis	-MicroFET 2 hand-held dynamometer (*ProCare, Groningen*) -Continuous variable -Kgf -Reliable and valid (10)
Proprioception	-Sitting position with hip and knee in 90°, upper leg fully supported by the table -Repositioning error during a knee joint position sense test (20°, 45° and 70° flexed knee) -Twice assessed, mean of 6 trials used for analysis	-Plurimeter *(Dr. Rippstein, Switzerland)* -Continuous variable -° of knee angle -Reliable (11)
Functional symptoms	-Questionnaire: questions related to stiffness, noises and mobility of the knee	-KOOS subscale symptoms -Continuous variable -5-point Likert scale: 0 (no symptoms) to 4 (always symptoms) for question 1 to 5, 4 (always) to 1 (never) for question 6 and 7 -Valid and reliable (12)
Physical function	-Questionnaire: asking questions related to different activities -Sum of subscales 'walking and standing', 'standard activities', 'advanced activities' and 'discretionary activities	-KSSS Functional Score -Continuous variable -Scored 0 (impossible to perform any activities) – 120 (possible to perform any activity) -Valid and reliable (15)
	-Sitting position with arms resting next to the body -Standing up and again sitting down as much as possible without support in 30s	-30 CST -Continuous variable -Number of times to stand up -Reliable (16)
Pain-related variables		
Pain intensity	-Questionnaire: questions related to pain intensity and specific movements during previous months of the knee that would undergo surgery	-KOOS subscale pain -Continuous variable -5-point Likert scale: 0 (no pain) to 4 (unbearable pain) -Valid and reliable (12)
	-Scale to measure pain intensity in rest at one moment	-Numeric pain rating scale -Continuous variable -11-point Likert scale: 0 (no pain) to 10 (unbearable pain) -Valid and reliable (17)
Pain symptoms	-3 scales related to pain during walking on ground, pain during walking on stairs and how 'normal' the knee feels	-KSSS Symptom Score -Continuous variable -Scored 0 (no pain) – 25 (worst pain) -Valid and reliable (15)

Table S1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Pain-related variables (continued)		
Sensitization associated symptoms	-Questionnaire: questions related to self-reported central sensitization -Total score was used for analysis	-Central Sensitization Inventory -Continuous variable -5-point Likert scale: 0 (no central sensitization present) to 4 (most central sensitization symptom present) -Reliable (18)
Number of pain locations	To draw their pain on a body chart by crossing all body parts that were painful during the last week	-Pain drawings on body chart -Continuous variable -Number of body parts -Valid and reliable (19)
Mechanical PPT	-Supine lying position -The probe (1cm2) was placed perpendicular to the test surface and pressure increased with a speed of 9.8 Newton/second until the subject reported a first feeling of pain/discomfort at the location of the stimulus (+/- 1/10 NRS). -Repeated after 30s (2 trials), mean used for analysis Location: Local hyperalgesia: - Medial joint-space dominant side - Lateral joint-space dominant side Widespread hyperalgesia: - m. Tibialis Anterior dominant side - m. ECRL of non-dominant side - Forehead	-Hand-held pressure algometer *(Wagner FDX 25 Force Gage, USA)* -Continuous variable -Newton/second -Reliable (22,23)
Thermal allodynia	-Supine lying position -At the skin overlying the medial and lateral joint-space of the affected knee (local thermal allodynia) and m. ECRL of non-dominant side (widespread thermal allodynia) -The executive researcher rolled the thermoroller for 10s over the skin and participant had to score their pain intensity felt at the location of the stimulus	-Thermal rollers (Rolltemp II) with a roller of 25°C and 40°C -Continuous variable -NRS: 0 (no pain) to 10 (unbearable pain) -Recommended to test abnormal thermal sensation (24)
Temporal summation	-Supine lying position -At the skin overlying the medial joint-space of the affected knee (local temporal summation) and the dorsal wrist of the affected side (widespread temporal summation) -30 repeated pinpricks with pace of 1 pinprick/s -Pain NRS score felt at the location of the stimulus given by subject on first and last pinprick the subject -The differences of the NRS scores were calculated and used for analysis.	- Von Frey monofilament 60g -Continuous variable -NRS: 0 (no pain) to 10 (unbearable pain) -Reliable (25,26)

Table S1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Pain-related variables (continued)		
CPM	-Sitting position, lower arms supported, heat thermodes around the participant's wrist -The device searched for a temperature equal to a pain intensity NRS score of 4/10 (until a maximum of 46°C). This identified temperature (or 46°C when the 4/10 on a NRS was not reached) was used as test stimulus. The participant had to score the test stimulus on a NRS 4 times. After a pause of 120 seconds, a conditioning stimulus (with a temperature of 0.5°C more than the test stimulus) was added for 65 seconds and 20 seconds after its initiation, the test stimulus was repeated. Again, the participants had to score their pain for 4 times, but only on the test site. If the NRS at 46°C and the mean of the NRS of test stimulus was equal to zero, the participant was excluded for analysis of this variable. -Percentage change ((absolute score/NRS score during test stimulus)*100) scores were used for analysis.	-Q-sense CPM (*Medoc, USA*) -Continuous variable -NRS: 0 (no pain) to 10 (unbearable pain) -Reliability to better confirmed(26)
Psychological variables		
Pain catastrophizing	-Questionnaire: questions related to pain catastrophizing -Three subdomains: magnification, rumination and helplessness -Total score was used for the analysis	-Pain Catastrophizing Scale -Continuous variable -5-point Likert scale: 0 (not at all) to 4 (all the time) -Valid and reliable (28,29)
Depression Anxiety	-Questionnaire: questions related to depression and anxiety -Two subscales : depression and anxiety -Scores of two subscales were used for analysis	-Hospital Anxiety and Depression Scale -Continuous variable -4-point Likert scale: 0 to 3 (variable meaning per item) -Valid and reliable (30)
Expectations	-Questionnaire: questions related to surgery result expectation -Subscale 'expectations' was used for analysis	-Knee Society Scoring System Score -Continuous variable -6-point Likert scale: 0 (no expectation) to 5 (high positive expectations) -Valid and reliable (15)
Satisfaction	-Questionnaire: questions related to satisfaction about knee complaint -Subscale 'satisfaction' was used for analysis	-Knee Society Scoring System Score -Continuous variable -5 items scored from 0 (no expectations) to 8 (high positive expectations) -Valid and reliable (15)

Table S1 (continued)

Variable	Measurement method	-Measurement device -Data type -Scoring -Reference to psychometric properties
Psychological (continued)		
Consequences	-Questionnaire: questions related to consequences of KOA complaint	- Illness perception questionnaire : subscales
Timeline	-Questionnaire: questions related to timeline of KOA complaint	-Continuous variable -6 items scored from 1 (strongly disagree) to 5 (strongly agree) -Reliable, expect for subscale 310ensitiza (31)
Personal control	-Questionnaire: questions related to personal control over the KOA disease	
Treatment control	-Questionnaire: questions related to treatment control over the KOA treatment	
Emotional representation	-Questionnaire: questions related to emotional representation	
Illness cohorence	-Questionnaire: questions related to illness coherence	
Identity	-Questionnaire: questions related to experienced symptom related (or not) to the disease	-Illness perception questionnaire : subcale identity -Continuous variable -9 symptoms related to illness scored 0 (no) or 1 (yes) -Reliable (31)
Causes of KOA	-Questionnaire: questions related to causes of KOA complaint	- Illness perception questionnaire : subcale causes -Continuous variable -Every question scored separately from 1 (strongly disagree) to 5 (strongly agree), no total score -Reliable (31)
Social variables		
Work	-Work level including pension, self-employed, white-collar worker, laborer, unemployed, or other	- Demographic questionnaire -Nominal variable -Scored from 1 to 6
Education	-Educational level going from no degree, primary school degree, technical secondary school degree, higher secondary school degree, high school degree, university degree to other	- Demographic questionnaire -Ordinal variable -Scored from 1 to 7
Marital status	-Marital status including married, divorced, single, widow(er) or other	- Demographic questionnaire -Nominal variable -Scored from 1 to 5

Abbreviations: BPS = biopsychosocial, KOA = knee osteoarthritis, AP = anterior-posterior, MRI = magnetic resonance images, K&L scale = Kellgren and Lawrence scale, N/A = not applicable, BMI = body mass index, Hb1Ac = glycated hemoglobin (presence of diabetes type 2), KSSS = Knee Society Scoring System, s= second, 30CST = 30s timed chair stand test, KOOS = Knee Osteoarthritis Outcome and Index Score, ECRL = Extensor capri radialis longus, g = grams, NRS = numeric rating scale, h = hour, PPT = pressure pain threshold, CPM = conditioned pain modulation, kgf = kilogram force, mg/l = milligrams/liter, SPS = somatosensory processing signs

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Table S2: Demographics and number of missing values total KOA sample

Variable	Mean +/- SD or N (%) (n=197)	N (%) missing
Continuous variables		
Age	65.35 +/- 7.67	0
BMI (kg/m^2)	29.97 +/- 5.31	0
PPT m. Tibialis anterior (Ne)	50.06 +/- 23.45	0
PPT medial knee joint-line (Ne)	42.12 +/- 22.53	0
PPT lateral knee joint-line (Ne)	46.99 +/- 24.63	0
PPT m. ECRL (Ne)	37.30 +/- 17.15	0
PPT forehead (Ne)	30.17 +/- 12.73	23 (11.86)
TS medial knee joint-line (Diff in NRS)	1.25 +/- 1.99	0
After sensation medial knee joint-line (0-10)	0.43 +/- 1.15	0
TS medial wrist (Diff in NRS)	1.06 +/- 1.63	0
Cold allodynia medial knee joint-line (0-10)	0.36 +/- 0.97	1 (0.51)
Heat allodynia medial knee joint-line (0-10)	0.87 +/- 1.52	1 (0.51)
Cold allodynia lateral knee joint-line (0-10)	0.30 +/- 0.96	1 (0.51)
Heat allodynia lateral knee joint-line (0-10)	0.41 +/- 1.14	1 (0.51)
Cold allodynia m. ECRL (0-10)	0.20 +/- 0.79	1 (0.51)
Heat allodynia m. ECRL (0-10)	0.48 +/- 1.16	1 (0.51)
CPM relative score (%)	14.39 +/- 66.14	15 (7.61)
Strength m. Quadriceps (kgf)	27.52 +/- 12.99	0
Strength m. Hamstrings (kgf)	11.94 +/- 5.92	0
Proprioception (°)	4.47 +/- 2.09	3 (1.52)
30s chair stand test (N)	10.76 +/- 4.06	2 (1.02)
Hba1c value (%)	5.58 +/- 0.59	16 (8.12)
Bodychart (N)	3.47 +/- 2.27	0
NRS pain in rest (0-10)	4.60 +/- 2.67	0
IPQR 313ensitiz score (0-14)	2.12 +/- 1.42	0
IPQR Timeline (6-30)	17.87 +/- 5.28	0
IPQR Consequences (6-30)	19.46 +/- 4.21	0
IPQR personal control (6-30)	19.70 +/- 3.98	0
IPQR treatment control (5-25)	18.16 +/- 3.08	0
IPQR Illness 313ensitiza (5-25)	18.74 +/- 2.14	0
IPQR Timeline cyclical (4-20)	11.95 +/- 3.84	0
IPQR Emotional representations (6-30)	15.80 +/- 4.58	0
PCS rumination (0-16)	6.26 +/- 3.84	1 (0.51)
PCS magnification (0-12)	2.73 +/- 2.52	1 (0.51)
PCS 313ensitizatio (0-24)	7.36 +/- 5.08	1 (0.51)
PCS total score (0-52)	16.35 +/- 10.41	1 (0.51)
HADS fear (0-21)	5.31 +/- 3.94	0
HADS depression (0-21)	5.07 +/- 3.20	0
KSSS symptoms (0-20)	8.46 +/- 4.67	0
KSSS satisfaction (0-40)	15.40 +/- 7.31	1 (0.51)
KSSS expectations (3-15)	13.95 +/- 1.61	1 (0.51)
KSSS functional score (0-100)	43.14 +/- 15.13	1 (0.51)
KOOS subscale symptoms (0-20)	48.85 +/- 17.82	1 (0.51)
KOOS subscale pain (0-100)	43.82 +/- 15.30	1 (0.51)
CSI (0-100)	28.23 +/- 12.99	1 (0.51)
Fat mass (%)	35.04 +/- 8.92	83 (42.13)
Lean mass (%)	64.96 +/- 8.92	83 (42.13)
CRP-value (mg/L)	6.75 +/- 20.12	109 (55.33)
KOOS subscale pain one-year postoperative	72.76 +/- 24.57	41 (20.80)

Table S2 (continued)

Variable		Mean +/- SD or N (%) (n=197)	N (%) missing
Categorical variables			
Sex	Man	102 (52)	0
	Woman	95 (48)	
Grade of KOA	K&L 1	3 (1.50)	6 (3.00)
	K&L 2	40 (20.30)	
	K&L 3	68 (34.50)	
	K&L 4	80 (40.60)	
Education	No degree	11 (5.60)	0
	Primary school	11 (5.60)	
	Technical secondary school	46 (23.40)	
	Higher secondary school	24 (12.20)	
	High school	48 (24.37)	
	University	16 (8.10)	
	Other	41 (20.80)	
Work	Pension	104 (52.80)	1 (0.50)
	Self-employed	14 (7.10)	
	White-collar worker	26 (13.20)	
	Laborer	25 (12.70)	
	Unemployed	2 (1.00)	
	Other	25 (12.70)	
Marital status	Married	141 (71.60)	1 (0.50)
	Divorced	17 (8.60)	
	Single	8 (4.10)	
	Widow(er)	18 (9.10)	
	Other	12 (6.10)	

Abbreviations: SD= standard deviation, N= number, BMI= body mass index, kg/m^2= kilograms/squared meter, PPT= pressure pain threshold, m. = musculus, Ne= Newton, ECRL= extensor carpi radialis longus, TS= temporal summation, Diff= difference, NRS= numeric rating scale, CPM= conditioned pain modulation, kgf= kilograms force, Hb1ac= glycated hemoglobin, IPQR= illness perceptions questionnaire revised, PCS= pain catastrophizing scale, HADS= hospitality anxiety and depression scale, KSSS= knee society scoring system, KOOS= knee injury and osteoarthritis outcome scale, CSI= central sensitization inventory, CRP= C-reactive protein, K&L= Kellgren and Lawrence scale

Supplementary Table S3: Differences between knee osteoarthritis participants with 'probable', 'possible', or 'no' nociplastic pain (continuous variables) at baseline and one-year postoperative (4 pain locations approach)

Variable Continuous variables	Probable nociplastic pain (n = 30) Estimated mean (95%CI)	Possible nociplastic pain (n= 20) Estimated mean (95%CI)	No nociplastic pain (n= 147) Estimated mean (95%CI)	P-value	Post-hoc
Demographic variable					
Age	61.83 (59.14; 64.53)	64.70 (61.39; 68.01)	66.16 (64.94; 67.38)	0.017	/
Metabolic and inflammatory variables					
BMI (kg/m^2)	29.85 (27.90; 31.79)	28.45 (26.13, 30.77)	30.21 (29.35; 31.08)	0.380	/
Hba1c value (%)	5.64 (5.40; 5.88)	5.48 (5.21; 5.76)	5.59 (5.48; 5.69)	0.634	/
Pain-related variables					
Bodychart (N)	6.46 (5.83; 7.09)	5.08 (4.33; 5.83)	2.65 (2.37; 2.93)	<0.001*	Probable vs. no + possible vs. no : <0.001*, probable vs. possible: 0.019*
NRS pain in rest (0-10)	4.88 (3.90; 5.56)	5.38 (4.21; 6.55)	4.46 (4.02; 4.89)	0.308	/
KOOS subscale pain (0-100)	38.09 (32.60; 43.57)	44.84 (38.29; 51.38)	44.89 (42.44; 47.34)	0.088	/
PPT m. Tibialis anterior (Ne)	42.65 (34.98; 50.31)	47.56 (38.41; 56.70)	51.46 (48.04; 54.87)	0.118	/
PPT MK joint-line (Ne)	30.91 (23.16; 38.65)	38.70 (29.46; 47.94)	44.59 (41.15; 48.04)	0.007*	Probable vs. no: 0.006*
PPT LK joint-line (Ne)	36.49 (28.06; 44.92)	44.74 (34.68; 54.80)	49.35 (45.60; 53.10)	0.026	/
PPT m. ECRL (Ne)	30.73 (25.12; 36.34)	35.41 (28.72; 42.10)	38.33 (35.84; 40.83)	0.055	/
PPT forehead (Ne)	25.00 (20.42; 29.59)	28.32 (22.64; 34.01)	31.40 (29.29; 33.52)	0.038	/
TS MK joint-line (Diff in NRS)	2.24 (1.55; 2.93)	2.22 (1.40; 3.04)	0.94 (0.63; 1.24)	<0.001*	Probable vs. no: 0.003*, possible vs. no: 0.014*
After sensation medial knee (0-10)	1.15 (0.75; 1.54)	1.12 (0.65; 1.59)	0.19 (0.02; 0.37)	<0.001*	Probable vs. no: <0.001*, possible vs. no: 0.001*
TS medial wrist (Diff in NRS)	1.83 (1.24; 2.42)	1.36 (0.66; 2.06)	0.86 (0.60; 1.13)	0.012*	Probable vs. no: 0.012*
After sensation medial wrist (0-10)	0.27 (0.04; 0.50)	0.44 (0.17; 0.71)	0.11 (0.01; 0.21)	0.062	/
Cold allodynia MK joint-line (0-10)	1.04 (0.70; 1.39)	0.56 (0.15; 0.97)	0.20 (0.05; 0.36)	<0.001*	Probable vs. no: <0.001*
Heat allodynia MK joint-line (0-10)	1.87 (1.32; 2.41)	1.28 (0.64; 1.93)	0.62 (0.38; 0.87)	<0.001*	Probable vs. no: <0.001*
Cold allodynia LK joint-line (0-10)	0.96 (0.61; 1.30)	0.30 (-0.11; 0.71)	0.17 (0.02; 0.32)	<0.001*	Probable vs. no: <0.001*, probable vs. possible: 0.046*
Heat allodynia LK joint-line (0-10)	1.22 (0.80; 1.63)	0.53 (0.03; 1.02)	0.24 (0.05; 0.43)	<0.001*	Probable vs. no: <0.001*
Cold allodynia m. ECRL (0-10)	0.51 (0.22; 0.81)	0.15 (-0.20; 0.50)	0.15 (0.02; 0.29)	0.093	/
Heat allodynia m. ECRL (0-10)	1.09 (0.67; 1.52)	0.83 (0.33; 1.34)	0.33 (0.14; 0.52)	0.003*	Probable vs. no: 0.005*
CPM relative score (%)	7.89 (-16.49; 32.26)	43.02 (12.93; 73.12)	12.61 (1.40; 23.82)	0.133	/
CSI (0-100)	40.30 (36.11; 44.49)	26.47 (21.47; 31.47)	23.30 (24.44; 28.17)	<0.001*	Probable vs. no + probable vs. possible : <0.001*
Functional variables					
Strength m. Quadriceps (kgf)	23.56 (19.62; 27.49)	27.39 (22.70; 32.09)	28.02 (26.27; 29.77)	0.137	/
Strength m. Hamstrings (kgf)	9.95 (8.00; 11.90)	10.15 (7.73; 12.48)	12.48 (11.31; 13.34)	0.027	/
Proprioception (°)	4.30 (3.52; 5.08)	5.05 (4.14; 5.97)	4.41 (4.07; 4.76)	0.370	/

Supplementary Table S3 (continued)

Variable Continuous variables	Probable nociplastic pain (n = 30) Estimated mean (95%CI)	Possible nociplastic pain (n= 20) Estimated mean (95%CI)	No nociplastic pain (n= 147) Estimated mean (95%CI)	P-value	Post-hoc
Functional variables (continued)					
30s chair stand test (N)	9.86 (8.37; 11.35)	10.39 (8.62; 12.17)	10.98 (10.32; 11.64)	0.380	/
KSSS symptoms (0-20)	8.10 (6.43; 9.77)	7.60 (5.61; 9.60)	8.63 (7.89; 9.38)	0.590	/
KSSS functional score (0-100)	37.58 (32.15; 43.02)	43.46 (36.98; 49.94)	44.09 (41.67; 46.51)	0.106	/
KOOS subscale symptoms (0-100)	9.87 (8.60; 11.14)	10.21 (8.70; 11.72)	10.32 (9.76; 10.89)	0.817	/
Psychological variables					
IPQR identity score (0-14)	2.21 (1.69; 2.73)	2.15 (1.53; 2.77)	2.10 (1.87; 2.34)	0.933	/
IPQR Timeline (6-30)	19.04 (17.09; 20.99)	18.39 (16.07; 20.72)	17.54 (16.68; 18.41)	0.363	/
IPQR Consequences (6-30)	19.33 (17.79; 20.87)	19.41 (17.57; 21.24)	19.47 (18.79; 20.16)	0.986	/
IPQR personal control (6-30)	19.82 (18.35; 21.29)	20.29 (18.53; 22.04)	19.59 (18.93; 20.24)	0.757	/
IPQR treatment control (5-25)	17.86 (16.72; 18.99)	18.52 17.26; 19.97)	18.15 (17.65; 18.66)	0.700	/
IPQR Illness cohorence (5-25)	19.31 (18.53; 20.09)	18.39 (17.46; 19.33)	18.66 (18.31; 19.01)	0.256	/
IPQR Timeline cyclical (4-20)	11.92 (10.50; 13.34)	12.49 (10.80; 14.19)	11.98 (11.26; 12.52)	0.808	/
IPQR Emotional representations (6-30)	17.61 (15.96; 19.26)	14.73 (12.76; 16.70)	15.60 (14.86; 16.33)	0.051	/
PCS rumination (0-16)	7.42 (6.01; 8.82)	5.58 (3.82; 7.34)	6.12 (5.49; 6.74)	0.177	/
PCS magnification (0-12)	3.70 (2.78; 4.62)	3.25 (2.13; 4.37)	2.45 (2.04; 2.86)	0.039	/
PCS helplesness (0-24)	9.10 (7.26; 10.45)	7.31 (5.07; 9.56)	7.01 (6.19; 7.83)	0.137	/
PCS total score (0-52)	20.22 (16.44; 24.00)	16.14 (11.54; 20.74)	15.58 (13.90; 17.26)	0.097	/
HADS fear (0-21)	7.13 (5.73; 8.52)	6.15 (4.49; 7.81)	4.85 (4.23; 5.47)	0.011*	Probable vs. no: 0.013*
HADS depression (0-21)	6.88 (5.73; 8.04)	5.10 (3.73; 6.48)	4.69 (4.18; 5.20)	0.004*	Probable vs. no: 0.003*
KSSS satisfaction (0-40)	12.95 (10.32; 15.57)	14.46 (11.33; 17.60)	15.99 (14.81; 17.16)	0.110	/
KSSS expectations (3-15)	13.48 (12.89; 14.07)	14.18 (13.42; 14.83)	14.02 (13.76; 14.29)	0.234	/
One year postoperative outcome variable					
KOOS subscale pain	58.56 (48.41; 68.71)	70.75 (58.39; 83.11)	75.09 (70.66; 79.52)	0.005*	Probable vs. no: 0.004*

Table 4. *significant difference (p<0.017). All variables are adjusted for sex and age (except age itself). Abbreviations: BMI= body mass index. Kg/m2= kilograms/squared meter. PPT= pressure pain threshold. M. = musculus. Ne= Newton. ECRL= extensor carpi radialis longus. TS= temporal summation. Diff= difference. NRS= numeric rating scale. CPM= conditioned pain modulation. Kgf= kilograms force. Hb1ac= glycated hemoglobin. IPQR= illness perceptions questionnaire revised. PCS= pain catastrophizing scale. HADS= hospitality anxiety and depression scale. KSSS= knee society scoring system. KOOS= knee injury and osteoarthritis outcome scale. CSI= central sensitization inventory, MK= medial knee, LK= lateral knee.

Supplementary Table S4: Differences between knee osteoarthritis participants with 'probable', 'possible', or 'no' nociplastic pain (categorical variables) at baseline and one-year postoperative (4 pain locations approach)

Variable		Probable nociplastic pain (n = 30)	Possible nociplastic pain (n = 20)	No nociplastic pain (n = 147)	P-value	Post-hoc
Categorical variables			**N (%)**			
Demographic variable						
Sex	Man	9 (30.00)	8 (40.00)	85 (57.82)	0.011*	Probable vs. no: 0.005*
	Woman	21 (70.00)	12 (60.00)	62 (42.18)		
Structural variable						
Grade of KOA	K&L 1	1 (3.33)	0 (0.00)	2 (0.01)	0.527	/
	K&L 2	10 (33.33)	4 (20.00)	28 (19.05)		
	K&L 3	10 (33.33)	5 (25.00)	55 (37.41)		
	K&L 4	9 (30.00)	11 (55.00)	62 (42.18)		
Social variables						
Education	No degree	3 (10.00)	1 (5.00)	7 (4.76)	0.757	/
	Primary school	1 (3.33)	2 (10.00)	8 (5.44)		
	Technical secondary school	5 (16.67)	3 (15.00)	38 (25.85)		
	Higher secondary school	3 (10.00)	3 (15.00)	19 (12.93)		
	High school	9 (30.00)	8 (40.00)	30 (20.41)		
	University	3 (10.00)	0 (0.00)	13 (8.84)		
	Other	6 (20.00)	3 (15.00)	32 (21.77)		
Work	Pension	9 (30.00)	10 (50.00)	86 (58.50)	0.296	/
	Self-employed	5 (16.67)	4 (20.00)	5 (3.40)		
	White-collar worker	6 (20.00)	2 (10.00)	18 (12.24)		
	Laborer	4 (13.33)	2 (10.00)	19 (12.93)		
	Unemployed	0 (0.00)	0 (0.00)	2 (1.36)		
	Other	6 (20.00)	2 (10.00)	17 (11.56)		
Marital status	Married	20 (66.67)	15 (75.00)	107 (72.79)	0.465	/
	Divorced	3 (10.00)	2 (10.00)	12 (8.16)		
	Single	3 (10.00)	0 (0.00)	5 (3.40)		
	Widow(er)	1 (3.33)	3 (15.00)	14 (9.52)		
	Other	3 (10.00)	0 (0.00)	9 (6.12)		

Table 5. * significant difference (p<0.017). All variables are adjusted for age and sex (except sex itself).
Abbreviations: K&L= Kellgren and Lawrence scale

Supplementary Table S5: Differences between knee osteoarthritis participants with 'probable', 'possible', or 'no' nociplastic pain (continuous variables) at baseline and one-year postoperative (3 pain locations approach)

Variable	Probable nociplastic pain (n = 46)	Possible nociplastic pain (n= 36)	No nociplastic pain (n= 115)	P-value	Post-hoc
Continuous variables		**Estimated mean (95%CI)**			
Demographic variable					
Age	62.41 (60.25; 64.58)	64.58 (62.14; 67.03)	66.77 (65.40; 68.13)	0.004*	Probable vs. no: 0.003*
Metabolic and inflammatory variables					
BMI (kg/m^2)	29.84 (28.28; 31.41)	28.55 (26.83; 30.27)	30.48 (29.50; 31.46)	0.165	/
Hba1c value (%)	5.65 (5.46; 5.84)	5.42 (5.22; 5.63)	5.61 (5.49; 5.72)	0.165	/
Pain-related variables					
Bodychart (N)	5.24 (4.67; 5.81)	4.26 (3.63; 4.89)	2.53 (2.17; 2.89)	<0.001*	Probable vs. no + possible vs. no: <0.001*
NRS pain in rest (0-10)	5.10 (4.31; 5.88)	5.17 (4.31; 6.03)	4.25 (3.75; 4.74)	0.086	/
KOOS subscale pain (0-100)	39.07 (34.65; 43.49)	44.00 (39.14; 48.86)	45.72 (42.93; 48.51)	0.053	
PPT m. Tibialis anterior (Ne)	46.82 (39.92; 52.34)	46.82 (39.99; 53.65)	52.05 (48.15; 55.96)	0.206	/
PPT MK joint-line (Ne)	33.36 (27.12; 39.61)	40.01 (33.14; 46.87)	45.93 (42.00; 49.85)	0.005*	Probable vs. no: 0.004*
PPT LK joint-line (Ne)	40.92 (34.08; 47.75)	43.44 (35.93; 50.96)	50.41 (46.11; 54.70)	0.052	/
PPT m. ECRL (Ne)	32.64 (28.12; 37.16)	34.56 (29.59; 39.54)	39.30 (36.46; 42.14)	0.038	/
PPT forehead (Ne)	27.74 (23.95; 31.53)	29.34 (25.01; 33.68)	31.30 (28.92; 33.68)	0.265	/
TS MK joint-line (Diff in NRS)	1.78 (1.22; 2.35)	1.78 (1.16; 2.41)	0.90 (0.54; 1.25)	0.010*	Probable vs. no: 0.036*
After sensation medial knee (0-10)	0.75 (0.42; 1.08)	0.74 (0.38; 1.10)	0.21 (0.00; 0.42)	0.007*	Probable vs. no: 0.027*, possible vs. no: 0.043*
TS medial wrist (Diff in NRS)	1.63 (1.16; 2.11)	1.13 (0.61; 1.65)	0.81 (0.51; 1.11)	0.021	/
After sensation medial wrist (0-10)	0.19 (0.00; 0.37)	0.24 (0.04; 0.45)	0.14 (0.02; 0.26)	0.679	/
Cold allodynia MK joint-line (0-10)	0.78 (0.50; 1.07)	0.39 (0.08; 0.70)	0.19 (0.01; 0.38)	0.004*	Probable vs. no: 0.003*
Heat allodynia MK joint-line (0-10)	1.53 (1.09; 1.97)	1.18 (0.69; 1.66)	0.53 (0.25; 0.81)	<0.001*	Probable vs. no: <0.001*
Cold allodynia LK joint-line (0-10)	0.61 (0.32; 0.90)	0.27 (-0.04; 0.59)	0.19 (0.01; 0.37)	0.053	/
Heat allodynia LK joint-line (0-10)	0.78 (0.44; 1.13)	0.42 (0.04; 0.80)	0.27 (0.05; 0.49)	0.050	/
Cold allodynia m. ECRL (0-10)	0.35 (0.11; 0.59)	0.22 (-0.4; 0.48)	0.15 (-0.01; 0.30)	0.388	/
Heat allodynia m. ECRL (0-10)	0.85 (0.50; 1.20)	0.68 (0.30; 1.06)	0.30 (0.08; 0.51)	0.019	/
CPM relative score (%)	4.77 (-14.97; 24.51)	34.26 (12.22; 56.30)	13.07 (0.25; 25.89)	0.124	/
CSI (0-100)	38.78 (35.49; 42.07)	24.38 (20.77; 28.00)	25.59 (23.52; 27.66)	<0.001*	Probable vs. no + probable vs. possible: <0.001*
Functional variables					
Strength m. Quadriceps (kgf)	22.23 (19.12; 25.33)	27.35 (23.94; 30.77)	29.29 (27.34; 31.24)	0.001*	Probable vs. no: <0.001*
Strength m. Hamstrings (kgf)	10.44 (8.86; 12.02)	10.97 (9.24; 12.71)	12.70 (11.71; 13.69)	0.041	/
Proprioception (°)	4.54 (3.91; 5.16)	4.73 (4.05; 5.41)	4.35 (3.96; 4.74)	0.605	/
30s chair stand test (N)	9.45 (8.26; 10.64)	10.80 (9.50; 12.11)	11.16 (10.51; 12.00)	0.049	/
KSSS symptoms (0-20)	8.06 (6.71; 9.41)	8.24 (6.76; 9.72)	8.67 (7.82; 9.51)	0.738	/
KSSS functional score (0-100)	37.12 (32.81; 41.48)	43.43 (38.67; 48.20)	45.28 (42.55; 48.01)	0.010*	Probable vs. no: 0.007*

Supplementary Table S5 (continued)

Variable	Probable nociplastic pain (n = 46)	Possible nociplastic pain (n= 36)	No nociplastic pain (n= 115)	P-value	Post-hoc
Continuous variables		**Estimated mean (95%CI)**			
Functional variables (continued)					
KOOS subscale symptoms (0-100)	9.99 (8.97; 11.01)	10.35 (9.22; 11.47)	10.32 (9.67; 10.96)	0.856	/
Psychological variables					
IPQR identity score (0-14)	2.49 (2.07; 2.90)	1.87 (1.42; 2.33)	2.06 (1.80; 2.32)	0.118	/
IPQR Timeline (6-30)	19.47 (17.90; 21.03)	17.54 (15.82; 19.26)	17.31 (16.33; 18.29)	0.077	/
IPQR Consequences (6-30)	20.63 (19.40; 21.85)	18.85 (17.50; 20.20)	19.15 (18.38; 19.92)	0.095	/
IPQR personal control (6-30)	19.63 (18.45; 20.82)	20.22 (18.91; 21.53)	19.55 (18.80; 20.30)	0.682	/
IPQR treatment control (5-25)	17.69 (16.78; 18.60)	18.87 (17.86; 19.87)	18.12 (17.55; 18.69)	0.277	/
IPQR Illness cohorence (5-25)	19.21 (18.58; 19.84)	18.56 (17.86; 19.25)	18.60 (18.20; 18.99)	0.249	/
IPQR Timeline cyclical (4-20)	11.27 (10.13; 12.41)	11.87 (10.61; 13.13)	12.26 (11.55; 12.98)	0.366	/
IPQR Emotional representations (6-30)	17.55 (16.23; 18.87)	14.38 (12.93; 15.82)	15.57 (14.74; 16.40)	0.005*	Probable vs. no: 0.047*, probable vs. possible: 0.005*
PCS rumination (0-16)	7.28 (6.15; 8.41)	5.52 (4.24; 6.80)	6.08 (5.37; 6.79)	0.093	/
PCS magnification (0-12)	3.86 (3.13; 4.60)	2.64 (1.82; 3.45)	2.29 (1.83; 2.75)	0.003*	Probable vs. no: 0.002*
PCS helplesness (0-24)	9.53 (8.07; 10.99)	6.86 (5.23; 8.49)	6.65 (5.73; 7.57)	0.005*	Probable vs. no: 0.005*, probable vs. possible: 0.043*
PCS total score (0-52)	20.67 (17.66; 23.69)	15.01 (11.66; 18.36)	15.02 (13.13; 16.91)	0.007*	Probable vs. no: 0.008*, probable vs. possible: 0.039*
HADS fear (0-21)	6.67 (5.43; 7.80)	5.16 (3.92; 6.40)	4.85 (4.14; 5.56)	0.032	/
HADS depression (0-21)	6.55 (5.62; 7.48)	4.66 (3.64; 5.67)	4.60 (4.02; 5.19)	0.002*	Probable vs. no: 0.002*, probable vs. possible: 0.022*
KSSS satisfaction (0-40)	13.64 (11.52; 15.77)	14.97 (12.63; 17.31)	16.18 (14.84; 17.53)	0.148	/
KSSS expectations (3-15)	13.60 (13.12; 14.08)	14.06 (13.53; 14.59)	14.06 (13.75; 14.36)	0.260	/
One year postoperative outcome variable					
KOOS subscale pain	61.52 (53.81; 69.23)	73.60 (54.42; 82.79)	75.91 (70.72; 81.11)	0.004*	Probable vs. no: 0.004*

Table 4. *significant difference (p<0.019). All variables are adjusted for sex and age (except age itself). Abbreviations: BMI= body mass index. Kg/m2= kilograms/squared meter. PPT= pressure pain threshold. M. = musculus. Ne= Newton. ECRL= extensor carpi radialis longus. TS= temporal summation. Diff= difference. NRS= numeric rating scale. CPM= conditioned pain modulation. Kgf= kilograms force. Hb1ac= glycated hemoglobin. IPQR= illness perceptions questionnaire revised. PCS= pain catastrophizing scale. HADS= hospitality anxiety and depression scale. KSSS= knee society scoring system. KOOS= knee injury and osteoarthritis outcome scale. CSI= central sensitization inventory, MK= medial knee, LK= lateral knee.

Supplementary Table S6: Differences between knee osteoarthritis participants with 'probable', 'possible', or 'no' nociplastic pain (categorical variables) at baseline and one-year postoperative (3 pain locations approach)

Variable		Probable nociplastic pain (n = 30)	Possible nociplastic pain (n = 36)	No nociplastic pain (n = 115)	P-value	Post-hoc
Categorical variables			**N (%)**			
Demographic variable						
Sex	Man	16 (34.78)	17 (47.22)	46 (40.00)	0.012*	Probable vs. no: 0.004*
	Woman	30 (65.22)	19 (52.78)	69 (60.00)		
Structural variable						
Grade of KOA	K&L 1	3 (6.52)	0 (0.00)	0 (0.00)	0.035	/
	K&L 2	14 (30.43)	5 (13.89)	23 (20.00)		
	K&L 3	13 (28.26)	15 (41.67)	42 (36.52)		
	K&L 4	16 (34.78)	16 (44.44)	50 (43.48)		
Social variables						
Education	No degree	3 (6.52)	1 (2.78)	7 (6.09)	0.794	/
	Primary school	2 (4.35)	2 (5.56)	7 (6.09)		
	Technical secondary school	13 (28.26)	6 (16.67)	27 (23.48)		
	Higher secondary school	5 (10.87)	7 (19.44)	13 (11.30)		
	High school	10 (21.74)	10 (27.78)	27 (23.48)		
	University	3 (6.52)	1 (2.78)	12 (10.43)		
	Other	10 (21.74)	9 (25.00)	22 (19.13)		
Work	Pension	16 (34.78)	16 (44.44)	43 (37.39)	0.051	/
	Self-employed	6 (13.04)	4 (11.11)	4 (3.48)		
	White-collar worker	9 (19.57)	4 (11.11)	13 (11.30)		
	Laborer	6 (13.04)	7 (19.44)	12 (10.43)		
	Unemployed	0 (0.00)	1 (2.78)	1 (0.01)		
	Other	9 (19.57)	4 (11.11)	12 (10.43)		
Marital status	Married	32 (69.57)	25 (69.44)	85 (73.91)	0.660	/
	Divorced	4 (8.70)	4 (11.11)	9 (7.83)		
	Single	3 (6.52)	1 (2.78)	4 (3.48)		
	Widow(er)	2 (4.35)	5 (13.89)	11 (9.57)		
	Other	5 (10.87)	1 (2.78)	6 (5.22)		

Table 5. *significant difference (p<0.017). All variables are adjusted for age and sex (except sex itself).
Abbreviations: K&L= Kellgren and Lawrence scale

Supplementary material Chapter 4

Table S1: Quality assessment PPT and PTT

Study	1	2	3	4	5	6	Overall RoB	LoE
Pressure thresholds								
Aranda-Villalobos et al., 2013 (37)	Low	Low	Low	Low	Low	Moderate	**Low**	1b
Arendt-Nielsen et al., 2018 (24)	Low	High	Low	Low	Low	Low	**High**	2b
Bjurström et al., 2022 (25)	Low	Low	Low	Moderate	N/A	Low	**Low**	2b
Feldreich et al., 2017 (26)	High	High	Moderate	Moderate	N/A	Low	**High**	2b
Graven-Nielsen et al., 2012 (44)	High	High	Low	Moderate	N/A	Moderate	**High**	2b
Izumi et al., 2017 (38)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Kadum et al., 2018 (28)	Low	High	Low	Moderate	Low	Low	**High**	2b
Kosek et al., 2000a (40)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Kosek et al., 2000b (39)	Moderate	High	Low	Moderate	N/A	Moderate	**High**	2b
Kosek et al., 2013 (29)	Low	Low	Low	Moderate	Low	Moderate	**Moderate**	1b
Kurien et al., 2018 (41)	Low	Moderate	Low	Low	N/A	Low	**Low**	1b
Larsen et al., 2021 (30)	Low	High	Low	Low	High	Low	**High**	2b
Lewis et al., 2018 (31)	Low	Low	Low	Moderate	N/A	Low	**Low**	1b
Martinez et al., 2007 (32)	High	High	Low	Moderate	N/A	Low	**High**	2b
Petersen et al., 2015 (42)	Moderate	Low	Low	Moderate	N/A	Low	**Moderate**	2b
Skou et al., 2016 (33)	Low	Moderate	Low	Low	Low	Low	**Low**	1b
Tschugg et al., 2016 (34)	High	High	Low	Moderate	N/A	Low	**High**	2b
Tschugg et al., 2017 (35)	High	High	Low	Moderate	N/A	Low	**High**	2b
Vaegter et al., 2017 (36)	Moderate	Moderate	Low	Low	N/A	Low	**Moderate**	1b
Wilder-Smith et al., 1996 (43)	High	High	Low	Moderate	N/A	Low	**High**	2b

Bias due to 1 = Study participation, 2 = Study attrition, 3 = Prognostic factor measurement, 4 = Outcome measurement, 5 = Study confounding, 6= Statistical analysis and reporting. Abbreviations: RoB, risk of bias; LoE, level of evidence; N/A, not applicable; PPT, pressure pain threshold; PTT, pain tolerance threshold

Table S2: Static QST – Pressure thresholds

SPS sign	MSK disorder	FU	Study	Change in SPS (local)	Change in SPS (widespread)	Level of recommendation
PPT (pressure or cuff)	Hip OA	<3m	Izumi et al., 2017 (38)	+ (pressure), / cuff	+ (pressure), / cuff	**Conflicting**
		≥3m	Aranda-Villalobos et al., 2013 (37)	+	+	**Conflicting**
			Bjurström et al., 2022 (25)	+	+	
			Kosek et al., 2000a (40)	+	+*	
			Kosek et al., 2000b (39)	+**	+**	
			Kosek et al., 2013 (29)	/	/	
	Knee OA	<3m	Graven-Nielsen et al., 2012 (44)	+	+	**Local = conflicting** **Widespread = moderate for positive change**
			Petersen et al., 2015 (42)	+	+***	
			Lewis et al., 2018 (31)	/		
		≥3m	Graven-Nielsen et al., 2012 (44)	+	+	**Conflicting**
			Skou et al., 2016 (33)	+	+	
			Arendt-Nielsen et al., 2018 (41)	+	+	
			Petersen et al., 2015 (42)	+	+***	
			Vaegter et al., 2017 (36)	+/-	+/-	
			Kurien et al., 2018 (41)	+, cuff /	/	
			Kosek et al., 2013 (29)	/	/	
			Larsen et al., 2021 (30)	/		
			Lewis et al., 2018 (31)	/		
	Closed lock TMJ	≥3m	Feldreich et al., 2017 (26)	/	/	**Weak for no change**
	Disc herniation	<3m	Wilder-Smith et al., 1996 (43)	-/	/	**Conflicting**
			Tschugg et al., 2016 (34)	+**	+**	
		≥3m	Tschugg et al., 2016 (34)	+**	+**	**Moderate for positive change**
			Tschugg et al., 2017 (35)	+**	+**	
PTT (pressure or cuff)	Hip OA	≥3m	Bjurström et al., 2022 (25)	+	+	**Moderate for positive change**
	Knee OA	<3m	Graven-Nielsen et al., 2012 (44)	/	/	**Weak for no change**
		≥3m	Graven-Nielsen et al., 2012 (44)	/	/	**Strong for no change**
			Kurien et al., 2018 (41)	/	/	
			Vaegter et al., 2017 (36)	/	/	
	Disc herniation	<3m	Wilder-Smith et al., 1996 (43)	-5d, + 4h, +6h		**Conflicting**

Abbreviations: QST, quantitative sensory testing; SPS, somatosensory processing system; MSK, musculoskeletal; PPT, pressure pain threshold; PTT, pressure pain tolerance threshold; OA, osteoarthritis; m, month; +, positive (means increase in PPT or PTT); -, negative (means decrease in PPT or PTT); /, no difference; +/-, some local or widespread locations, not all; empty cell, not measured; *= ipsilateral side, not contralateral side; **= location not specified; *** = except for low pain group

Table S3: Quality assessment thermal and other thresholds

Study	1	2	3	4	5	6	Overall RoB	LoE
Thermal thresholds								
Izumi et al., 2017 (38)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Kosek et al., 2000a (40)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Kosek et al., 2000b (39)	Moderate	High	Low	Moderate	N/A	Moderate	**High**	2b
Martinez et al., 2007 (32)	High	High	Low	Moderate	N/A	Low	**High**	2b
Tschugg et al., 2016 (34)	High	High	Low	Moderate	N/A	Low	**High**	2b
Tschugg et al., 2017 (35)	High	High	Low	Moderate	N/A	Low	**High**	2b
Other thresholds								
Izumi et al., 2017 (38)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Bjurström et al., 2022 (25)	Low	Low	Low	Moderate	N/A	Low	**Low**	2b
Feldreich et al., 2017 (26)	High	High	Moderate	Moderate	N/A	Low	**High**	2b
Kadum et al., 2018 (28)	Low	High	Low	Moderate	Low	Low	**High**	2b
Martinez et al., 2007 (32)	High	High	Low	Moderate	N/A	Low	**High**	2b
Tschugg et al., 2016 (34)	High	High	Low	Moderate	N/A	Low	**High**	2b
Tschugg et al., 2017 (35)	High	High	Low	Moderate	N/A	Low	**High**	2b
Wilder-Smith et al., 1996 (43)	High	High	Low	Moderate	N/A	Low	**High**	2b

Bias due to 1 = Study participation, 2 = Study attrition, 3 = Prognostic factor measurement, 4 = Outcome measurement, 5 = Study confounding, 6= Statistical analysis and reporting. Abbreviations: RoB, risk of bias; LoE, level of evidence; N/A, not applicable; CDT, cold detection threshold; WDT, warmth detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; EDT, electrical detection threshold; EPT, electrical pain threshold; VDT, vibration detection threshold

Table S4: Static QST – Thermal thresholds

SPS sign	MSK	FU	Study	Change in SPS (local)	Change in SPS (widespread)	Level of recommendation
CDT	Hip OA	<3m	Izumi et al., 2017 (38)	/		**Weak for no change**
		≥3m	Kosek et al., 2000a (40)	/	/	**Conflicting**
			Kosek et al., 2000b (39)	+**	+**	
	Disc herniation	<3m	Tschugg et al., 2016 (34)	/	/	**Weak for no change**
		≥3m	Tschugg et al., 2017 (35)	+**	+**	**Moderate for positive change**
			Tschugg et al., 2016 (34)	+**	+**	
WDT	Hip OA	<3m	Izumi et al., 2017 (38)	/		**Weak for no change**
		≥3m	Kosek et al., 2000a (40)	+*	+*	**Conflicting**
			Kosek et al., 2000b (39)	/	/	
	Disc herniation	<3m	Tschugg et al., 2016 (34)	/	/	**Weak for no change**
		≥3m	Tschugg et al., 2017 (35)	/	/	**Moderate for no change**
			Tschugg et al., 2016 (34)	/	/	
HPT	Hip OA	<3m	Izumi et al., 2017 (38)	/		**Weak for no change**
		≥3m	Kosek et al., 2000a (40)	/	/	**Moderate for no change**
			Kosek et al., 2000b (39)	/	/	
	Knee OA	<3m	Martinez et al., 2007 (32)	/	/	**Weak for no change**
		≥3m	Martinez et al., 2007 (32)	/	/	**Weak for no change**
	Disc herniation	<3m	Tschugg et al., 2016 (34)	/	/	**Weak for no change**
		≥3m	Tschugg et al., 2017 (35)	/	/	**Moderate for no change**
			Tschugg et al., 2016 (34)	/	/	
CPT	Hip OA	<3m	Izumi et al., 2017 (38)	/		**Weak for no change**
		≥3m	Kosek et al., 2000a (40)	/	/	**Moderate for no change**
			Kosek et al., 2000b (39)	/	/	
	Knee OA	<3m	Martinez et al., 2007 (32)	-	/	**Local = weak for negative change, widespread= weak for no change**
		≥3m	Martinez et al., 2007 (32)	/	/	**Weak for no change**
	Disc herniation	<3m	Tschugg et al., 2016 (34)	/	/	**Weak for no change**
		≥3m	Tschugg et al., 2017 (35)	/	/	**Moderate for no change**
			Tschugg et al., 2016 (34)	/	/	
Warm supra-threshold	Knee OA	<3m	Martinez et al., 2007 (32)	/	/	**Weak for no change**

Table S4 (continued)

SPS sign	MSK	FU	Study	Change in SPS (local)	Change in SPS (widespread)	Level of recommendation
Warm supra-threshold	Knee OA	≥3m	Martinez et al., 2007 (32)	/	/	**Weak for no change**
Cold supra-threshold	Knee OA	<3m	Martinez et al., 2007 (32)	/	/	**Weak for no change**
		≥3m	Martinez et al., 2007 (32)	/	/	**Weak for no change**

Abbreviations : QST, quantitative sensory testing; SPS, somatosensory processing system; MSK, musculoskeletal; ; OA, osteoarthritis; CDT, cold detection threshold; WDT, warmth detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; m, month; +, positive; -, negative; /, no difference; empty cell, not measured; *= ipsilateral side, not contralateral side; **= location not specified

Table S5: Static QST – Other thresholds

SPS sign	MSK disorder	FU	Study	Change in SPS (local)	Change in SPS (widespread)	Level of recommendation
Pinprick pain threshold	Hip OA	<3m	Izumi et al., 2017 (38)	/		**Weak for no change**
		≥3m	Bjurström et al., 2022 (25)	/	+	**Local = moderate for no change, Widespread = moderate for positive change**
	Knee OA	<3m	Martinez et al., 2007 (32)	-	-	**Weak for negative change**
		≥3m	Martinez et al., 2007 (32)	/	/	**Weak for no change**
	Disc herniation	<3m	Tschugg et al., 2016 (34)	/	/	**Weak for no change**
		≥3m	Tschugg et al., 2017 (35)	+**	+**	**Moderate for positive change**
			Tschugg et al., 2016 (34)	+**	+**	
EDT	Closed lock TMJ	≥3m	Feldreich et al., 2017 (26)	/	/	**Weak for no change**
EPT	Closed lock TMJ	≥3m	Feldreich et al., 2017 (26)	/	/	**Weak for no change**
	Shoulder OA	<3m	Kadum et al., 2018 (28)	~~/~~	/	**Weak for no change**
		≥3m	Kadum et al., 2018 (28)	~~/~~	/	**Weak for no change**
VDT	Disc herniation	<3m	Tschugg et al., 2016 (34)	+**	+**	**Weak for positive change**
		≥3m	Tschugg et al., 2017 (35)	+***(**)	+***(**)	**Conflicting**
			Tschugg et al., 2016 (34)	/	/	
Light-touch detection threshold	Hip OA	≥3m	Kosek et al., 2000a (40)	+	+*	**Moderate for positive change**
			Kosek et al., 2000b (39)	+**	+**	
	Disc herniation	<3m	Tschugg et al., 2016 (34)	+**	+**	**Conflicting**
			Wilder-Smith et al., 1996 (43)	/	/	
		≥3m	Tschugg et al., 2017 (35)	+**	+**	**Moderate for positive change**
			Tschugg et al., 2016 (34)	+**	+**	

Abbreviations : QST, quantitative sensory testing; SPS, somatosensory processing system; MSK, musculoskeletal; EDT, electrical detection threshold; EPT, electrical pain threshold; VDT, vibration detection threshold; OA, osteoarthritis; m, month; +, positive; -, negative; /, no difference; empty cell, not measured; *= ipsilateral side, not contralateral side; **= location not specified; ***, group without sensory loss

Table S6: Quality assessment dynamic QST and other SPS measurements

Study	1	2	3	4	5	6	Overall RoB	LoE
Temporal summation								
Izumi et al., 2017 (38)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Bjurström et al., 2022 (25)	Low	Low	Low	Moderate	N/A	Low	**Low**	2b
Lewis et al., 2018 (61)	Low	Low	Low	Moderate	N/A	Low	**Low**	1b
Kurien et al., 2018 (41)	Low	Moderate	Low	Low	N/A	Low	**Low**	1b
Spatial summation								
Izumi et al., 2017 (38)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Graven-Nielsen et al., 2012 (44)	High	High	Low	Moderate	N/A	Moderate	**High**	2b
CPM								
Izumi et al., 2017 (38)	Moderate	High	Low	Moderate	N/A	Low	**High**	2b
Bjurström et al., 2022 (25)	Low	Low	Low	Moderate	N/A	Low	**Low**	2b
Graven-Nielsen et al., 2012 (44)	High	High	Low	Moderate	N/A	Moderate	**High**	2b
Lewis et al., 2018 (61)	Low	Low	Low	Moderate	N/A	Low	**Low**	1b
Kurien et al., 2018 (41)	Low	Moderate	Low	Low	N/A	Low	**Low**	1b
Larsen et al., 2021 (30)	Low	High	Low	Low	High	Low	**High**	2b
Vaegter et al., 2017 (36)	Moderate	Moderate	Low	Low	N/A	Low	**Moderate**	1b
CSI								
Huysmans et al., 2021 (27)	Low	High	Low	Low	Low	Low	**High**	2b
EIA								
Kosek et al., 2013 (29)	Low	Low	Low	Moderate	Low	Moderate	**Moderate**	1b
Vaegter et al., 2017 (36)	Moderate	Moderate	Low	Low	N/A	Low	**Moderate**	1b
Dynamic pain								
Martinez et al., 2007 (32)	High	High	Low	Moderate	N/A	Low	**High**	2b

Bias due to 1 = Study participation, 2 = Study attrition, 3 = Prognostic factor measurement, 4 = Outcome measurement, 5 = Study confounding, 6= Statistical analysis and reporting. Abbreviations: RoB, risk of bias; LoE, level of evidence; N/A, not applicable; CPM, conditioned pain modulation; CSI, Central Sensitization Index; EIA, exercise induced analgesia

Table S7: Dynamic QST

SPS sign	MSK	FU	Study	Change in SPS	Level of recommendation
Temporal summation	Hip OA	<3m	Izumi et al., 2017 (38)	+	**Weak for positive change**
		≥3m	Bjurström et al., 2022 (25)	+	**Moderate for positive change**
	Knee OA	<3m	Lewis et al., 2018 (31)	+	**Moderate for positive change**
		≥3m	Kurien et al., 2018 (41)	+	**Strong for positive change**
			Lewis et al., 2018 (31)	+	
Spatial summation	Hip OA	<3m	Izumi et al., 2017 (38)	+	**Weak for positive change**
	Knee OA	<3m	Graven-Nielsen et al., 2012 (62)	+	**Weak for positive change**
		≥3m	Graven-Nielsen et al., 2012 (62)	+	**Weak for positive change**
CPM	Hip OA	<3m	Izumi et al., 2017 (38)	/	**Weak for no change**
		≥3m	Bjurström et al., 2022 (25)	/	**Moderate for no change**
	Knee OA	<3m	Graven-Nielsen et al., 2012 (62)	+	**Moderate for positive change**
			Lewis et al., 2018 (31)	+	
		≥3m	Graven-Nielsen et al., 2012 (62)	+	**Conflicting**
			Lewis et al., 2018 (31)	+	
			Kurien et al., 2018 (41)	/	
			Larsen et al., 2021 (30)	/	
			Vaegter et al., 2017 (36)	/	

Abbreviations: QST, quantitative sensory testing; SPS, somatosensory processing system; MSK, musculoskeletal; CPM, conditioned pain modulation; OA, osteoarthritis; m, month; +, positive; /, no difference

Table S8: Other SPS measurements

SPS sign	MSK	FU	Study	Change in SPS	Level of recommendation
CSI	Knee OA	<3m	Huysmans et al., 2021 (27)	+	**Weak for positive change**
		≥3m	Huysmans et al., 2021 (27)	+	**Weak for positive change**
EIA	Knee and Hip OA	≥3m	Kosek et al., 2013 (29)	+	**Knee: conflicting, hip weak for positive change**
	Knee OA	≥3m	Vaegter et al., 2017 (36)	/	**Weak for no change**
Dynamic pain	Knee OA	<3m	Martinez et al., 2007 (32)	/	**Weak for no change**
		≥3m	Martinez et al., 2007 (32)	/	**Weak for no change**

Abbreviations: SPS, somatosensory processing system; MSK, musculoskeletal; CSI, central sensitization index; EIA, exercise induced analgesia; OA, osteoarthritis; m, month; +, positive; /, no difference

Supplementary material Chapter 5

Table S1: missing value analysis

Variable	Number of participants	Mean	Standard Deviation	Missing (count)	Missing (percent)
Age	223	65,52	7,66	0	0
BMI BL	220	29,99	5,25	3	1,3
Hospital	223	/	/	0	0
OA-grade	214	/	/	9	4,0
sex	219	/	/	0	0
PPT m. Tibialis anterior BL	220	50,89	24,81	3	1,3
PPT m. Tibialis anterior FU2	173	55,22	28,42	50	22,4
PPT medial knee BL	220	42,83	23,71	3	1,3
PPT medial knee FU2	173	44,83	22,91	50	22,4
PPT lateral knee BL	220	48,06	26,58	3	1,3
PPT lateral knee FU2	173	51,42	26,34	50	22,4
PPT m. ECRL BL	220	37,55	17,24	3	1,3
PPT m. ECRL FU2	173	39,91	16,89	50	22,4
PPT forehead BL	185	30,18	12,73	38	17,0
PPT forehead FU2	164	31,87	11,09	59	26,5
TS medial knee BL	220	1,23	2,02	3	1,3
TS medial knee FU2	172	0,69	1,57	51	22,9
TS medial wrist BL	219	0,98	1,56	4	1,8
TS medial wrist FU2	172	0,65	1,17	51	22,9
Cold allodynia medial knee BL	219	0,36	0,96	4	1,8
Cold allodynia medial knee FU2	173	0,17	0,63	50	22,4
Heat allodynia medial knee BL	219	0,82	1,46	4	1,8
Heat allodynia medial knee FU2	173	0,55	1,14	50	22,4
Cold allodynia lateral knee BL	219	0,27	0,91	4	1,8
Cold allodynia lateral knee FU1	181	0,12	0,42	42	18,8
Cold allodynia lateral knee FU2	173	0,08	0,35	50	22,4
Heat allodynia lateral knee BL	219	0,37	1,09	4	1,8
Heat allodynia lateral knee FU2	173	0,19	0,63	50	22,4
Cold allodynia m. ECRL BL	219	0,19	0,76	4	1,8
Cold allodynia m. ECRL FU2	173	0,15	0,58	50	22,4
Heat allodynia m. ECRL BL	219	0,48	1,10	4	1,8
Heat allodynia m. ECRL FU2	173	0,39	0,91	50	22,4
CPM relative score BL	201	9,94	48,31	24	10,8
CPM relative score FU2	148	6,27	54,49	75	33,6
CSI BL	211	28,06	13,14	12	5,4
CSI FU2	168	23,40	13,81	55	24,7
KOOS subscale pain BL	211	44,07	15,31	12	5,4
KOOS subscale pain FU1	174	15,45	9,35	49	22,0
KOOS subscale pain FU2	168	73,45	24,15	55	24,7

Abbreviations: OA= osteoarthritis, BMI = body mass index, KOOS = Knee Osteoarthritis Outcome and Index Score, CSI= Central Sensitization Inventory, m. = musculus, ECRL = Extensor capri radialis longus, PPT = pressure pain threshold, TS = temporal summation, CPM = conditioned pain modulation, CRP= creatinine phosphate, BL= baseline, FU1= follow-up 1, FU2= follow-up 2

Supplementary Table S2: correlation coefficients between quantitative sensory testing variables at baseline

	PPT m. TA	PPT mk	PPT lk	PPT m. ECRL	PPT forehead	TS mk	TS mw	CPM	TH cold mk	TH heat mk	TH cold lk	TH heat lk	TH cold m. ECRL	TH heat m. ECRL
PPT m. TA	1	0,796	0,805	0,726	0,656	-0,35	-0,223	-0,066	-0,175	-0,189	-0,213	-0,237	-0,148	-0,091
PPT mk	0,796	1	0,764	0,652	0,597	-0,306	-0,171	-0,131	-0,239	-0,221	-0,209	-0,23	-0,152	-0,106
PPT lk	0,805	0,764	1	0,721	0,694	-0,313	-0,27	-0,017	-0,271	-0,276	-0,265	-0,299	-0,232	-0,169
PPT m. ECRL	0,726	0,652	0,721	1	0,728	-0,326	-0,291	-0,043	-0,205	-0,192	-0,254	-0,261	-0,214	-0,176
PPT forehead	0,656	0,597	0,694	0,728	1	-0,318	-0,287	-0,01	-0,277	-0,219	-0,311	-0,291	-0,293	-0,243
TS mk	-0,35	-0,306	-0,313	-0,326	-0,318	1	0,418	0,064	0,166	0,118	0,209	0,157	0,098	0,061
TS mw	-0,223	-0,171	-0,27	-0,291	-0,287	0,418	1	-0,017	0,103	0,119	0,188	0,15	0,12	0,074
CPM	-0,066	-0,131	-0,017	-0,043	-0,01	0,064	-0,017	1	-0,019	-0,066	-0,092	-0,051	-0,154	-0,156
TH cold mk	-0,175	-0,239	-0,271	-0,205	-0,277	0,166	0,103	-0,019	1	0,517	0,708	0,471	0,575	0,355
TH heat mk	-0,189	-0,221	-0,276	-0,192	-0,219	0,118	0,119	-0,066	0,517	1	0,395	0,702	0,391	0,66
TH cold lk	-0,213	-0,209	-0,265	-0,254	-0,311	0,209	0,188	-0,092	0,708	0,395	1	0,49	0,664	0,355
TH heat lk	-0,237	-0,23	-0,299	-0,261	-0,291	0,157	0,15	-0,051	0,471	0,702	0,49	1	0,411	0,623
TH cold m. ECRL	-0,148	-0,152	-0,232	-0,214	-0,293	0,098	0,12	-0,154	0,575	0,391	0,664	0,411	1	0,475
TH heat m. ECRL	-0,091	-0,106	-0,169	-0,176	-0,243	0,061	0,074	-0,156	0,355	0,66	0,355	0,623	0,475	1

Abbreviations: CPM = conditioned pain modulation, CSI = Central Sensitization Index, ECRL = m. Extensor Carpi Radialis Longus, lk = lateral knee, mk = medial knee, mw = medial wrist, m. = musculus, PPT = pressure pain threshold, TA = m. Tibialis Anterior, TH = thermal hypersensitivity, TS = temporal summation

Table S3: correlation coefficients between quantitative sensory testing variables at one-year postoperative

	PPT m. TA	PPT mk	PPT lk	PPT m. ECRL	PPT forehead	TS mk	TS mw	CPM	TH cold mk	TH heat mk	TH cold lk	TH heat lk	TH cold m. ECRL	TH heat m. ECRL
PPT m. TA	1	0,734	0,686	0,586	0,526	-0,144	-0,175	0,075	-0,037	-0,027	-0,025	-0,014	0,015	-0,012
PPT mk	0,734	1	0,711	0,647	0,655	-0,233	-0,21	0,022	-0,122	-0,166	-0,05	-0,156	-0,086	-0,082
PPT lk	0,686	0,711	1	0,496	0,586	-0,168	-0,167	0,034	-0,047	-0,04	0,007	-0,045	-0,043	-0,091
PPT m. ECRL	0,586	0,647	0,496	1	0,65	-0,173	-0,209	0,069	-0,144	-0,16	-0,108	-0,143	-0,149	-0,108
PPT forehead	0,526	0,655	0,586	0,65	1	-0,249	-0,223	0,04	-0,148	-0,222	-0,118	-0,13	-0,176	-0,203
TS mk	-0,144	-0,233	-0,168	-0,173	-0,249	1	0,501	-0,007	0,148	0,149	0,148	0,203	0,208	0,199
TS mw	-0,175	-0,21	-0,167	-0,209	-0,223	0,501	1	-0,1	0,374	0,268	0,195	0,261	0,265	0,363
CPM	0,075	0,022	0,034	0,069	0,04	-0,007	-0,1	1	-0,03	-0,01	0,003	-0,041	-0,021	-0,069
TH cold mk	-0,037	-0,122	-0,047	-0,144	-0,148	0,148	0,374	-0,03	1	0,655	0,61	0,594	0,659	0,602
TH heat mk	-0,027	-0,166	-0,04	-0,16	-0,222	0,149	0,268	-0,01	0,655	1	0,438	0,64	0,631	0,725
TH cold lk	-0,025	-0,05	0,007	-0,108	-0,118	0,148	0,195	0,003	0,61	0,438	1	0,336	0,576	0,327
TH heat lk	-0,014	-0,156	-0,045	-0,143	-0,13	0,203	0,261	-0,041	0,594	0,64	0,336	1	0,538	0,557
TH cold m. ECRL	0,015	-0,086	-0,043	-0,149	-0,176	0,208	0,265	-0,021	0,659	0,631	0,576	0,538	1	0,652
TH heat m. ECRL	-0,012	-0,082	-0,091	-0,108	-0,203	0,199	0,363	-0,069	0,602	0,725	0,327	0,557	0,652	1

Abbreviations: CPM = conditioned pain modulation, CSI = Central Sensitization Index, ECRL = m. Extensor Carpi Radialis Longus, lk = lateral knee, mk = medial knee, mw = medial wrist, m. = musculus, PPT = pressure pain threshold, TA = m. Tibialis Anterior, TH = thermal hypersensitivity, TS = temporal summation

Supplementary material Chapter 6

Table S1: correlation coefficients between predictors part 1

	Age	Education	BMI	**PPT m. TA**	**PPT mk**	**PPT lk**	**PPT m. ECRL**	**PPT forehead**	TS mk	TS mw	CPM	Strength m. Quadriceps	Strength m. Hamstrings	Proprio-ception	30s CST	Hb1Ac
Age	1	0,086	-0,144	0,095	0,025	0,033	0,031	0,118	-0,049	0,004	-0,068	-0,125	-0,071	0,145	-0,06	0,042
Education	0,086	1	0,018	-0,087	-0,127	-0,078	-0,011	-0,059	-0,021	0,015	-0,117	-0,013	-0,058	-0,192	0,13	0,116
BMI	-0,144	0,018	1	-0,108	-0,054	-0,055	0,06	-0,077	0,055	-0,053	0,093	0,111	0,113	-0,024	-0,2	0,161
PPT m. TA	0,095	-0,087	-0,108	1	**0,796**	**0,805**	**0,726**	0,656	-0,35	-0,223	-0,066	0,342	0,329	-0,033	0,208	-0,085
PPT mk	0,025	-0,127	-0,054	**0,796**	1	**0,764**	0,652	0,597	-0,306	-0,171	-0,131	0,343	0,316	-0,026	0,303	-0,146
PPT lk	0,033	-0,078	-0,055	**0,805**	**0,764**	1	**0,721**	0,694	-0,313	-0,27	-0,017	0,413	0,428	-0,017	0,23	-0,05
PPT m. ECRL	0,031	-0,011	0,06	**0,726**	0,652	**0,721**	1	**0,728**	-0,326	-0,291	-0,043	0,345	0,327	-0,028	0,147	-0,051
PPT forehead	0,118	-0,059	-0,077	0,656	0,597	0,694	**0,728**	1	-0,318	-0,287	-0,01	0,258	0,433	-0,098	0,222	0,072
TS mk	-0,049	-0,021	0,055	-0,35	-0,306	-0,313	-0,326	-0,318	1	0,418	0,064	-0,162	-0,215	0,045	-0,086	0,045
TS mw	0,004	0,015	-0,053	-0,223	-0,171	-0,27	-0,291	-0,287	0,418	1	-0,017	-0,203	-0,205	-0,032	-0,139	0,015
CPM	-0,068	-0,117	0,093	-0,066	-0,131	-0,017	-0,043	-0,01	0,064	-0,017	1	-0,048	-0,022	-0,05	-0,124	-0,004
Strength m. Quadriceps	-0,125	-0,013	0,111	0,342	0,343	0,413	0,345	0,258	-0,162	-0,203	-0,048	1	0,685	-0,029	0,461	0,009
Strength m. Hamstrings	-0,071	-0,058	0,113	0,329	0,316	0,428	0,327	0,433	-0,215	-0,205	-0,022	0,685	1	-0,109	0,371	-0,001
Proprioception	0,145	-0,192	-0,024	-0,033	-0,026	-0,017	-0,028	-0,098	0,045	-0,032	-0,05	-0,029	-0,109	1	-0,013	-0,033
30s CST	-0,06	0,13	-0,2	0,208	0,303	0,23	0,147	0,222	-0,086	-0,139	-0,124	0,461	0,371	-0,013	1	-0,018
Hb1Ac	0,042	0,116	0,161	-0,085	-0,146	-0,05	-0,051	0,072	0,045	0,015	-0,004	0,009	-0,001	-0,033	-0,018	1
Number of pain locations	-0,157	-0,065	0,08	-0,196	-0,196	-0,172	-0,181	-0,169	0,11	0,126	0,071	-0,189	-0,174	-0,047	-0,18	0,03
IPQR Identity	-0,079	0,066	0,147	-0,099	-0,152	-0,178	-0,103	-0,064	0,041	0,079	-0,094	-0,234	-0,128	-0,154	-0,037	0,031
IPQR timeline	-0,068	-0,008	-0,07	0,048	-0,004	0,019	-0,035	-0,051	0,118	0,052	-0,026	0,064	0,018	-0,078	-0,064	-0,106

Table S1 (continued)

	Age	Education	BMI	PPT m. TA	PPT mk	PPT lk	PPT m. ECRL	PPT forehead	TS mk	TS mw	CPM	Strength m. Quadriceps	Strength m. Hamstrings	Proprio-ception	30s CST	Hb1Ac
IPQR consequences	-0,175	-0,105	0,109	-0,002	-0,05	-0,004	0,058	0,003	0,02	0,048	-0,083	0,014	-0,064	-0,051	-0,143	-0,068
IPQR personal control	-0,071	-0,016	0,046	0,075	0,111	0,036	0,043	0,024	-0,131	-0,026	-0,136	0,161	0,088	0,069	0,134	-0,025
IPQR treatment control	0,037	-0,032	-0,137	0,038	0,042	-0,01	-0,028	0,006	-0,099	0,044	-0,105	0,034	0,057	0,165	0,108	-0,05
IPQR illness coherence	-0,077	-0,015	-0,058	-0,07	-0,095	-0,02	-0,132	-0,068	0,035	0,071	-0,118	0,091	0,081	0,011	0,176	-0,023
IPQ timeline cyclical	0,049	-0,054	-0,048	0,033	0,059	-0,01	0,013	-0,04	-0,059	-0,128	-0,074	-0,007	-0,061	0,107	0,001	-0,063
IPQR emotional representations	-0,179	-0,049	0,259	-0,121	-0,154	-0,149	0,029	-0,053	0,104	0,075	0,017	-0,135	-0,145	-0,098	-0,196	0,021
PCS	-0,136	-0,187	0,199	-0,092	-0,098	-0,083	-0,05	-0,079	0,116	0,127	0,061	-0,069	-0,143	0,002	-0,128	0,101
HADS anxiety	-0,097	-0,135	0,075	-0,208	-0,141	-0,163	-0,101	-0,096	0,096	0,119	0,042	-0,16	-0,181	0,005	-0,223	0,023
HADS depression	-0,095	-0,13	0,113	-0,028	-0,017	0,047	0,062	0,046	0,059	0,035	-0,037	-0,006	-0,087	-0,037	-0,233	0,047
KSSS symptoms	0,256	0,056	-0,093	0,06	0,023	0,039	0,047	-0,045	-0,043	-0,01	-0,144	0,083	0,02	0,047	0,11	0,073
KSSS satisfaction	0,202	-0,039	-0,162	0,175	0,139	0,193	0,149	0,082	-0,085	-0,024	-0,022	0,18	0,156	0,097	0,099	-0,019
KSSS functional score	0,072	0,022	-0,218	0,159	0,197	0,236	0,164	0,145	-0,173	-0,106	-0,013	0,249	0,237	0,115	0,28	-0,078
KOOS symptoms	0,248	0,077	0,047	0,027	0,003	0,044	0,086	0,041	-0,096	-0,126	0,019	0,071	0,137	0,149	0,067	0,037
CSI	-0,195	0,015	0,122	-0,222	-0,259	-0,176	-0,227	-0,195	0,182	0,136	-0,055	-0,208	-0,197	-0,07	-0,21	0,182
KOOS subscale pain	0,202	0,029	-0,093	0,134	0,172	0,175	0,211	0,13	-0,098	-0,082	0,011	0,201	0,167	0,086	0,138	-0,019
K-L scale	0,056	-0,024	-0,002	0,141	0,197	0,191	0,158	0,106	-0,092	0,063	-0,027	0,189	0,152	-0,09	0,173	-0,052

Table S1 (continued)

	Age	Education	BMI	PPT m. TA	PPT mk	PPT lk	PPT m. ECRL	PPT forehead	TS mk	TS mw	CPM	Strength m. Quadriceps	Strength m. Hamstrings	Proprio-ception	30s CST	Hb1Ac
Marital status	-0,058	-0,066	-0,029	-0,089	-0,054	-0,042	-0,124	-0,124	0,11	0,075	0,055	-0,073	-0,115	0,064	-0,005	-0,035
Work	-0,662	0,018	0,213	-0,107	-0,086	-0,082	-0,052	-0,146	0,011	0,002	0,023	0,103	0,039	-0,091	-0,01	-0,072
TS after sens mk	-0,114	0,032	-0,003	-0,24	-0,224	-0,269	-0,224	-0,207	0,356	0,141	-0,046	-0,211	-0,274	0,032	-0,109	0,014
TS after sens mw	-0,149	-0,02	-0,106	-0,058	-0,03	-0,134	-0,129	-0,127	0,148	0,26	-0,052	-0,077	-0,17	0,03	-0,055	-0,109
TH cold mk	-0,139	-0,048	-0,053	-0,175	-0,239	-0,271	-0,205	-0,277	0,166	0,103	-0,019	-0,148	-0,234	0,033	-0,123	-0,01
TH heat mk	-0,014	-0,033	-0,022	-0,189	-0,221	-0,276	-0,192	-0,219	0,118	0,119	-0,066	-0,091	-0,178	-0,049	-0,042	0,023
TH cold lk	-0,143	-0,07	0,004	-0,213	-0,209	-0,265	-0,254	-0,311	0,209	0,188	-0,092	-0,133	-0,186	-0,014	-0,115	-0,042
TH heat lk	-0,057	-0,1	0,033	-0,237	-0,23	-0,299	-0,261	-0,291	0,157	0,15	-0,051	-0,06	-0,217	-0,098	-0,102	-0,012
TH cold m. ECRL	-0,088	-0,009	-0,092	-0,148	-0,152	-0,232	-0,214	-0,293	0,098	0,12	-0,154	-0,048	-0,125	0	-0,069	-0,087
TH heat m. ECRL	0,036	-0,06	-0,093	-0,091	-0,106	-0,169	-0,176	-0,243	0,061	0,074	-0,156	-0,031	-0,18	0,019	-0,004	-0,017
KSSS expectations	0,032	-0,07	0,051	0,001	-0,015	0,004	-0,031	-0,113	-0,054	-0,005	0,008	0,044	0,008	0,128	0,064	-0,065
Sex	0,042	-0,16	-0,041	0,384	0,271	0,353	0,311	0,248	-0,259	-0,111	-0,069	0,556	0,443	0,011	0,147	-0,079

Abbreviations: 30CST = 30 seconds chair stand test, BMI = body mass index, CPM = conditioned pain modulation, CSI = Central Sensitization Index, ECRL = m. Extensor Carpi Radialis Longus, HADS = Hospital Anxiety and Depression Scale, Hb1Ac = glycated hemoglobin, IPQR = illness perceptions questionnaire revised, KSSS = Knee Society Scoring System, KOOS = Knee Injury and Osteoarthritis Outcome Score, lk = lateral knee, mk = medial knee, mw = medial wrist, m. = musculus, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold, TA = m. Tibialis Anterior, TH = thermal hypersensitivity, TS = temporal summation

Table S2: correlation coefficients between predictors part 2

	Number of pain locations	IPQR Identity	IPQR timeline	IPQR consequences	IPQR personal control	IPQR treatment control	IPQR illness coherence	IPQ timeline cyclical	IPQR emotional representations	PCS	HADS anxiety	HADS depression	KSSS symptoms	KSSS satisfaction	KSSS functional score
Age	-0,157	-0,079	-0,068	-0,175	-0,071	0,037	-0,077	0,049	-0,179	-0,136	-0,097	-0,095	0,256	0,202	0,072
Education	-0,065	0,066	-0,008	-0,105	-0,016	-0,032	-0,015	-0,054	-0,049	-0,187	-0,135	-0,13	0,056	-0,039	0,022
BMI	0,08	0,147	-0,07	0,109	0,046	-0,137	-0,058	-0,048	0,259	0,199	0,075	0,113	-0,093	-0,162	-0,218
PPT m. TA	-0,196	-0,099	0,048	-0,002	0,075	0,038	-0,07	0,033	-0,121	-0,092	-0,208	-0,028	0,06	0,175	0,159
PPT mk	-0,196	-0,152	-0,004	-0,05	0,111	0,042	-0,095	0,059	-0,154	-0,098	-0,141	-0,017	0,023	0,139	0,197
PPT lk	-0,172	-0,178	0,019	-0,004	0,036	-0,01	-0,02	-0,01	-0,149	-0,083	-0,163	0,047	0,039	0,193	0,236
PPT m. ECRL	-0,181	-0,103	-0,035	0,058	0,043	-0,028	-0,132	0,013	0,029	-0,05	-0,101	0,062	0,047	0,149	0,164
PPT forehead	-0,169	-0,064	-0,051	0,003	0,024	0,006	-0,068	-0,04	-0,053	-0,079	-0,096	0,046	-0,045	0,082	0,145
TS mk	0,11	0,041	0,118	0,02	-0,131	-0,099	0,035	-0,059	0,104	0,116	0,096	0,059	-0,043	-0,085	-0,173
TS mw	0,126	0,079	0,052	0,048	-0,026	0,044	0,071	-0,128	0,075	0,127	0,119	0,035	-0,01	-0,024	-0,106
CPM	0,071	-0,094	-0,026	-0,083	-0,136	-0,105	-0,118	-0,074	0,017	0,061	0,042	-0,037	-0,144	-0,022	-0,013
Strength m. Quadriceps	-0,189	-0,234	0,064	0,014	0,161	0,034	0,091	-0,007	-0,135	-0,069	-0,16	-0,006	0,083	0,18	0,249
Strength m. Hamstrings	-0,174	-0,128	0,018	-0,064	0,088	0,057	0,081	-0,061	-0,145	-0,143	-0,181	-0,087	0,02	0,156	0,237
Proprioception	-0,047	-0,154	-0,078	-0,051	0,069	0,165	0,011	0,107	-0,098	0,002	0,005	-0,037	0,047	0,097	0,115
30s CST	-0,18	-0,037	-0,064	-0,143	0,134	0,108	0,176	0,001	-0,196	-0,128	-0,223	-0,233	0,11	0,099	0,28
Hb1Ac	0,03	0,031	-0,106	-0,068	-0,025	-0,05	-0,023	-0,063	0,021	0,101	0,023	0,047	0,073	-0,019	-0,078
Number of pain locations	1	0,041	0,081	0,031	0,016	-0,064	0,004	0,07	0,242	0,241	0,322	0,245	-0,101	-0,215	-0,185
IPQR Identity	0,041	1	0,02	0,25	0,075	-0,112	0,023	-0,044	0,274	0,145	0,162	0,127	-0,211	-0,265	-0,17
IPQR timeline	0,081	0,02	1	-0,14	-0,321	-0,009	0,005	0,136	0,115	0,133	0,144	-0,039	0,032	-0,03	-0,14

Table S2 (continued)

	Number of pain locations	IPQR Identity	IPQR timeline	IPQR consequences	IPQR personal control	IPQR treatment control	IPQR illness coherence	IPQ timeline cyclical	IPQR emotional representations	PCS	HADS anxiety	HADS depression	KSSS symptoms	KSSS satisfaction	KSSS functional score
IPQR consequences	0,031	0,25	0,229	1	-0,036	-0,16	-0,045	-0,047	0,481	0,28	0,231	0,324	-0,255	-0,256	-0,323
IPQR personal control	0,016	0,075	-0,14	-0,036	1	0,306	0,106	0,241	0,006	0,018	0,052	-0,027	0,06	0,065	0,192
IPQR treatment control	-0,064	-0,112	-0,321	-0,16	0,306	1	0,154	0,052	-0,23	-0,141	-0,058	-0,186	0,092	0,09	0,27
IPQR illness coherence	0,004	0,023	-0,009	-0,045	0,106	0,154	1	-0,204	-0,147	-0,139	-0,154	-0,131	0,032	0,045	0,057
IPQ timeline cyclical	0,07	-0,044	0,005	-0,047	0,241	0,052	-0,204	1	0,097	0,071	0,188	0,157	0,152	0,087	0,079
IPQR emotional representations	0,242	0,274	0,136	0,481	0,006	-0,23	-0,147	0,097	1	0,527	0,612	0,456	-0,217	-0,263	-0,309
PCS	0,241	0,145	0,115	0,28	0,018	-0,141	-0,139	0,071	0,527	1	0,555	0,479	-0,2	-0,174	-0,281
HADS anxiety	0,322	0,162	0,133	0,231	0,052	-0,058	-0,154	0,188	0,612	0,555	1	0,61	-0,142	-0,147	-0,136
HADS depression	0,245	0,127	0,144	0,324	-0,027	-0,186	-0,131	0,157	0,456	0,479	0,61	1	-0,133	-0,127	-0,236
KSSS symptoms	-0,101	-0,211	-0,039	-0,255	0,06	0,092	0,032	0,152	-0,217	-0,2	-0,142	-0,133	1	0,605	0,444
KSSS satisfaction	-0,215	-0,265	0,032	-0,256	0,065	0,09	0,045	0,087	-0,263	-0,174	-0,147	-0,127	0,605	1	0,55
KSSS functional score	-0,185	-0,17	-0,03	-0,323	0,192	0,27	0,057	0,079	-0,309	-0,281	-0,136	-0,236	0,444	0,55	1
KOOS symptoms	-0,099	-0,173	-0,132	-0,121	0,018	-0,002	0,027	-0,019	-0,138	-0,046	-0,077	-0,054	0,232	0,205	0,189
CSI	0,459	0,318	0,15	0,234	0,066	-0,164	-0,039	0,065	0,456	0,411	0,588	0,489	-0,186	-0,277	-0,296
KOOS subscale pain	-0,202	-0,178	-0,072	-0,255	0,18	0,158	0,06	0,096	-0,231	-0,246	-0,1	-0,132	0,535	0,692	0,66
K-L scale	-0,028	-0,127	0,008	-0,087	-0,041	0,032	-0,163	0,027	-0,014	-0,135	-0,093	-0,136	-0,052	0,063	0,169
Marital status	0,009	-0,024	-0,089	0,025	-0,06	0,035	0,022	0,103	-0,1	-0,029	0,031	0,043	0,026	-0,034	0,019

Table S2 (continued)

	Number of pain locations	IPQR Identity	IPQR timeline	IPQR consequences	IPQR personal control	IPQR treatment control	IPQR illness coherence	IPQ timeline cyclical	IPQR emotional representations	PCS	HADS anxiety	HADS depression	KSSS symptoms	KSSS satisfaction	KSSS functional score
Work	0,18	0,115	-0,066	0,041	0,159	0,021	-0,077	0,008	-0,19	0,145	0,057	-0,022	0,043	-0,212	-0,151
TS after sens mk	0,158	0,108	0,078	0,163	0,094	0,025	0,065	-0,006	-0,009	0,048	0,012	0,096	-0,002	-0,121	-0,106
TS after sens mw	0,042	-0,021	0,079	0,017	0,025	0,057	0,104	-0,078	0,047	0,006	0,008	-0,005	-0,164	0,02	0,075
TH cold mk	0,181	0,064	0,077	0,075	0,108	0,047	0,066	0,082	0,105	0,141	0,174	0,169	0,079	-0,098	-0,132
TH heat mk	0,083	0,104	0,084	0,071	0,152	0,072	0,019	0,08	-0,042	0,114	0,14	0,14	0,138	0,009	-0,108
TH cold lk	0,133	0,084	0,016	0,044	0,093	-0,009	0,034	0,082	0,047	0,053	0,161	0,093	0,083	-0,072	-0,142
TH heat lk	0,108	0,047	0,063	0,064	0,192	0,015	-0,059	0	-0,019	0,196	0,204	0,154	0,115	0,019	-0,102
TH cold m. ECRL	0,118	0,024	0,084	0,046	0,109	-0,014	0,019	0,04	0,079	0,068	0,082	0,098	0,045	0,031	-0,085
TH heat m. ECRL	0,042	0,017	0,082	0,023	0,09	-0,01	-0,012	0,063	0,005	0,045	0,042	0,049	0,106	0,023	-0,072
KSSS expectations	-0,085	-0,127	-0,258	-0,031	0,029	-0,009	0,147	0,07	-0,153	-0,037	-0,004	-0,127	-0,121	0,046	0,043
Sex	-0,16	-0,115	0,019	-0,162	0,084	0,049	0,074	0,114	-0,052	-0,102	-0,031	-0,211	-0,008	0,074	0,056

Abbreviations: 30CST = 30 seconds chair stand test, BMI = body mass index, CPM = conditioned pain modulation, CSI = Central Sensitization Index, ECRL = m. Extensor Carpi Radialis Longus, HADS = Hospital Anxiety and Depression Scale, Hb1Ac = glycated hemoglobin, IPQR = illness perceptions questionnaire revised, KSSS = Knee Society Scoring System, KOOS = Knee Injury and Osteoarthritis Outcome Score, lk = lateral knee, mk = medial knee, mw = medial wrist, m. = musculus, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold, TA = m. Tibialis Anterior, TH = thermal hypersensitivity, TS = temporal summation

Table S3: correlation coefficients between predictors part 3

	KOOS symptoms	CSI	KOOS subscale pain	K-L scale	Marital status	Work	TS after sens mk	TS after sens mw	**TH cold mk**	**TH heat mk**	**TH cold lk**	**TH heat lk**	TH cold m. ECRL	TH heat m. ECRL	KSSS expectations	Sex
Age	0,248	-0,195	0,202	0,056	-0,058	-0,662	-0,114	-0,149	-0,139	-0,014	-0,143	-0,057	-0,088	0,036	0,032	0,042
Education	0,077	0,015	0,029	-0,024	-0,066	0,018	0,032	-0,02	-0,048	-0,033	-0,07	-0,1	-0,009	-0,06	-0,07	-0,16
BMI	0,047	0,122	-0,093	-0,002	-0,029	0,213	-0,003	-0,106	-0,053	-0,022	0,004	0,033	-0,092	-0,093	0,051	-0,041
PPT m. TA	0,027	-0,222	0,134	0,141	-0,089	-0,107	-0,24	-0,058	-0,175	-0,189	-0,213	-0,237	-0,148	-0,091	0,001	0,384
PPT mk	0,003	-0,259	0,172	0,197	-0,054	-0,086	-0,224	-0,03	-0,239	-0,221	-0,209	-0,23	-0,152	-0,106	-0,015	0,271
PPT lk	0,044	-0,176	0,175	0,191	-0,042	-0,082	-0,269	-0,134	-0,271	-0,276	-0,265	-0,299	-0,232	-0,169	0,004	0,353
PPT m. ECRL	0,086	-0,227	0,211	0,158	-0,124	-0,052	-0,224	-0,129	-0,205	-0,192	-0,254	-0,261	-0,214	-0,176	-0,031	0,311
PPT forehead	0,041	-0,195	0,13	0,106	-0,124	-0,146	-0,207	-0,127	-0,277	-0,219	-0,311	-0,291	-0,293	-0,243	-0,113	0,248
TS mk	-0,096	0,182	-0,098	-0,092	0,11	0,011	0,356	0,148	0,166	0,118	0,209	0,157	0,098	0,061	-0,054	-0,259
TS mw	-0,126	0,136	-0,082	0,063	0,075	0,002	0,141	0,26	0,103	0,119	0,188	0,15	0,12	0,074	-0,005	-0,111
CPM	0,019	-0,055	0,011	-0,027	0,055	0,023	-0,046	-0,052	-0,019	-0,066	-0,092	-0,051	-0,154	-0,156	0,008	-0,069
Strength m. Quadriceps	0,071	-0,208	0,201	0,189	-0,073	0,103	-0,211	-0,077	-0,148	-0,091	-0,133	-0,06	-0,048	-0,031	0,044	0,556
Strength m. Hamstrings	0,137	-0,197	0,167	0,152	-0,115	0,039	-0,274	-0,17	-0,234	-0,178	-0,186	-0,217	-0,125	-0,18	0,008	0,443
Proprioception	0,149	-0,07	0,086	-0,09	0,064	-0,091	0,032	0,03	0,033	-0,049	-0,014	-0,098	0	0,019	0,128	0,011
30s CST	0,067	-0,21	0,138	0,173	-0,005	-0,010	-0,109	-0,055	-0,123	-0,042	-0,115	-0,102	-0,069	-0,004	0,064	0,147
Hb1Ac	0,037	0,182	-0,019	-0,052	-0,035	-0,072	0,014	-0,109	-0,01	0,023	-0,042	-0,012	-0,087	-0,017	-0,065	-0,079
Number of pain locations	-0,099	0,459	-0,202	-0,028	0,009	0,180	0,158	0,042	0,181	0,083	0,133	0,108	0,118	0,042	-0,085	-0,16
IPQR Identity	-0,192	0,113	-0,508	-0,087	0,025	0,041	0,163	0,017	0,075	0,071	0,044	0,064	0,046	0,023	-0,031	-0.162
IPQR timeline	-0,132	0,15	-0,072	0,008	-0,089	-0,066	0,078	0,079	0,077	0,084	0,016	0,063	0,084	0,082	-0,258	0,019
IPQR consequences	-0,121	0,234	-0,255	-0,041	-0,06	0,159	0,094	0,025	0,108	0,152	0,093	0,192	0,109	0,09	0,029	0,084
IPQR personal control	0,018	0,066	0,18	0,032	0,035	0,021	0,025	0,057	0,047	0,072	-0,009	0,015	-0,014	-0,01	-0,009	0,049
IPQR treatment control	-0,002	-0,164	0,158	-0,163	0,022	-0,077	0,065	0,104	0,066	0,019	0,034	-0,059	0,019	-0,012	0,147	0,074
IPQR illness coherence	0,027	-0,039	0,06	0,027	0,103	0,008	-0,006	-0,078	0,082	0,08	0,082	0	0,04	0,063	0,07	0,114

Table S3 (continued)

	KOOS symptoms	CSI	KOOS subscale pain	K-L scale	Marital status	Work	TS after sens mk	TS after sens mw	**TH cold mk**	**TH heat mk**	**TH cold lk**	**TH heat lk**	TH cold m. ECRL	TH heat m. ECRL	KSSS expectations	Sex
IPQ timeline cyclical	-0,019	0,065	0,096	-0,014	-0,1	-0,19	-0,009	0,047	0,105	-0,042	0,047	-0,019	0,079	0,005	-0,153	-0,052
IPQR emotional representations	-0,138	0,456	-0,231	-0,135	-0,029	0,145	0,048	0,006	0,141	0,114	0,053	0,196	0,068	0,045	-0,037	-0,102
PCS	-0,046	0,411	-0,246	-0,093	0,031	0,057	0,012	0,008	0,174	0,14	0,161	0,204	0,082	0,042	-0,004	-0,031
HADS anxiety	-0,077	0,588	-0,1	-0,136	0,043	-0,022	0,096	-0,005	0,169	0,14	0,093	0,154	0,098	0,049	-0,127	-0,211
HADS depression	-0,054	0,489	-0,132	-0,052	0,026	0,043	-0,002	-0,164	0,079	0,138	0,083	0,115	0,045	0,106	-0,121	-0,008
KSSS symptoms	0,232	-0,186	0,535	0,063	-0,034	-0,212	-0,121	0,02	-0,098	0,009	-0,072	0,019	0,031	0,023	0,046	0,074
KSSS satisfaction	0,205	-0,277	0,692	0,169	0,019	-0,151	-0,106	0,075	-0,132	-0,108	-0,142	-0,102	-0,085	-0,072	0,043	0,056
KSSS functional score	0,189	-0,296	0,66	0,149	-0,082	-0,089	-0,025	0,13	-0,093	-0,1	-0,147	-0,115	-0,024	-0,032	0,024	0,191
KOOS symptoms	1	-0,138	0,261	0,172	-0,056	-0,127	-0,086	-0,083	-0,083	-0,001	-0,076	-0,073	-0,051	-0,024	0,008	0,136
CSI	-0,138	1	-0,234	-0,199	0,067	0,132	0,097	-0,022	0,1	0,124	0,071	0,174	0,103	0,092	-0,141	-0,27
KOOS subscale pain	0,261	-0,234	1	0,157	0,067	-0,212	-0,079	0,052	-0,152	-0,081	-0,23	-0,143	-0,092	-0,068	0,021	0,077
K-L scale	0,172	-0,199	0,157	1	-0,065	0,078	-0,106	0,02	-0,078	-0,103	-0,019	-0,104	-0,056	-0,072	0,031	0,174
Marital status	-0,056	0,067	0,067	-0,065	1	0,064	0,147	0,063	0,091	0,008	0,093	0,107	0,042	0,049	-0,005	-0,105
Work	-0,127	0,132	-0,212	0,078	0,064	1	0,089	0,058	0,125	-0,001	0,178	0,03	0,029	-0,097	0,032	-0,035
TS after sens mk	-0,086	0,097	-0,079	-0,106	0,147	0,089	1	0,384	0,366	0,204	0,254	0,188	0,155	0,149	0,021	-0,191
TS after sens mw	-0,083	-0,022	0,052	0,02	0,063	0,058	0,384	1	0,179	0,12	0,138	0,19	0,256	0,146	-0,01	-0,097
TH cold mk	-0,083	0,1	-0,152	-0,078	0,091	0,125	0,366	0,179	1	0,517	**0,708**	0,471	0,575	0,355	-0,097	-0,01
TH heat mk	-0,001	0,124	-0,081	-0,103	0,008	-0,001	0,204	0,12	0,517	1	0,395	**0,702**	0,391	0,66	-0,122	0,066
TH cold lk	-0,076	0,071	-0,23	-0,019	0,093	0,178	0,254	0,138	**0,708**	0,395	1	0,49	0,664	0,355	-0,038	-0,041

Table S3 (continued)

	KOOS symptoms	CSI	KOOS subscale pain	K-L scale	Marital status	Work	TS after sens mk	TS after sens mw	**TH cold mk**	**TH heat mk**	**TH cold lk**	**TH heat lk**	TH cold m. ECRL	TH heat m. ECRL	KSSS expectations	Sex
TH heat lk	-0,073	0,174	-0,143	-0,104	0,107	0,03	0,188	0,19	0,471	**0,702**	0,49	1	0,411	0,623	-0,041	0,053
TH cold m. ECRL	-0,051	0,103	-0,092	-0,056	0,042	0,029	0,155	0,256	0,575	0,391	0,664	0,411	1	0,475	-0,08	-0,005
TH heat m. ECRL	-0,024	0,092	-0,068	-0,072	0,049	-0,097	0,149	0,146	0,355	0,66	0,355	0,623	0,475	1	-0,125	0,075
KSSS expectations	0,008	-0,141	0,021	0,031	-0,005	0,032	0,021	-0,01	-0,097	-0,122	-0,038	-0,041	-0,08	-0,125	1	0,128
Sex	0,136	-0,27	0,077	0,174	-0,105	-0,035	-0,191	-0,097	-0,01	0,066	-0,041	0,053	-0,005	0,075	0,128	1

Abbreviations: 30CST = 30 seconds chair stand test, BMI = body mass index, CPM = conditioned pain modulation, CSI = Central Sensitization Index, ECRL = m. Extensor Carpi Radialis Longus, HADS = Hospital Anxiety and Depression Scale, Hb1Ac = glycated hemoglobin, IPQR = illness perceptions questionnaire revised, KSSS = Knee Society Scoring System, KOOS = Knee Injury and Osteoarthritis Outcome Score, lk = lateral knee, mk = medial knee, mw = medial wrist, m. = musculus, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold, TA = m. Tibialis Anterior, TH = thermal hypersensitivity, TS = temporal summation

Supplementary material Chapter 7

Supplementary digital material 1: Osteoarthritis related key-terms

All Dutch & English Key-terms: artrose, arthrose, arthrosis, 341ensitizatio, coxarthrosis, coxartrose, coxartrosis, degeneratie, discogeen, discogene, facetartrose, facetarthrose, facetartrosis, failed back, FBSS, foramen vernauwing, foramen, gonarthrose, gonarthrosis, heupprothese, kanaalstenose, knieprothese, modic, omoartrose, 341ensitiza, recessus vernauwing, slijtage, total hip prosthesis, total knee 341ensitizatio, total knee prosthesis, tussenwervelschijf versmalling

Supplementary digital material 2: Supplementary Table I: Possible predictors found in the expert-brainstorm session, literature review and Dutch Dataset Pain Rehabilitation

Brainstorm experts in the field	Literature review	Dutch Dataset Pain Rehabilitation (compulsory and optional part)
• Depression • To take responsibility for the treatment • Level of limitation • Avoidance • Pain intensity • Pain duration • Pain experience • Absence of work • Motivation • Communication with treatment team • Openness and hostility • To be motivated to participate in the treatment • Having confidence in the treatment team to make decisions about the rehabilitation procedure	• Emotional factors • Cognitive and behaviour factors • Self-reported physical function/physical limitations • Number of pain locations • Pain intensity • Pain duration • Age • Work level • Educational level	• General amnestic questionnaire (age, sex, body mass index, other chronic diseases, alcohol, smoking, drugs, use of medication, living situation, having children, highest education level) • Pain location • Pain duration • Pain intensity (mean) • Pain intensity (peak) • Level of cognitive problems • Work status • Working capacity • Receiving payment benefits • Help request • Adverse effects • Physical activity • Influence of pain on mood • Help needed for daily activities • Adjustments at home • Use of help devices • Experienced drastic events • Activities during a normal day • Pain Catastrophizing Scale • Hospital Anxiety and Depression Scale • Douleur Neuropathique-questionnaire • Pain Disability Index • Short-form 12 physical component • Short-form 12 mental component • Psychological stress • Sleep problems (Checklist individual strength) • Global perceived effect • Psychological inflexibility pain scale • Pain self-efficacy questionnaire • llness perceptions questionnaire-short version • Fear avoidance beliefs questionnaire

Abbreviations: PDI= pain disability index, HADS= hospital anxiety and depression scale, PCS= pain catastrophizing scale, PIPS= psychological inflexibility pain scale, SF12= short-form 12, PSEQ= pain self-efficacy questionnaire, CIS= Checklist individual strength, IPQK= illness perceptions questionnaire-short version

Supplementary digital material 3: Supplementary Table II: Potential predictor variables included in model development + references

Potential predictor (all measured at baseline)	Measurement method
Age	-General questionnaire DDPR
Sex	-General questionnaire DDPR -1= male, 2= female
Number of pain locations	-A list with 10 body regions -Scored from 1 to maximum 10 body regions
Body Mass Index (kg/m^2)	-Calculated with body weight and height assessed by physiotherapist
Disability/physical function	-Total score PDI (1) -0 (no limitations) to 10 (completely limited)
Pain duration	-General questionnaire DDPR -Time since symptoms started: 0= 0-2 years ago, 1= 2-5 years ago, 2= more than 5 years ago
Pain severity (average)	-Average pain during the last week- general questionnaire DDPR -Numeric rating scale -0 (no pain) to 10 (worst imaginable pain)
Pain severity (worst)	-Worst pain during the last week- general questionnaire DDPR -Numeric rating scale -0 (no pain) to 10 (worst imaginable pain)
Use of pain medication	-General questionnaire DDPR, -0= no, 1= yes
Highest education level	-General questionnaire DDPR -1= low (no education, primary school or pre-vocational secondary education), 2= medium (secondary vocational or senior general secondary education, or higher professional education or university not completed), 3= high (higher professional education, university or postdoctoral education)
Self-rated work capacity	-Numeric rating scale -0=not able to work at all, 10= able to work as in my best period
Alcohol use	-General questionnaire DDPR -0= no, 1= yes
Smoking	-General questionnaire DDPR -0= no, 1= yes
Drugs (not medication)	-General questionnaire DDPR -0= no, 1= yes
Fatigue	-Measures subjective tiredness -Total score CIS (2) -1 (no fatigue) to 7 (extreme fatigue)
Anxiety	-Measures feelings of anxiety -HADS subscale anxiety (3) -0 to 3 (variable meaning per item)
Depression	-Measures feelings of depression -HADS subscale depression (3) -0 to 3 (variable meaning per item)
Consequences	-Measures illness perceptions about consequences of disease -IPQK subscale consequences (4) -0 (no influence) to 10 (many influence)
Timeline	-Measures illness perceptions about timeline of disease -IPQK subscale timeline (4) -0 (very short) to 10 (my whole life)

Supplementary digital material 3: Supplementary Table II (continued)

Potential predictor (all measured at baseline)	Measurement method
Treatment control	-Measures illness perceptions about treatment control of disease -IPQK subscale treatment control (4) -0 (not at all) to 10 (very much)
Identity	-Measures illness perceptions about identity of disease -IPQK subscale identity (4) -0 (no complaints) to 10 (very serious complaints)
Illness concern	-Measures illness perceptions about concerns about disease -IPQK subscale illness concern (4) -0 (not worried) to 10 (very much worried)
Coherence	-Measures illness perceptions about coherence of disease -IPQK subscale coherence (4) -0 (no understanding) to 10 (very much understanding)
Emotional representation	-Measures illness perceptions about emotional representation -IPQK subscale emotional representation (4) -0 (no influence) to 10 (many influence)
Pain catastrophizing	-Measures to what degree patient experiences catastrophizing -Total score PCS (5) -0 (not at all) to 4 (all the time)
Avoidance	-Measures aspects of psychological inflexibility (avoidance) -PIPS subscale avoidance (6) -0 (never true) to 7 (always true)
Cognitive fusion	-Measures aspects of psychological inflexibility (cognitive fusion) -PIPS subscale cognitive fusion (6) -0 (never true) to 7 (always true)
Self-efficacy	-Measures confidence of being able to perform daily tasks despite the pain -Total score PSEQ (7) -0 (not at all confident) to 6 (completely confident)
Hostility	-Measures to what degree patient was bothered by 90 psychological and physical symptoms -SCL90 subscale hostility (8) -1 (completely not) to 5 (really bad)
Mental health	-Measures general mental health status -Mental Component Summary SF12 (9) -Likert scale is item dependent, scored from 0-50 (higher scores is better mental health)
Physical health	-Measures general physical health status -Physical Component Summary SF12 (9) -Likert scale is item dependent, scored from 0-50 (higher scores is better physical health)

Abbreviations: kg/m2= kilograms/square meter, PDI= pain disability index, CIS= Checklist individual strength, HADS= hospital anxiety and depression scale, IPQK= illness perceptions questionnaire-short version, PCS= pain catastrophizing scale, PIPS= psychological inflexibility pain scale, PSEQ= pain self-efficacy questionnaire, SCL90= symptom checklist – 90 items, SF12= short-form 12, DDPR= Dutch Dataset Pain Rehabilitation

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Supplementary digital material 4: Supplementary Table III: Performance measures of the final model for 5 imputed datasets

Imputed number	-2 log likelihood	Cox & Snell R Square	Nagelkerke R Square
Original data	584.578	0.20	0.27
1	705.424	0.17	0.23
2	711.944	0.18	0.24
3	718.147	0.17	0.22
4	706.497	0.18	0.25
5	718.978	0.17	0.22

Supplementary material Chapter 8

Appendix S1: References of previous systematic reviews including preoperative rehabilitation in patients with KOA awaiting TKA (75-110)

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Table S1: Search query (Web Of Science and Scopus)

	Key words
Group 1 (P)	(((Knee Prosthesis OR (knee AND prosthesis)) OR 'Knee Replacement Arthroplasty' OR (Knee AND replacement AND arthroplasty)) OR (knee arthroplasty OR (knee AND arthroplasty) OR knee replacement OR (knee and replacement) OR knee surgery OR (knee AND surgery))))
Group 2 (I)	(((((Preoperative Period OR Preoperative Care) OR (preoperati* OR pre-operati* OR presurgical OR pre-surgical OR pre-surger* OR pre-surgical OR pre-surgically OR preadmission)) AND ((((((‘Physical Therapy Specialty’ OR (physical AND therapy) OR ‘Physical Therapy Modalities’ OR (physical AND therapy AND modalities) OR ‘Cognitive Behavioral Therap*’ OR (Cognitive AND behavioral AND therapy) OR Acupuncture Therap* OR (acupuncture AND therapy) OR Exercise Therap* OR (Exercise AND Therapy) OR Behavior Therap* OR (Behavior AND Therapy) OR Cryotherap* OR Soft Tissue therap* OR (Soft AND Tissue AND therapy) OR ‘Acceptance and Commitment Therap*’) OR (‘Exercise Movement Techniques’ OR Resistance Training OR (resistance AND training) OR Exercis*)) OR (Rehabilitation OR Telerehabilitation)) OR (Orthopedic Manipulation OR (Orthopedic AND Manipulation) OR Musculoskeletal Manipulations OR (Musculoskeletal AND Manipulations)) OR Dry Needling) OR (physical therap* OR 348ensitization* OR cognitive therap* OR (Cognitive AND therapy) OR acupuncture OR manual therap* OR (manual AND therapy) OR mobilization OR mobilizations OR mobilisation OR mobilisations OR behaviour therap* OR (behaviour AND therapy) OR strength training OR (strength AND training) OR conservative therap* OR (conservative AND therapy) OR ‘graded activity’ OR (graded AND activity) OR ‘graded exposure’ OR (graded AND exposure) OR ‘graded exercise’ OR (graded AND exercise) OR pain education OR (pain AND education) OR participant education OR (participant AND education))))
Group 3 (O)	((((((Pain OR Musculoskeletal Pain OR (musculoskeletal AND pain) OR Chronic Pain OR (chronic AND pain)) OR ‘Disability Evaluation’ OR disability) OR Activities of Daily Living OR activities OR (activities AND daily AND living)) OR Quality of Life OR (quality AND life)) OR (Personal Satisfaction OR (personal AND satisfaction) OR Participant Satisfaction OR (participant AND satisfaction))) OR (functioning OR activities OR participation OR satisfaction OR disability)))
Group 4 (S)	(((‘Pragmatic Clinical Trial’ OR ‘Controlled Clinical Trial’ OR ‘Randomized Controlled Trial’ OR (randomized AND controlled AND trial) OR (randomized AND controlled) OR Clinical Trial OR (clinical AND trial) OR Cross-Over Studies OR (cross-over AND studies)) OR (Cross-Sectional Studies OR (cross-sectional AND studies) OR Cohort Studies OR (cohort AND studies) OR Longitudinal Studies OR (longitudinal AND studies) OR Follow-Up Studies OR (follow-up AND studies) OR Case-Control Studies OR (case-control AND studies) OR Prospective Studies OR (prospective AND studies))) OR (‘randomised controlled trial’ OR (randomised AND controlled AND trial) OR (randomised AND controlled))))

Table S2: Search query (Embase)

	Key words
Group 1 (P)	('knee prosthesis'/exp OR 'knee arthroplasty'/exp OR ((((knee:ab,ti AND arthroplasty:ab,ti OR knee:ab,ti) AND prosthesis:ab,ti OR knee:ab,ti) AND replacement:ab,ti OR knee:ab,ti) AND surgery:ab,ti)
Group 2 (I)	('preoperative care'/exp OR 'preoperative education'/exp OR (preoperative:ab,ti OR 'pre operative':ab,ti OR presurgical:ab,ti OR 'pre surgery':ab,ti OR preadmission:ab,ti)) AND ('acupuncture'/exp OR 'conservative treatment'/exp OR 'motivational interviewing'/exp OR 'cryotherapy'/exp OR 'kinesiotherapy'/exp OR 'physiotherapy'/exp OR 'cognitive rehabilitation'/exp OR 'behavior therapy'/exp OR 'cognitive behavioral therapy'/exp OR 'client centered therapy'/exp OR 'exercise'/exp OR 'cognitive therapy'/exp OR 'telerehabilitation'/exp OR 'rehabilitation'/exp OR 'manipulative medicine'/exp OR 'dry needling'/exp OR 'graded exercise therapy'/exp OR ((((((((((((((((physical:ti,ab AND therapy:ti,ab OR physiotherapy:ti,ab OR behaviour:ti,ab) AND therapy:ti,ab OR cryotherapy:ti,ab OR soft:ti,ab) AND tissue:ti,ab AND therapy:ti,ab OR 'acceptance and commitment':ti,ab OR cognitive:ti,ab) AND behavioral:ti,ab AND therapy:ti,ab OR cognitive:ti,ab) AND therapy:ti,ab OR acupuncture:ti,ab OR exercise:ti,ab) AND therapy:ti,ab OR manual:ti,ab) AND therapy:ti,ab OR mobilization:ti,ab OR mobilisation:ti,ab OR behavior:ti,ab) AND therapy:ti,ab OR resistance:ti,ab) AND training:ti,ab OR strength:ti,ab) AND training:ti,ab OR conservative:ti,ab) AND therapy:ti,ab OR graded:ti,ab) AND activity:ti,ab OR graded:ti,ab) AND exposure:ti,ab OR graded:ti,ab) AND exercise:ti,ab OR pain:ti,ab) AND education:ti,ab OR participant:ti,ab) AND education:ti,ab))
Group 3 (O)	('chronic pain'/exp OR 'hyperalgesia'/exp OR 'allodynia'/exp OR 'nociceptive pain'/exp OR 'postoperative pain'/exp OR 'disability'/exp OR 'human activities'/exp OR 'quality of life'/exp OR 'participant satisfaction'/exp OR ((pain:ti,ab OR functioning:ti,ab OR 'activities of daily living':ti,ab OR activities:ti,ab OR participation:ti,ab OR quality:ti,ab) AND of:ti,ab AND life:ti,ab OR satisfaction:ti,ab OR disability:ti,ab)
Group 4 (S)	('clinical trial'/exp OR 'intervention study'/exp OR 'longitudinal study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cross-sectional study'/exp OR 'cohort analysis'/exp OR (((((((((clincal:ti,ab AND trial:ti,ab OR randomized:ti,ab) AND controlled:ti,ab AND trial:ti,ab OR randomised:ti,ab) AND controlled:ti,ab AND trial:ti,ab OR cohort:ti,ab) AND studies:ti,ab OR prospective:ti,ab) AND studies:ti,ab OR longitudinal:ti,ab) AND studies:ti,ab OR 'follow up':ti,ab) AND studies:ti,ab OR 'case control':ti,ab) AND studies:ti,ab OR 'cross sectional':ti,ab) AND studies:ti,ab)

Curriculum Vitae

GENERAL INFORMATION

Name	Vervullens Sophie
Date of birth	14 July 1995
Place of birth	Wilrijk, Belgium

WORKING EXPERIENCE

2020-Current	Joint PhD-Researcher University of Antwerp, Belgium and University of Maastricht, The Netherlands
2019-2020	Self-employed physiotherapist Kine Expo, Antwerp, Belgium
2018-2020	Self-employed physiotherapist Chiron, Aartselaar, Belgium

EDUCATION

2018-2019	Postgraduate Manual Therapy, University of Ghent, Belgium
2016-2018	Master Rehabilitation Sciences and Physiotherapy, Catholic University of Leuven, Belgium
2013-2016	Bachelor Rehabilitation Sciences and Physiotherapy, University of Antwerp, Belgium
2007-2013	Secondary school diploma: Latin-Math, Sint-Ritacollege Kontich, Belgium

COURSES

2024	Applying for a job, Antwerp Doctoral School
2023	Grow your further career, Antwerp Doctoral School
2023	Pain neuroscience education, Brussel University
2023	Missing data analysis in R, Flames
2022	Inside a company, Antwerp Doctoral School
2022	Biomedical sources, Antwerp Doctoral School
2022	Graphical presentation of research data, Antwerp Doctoral School
2022	Introduction to R, STATUA Antwerp
2022	Handling categorical data with logistic regression, STATUA Antwerp
2022	Excel intermediate tips & tricks, Antwerp Doctoral School
2021	Linear mixed models in JMPSAS, STATUA Antwerp
2021	Linear regression and ANOVA, STATUA Antwerp
2021	Writing academic papers in English, Antwerp Doctoral School
2021	Communicating effectively academic context, Antwerp Doctoral School
2021	Timemanagement, Antwerp Doctoral School
2021-2022	Good Academic Research Practices ‘Mind the Gap’
2021	Good Clinical Practices (ICH-GCP-E6R2)
2019-2020	Manual Lymphatic Drainage a.m. Vodder: 2020

SCIENTIFIC PUBLICATIONS

First author

2024 Accepted in Annals of Physical and Rehabilitation Medicine – Vervullens S., Meert L., Smeets R.J.E.M., Van der Nest G., Verbrugghe J., Verdonk P., Rahusen F, Meeus M. A biopsychosocial approach to phenotype knee osteoarthritis patients awaiting total knee arthroplasty: a cross-sectional study

2024 Vervullens S, Meert L, Meeus M, Heusdens CHW, Verdonk P, Foubert A, Abatih E, Durnez L, Verbrugghe J, Smeets Rob J.E.M. Application of the IASP Grading System to Identify Underlying Pain Mechanisms in Patients with Knee Osteoarthritis: A Prospective Cohort Study. The Clinical Journal of Pain ():10.1097/AJP.0000000000001234, July 17, 2024.

2024 Vervullens S, Meert L, Smeets RJEM, Verbrugghe J, Baert I, Rahusen FTG, et al. Preoperative glycaemic control, number of pain locations, structural knee damage, self-reported central 351ensitization, satisfaction and personal control are predictive of 1-year postoperative pain, and change in pain from pre- to 1-year posttotal knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2024 May 15

2024 Vervullens S, Meert L, Smeets RJEM, Verbrugghe J, Verdonk P, Meeus M. Does pain intensity after total knee arthroplasty depend on somatosensory functioning in knee osteoarthritis patients? A prospective cohort study. Clin Rheumatol. 2024 Jun 1;43(6):2047–59.

2023 Vervullens S, Breugelmans L, Beckers L, VAN Kuijk SM, VAN Hooff M, Winkens B, et al. Clinical prediction model for interdisciplinary biopsychosocial rehabilitation in osteoarthritis patients. Eur J Phys Rehabil Med. 2023 Dec 7

2022 Vervullens S, Meert L, Baert I, Smeets RJEM, Verdonk P, Rahusen F, et al. Prehabilitation before total knee arthroplasty: A systematic review on the use and efficacy of stratified care. Ann Phys Rehabil Med. 2022 Sep 14;101705.

2022 Vervullens S, Haenen V, Meert L, Meeus M, Smeets RJEM, Baert I, et al. Personal influencing factors for pressure pain threshold in healthy people: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2022 Jun 11;139:104727

2022 Vervullens S, Meert L, Meeus M, Baert I, Heusdens CHW, Caethoven C, et al. The evolution of somatosensory processing signs after nociceptive targeted surgery in patients with musculoskeletal disorders: a systematic review. PAIN. 2022 May 13;10.1097/j.pain.0000000000002867.

2022 Vervullens S, Meert L, Baert I, Delrue N, Heusdens CHW, Hallemans A, et al. The effect of one dry needling session on pain, central pain processing, muscle co-contraction and gait characteristics in patients with knee osteoarthritis: a randomized controlled trial. Scandinavian Journal of Pain. 2022 Apr 1;22(2):396–409

Second author

2024 Meert L, Mertens MG, Meeus M, Vervullens S, Baert I, Beckwée D, et al. Identification of Metabolic Factors and Inflammatory Markers Predictive of Outcome after Total Knee Arthroplasty in Patients with Knee Osteoarthritis: A Systematic Review. International Journal of Environmental Research and Public Health. 2023 Jan;20(10):5796.

2023 Meert L, Mertens MG, Meeus M, Vervullens S, Baert I, Beckwée D, et al. Identification of Metabolic Factors and Inflammatory Markers Predictive of Outcome after Total Knee Arthroplasty in Patients with Knee Osteoarthritis: A Systematic Review. International Journal of Environmental Research and Public Health. 2023 Jan;20(10):5796.

2021 Meert L, Vervullens S, Smeets RJEM, Nijs J, Meeus M. Nociplastische pijn bij knieartrose. Physios. 2021 Jun 22;13(2):15–26.

PUBLISHED ABSTRACTS

2023 Vervullens S, Meert L, Nest GV der, Verbrugghe J, Verdonk P, Rahussen F, et al. Pos0410 a Biopsychosocial Approach to Phenotype Knee Osteoarthritis Patients Awaiting Total Knee Arthroplasty: A Cross-Sectional Study. Annals of the Rheumatic Diseases. 2023 Jun 1;82(Suppl 1):460–1.

2021 Vervullens S, Meert L, Baert I, Delrue N, Heusdens K, Hallemans A, et al. POS1096 THE EFFECT OF ONE DRY NEEDLING SESSION ON PAIN AND CENTRAL PAIN PROCESSING IN PATIENTS WITH KNEE OSTEOARTHRITIS: A RANDOMIZED CONTROLLED TRIAL. Annals of the Rheumatic Diseases. 2021 Jun 1;80(Suppl 1):828–828.

WEBSITE PUBLICATIONS

2023 Blog Pain in Motion: INDIVIDUALIZED CARE IN CHRONIC PAIN RESEARCH. http://paininmotion.be/blog/detail/individualized-care-chronic-pain-research

2022 Blog MOVANT University of Antwerp: IS KNEE OSTEOARTHRITIS ALWAYS CHRONIC SECONDARY PAIN? http://www.paininmotion.be/blog/detail/knee-osteoarthritis-always-chronic-secondary-pain

2021 Blog Pain in Motion: SAME DIAGNOSIS ≠ SAME TREATMENT. https://www.uantwerpen.be/en/research-groups/movant/blog/samediagnosis/

PRESENTATIONS AT INTERNATIONAL CONGRESSES

Invited speaker

2024 Prognostic factors for chronic pain after total knee arthroplasty, EFIC summit, Online

Oral presentations

2023 Clinical prediction model for interdisciplinary biopsychosocial rehabilitation in osteoarthritis patients, DCRM congress, s' Hertogenbosch, The Netherlands

2022 Vervullens S., Meert L., Baert I., Smeets R.J.E.M., Verdonk P., Rahusen F., Meeus M. Prehabilitation before total knee arthroplasty: A systematic review on the use and efficacy of stratified care. EFIC congress, Dublin, Ireland

Poster presentations

2023 Vervullens S., Meert L., Smeets R.J.E.M., Van der Nest G., Verbrugghe J., Verdonk P., Rahusen F, Meeus M. A biopsychosocial approach to phenotype knee osteoarthritis patients awaiting total knee arthroplasty: a cross-sectional study., EULAR congress, Milan, Italy

2023 Vervullens S., Meert L., Smeets R.J.E.M., Van der Nest G., Verbrugghe J., Verdonk P., Rahusen F, Meeus M. A biopsychosocial approach to phenotype knee osteoarthritis patients awaiting total knee arthroplasty: a cross-sectional study., CAPHRI research day, Maastricht, the Netherlands

2022 Vervullens S., Haenen V., Meert L., Meeus M., Smeets R.J.E.M., Baert I., et al. Personal influencing factors for pressure pain threshold in healthy people : a systematic review and meta-analysis. PSIM congress, Maastricht, the Netherlands

2021 Vervullens S., Meert L., Baert I., Delrue N., Heusdens C.H.W., Hallemans A., Van Criekinge T., Smeets R.J.E.M., De Meulemeester K., The Effect of One Dry Needling Session on Pain and Central Pain Processing in Patients With Knee Osteoarthritis: a Randomized Controlled Trial., EULAR congress, ONLINE

2021 Vervullens S., Meert L., Baert I., Delrue N., Heusdens C.H.W., Hallemans A., Van Criekinge T., Smeets R.J.E.M., De Meulemeester K., The Effect of One Dry Needling Session on Pain and Central Pain Processing in Patients With Knee Osteoarthritis: a Randomized Controlled Trial., IASP congress, ONLINE

JOURNAL REVIEWING

2024 Journal of Pain Research

2023 Musculoskeletal Science & Practice

GRANTS & AWARDS

2023 Best presentation award at DCRM congress, 's Hertogenbosch, The Netherlands

2022 FWO Travel Grant EFIC congress, Dublin, Ireland

TEACHING EXPERIENCE

2022-2024	Bachelor thesis scientific research: how to write a systematic review – 3rd Bachelor students, University of Antwerp, Belgium
2020-2024	Pain management: pain science education & pain management in osteoarthritis – 2nd Master students, University of Antwerp, Belgium
2023	Osteoarthritis: the modern approach – graduated physiotherapists, Randstad Maassluis, The Netherlands

THESIS SUPERVISION

2020-2024	Supervision of 1st and 2nd master theses, University of Antwerp, Belgium
2020-2024	Supervision of 3rd bachelor theses, University of Antwerp, Belgium

SCIENCE COMMUNICATION TO A BROAD PUBLIC

2022	'Proefkot' science communication for children, University of Antwerp, Belgium
2021	Finalist 'Pitch your PhD', University of Maastricht, The Netherlands
2021	Finalist PRESS>>SPEAK presentation contest, University of Antwerp, Belgium

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