Can Preoperative Qualitative Sensory Testing Predict Persistent Post-operative Knee Pain following Total Knee Replacement? – A Systematic Review

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TITLE PAGE

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ABSTRACT

Objective: To investigate whether pre-operative Quantitative Sensory Testing (QST) can identify patients who experience persistent post-operative knee pain following Total Knee Replacement (TKR).

Data sources: PubMed, EMBASE, CINAHL, EBSCO and grey literature.

Study selection: 1056 studies were retrieved. The title and abstracts were screened by two independent reviewers, of which 45 were retrieved for full text analysis and 16 studies were included. Studies of any design were included if they recruited adults who underwent TKR; completed any component of the German Research Network on Neuropathic Pain QST or conditioned pain modulation testing preoperatively and assessed post-surgical joint pain using a self-reported outcome measure at a minimum of three months post TKR.

Data extraction: Data was independently extracted by two researchers. Disagreements were resolved through consensus. The extracted data was recorded in a predefined spreadsheet. Domains included demographic data, type and site of QST, pain outcome measure, follow up duration, statistical methods and associative data. Two independent reviewers assessed the quality of studies using Quality in Prognosis risk of bias tool and the certainty of evidence using the GRADE framework.

Data synthesis: Sixteen cohort studies met the eligibility criteria (n=2051 patients). Data was analysed narratively because of the heterogeneity across the QST procedures (mechanical and thermal detection and pain thresholds, conditioned pain modulation and temporal summation of pain), measures of reporting pain (Western Ontario and McMaster Universities Osteoarthritis Index, visual analogue scale and numeric pain rating score) and follow up time points (3 to 18 months).

Conclusions: Due to the heterogeneity and low-moderate quality studies included, it remains unclear whether QST can identify patients who are likely to experience persistent postoperative joint pain following TKR.

MANUSCRIPT

INTRODUCTION

In the United Kingdom (UK) National Health Service (NHS) the largest waiting lists are for people with bone and joint (orthopaedic) pain. As of January 2024, there are more than 800,000 people currently waiting to see an orthopaedic clinician, of which 45% have been waiting longer than 18-weeks [55]. One of the most common orthopaedic operations is a total knee replacement [56]. Around 110,000 total knee replacements are conducted each year in the NHS, primarily to treat knee arthritis, at a cost the NHS around £770 million each year for the NHS [57]. Projections from the National Joint Registry (2022) anticipate an increase of 36.6% in the number of TKR surgeries by the year 2060[38.] The most common reason that individuals undergo a total knee replacement is pain relief. However, between 10-34% of patients experience pain which persists beyond three months following their knee replacement, for which there is no evidence-based treatment. People who experience persistent pain following total knee replacement are more likely to be dissatisfied with the outcome of their surgery. At one year following surgery, 17% of patients, report that they regret their decision to have a knee replacement [38]. Therefore, around 20,000 people a year in the UK have a total knee replacement in the NHS that will not benefit them, at a cost of around £140 million [57].

In recent years, much research has been undertaken to understand whether it is possible to identify patients who are likely to experience poor outcomes following total knee replacement, prior to

surgery. The results of this research have been inconsistent and not led to any significant changes to care pathways for people undergoing total knee replacement.

Quantitative Sensory Testing (QST) uses a group of non-invasive, quantifiable sensory stimuli procedures can provide insight into a person's somatosensory nerve system function and integrity [3, 20]. Quantitative sensory testing quantifies these altered responses by utilising various stimuli to assess perceptions of proprioception, touch, pinprick/blunt pressure sensitivity, vibration, as well as sensitivity to heat or cold stimuli [3, 20]. It is suggested that people who may have altered nociceptive activity, may be more likely to experience persistent post-operative pain [20]. If QST is able to identify individuals who are likely to experience persistent post-operative pain following total knee replacement, it could significantly reduce the burden of unsuccessful surgeries on both individuals and society by improving patient selection for surgery and informing future intervention development. A recent systematic review suggested that QST may have the potential to identify patients, who are likely to develop persistent post-operative pain from orthopaedic surgery [20]. This systematic review aims to understand whether pre-operative QST can identify people who will experience persistent post-operative pain following total knee replacement.

METHODS

This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA)[41].

Search Strategy

A systematic search was performed of four databases (EMBASE, CINAHL, SCOPUS, PubMed) and grey literature on 29th March 2023 and updated on 30th January 2024 using a search strategy with components of quantitative sensory testing, persistent postoperative pain and total knee replacement. An example of the search strategy employed in the PubMed database can be found in Figure 1. A manual search of reference lists of the acquired articles, along with relevant systematic reviews and meta-analyses was completed to identify studies that may not have been found through the initial search. No contact with expert authors in the field was attempted. After importing identified studies into EndNote X9 (Clarivate Analytics) and eliminating duplicates, a comprehensive assessment was carried out by the two researchers (V.K and G.F) blinded to reduce risk of bias and increase reliability. The titles and abstracts of the retrieved studies were scrutinised to determine inclusion. Finally, the full-text versions of the selected studies were obtained and analysed independently to assess their eligibility. Any differences that arose were resolved through consensus.

[INSERT FIGURE 1]

Eligibility criteria

Studies were included if they met all the following criteria:

- A study population of adults (aged 18 years and above) who underwent total knee replacement (TKR).
- Completed any component of the German Research Network on Neuropathic Pain (DFNS)
- Assessed post-surgical pain using a self-reported outcome measure at a minimum of 3 months after TKR (in accordance with the ICD-11 definition)[4]
- Statistically associated or correlated preoperative QST and the above-stated pain outcome measure.

Studies were excluded if they met the following exclusion criteria:

- Animal or cadaveric studies
- Commentaries, editorials, single case studies, reports or laboratory data, books or book chapters, letters, conference posters or proceedings or study protocols.

Assessment of Methodological Quality

The methodological quality of the included studies was assessed independently by 2 reviewers (V.K and G.F) using the Quality In Prognostic Studies (QUIPS) tool.[42] The QUIPS tool was deemed suitable since it is specifically aimed at assessing the risk of bias in studies investigating prognostic factors in line with the recommendations of the Cochrane Prognosis Methods Group.[51] This tool focuses on 6 domains that include study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting with the final risk of bias of the study graded as low, moderate, or high.

143

144 *Data extraction and synthesis*

145 Data was independently extracted by two researchers (V.K and G.F). The extracted data was
146 recorded in a predefined spreadsheet based on the works of previous research [19,20] included
147 bibliographical and demographic data, total number of participants, type and site of QST, pain
148 outcome measure, follow up duration, the type of statistical method used to investigate association
149 and its findings. Any disagreements that arose were resolved through consensus. Significant
150 heterogeneity was observed in the administration of QST protocols and pain outcome measures
151 employed among the individual studies. On performing the chi-square test of homogeneity test, an
152 I^2 value of 65% denoted substantial heterogeneity. Therefore, a meta-analysis was not
153 recommended, and a narrative synthesis of the findings was performed.

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155

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RESULTS

Study Selection

The search strategy retrieved 1056 studies and three studies from the electronic databases and grey literature, respectively (Figure 2). On removing 579 duplicates, the title and abstracts of the remaining 493 studies were screened, of which 45 were retrieved for full text analysis. Interrater reliability between the two reviewers was measured using a weighted Kappa statistic on a sample of included papers (n=10). The agreement rate was deemed substantial (>90%)(k =0.80). Sixteen studies met the inclusion criteria with the most common reasons for exclusion (29 studies) being: association of QST and chronic pain outcomes not analysed (45%), insufficient data (31%), revision replacement (17%) and change in pain reported as a measure (1%).

[INSERT FIGURE 2]

Study Characteristics

This systematic review reports 16 studies, all of which were classified as prospective cohort studies. Most studies (n=8) originated from Denmark[11,26,27,28,31] and the United Kingdom[24,25,43] and were published between the years 2007 to 2022. Table 3 demonstrates the characteristics of these included studies. The 16 studies sampled a total of 2051 patients who underwent primary unilateral TKR. Sample sizes ranged between 14 to 300 with a median of 128. The patients had a median age of 68 years, ranging from 62 to 73 years. All studies included in this analysis followed a longitudinal cohort design and investigated a population diagnosed with osteoarthritis. The majority of the participants were female, accounting for 60% (1231) of the total sample.

Preoperative QST Assessment

Type of QST

This systematic review describes the utilisation of 14 QST modalities, including static modalities such as mechanical (three tests), thermal (six tests), and electrical (two tests), as well as dynamic (two tests). Mechanical QST was the most commonly reported test modality (12/16 studies), followed by dynamic measures (10/16 studies).

Test timing

Not all studies reported the timing at which preoperative QST was performed; those that did (four studies) reported times ranging from 57 (average), 17 (average) days to 1-2 weeks prior to surgery.

PPSP Assessment

Outcomes

The most commonly reported outcome measures were validated questionnaires on pain and disability such as the Visual Analog Scale[8,11,24,26,27,29,31] (seven studies), Western Ontario and McMaster Universities Osteoarthritis Index Pain sub-scale[23,25,32,34,35,43] (six studies) and the Numerical Rating Scales[28,30,44] (three studies).

Assessment timing

Only studies assessing postoperative pain at a minimum of 3 months following surgery were included, in accordance with the defined criteria for persistent postsurgical pain (PPSP).[4] Pain assessments were conducted within a timeframe ranging from 3 months to 18 months following the total knee replacement surgery. The time period most frequently reported was 6 months[23,24,28,30,32,34,35,44] (eight studies) followed by 12 months[11,21,23,25,26,31] (six studies). Additionally, two studies reported time frames of 4 and 18 months[8,28], respectively.

Preoperative QST Association with PPSP

Mechanical

The assessment of mechanical quantitative sensory testing is commonly conducted using Frey filaments, whereas the determination of pain threshold is typically performed using blunt pin pricks and pressure cuffs.[22] Pressure pain threshold (PPT) was the most frequently administered

test[11,23,24,25,26,27,28,30,32,35,43] (11 studies) along with pressure tolerance threshold (PTT) and mechanical pain threshold (MPT) reported in three[26,27,28] and two[29,30] studies respectively.

PPT

While 11 studies used PPT as part of their preoperative quantitative sensory testing protocol, seven studies[11,23,24,25,30,32,43] provided data of its association with postoperative pain. Of these, only five studies[23,24,25,32,43] revealed statistically significant associations. Interestingly, Leung et al (2019)[23] found PPT to be correlated to post operative pain at 12 months but not at 6 months. This was corroborated with the findings of Kurien et al (2018)[24] and Wylde et al (2015)[25] who found statistically significant associations with PPT when correlated with pain at 12 months. The overall quality of evidence for PPT within this review was judged to be low. Details of statistical associations are summarised in Table 4.

PTT

Three studies reported the use of PTT preoperatively.[26,27,28] Although, it should be noted that one of these studies did not investigate the relationship between PTT and pain.[27]. Furthermore, out of the other two investigations [26,28], only one was found to have achieved statistical significance. Petersen et al. (2016)[26] performed a regression analysis to ascertain the prediction of postoperative pain and found that at 12 months, PTT was an independent parameter for predicting persistent post-operative pain (R=-0.222, P=0.034). Overall, these inconsistencies contributed to the quality of evidence for PTT to be very low.

242 ***MPT***

243 The results of both studies investigating the mechanical pain threshold at 4 and 6 months [29,30]
244 following surgery did not reveal any statistically significant associations with post-surgical pain.
245 The quality of evidence was assessed as low as measured by GRADE.

246

247 **Thermal**

248 Thermal modalities of QST typically involve the application of heat or cold stimuli to the skin
249 surface. This is commonly achieved by utilising Peltier elements (semiconductor junctions that
250 create temperature gradient through electric current). Additional non-standardized techniques are
251 also employed to cool or heat the skin, including the utilisation of radiant heat, ice application, or
252 limb water immersion. Thermal modalities of QST were reported in 5/16 studies (31.25%).

253

254 ***Cold Stimulus (CPT, CDT, STCPI)***

255 No statistically significant correlations were reported for all three measures: cold detection
256 threshold (CDT)[31] (R=0.025, P>0.05), cold pain tolerance (CPT)[32] (P=0.84), suprathreshold cold
257 pain intensity (STCPI)[29]. The quality of evidence for the only three studies [29,31,32] that reported
258 thermal QSTs was determined to be very low.

259

260 ***Heat Stimulus (WDT, HPT, STHPI)***

261 Heat pain threshold (HPT) was most commonly reported (four studies)[29,30,31,43] followed by warm
262 detection threshold (WDT) (one study)[31] and suprathreshold heat pain intensity (STHPI) (one
263 study).[29] The quality of evidence for WDT and STHPI was judged to be very low. Although only

17% (1/6) of the studies reported a correlation with postoperative pain, the overall certainty of the evidence was rated as moderate.

Electrical

A study conducted by Lundblad et al. (2008)[8] is currently the sole study to investigate the electrical QST modalities in the context of chronic pain and post-total knee replacement outcomes. The study revealed a strong correlation between the electrical pain threshold (EPT) and electrical detection threshold (EDT) with pain at 18 months post TKR. The statistical analysis showed that the association was significant for both EDT (P = 0.045) and EPT (P = 0.012). Furthermore, the logistic regression model indicated that EPT was a strong predictor of pain (p= 0.01). The certainty of evidence was rated very low, primarily because of significant concerns in various domains such as imprecision. To improve the informational robustness, further studies involving a larger number of participants are required.

Dynamic

Dynamic measures were the second most commonly reported QST modality in 10/16 studies (62.5%). The constituted measures such as Conditioned Pain Modulation (CPM) were utilised in 9/16 studies and Temporal Summation of Pain (TSP) in 6/16 studies.

CPM

Conditioned pain modulation was associated with chronic post-operative pain in only 3/9 (33%) studies.[4,27,28] Vaegter et al. (2017)[28] and Durstler et al. (2021)[44] observed that preoperative CPM was found statistically significant at 6 months for postoperative pain, while Larsen et al. (2021)[27]

reported this association at 12 months. Additionally, there was no standardisation of conditions in which test stimulus and conditioning stimulus were reported across all 9 studies. The overall quality of evidence for the use of CPM within this review was judged to be low.

TSP

TSP was found to be predictive of persistent post surgical pain in 3/6 studies (50%) at a minimum of 6 to 12 months post TKR[11,24,31]. Kurien et al. (2018) [24] evaluated preoperative TSP with the use of cuff algometry and monofilaments. Although both methods correlated positively with post-operative pain at 6 months, the correlation between TSP elicited using monofilaments and post-operative pain was stronger. Petersen et al. found significant correlations between TSP and post-surgical pain at 12 months in both their initial study[11] ($r = 0.24$, $P = 0.037$) and a subsequent 3-year follow-up study[31] ($r = 0.193$, $P = 0.013$). In univariate linear regression analyses, they observed similar results with significant crude coefficients of 0.311 ($P = 0.037$) and significant P-values of 0.023, respectively. However, these associations were not found in the multivariate model. The remaining three studies [26,34,35] did not find any association between TSP and post-surgical pain. Certainty of evidence for TSP was deemed moderate.

Risk of Bias

Overall, eight studies[11,24,26,29,31,32,43] exhibited moderate bias, three were high[8,23,28] and six[25,27,30,34,35,44] were low. Cohen's kappa was used to measure inter-rater reliability between the two reviewers in QUIPS bias evaluations with a result of 0.82 indicating a relatively high level of agreement. Disagreements in judgement were prevalent in the confounding factors domain, which consequently scored the highest risk out of the other domains as well, owing to most of the studies'

lack of clarity in describing confounding variables. These were subsequently resolved by consensus. Furthermore, the statistical analyses and reporting in the included studies were inconsistent, resulting in a moderate risk of bias within QUIP's statistical analysis/reporting domain. Contrarily, the domains study participation and study attrition were judged to be of low risk of bias because of clear description of the population, transparent reporting of recruitment strategies and adequate accounting for participant losses to follow up. Although the use of standardised QST protocols such as the DFNS was not used in all the included studies, given the proven reliability and validity of assessment measures a low rating of risk was found in the prognostic and outcome measures domain. Individual risk of bias of the included studies can be found in Table 2 with the overall risk of bias of each domain demonstrated in Figure 3.

Certainty of Evidence

Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, the certainty of evidence for each QST modality was evaluated. The guideline recommended by Lorio et al [36] for conducting GRADE evaluations of prognostic studies was used to make decisions in accordance with the objectives of this review. The highest quality of evidence was found in TSP and HPT which were graded as moderate, followed by CPM, PPT and MPT graded as low-quality evidence. Majority of the QST modalities described within this review appeared to be of very low certainty of evidence. High risk of bias and high imprecision ratings were the most frequent reasons for downgrading the evidence's certainty. Explanations for all evaluations are described in the summary of findings in Table 5 in the Appendix.

333

DISCUSSON

Previous systematic reviews have explored the relationship between presurgical QST and both acute and chronic post-surgical pain in total joint arthroplasties[19] and other surgeries.[6] However, this is the first systematic review to exclusively examine the relationship between presurgical QST and persistent post-surgical pain in patients who have undergone TKR. The current review is also the first to investigate which QST measures were most predictive of this relationship and aimed to evaluate the certainty of presenting evidence.

Among the 16 studies included a total of 13 QST measures were identified across four sub-types: mechanical, thermal, electrical, and dynamic. Given the variation in the timing of pain assessments, spanning from 3 to 18 months post-surgery, and the predominant use of non-standardized QST methods across most of the studies the evidence was narratively synthesised in this review.

In the current review, mechanical measures were the most reported (n=12) wherein three measures—MPT, PPT and cPTT were utilised for preoperative QST. Among these measures, PPT seemed to demonstrate the most consistent correlation with persistent post-surgical pain (PPSP) in 5 out of 11 studies (45%). This percentage is lower compared to a recent systematic review[19], in which pressure stimuli were found to be correlated with post-surgical pain in 8 out of 12 studies (67%). These variations may be attributed to differences in the timing of pain onset and the inclusion of other joint arthroplasties within their study population. Furthermore, the selection of QST sites appears to influence pain outcomes, which may be inferred from the findings of one of the included studies,[43] revealing significant associations between PPT and PPSP in the forearm but

not in the knee. The remaining measures, MPT and cPTT, yielded inconsistent results. MPT, in particular, demonstrated no significant correlation with PPSP, and the quality of evidence with regard to these findings was notably low.

The evidence for thermal QST presented conflicting findings overall. Among the three heat stimulus measures (WDT, HPT, STHPI), only 17% (1/6) of the studies reported a correlation with postoperative pain. The only study to demonstrate a positive correlation was specifically associated with the HPT measure, and the certainty of the evidence for it was rated as moderate, in contrast to the very low quality of evidence for WDT and STHPI. One study found no association between STHPI and persistent postsurgical pain (PPSP)[29]. However, a systematic review[15] has reported a strong correlation between STHPI and acute postsurgical pain in various surgeries such as total knee replacement[52], elective gynaecological surgeries,[14,53] herniotomy,[54] and thoracic surgeries.[10] These discrepancies suggest that sensitivity to heat stimuli may indeed be dependent upon the timing of pain onset and type of surgery. Previous research has established that cold stimulus measures of thermal QST serve as strong predictors for neuropathic pain[45] and musculoskeletal disorders such as whiplash injuries[46]. However, within the context of postsurgical pain, our review examined three studies[29 31 32] investigating cold stimulus measures (CPT, CDT and STCPI) found no significant correlations with PPSP in patients who underwent TKR with the quality of evidence supporting these correlations judged as very low. Interestingly, these results align with findings from three other reviews[6,19,47], all of which failed to establish any meaningful association between cold stimuli and the development of PPSP.

Whilst only one study reported electrical QST measures,[8] utilising EPT and EDT, the study reported that lower EPT was associated with PPSP following TKR. Electrical QST measures have also demonstrated predictive value for surgical pain in procedures like caesarean sections,[49,50] albeit primarily for acute postoperative pain. In the literature, while one study[16] suggested that electrical measures correlated more strongly with post-surgical pain compared to mechanical and thermal measures, recent systematic reviews have reported inconsistent associations with post-surgical pain. Notably, due to a high risk of bias related to study attrition, the quality of evidence was rated as low.

Dynamic measures were the second most frequently employed QST modality in 10 out of 16 studies. While conditioned pain modulation (CPM) showed an association with chronic post-operative pain in only 3 out of 9 studies (33%)[4,27,28], the temporal summation of pain (TSP) emerged as a slightly more consistent predictor of persistent post-surgical pain, being found in 3 out of 6 studies (50%)[11,24,31]. It should be noted that the limited association of CPM with persistent post-surgical pain aligns with findings from previous works[6,19]. These findings were rated as having a very low quality of evidence, primarily due to the lack of standardisation in the conditions under which the test stimulus and conditioning stimulus were administered across all 9 studies. In contrast, the evidence supporting TSP was rated as moderate. Coupled with the clinical feasibility of administering TSP and its stronger association with persistent post-surgical pain, the moderate level of evidence makes it the most suitable QST measure among those reported in this review.

It's crucial to highlight that certain confounding factors, such as gender, were not considered in the sixteen studies investigating the development of PPSP. This may be significant given that 60% of

the participants (n=1231) in this review were female. A meta-analysis[37] of postoperative pain predictors in TKR has shown that the female gender is moderately associated with increased postoperative pain severity. This suggests that gender may indeed be a confounding factor that influences both postoperative pain outcomes and preoperative pain sensitivity and should be taken into account when investigating their relationship with QST.

Our study offers several advantages compared to previous research. Unlike earlier reviews assessing the body of evidence for quantitative sensory testing (QST), our review employs tools that are well-suited for prognostic studies, such as QUIPS, and conducts GRADE assessments to evaluate the quality of evidence for each QST measure. However, it is important to consider certain limitations when interpreting the findings of this study. Firstly, administration of most QST measures relied on unstandardised protocols with a limited number of studies and small participant cohorts, potentially impacting generalizability and results. Additionally, significant heterogeneity existed in the statistical methods used; some studies employed univariate analyses while others utilised multivariate approaches, introducing challenges in result comparison. Moreover, some studies did not report p-values and other non-significant findings, reducing the transparency and reliability of results and resulting in a moderate to high risk of bias.

This systematic review was unable to establish an association between QST and PPSP based on and therefore are unable to make recommendations for clinical practice currently. However, the heterogeneity QST methods, and the poor quality of the research suggests that more needs to be done to standardise procedures and then test in a substantive cohort study. The aforementioned limitations substantially diminish the overall quality of evidence for the reported QST measures,

425 resulting in a very low level of certainty of these recommendations. Despite the low level of
426 evidence and confounding factors, preoperative QST screening holds promise for individual risk
427 assessment of persistent postoperative pain due to its ability to differentiate between peripheral and
428 central pain contributors[48]. The clinical implications of this review particularly concern patients
429 with osteoarthritis undergoing TKR. The results provide a graded assessment of evidence quality,
430 offering the potential to enhance clinician's decision-making and cost-effectiveness in the adoption
431 of QST. This would reduce the practical limitations of conducting a battery of preoperative tests,
432 instead streamlining the process, allowing for earlier and more efficient identification of patients
433 at risk of developing PPSP.

CONCLUSION

Despite the overall quality of evidence being very low, preoperative QST holds some potential for identifying patient pain profiles at risk of developing PPSP in the preoperative stage. Although mechanical and dynamic QSTs have been widely reported within pain literature, the findings of this review found electrical QST to be consistent in predicting persistent pain in one included study. However, the lack of sufficient evidence and the varied methodologies employed in its current usage render these recommendations inconclusive. The included studies were heterogeneous in study designs and included a small number of participants, which limits the applicability of findings to clinical practice. This review recommends future research employ robust methodologies to ensure consistent findings that may contribute to clinical relevance of QST within the niche of persistent pain.

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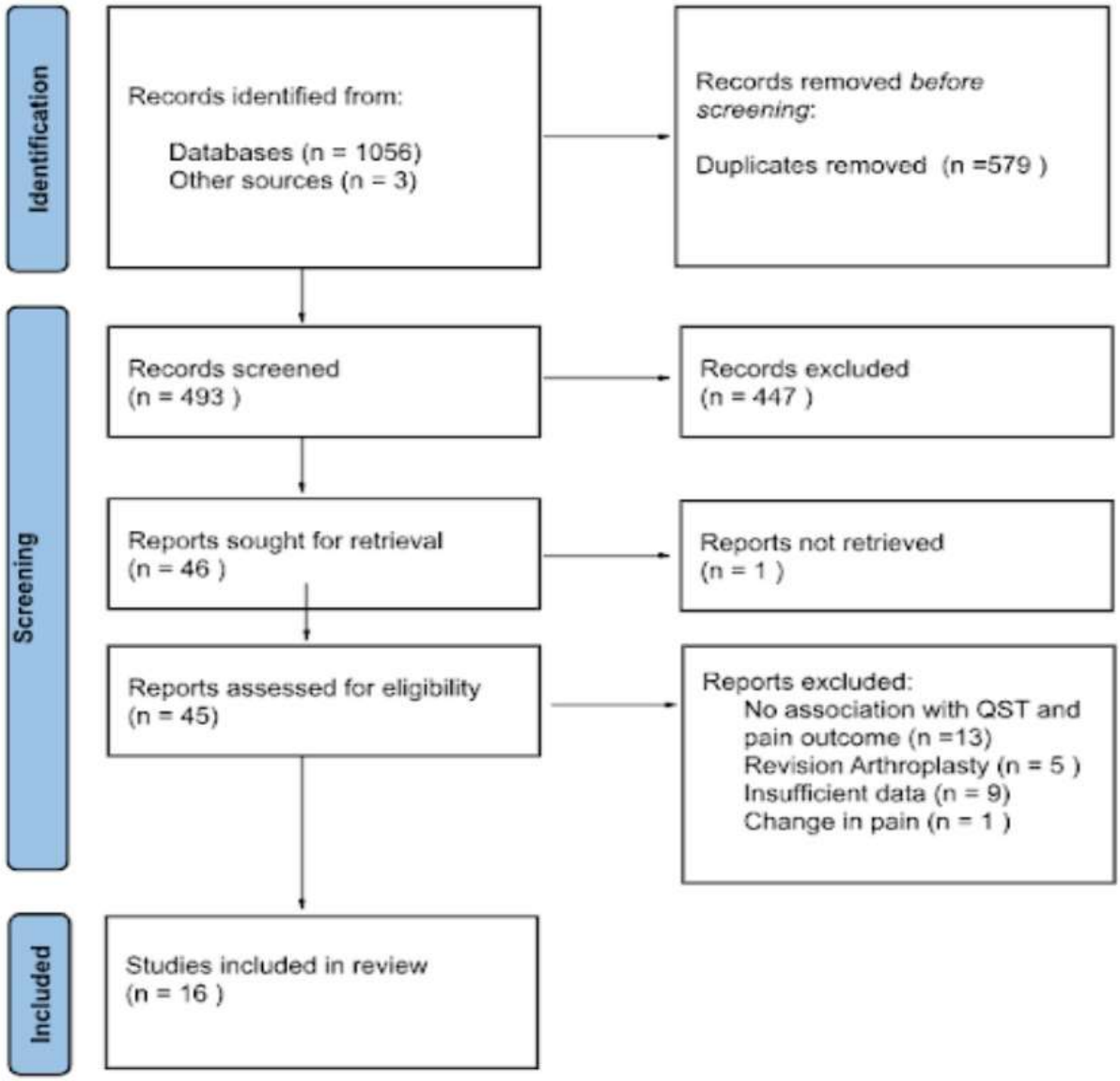
Figure 1. Pubmed search strategy

((QST OR Quantitative sensory OR Quantitative sensory test OR quantitative sensory testing OR thermal pain OR heat pain OR heat pain sensitivity OR heat detection threshold OR heat pain threshold OR heat pain tolerance OR warm detection OR cold pain OR cold pain sensitivity OR cold detection threshold OR cold pain threshold OR cold pain tolerance OR pressure pain sensitivity OR pressure pain threshold OR pressure pain tolerance OR electrical pain sensitivity OR electrical pain threshold OR electrical pain tolerance OR conditioned pain modulation OR temporal summation OR temporal summation of pain) AND (Total knee replacement OR Total knee replacement surgery OR TKR OR total knee replacement OR total knee replacement surgery OR TKR OR total knee joint replacement OR total knee joint replacement surgery OR tri-compartmental knee replacement surgery OR tri-compartmental knee joint replacement)) AND (postoperative pain OR Persistent postoperative pain OR pain after operation OR postsurgical pain OR Persistent postsurgical pain OR pain after surgery) **(N.B Free text)**

Figure 2: PRISMA flowchart



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718 **Appendix:** PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg.5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg.5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix Fig.1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg. 5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg. 5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Appendix Table 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pg. 5-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg. 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg. 5-6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg. 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg. 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a	Pg. 5

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Section and Topic	Item #	Checklist item	Location where item is reported
assessment		synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg. 6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg. 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pg. 6
Study characteristics	17	Cite each included study and present its characteristics.	Appendix Table 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Appendix Table 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg. 7-10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg. 7-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg. 6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg. 9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pg. 10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg. 10
	23b	Discuss any limitations of the evidence included in the review.	Pg. 11
	23c	Discuss any limitations of the review processes used.	Pg. 11
	23d	Discuss implications of the results for practice, policy, and future research.	Pg. 11-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg. 12
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg. 12
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Pg. 12
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg. 12
Competing interests	26	Declare any competing interests of review authors.	Pg. 12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pg. 12

Supplementary 1: Keywords used for search strategy (completed 29th March 2023)

Components	Terms
QST	QST, Quantitative sensory test, quantitative sensory testing, thermal pain, heat pain, heat pain sensitivity, heat detection threshold, heat pain threshold, heat pain tolerance, warm detection, cold pain, cold pain sensitivity, cold detection threshold, cold pain threshold, cold pain tolerance, pressure pain sensitivity, pressure pain threshold, pressure pain tolerance, electrical pain sensitivity, electrical pain threshold, electrical pain tolerance, conditioned pain modulation, temporal summation, temporal summation of pain
TKR	Total knee replacement, Total knee replacement surgery, TKR, total knee replacement, total knee replacement surgery, TKR, total knee joint replacement, total knee joint replacement surgery, tri-compartmental knee replacement surgery, tricompartmental knee joint replacement
Post operative pain	postoperative pain, persistent postoperative pain, pain after operation, postsurgical pain, persistent postsurgical pain, pain after surgery

SCOPUS search strategy

TITLE-ABS-KEY ("postoperative pain") OR TITLE-ABS-KEY ("persistent postoperative pain") OR TITLE-ABS-KEY ("pain after operation") OR TITLE-ABS-KEY ("postsurgical pain") OR TITLE-ABS-KEY ("persistent postsurgical pain") OR TITLE-ABS-KEY ("pain after surgery") AND TITLE-ABS-KEY ("total knee replacement") OR TITLE-ABS-KEY ("total knee replacement surgery") OR TITLE-ABS-KEY ("total knee replacement") OR TITLE-ABS-KEY ("total knee replacement

surgery") OR TITLE-ABS-KEY ("total knee joint replacement") OR TITLE-ABS-KEY ("total knee joint replacement surgery") OR TITLE-ABS-KEY ("tri-compartmental knee replacement surgery") OR TITLE-ABS-KEY ("tri-compartmental knee joint replacement") AND TITLE-ABS-KEY ("quantitative sensory testing") OR TITLE-ABS-KEY ("thermal pain") OR TITLE-ABS-KEY ("heat pain sensitivity") OR TITLE-ABS-KEY ("heat detection threshold") OR TITLE-ABS-KEY ("heat pain threshold") OR TITLE-ABS-KEY ("heat pain tolerance") OR TITLE-ABS-KEY ("warm detection") OR TITLE-ABS-KEY ("cold pain") OR TITLE-ABS-KEY ("cold pain sensitivity") OR TITLE-ABS-KEY ("cold detection threshold") OR TITLE-ABS-KEY ("cold pain threshold") OR TITLE-ABS-KEY ("cold pain tolerance") OR TITLE-ABS-KEY ("pressure pain sensitivity") OR TITLE-ABS-KEY ("pressure pain threshold") OR TITLE-ABS-KEY ("pressure pain tolerance") OR TITLE-ABS-KEY ("electrical pain sensitivity") OR TITLE-ABS-KEY ("electrical pain threshold") OR TITLE-ABS-KEY ("electrical pain tolerance") OR TITLE-ABS-KEY ("conditioned pain modulation") OR TITLE-ABS-KEY ("temporal summation") OR TITLE-ABS-KEY ("temporal summation of pain")

Table 2: QUIPS Tool (risk of bias for individual studies)

Articles	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Edwards et al 2022	Moderate	Moderate	Low	Low	Moderate	Moderate
Dürsteler et al 2021	Moderate	Low	Low	Low	Moderate	Low
Larsen et al 2021	Low	Low	Low	Low	Moderate	Moderate
Leung et al 2019	Low	Moderate	Moderate	Low	High	Low
Kurien et al 2019	Low	Low	Low	Moderate	Moderate	Moderate
Petersen et al 2018	Low	Moderate	Moderate	Low	Moderate	Low
Rice et al 2018	Low	Low	Low	Low	Moderate	Low
Bossmann 2017	Low	Moderate	Low	Low	Low	Moderate
Vaegter 2017	Low	Low	Low	Moderate	High	Moderate
Petersen et al. 2016	Low	Moderate	Low	Moderate	Moderate	Low
Wylde et al 2015	Low	Low	Low	Low	Moderate	Moderate
Petersen et al.	Low	Low	Low	Moderate	Moderate	Moderate

2015						
Noiseux et al 2014	Low	Low	Low	Low	Moderate	Moderate
Wylde et al 2013	Moderate	Low	Low	Moderate	Moderate	Moderate
Lundblad et al 2008	Low	High	Moderate	Moderate	Moderate	Moderate
Martinez et al 2007	Low	Low	Moderate	Low	Moderate	Moderate

Figure 3: Overall Risk of Bias

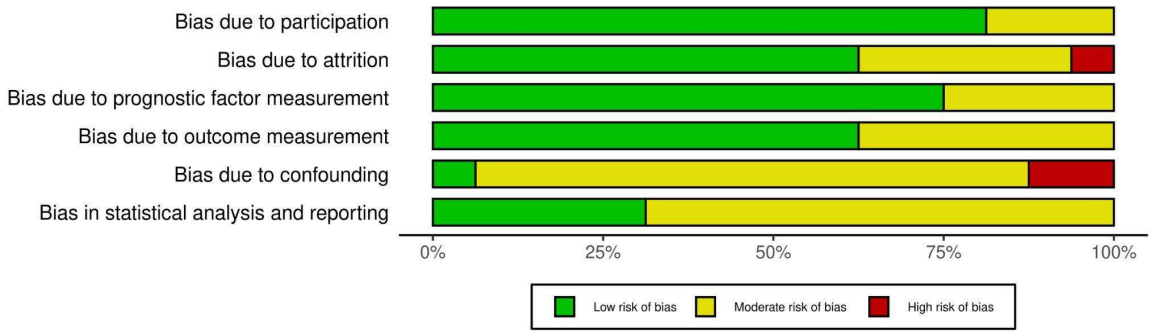

Table 3: Study Characteristics

	Author	Year	Country	Study design	Sample size	Male/Female	Mean Age	QST Parameters	QST test Site	Pain measure	Follow up Time
1	Edwards et al	2022	USA	Prospective cohort study	248	101/147	65.1	PPT, CPT, CPM	Trapezius, Patella, Middle phalanx of 3rd digit	WOMAC	6 months
2	Dürsteler et al	2021	Spain	Cohort study	146	39/107	73.1	CPM	Forearm	NRS	3 and 6 months
3	Larsen	2021	Denmark	Prospective cohort	131	58/73	67.73	CPM, PTT and PPT	Gastrocnemius	VAS	12 months
4	Leung	2019	Singapore	Cohort study	232	58/73	66	PPT	Knee	WOMAC	6 and 12 months
5	Kurien	2018	United Kingdom	prospective cohort	46	19/27	66.4	PPT, PTT, TSP, CPM	ECRL, Tibialis anterior, patella	VAS	6 months
6	Petersen	2018	Denmark	Prospective cohort	130	56/74	69.17	CDT, HPT, TSP, WDT	Tibialis anterior	VAS	12 months

7	D. A. Rice	2018	New Zealand	Prospective cohort study	300	156/144	69	TSP, PPT, and CPM	Knee Medial Joint Line	WOMAC	6 months
8	Bossmann	2017	Germany	Prospective cohort	56	19/37	68.8	CPM and TSP	Forearm	WOMAC	6 months
9	Vaegter et al	2017	Denmark	Prospective cohort	14	7/7	65.2	PPTs, PTT, CPM, and EIH	Quads, Biceps and Trapezius	NRS	6 months
10	Petersen et al.	2016	Denmark	Prospective cohort	103	37/66	69.15	PPT, PTT, TSP, and CPM	Tibialis anterior, ECRL, Patella	VAS	12 months
11	Wylde	2015	United Kingdom	Prospective cohort	234	114/125	69.1	PPT	Volar forearm	WOMAC	12 months
12	Petersen et al.	2015	Denmark	Prospective cohort	78	32/46	70	PPT, TSP, and CPM	Tibialis anterior, ECRL, Patella	VAS	12 months

13	Noiseux	2014	USA	Prospective cohort	193	68/128	61.68	MPT, HPT, and PPT	Patella	NRS	6 months
14	Wylde	2013	United Kingdom	Prospective cohort	51	22/29	68	HPT and PPT	Volar forearm and medial knee	WOMAC	13 months
15	Lundblad	2008	Sweden	Prospective cohort	69	34/35	68	EPT, EDT	Thumb and index finger	VAS	18 months
16	Martinez	2007	France	Prospective cohort	20	1/20	69	HPT, MPT, STHPI, STCPI	Knee	VAS	4 months

(CPT) Cold pressor test, (CDT) Cold detection test, (CPM) Conditioned pain modulation, (cPTT) Cuff pressure tolerance threshold (EDT) Electrical detection threshold, (EPT) Electrical pain threshold, (HPT) Heat pain threshold, (MPT) Mechanical pain threshold, (PPT) Pressure pain threshold, (STHPI)Suprathreshold heat pain intensity (STCPI)Suprathreshold cold pain intensity, (TSP) Temporal summation of pain, (WDT) Warm detection threshold

Table 4: Statistical data on association

	Author	Year	Sample size	QST Parameters	Pain measure	Statistical Method	Follow up Time	Findings	P value	95% CI (LL-UL)	R Square	R value
1	Edwards et al	2022	248	PPT, CPT, CPM	WOMAC	Univariate analysis	6 months	PPT	0.66			
								CPT	0.84			
								CPM	0.37			
								TSP	**0.02**			
						Multivariate regression			**0.01**	0.04-0.29	0.34	
2	Dürsteler et al	2021	146	CPM	NRS	Pearson correlation	3 months	CPM	**0.004**			
							6 months (at rest)	CPM	**0.038**			
3	Larsen	2021	131	CPM, PTT and PPT	VAS	Multivariate linear regression	12 months	CPM	**0.04**		0.0324	-0.18

								PTT	**0.034**			-0.222
4	Leung	2021	232	PPT	WOMAC	Pearson correlation	6 months	PPT	0.068			
				PPT			12 months	PPT	**0.012**			
5	Kurien	2018	46	PPT, PDT, TSP, CPM	VAS	Pearson correlation	6 months	PPT	**0.039**			-0.262
								TSP	**0.01**			0.343
6	Petersen	2018	130	CDT, HPT, TSP, WDT	VAS	Pearson correlations	12 months	TSP	**0.013**			0.193
								KL	**0.027**			-0.168
								WDT	**0.012**			0.195
								HPT	**0.012**			0.196
								CDT	>0.05			0.025
								CPT	>0.05			-0.002
7	D. A. Rice	2018	300	TSP, PPT, and CPM	WOMAC	Multivariate Stepwise logistic regression	6 months	TSP	0.36	0.98 to 1.05		

8	Bossmann	2017	56	CPM and TSP	WOMAC	Multivariate linear regression (ANCOVA)	6 months	CPM	**0.05**	-0.9 to -0.1		
								TSP	0.81	-3.2 to 3.7		
9	Vaegter et al	2017	14	PPTs, PTT, CPM, and EIH	NRS	Pearson's Correlation	6 months	CPM (U)	**0.035**		0.3249	0.57
								EIH			0.2809	0.52
10	Petersen et al.	2016	103	PPT, PTT, TSP, and CPM	VAS	Univariate analysis	12 months	PPT				-0.22
						Multivariate regression model		PPT			0.379	
11	Wylde	2015	234	PPT	WOMAC	Univariate linear regression (b)	12 months	PPT	**0.008**	0.74 to 4.80		
						Multivariate regression						-0.11
12	Petersen et al.	2015	78	PPT, TSP, and CPM	VAS	Pearson correlation	12 months	TSP	**0.037**			0.24

								CPM	0.123			-0.176
								PPT	**0.008**			-0.051
						Univariate linear regression		TSP	**0.037**			0.311
						Multivariate regression		TSP	0.052			0.289
13	Noiseux	2014	193	MPT, HPT, and PPT	NRS	Multivariate regression	6 months	MPT, HPT, PPT	>.10			
14	Wylde	2013	51	HPT and PPT	WOMAC	Spearman correlation	13 months	PPT knee	0.078			0.257
								PPT forearm	**0.008**			0.37
								HPT knee	0.368			0.13
								HPT forearm	0.094			0.237

15	Lundblad	2008	69	EPT, EDT	VAS	Multivariate logistic regression	18 months	EPT	**0.01**	1.69 to 50.07		
						Chi-squared test		EDT	**0.045**			
16	Martinez	2007	20	HPT, MPT, STHPI, STCPI	VAS	Spearman correlation	4 months	n.s	n.s			

Table 5: Summary of Findings

			GRADE							
Type of QST	Total no. of cohorts	Significant association	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall Quality	Explanation
Dynamic		**6/15 (40%)**								Moderate risk of bias for most domains
Conditioned pain modulation (CPM)	9	3/9	Observational studies	Serious	Serious	Not Serious	Not Serious	Serious	⊕⊕◯◯ Low	
Temporal summation of pain (TSP)	6	3/6	Observational studies	Serious	Serious	Not Serious	Not serious	Not Serious	⊕⊕⊕◯ Moderate	

Mechanical		**6/13 (46%)**								High risk of bias in 2 bias domains
Mechanical Pain Threshold (MPT)	2	0/2	Observational studies	Serious	Not serious	Not Serious	Serious	Serious	⊕⊕◯◯ Low	
Pressure Pain Threshold (PPT)	11	5/9	Observational studies	Very serious	Serious	Not Serious	Not serious	Not Serious	⊕⊕◯◯ Low	
Cuff pressure tolerance threshold (cPTT)	3	1/2	Observational studies	Very serious	serious	Not Serious	Very serious	Serious	⊕◯◯◯ Very low	
Thermal		**1/9 (11%)**								Evidence contain few studies and small

										number of participants across studies
Cold detection threshold (CDT)	1	0/1	Observational studies	Serious	Not Serious	Serious	Very serious	Serious	⨁◯◯◯ Very low	
Cold pressor test (CPT)	1	0/1	Observational studies	Very serious	Not Serious	Not Serious	Very serious	Serious	⨁◯◯◯ Very low	
Suprathreshold cold pain intensity (STCPI)	1	0/1	Observational studies	Serious	Not Serious	Not Serious	Very serious	Serious	⨁◯◯◯ Very low	
Warm detection threshold	1	0/1	Observational studies	Serious	Not Serious	Serious	Very serious	Serious	⨁◯◯◯ Very low	

(WDT)										
Heat pain threshold (HPT)	4	1/4	Observational studies	Serious	serious	Not Serious	not serious	Not Serious	⊕⊕⊕◯ Moderate	
Suprathreshold heat pain intensity (STHPI)	1	0/1	Observational studies	Serious	Not Serious	Not Serious	Very serious	Serious	⊕◯◯◯ Very low	
Electrical		**2/2 (100%)**								All studies show high risk of bias in 2 bias domains
Electrical detection threshold (EDT)	1	1/1	Observational studies	Very serious	Not Serious	Not Serious	Very serious	Not Serious	⊕◯◯◯ Very low	

Electrical pain threshold (EPT)	1	1/1	Observational studies	Very serious	Not Serious	Not Serious	Very serious	Not Serious	⨁◯◯◯ Very low	