

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

Mansfield, Michael; Kumar, Veneta; Stephens, Gareth

*Document Version*  
Peer reviewed version

*Citation for published version (Harvard):*  
Mansfield, M, Kumar, V & Stephens, G 2024, 'Can Preoperative Qualitative Sensory Testing Predict Persistent Post-operative Knee Pain following Total Knee Replacement? – A Systematic Review', *Physiotherapy Practice and Research*.

[Link to publication on Research at Birmingham portal](#)

## **General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## **Take down policy**

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

1 **TITLE PAGE**

2 **Article title:**

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

5

6

7 **Conflicting interests:**

8 All authors declare no conflict of interest.

9

10 **Word Count:** 3,510

11

12 **Keywords:** Quantitative Sensory Testing, Total Knee Replacement, Postoperative Pain,  
13 Systematic Review

14

15

16

17

18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40

## 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.

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

47  
48 **Conclusions:** Due to the heterogeneity and low-moderate quality studies included, it remains  
49 unclear whether QST can identify patients who are likely to experience persistent postoperative  
50 joint pain following TKR.

51

52

53

54

55

56 **MANUSCRIPT**

57  
58 **INTRODUCTION**

59  
60 In the United Kingdom (UK) National Health Service (NHS) the largest waiting lists are for people  
61 with bone and joint (orthopaedic) pain. As of January 2024, there are more than 800,000 people  
62 currently waiting to see an orthopaedic clinician, of which 45% have been waiting longer than 18-  
63 weeks<sup>55</sup>. One of the most common orthopaedic operations is a total knee replacement<sup>56</sup>. Around  
64 110,000 total knee replacements are conducted each year in the NHS, primarily to treat knee  
65 arthritis, at a cost the NHS around £770 million each year for the NHS<sup>57</sup>. Projections from the  
66 National Joint Registry (2022) anticipate an increase of 36.6% in the number of TKR surgeries by  
67 the year 2060<sup>38</sup>. The most common reason that individuals undergo a total knee replacement is pain  
68 relief. However, between 10-34% of patients experience pain which persists beyond three months  
69 following their knee replacement, for which there is no evidence-based treatment. People who  
70 experience persistent pain following total knee replacement are more likely to be dissatisfied with  
71 the outcome of their surgery. At one year following surgery, 17% of patients, report that they regret  
72 their decision to have a knee replacement<sup>38</sup>. Therefore, around 20,000 people a year in the UK  
73 have a total knee replacement in the NHS that will not benefit them, at a cost of around £140 million  
74<sup>57</sup>.

75  
76 In recent years, much research has been undertaken to understand whether it is possible to identify  
77 patients who are likely to experience poor outcomes following total knee replacement, prior to

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

80  
81 Quantitative Sensory Testing (QST) uses a group of non-invasive, quantifiable sensory stimuli  
82 procedures can provide insight into a person's somatosensory nerve system function and integrity  
83 <sup>3, 20</sup>. Quantitative sensory testing quantifies these altered responses by utilising various stimuli to  
84 assess perceptions of proprioception, touch, pinprick/blunt pressure sensitivity, vibration, as well  
85 as sensitivity to heat or cold stimuli <sup>3, 20</sup>. It is suggested that people who may have altered  
86 nociceptive activity, may be more likely to experience persistent post-operative pain <sup>20</sup>. If QST is  
87 able to identify individuals who are likely to experience persistent post-operative pain following  
88 total knee replacement, it could significantly reduce the burden of unsuccessful surgeries on both  
89 individuals and society by improving patient selection for surgery and informing future  
90 intervention development. A recent systematic review suggested that QST may have the potential  
91 to identify patients, who are likely to develop persistent post-operative pain from orthopaedic  
92 surgery <sup>20</sup>. This systematic review aims to understand whether pre-operative QST can identify  
93 people who will experience persistent post-operative pain following total knee replacement.

94  
95  
96

## METHODS

97  
98  
99 This systematic review was reported following the Preferred Reporting Items for Systematic  
100 Reviews and Meta-Analyses Statement (PRISMA)<sup>41</sup>.

101  
102 **Search Strategy**  
103 A systematic search was performed of four databases (EMBASE, CINAHL, SCOPUS, PubMed)  
104 and grey literature on 29th March 2023 and updated on 30th January 2024 using a search strategy  
105 with components of quantitative sensory testing, persistent postoperative pain and total knee  
106 replacement. An example of the search strategy employed in the PubMed database can be found in  
107 Figure 1. A manual search of reference lists of the acquired articles, along with relevant systematic  
108 reviews and meta-analyses was completed to identify studies that may not have been found through  
109 the initial search. No contact with expert authors in the field was attempted. After importing  
110 identified studies into EndNote X9 (Clarivate Analytics) and eliminating duplicates, a  
111 comprehensive assessment was carried out by the two researchers (V.K and G.F) blinded to reduce  
112 risk of bias and increase reliability. The titles and abstracts of the retrieved studies were scrutinised  
113 to determine inclusion. Finally, the full-text versions of the selected studies were obtained and  
114 analysed independently to assess their eligibility. Any differences that arose were resolved through  
115 consensus.

116  
117 [INSERT FIGURE 1]  
118

119 Eligibility criteria

120  
121 Studies were included if they met all the following criteria:

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

129  
130 Studies were excluded if they met the following exclusion criteria:

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

134  
135 *Assessment of Methodological Quality*

136 The methodological quality of the included studies was assessed independently by 2 reviewers  
137 (V.K and G.F) using the Quality In Prognostic Studies (QUIPS) tool.<sup>42</sup> The QUIPS tool was  
138 deemed suitable since it is specifically aimed at assessing the risk of bias in studies investigating  
139 prognostic factors in line with the recommendations of the Cochrane Prognosis Methods Group.<sup>51</sup>

140 This tool focuses on 6 domains that include study participation, study attrition, prognostic factor  
141 measurement, outcome measurement, study confounding, and statistical analysis and reporting  
142 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 <sup>19,20</sup> 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.

154

155

156

## RESULTS

157

158

### 159 Study Selection

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

168

[INSERT FIGURE 2]

169

170

171

172

173 **Study Characteristics**

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

182

183

184 **Preoperative QST Assessment**

185

186 **Type of QST**

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

191

192 **Test timing**

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

195

196

197 **PPSP Assessment**

198

199 **Outcomes**

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

204

205 **Assessment timing**

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

212

213 **Preoperative QST Association with PPSP**

214

215 **Mechanical**

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

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

221

222

### 223 ***PPT***

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

232

### 233 ***PTT***

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

241

242 ***MPT***

243 The results of both studies investigating the mechanical pain threshold at 4 and 6 months<sup>29,30</sup>  
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)<sup>31</sup> (R=0.025, P>0.05), cold pain tolerance (CPT)<sup>32</sup> (P=0.84), suprathreshold cold  
257 pain intensity (STCPI)<sup>29</sup>. The quality of evidence for the only three studies<sup>29,31,32</sup> 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)<sup>29,30,31,43</sup> followed by warm  
262 detection threshold (WDT) (one study)<sup>31</sup> and suprathreshold heat pain intensity (STHPI) (one  
263 study).<sup>29</sup> The quality of evidence for WDT and STHPI was judged to be very low. Although only

264 17% (1/6) of the studies reported a correlation with postoperative pain, the overall certainty of the  
265 evidence was rated as moderate.

266

### 267 **Electrical**

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

277

### 278 **Dynamic**

279 Dynamic measures were the second most commonly reported QST modality in 10/16 studies  
280 (62.5%). The constituted measures such as Conditioned Pain Modulation (CPM) were utilised in  
281 9/16 studies and Temporal Summation of Pain (TSP) in 6/16 studies.

282

### 283 **CPM**

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

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

290

## 291 **TSP**

292 TSP was found to be predictive of persistent post surgical pain in 3/6 studies (50%) at a minimum  
293 of 6 to 12 months post TKR<sup>11,24,31</sup>. Kurien et al. (2018)<sup>24</sup> evaluated preoperative TSP with the use  
294 of cuff algometry and monofilaments. Although both methods correlated positively with post-  
295 operative pain at 6 months, the correlation between TSP elicited using monofilaments and post-  
296 operative pain was stronger. Petersen et al. found significant correlations between TSP and post-  
297 surgical pain at 12 months in both their initial study<sup>11</sup> ( $r = 0.24$ ,  $P = 0.037$ ) and a subsequent 3-year  
298 follow-up study<sup>31</sup> ( $r = 0.193$ ,  $P = 0.013$ ). In univariate linear regression analyses, they observed  
299 similar results with significant crude coefficients of 0.311 ( $P = 0.037$ ) and significant P-values of  
300 0.023, respectively. However, these associations were not found in the multivariate model. The  
301 remaining three studies<sup>26,34,35</sup> did not find any association between TSP and post-surgical pain.  
302 Certainty of evidence for TSP was deemed moderate.

303

## 304 **Risk of Bias**

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



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

320

321

## 322 **Certainty of Evidence**

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

332



## DISCUSSION

334  
335  
336 Previous systematic reviews have explored the relationship between presurgical QST and both  
337 acute and chronic post-surgical pain in total joint arthroplasties<sup>19</sup> and other surgeries.<sup>6</sup> However,  
338 this is the first systematic review to exclusively examine the relationship between presurgical QST  
339 and persistent post-surgical pain in patients who have undergone TKR. The current review is also  
340 the first to investigate which QST measures were most predictive of this relationship and aimed to  
341 evaluate the certainty of presenting evidence.

342  
343 Among the 16 studies included a total of 13 QST measures were identified across four sub-types:  
344 mechanical, thermal, electrical, and dynamic. Given the variation in the timing of pain assessments,  
345 spanning from 3 to 18 months post-surgery, and the predominant use of non-standardized QST  
346 methods across most of the studies the evidence was narratively synthesised in this review.

347  
348 In the current review, mechanical measures were the most reported (n=12) wherein three  
349 measures—MPT, PPT and cPTT were utilised for preoperative QST. Among these measures, PPT  
350 seemed to demonstrate the most consistent correlation with persistent post-surgical pain (PPSP) in  
351 5 out of 11 studies (45%). This percentage is lower compared to a recent systematic review<sup>19</sup>, in  
352 which pressure stimuli were found to be correlated with post-surgical pain in 8 out of 12 studies  
353 (67%). These variations may be attributed to differences in the timing of pain onset and the  
354 inclusion of other joint arthroplasties within their study population. Furthermore, the selection of  
355 QST sites appears to influence pain outcomes, which may be inferred from the findings of one of  
356 the included studies,<sup>43</sup> revealing significant associations between PPT and PPSP in the forearm but

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

360  
361 The evidence for thermal QST presented conflicting findings overall. Among the three heat  
362 stimulus measures (WDT, HPT, STHPI), only 17% (1/6) of the studies reported a correlation with  
363 postoperative pain. The only study to demonstrate a positive correlation was specifically associated  
364 with the HPT measure, and the certainty of the evidence for it was rated as moderate, in contrast  
365 to the very low quality of evidence for WDT and STHPI. One study found no association between  
366 STHPI and persistent postsurgical pain (PPSP)<sup>29</sup>. However, a systematic review<sup>15</sup> has reported a  
367 strong correlation between STHPI and acute postsurgical pain in various surgeries such as total  
368 knee replacement<sup>52</sup>, elective gynaecological surgeries,<sup>14,53</sup> herniotomy,<sup>54</sup> and thoracic surgeries.<sup>10</sup>  
369 These discrepancies suggest that sensitivity to heat stimuli may indeed be dependent upon the  
370 timing of pain onset and type of surgery. Previous research has established that cold stimulus  
371 measures of thermal QST serve as strong predictors for neuropathic pain<sup>45</sup> and musculoskeletal  
372 disorders such as whiplash injuries<sup>46</sup>. However, within the context of postsurgical pain, our review  
373 examined three studies<sup>29 31 32</sup> investigating cold stimulus measures (CPT, CDT and STCPI) found  
374 no significant correlations with PPSP in patients who underwent TKR with the quality of evidence  
375 supporting these correlations judged as very low. Interestingly, these results align with findings  
376 from three other reviews<sup>6,19,47</sup>, all of which failed to establish any meaningful association between  
377 cold stimuli and the development of PPSP.

378

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

387  
388 Dynamic measures were the second most frequently employed QST modality in 10 out of 16  
389 studies. While conditioned pain modulation (CPM) showed an association with chronic post-  
390 operative pain in only 3 out of 9 studies (33%)<sup>4,27,28</sup>, the temporal summation of pain (TSP)  
391 emerged as a slightly more consistent predictor of persistent post-surgical pain, being found in 3  
392 out of 6 studies (50%)<sup>11,24,31</sup>. It should be noted that the limited association of CPM with persistent  
393 post-surgical pain aligns with findings from previous works<sup>6,19</sup>. These findings were rated as having  
394 a very low quality of evidence, primarily due to the lack of standardisation in the conditions under  
395 which the test stimulus and conditioning stimulus were administered across all 9 studies. In  
396 contrast, the evidence supporting TSP was rated as moderate. Coupled with the clinical feasibility  
397 of administering TSP and its stronger association with persistent post-surgical pain, the moderate  
398 level of evidence makes it the most suitable QST measure among those reported in this review.

399  
400 It's crucial to highlight that certain confounding factors, such as gender, were not considered in the  
401 sixteen studies investigating the development of PPSP. This may be significant given that 60% of

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

407  
408 Our study offers several advantages compared to previous research. Unlike earlier reviews  
409 assessing the body of evidence for quantitative sensory testing (QST), our review employs tools  
410 that are well-suited for prognostic studies, such as QUIPS, and conducts GRADE assessments to  
411 evaluate the quality of evidence for each QST measure. However, it is important to consider certain  
412 limitations when interpreting the findings of this study. Firstly, administration of most QST  
413 measures relied on unstandardised protocols with a limited number of studies and small participant  
414 cohorts, potentially impacting generalizability and results. Additionally, significant heterogeneity  
415 existed in the statistical methods used; some studies employed univariate analyses while others  
416 utilised multivariate approaches, introducing challenges in result comparison. Moreover, some  
417 studies did not report p-values and other non-significant findings, reducing the transparency and  
418 reliability of results and resulting in a moderate to high risk of bias.

419  
420 This systematic review was unable to establish an association between QST and PPSP based on  
421 and therefore are unable to make recommendations for clinical practice currently. However, the  
422 heterogeneity QST methods, and the poor quality of the research suggests that more needs to be  
423 done to standardise procedures and then test in a substantive cohort study. The aforementioned  
424 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<sup>48</sup>. 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

434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447

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.



448 **References**

- 449 1. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients  
450 report long-term pain after total hip or knee replacement for osteoarthritis? A systematic  
451 review of prospective studies in unselected patients. *BMJ Open*. 2012;2(1):e000435.  
452
- 453 2. Hall T, Briffa K, Schafer A, Tampin B, Moloney N. Quantitative sensory testing:  
454 implications for clinical practice [Internet]. Jull G, Moore A, Falla D, Lewis J, McCarthy  
455 C, Sterling M, editors. Macquarie University. United Kingdom: Elsevier; 2015 [cited 2023  
456 Aug 17]. p. 194–201. Available from:  
457 [https://researchers.mq.edu.au/en/publications/quantitative-sensory-testing-implications-](https://researchers.mq.edu.au/en/publications/quantitative-sensory-testing-implications-for-clinical-practice)  
458 [for-clinical-practice](https://researchers.mq.edu.au/en/publications/quantitative-sensory-testing-implications-for-clinical-practice)  
459
- 460 3. Cruz-Almeida Y, Fillingim RB. Can Quantitative Sensory Testing Move Us Closer to  
461 Mechanism-Based Pain Management? *Pain Medicine*. 2014 Jan;15(1):61–72.  
462
- 463 4. Schug SA, Lavand’homme P, Barke A, Korwisi B, Rief W, Treede RD. The IASP  
464 classification of chronic pain for ICD-11. *PAIN*. 2019 Jan;160(1):45–52.  
465
- 466 5. McMahon SE, Doran E, O’Brien S, Cassidy RS, Boldt JG, Beverland DE. Seventeen to  
467 Twenty Years of Follow-Up of the Low Contact Stress Rotating-Platform Total Knee  
468 Replacement With a Cementless Tibia in All Cases. *The Journal of Replacement* [Internet].

- 469 2019 Mar 1 [cited 2021 May 24];34(3):508–12. Available from:  
470 [https://www.replacementjournal.org/article/S0883-5403\(18\)31152-5/fulltext](https://www.replacementjournal.org/article/S0883-5403(18)31152-5/fulltext)  
471
- 472 6. Sangesland A, Støren C, Vaegter HB. Are preoperative experimental pain assessments  
473 correlated with clinical pain outcomes after surgery? A systematic review. *Scandinavian*  
474 *Journal of Pain*. 2017 Apr 1;15(1):44–52.  
475
- 476 7. Sakellariou VI, Poultsides LA, Ma Y, Bae J, Liu S, Sculco TP. Risk Assessment for Chronic  
477 Pain and Patient Satisfaction After Total Knee Replacement. *Orthopedics*. 2016 Jan  
478 1;39(1):55–62.  
479
- 480 8. Lundblad H, Kreicbergs A, Jansson KA. Prediction of persistent pain after total knee  
481 replacement for osteoarthritis. *The Journal of Bone and Joint Surgery British Volume*  
482 [Internet]. 2008 Feb 1;90(2):166–71. Available from:  
483 <https://pubmed.ncbi.nlm.nih.gov/18256082/>  
484
- 485 9. Tracy LM, Ioannou L, Baker KS, Gibson SJ, Georgiou-Karistianis N, Giummarra MJ.  
486 Meta-analytic evidence for decreased heart rate variability in chronic pain implicating  
487 parasympathetic nervous system dysregulation. *PAIN*. 2016 Jan;157(1):7–29.  
488
- 489 10. Weissman-Fogel I, Granovsky Y, Crispel Y, Ben-Nun A, Best LA, Yarnitsky D, et al.  
490 Enhanced Presurgical Pain Temporal Summation Response Predicts Post-Thoracotomy

- 491 Pain Intensity During the Acute Postoperative Phase. *The Journal of Pain*. 2009  
492 Jun;10(6):628–36.
- 493
- 494 11. Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical  
495 assessment of temporal summation of pain predicts the development of chronic  
496 postoperative pain 12 months after total knee replacement. *Pain*. 2015 Jan;156(1):55–61.
- 497
- 498 12. Chapman CR, Vierck CJ. The Transition of Acute Postoperative Pain to Chronic Pain: An  
499 Integrative Overview of Research on Mechanisms. *The Journal of Pain* [Internet]. 2017  
500 Apr;18(4):359.e1–38. Available from:  
501 <https://www.sciencedirect.com/science/article/pii/S1526590016303297>
- 502
- 503 13. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention.  
504 *The Lancet*. 2006 May;367(9522):1618–25.
- 505
- 506 14. Granot M, Lowenstein L, Yarnitsky D, Tamir A, Zimmer Etan Z. Postcesarean Section Pain  
507 Prediction by Preoperative Experimental Pain Assessment. *Anesthesiology*. 2003 Jun  
508 1;98(6):1422–6.
- 509
- 510 15. Abrishami A, Chan J, Chung F, Wong J. Preoperative Pain Sensitivity and Its Correlation  
511 with Postoperative Pain and Analgesic Consumption. *Anesthesiology* [Internet]. 2011 Feb  
512 [cited 2019 Dec 28];114(2):445–57. Available from:  
513 <https://anesthesiology.pubs.asahq.org/article.aspx?articleid=1933433>

- 514
- 515 16. Werner MU, Mjöbo HN, Nielsen PR, Rudin Å, Warner DS. Prediction of Postoperative  
516 Pain. *Anesthesiology*. 2010 Jun 1;112(6):1494–502.
- 517
- 518 17. Ip HYV, Abrishami A, Peng PWH, Wong J, Chung F. Predictors of Postoperative Pain and  
519 Analgesic Consumption. *Anesthesiology* [Internet]. 2009 Sep;111(3):657–77. Available  
520 from: <https://anesthesiology.pubs.asahq.org/article.aspx?articleid=1924225>
- 521
- 522 18. van Helmond N, Aarts HM, Timmerman H, Olesen SS, Drewes AM, Wilder-Smith OH, et  
523 al. Is Preoperative Quantitative Sensory Testing Related to Persistent Postsurgical Pain? A  
524 Systematic Literature Review. *Anesthesia & Analgesia* [Internet]. 2020 Oct 1 [cited 2023  
525 Aug 19];131(4):1146. Available from: [https://journals.lww.com/anesthesia-](https://journals.lww.com/anesthesia-analgesia/fulltext/2020/10000/is_preoperative_quantitative_sensory_testing.23.aspx)  
526 [analgesia/fulltext/2020/10000/is\\_preoperative\\_quantitative\\_sensory\\_testing.23.aspx](https://journals.lww.com/anesthesia-analgesia/fulltext/2020/10000/is_preoperative_quantitative_sensory_testing.23.aspx)
- 527
- 528
- 529 19. Paredes AC, Pinto JM, Almeida A, Pinto PR. Predictive value of quantitative sensory  
530 testing for acute and chronic postsurgical pain after total joint replacement. *Pain*. 2021 Jun  
531 29; Publish Ahead of Print.
- 532
- 533 20. Petersen KKS, Kilic K, Hertel E, Sejersgaard-Jacobsen TH, Jørgensen MK, Troelsen A, et  
534 al. Quantitative sensory testing as an assessment tool to predict the response to standard  
535 pain treatment in knee osteoarthritis: a systematic review and meta-analysis. *PAIN Reports*  
536 [Internet]. 2023 Aug 1 [cited 2023 Aug 20];8(4):e1079. Available from:

- 537 [https://journals.lww.com/painrpts/fulltext/2023/08000/quantitative\\_sensory\\_testing\\_as\\_an](https://journals.lww.com/painrpts/fulltext/2023/08000/quantitative_sensory_testing_as_an)  
538 [\\_assessment\\_tool.1.aspx](https://journals.lww.com/painrpts/fulltext/2023/08000/quantitative_sensory_testing_as_an)
- 539
- 540 21. Cornelius M, Walker J, Pejsa M, Hand M, Campbell C, Haythornthwaite J, et al. (201) Pre-  
541 surgical Quantitative Sensory Testing predicts persistent postoperative pain in total knee  
542 replacement patients. *The Journal of Pain*. 2015 Apr;16(4):S26.
- 543
- 544 22. .Braun M, Bello C, Riva T, Hönemann C, Doll D, Urman RD, et al. Quantitative Sensory  
545 Testing to Predict Postoperative Pain. *Current Pain and Headache Reports* [Internet]. 2021  
546 Jan 14;25(1):3. Available from: <https://pubmed.ncbi.nlm.nih.gov/33443676/>
- 547
- 548 23. Leung YY, Lim Z, Fan Q, Wylde V, Xiong S, Yeo SJ, et al. Pre-operative pressure pain  
549 thresholds do not meaningfully explain satisfaction or improvement in pain after knee  
550 replacement: a cohort study. *Osteoarthritis and Cartilage*. 2019 Jan;27(1):49–58.
- 551
- 552 24. Kurien T, Arendt-Nielsen L, Petersen KK, Graven-Nielsen T, Scammell BE. Preoperative  
553 Neuropathic Pain-like Symptoms and Central Pain Mechanisms in Knee Osteoarthritis  
554 Predicts Poor Outcome 6 Months After Total Knee Replacement Surgery. *The Journal of*  
555 *Pain*. 2018 Nov;19(11):1329–41.
- 556
- 557 25. Wylde V, Sayers A, Lenguerrand E, Gooberman-Hill R, Pyke M, Beswick AD, et al.  
558 Preoperative widespread pain sensitization and chronic pain after hip and knee replacement.  
559 *PAIN*. 2015 Jan;156(1):47–54.

- 560
- 561 26. Petersen KK, Graven-Nielsen T, Simonsen O, Laursen MB, Arendt-Nielsen L. Preoperative  
562 pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain  
563 relief after total knee replacement. *PAIN*. 2016 Jul;157(7):1400–6.
- 564 27. Larsen DB, Laursen M, Edwards RR, Simonsen O, Arendt-Nielsen L, Petersen KK. The  
565 Combination of Preoperative Pain, Conditioned Pain Modulation, and Pain Catastrophizing  
566 Predicts Postoperative Pain 12 Months After Total Knee Replacement. *Pain Medicine*. 2021  
567 Jan 7;22(7):1583–90.
- 568
- 569 28. Vaegter HB, Handberg G, Emmeluth C, Graven-Nielsen T. Preoperative Hypoalgesia After  
570 Cold Pressor Test and Aerobic Exercise is Associated With Pain Relief 6 Months After  
571 Total Knee Replacement. *The Clinical Journal of Pain*. 2017 Jun;33(6):475–84.
- 572
- 573 29. Martinez V, Fletcher D, Didier Bouhassira, Sessler DI, Chauvin M. The Evolution of  
574 Primary Hyperalgesia in Orthopedic Surgery: Quantitative Sensory Testing and Clinical  
575 Evaluation Before and After Total Knee Replacement. *Anesthesia & Analgesia*. 2007 Sep  
576 1;105(3):815–21.
- 577
- 578 30. Noiseux NO, Callaghan JJ, Clark CR, Zimmerman MB, Sluka KA, Rakel BA. Preoperative  
579 Predictors of Pain Following Total Knee Replacement. *The Journal of Replacement*. 2014  
580 Jul;29(7):1383–7.
- 581

- 582 31. Petersen KK, Simonsen O, Laursen MB, Arendt-Nielsen L. The Role of Preoperative  
583 Radiologic Severity, Sensory Testing, and Temporal Summation on Chronic Postoperative  
584 Pain Following Total Knee Replacement. *The Clinical Journal of Pain*. 2018  
585 Mar;34(3):193–7.  
586
- 587 32. Edwards RR, Campbell C, Schreiber KL, Meints S, Lazaridou A, Martel MO, et al.  
588 Multimodal prediction of pain and functional outcomes 6 months following total knee  
589 replacement: a prospective cohort study. *BMC Musculoskeletal Disorders*. 2022 Mar  
590 29;23(1).  
591
- 592 33. Cruz-Almeida Y, Fillingim R. PSYCHOLOGY, PSYCHIATRY & BRAIN  
593 NEUROSCIENCE SECTION Review Article Can Quantitative Sensory Testing Move Us  
594 Closer to Mechanism-Based Pain Management? 2014  
595
- 596 34. Bossmann T, Brauner T, Wearing S, Horstmann T. Predictors of chronic pain following  
597 total knee replacement in females and males: an exploratory study. *Pain Management*. 2017  
598 Sep;7(5):391–403.  
599
- 600 35. Rice DA, Kluger MT, McNair PJ, Lewis GN, Somogyi AA, BoroTKRnics R, et al.  
601 Persistent postoperative pain after total knee replacement: a prospective cohort study of  
602 potential risk factors. *British Journal of Anaesthesia*. 2018 Oct;121(4):804–12.  
603

- 604 36. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, et al. Use of GRADE for  
605 assessment of evidence about prognosis: rating confidence in estimates of event rates in  
606 broad categories of patients. *BMJ*. 2015 Mar 16;350(mar16 7):h870–0.  
607
- 608 37. Ip HYV, Abrishami A, Peng PWH, Wong J, Chung F. Predictors of Postoperative Pain and  
609 Analgesic Consumption. *Anesthesiology* [Internet]. 2009 Sep;111(3):657–77. Available  
610 from: <https://anesthesiology.pubs.asahq.org/article.aspx?articleid=1924225>  
611
- 612 38. Matharu G, Culliford D, Blom A, Judge A. Projections for primary hip and knee  
613 replacement surgery up to the year 2060: an analysis based on data from The National Joint  
614 Registry for England, Wales, Northern Ireland and the Isle of Man. *The Annals of The*  
615 *Royal College of Surgeons of England*. 2022 Jun;104(6):443–8.  
616
- 617 39. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and Molecular Mechanisms of  
618 Pain. *Cell* [Internet]. 2009 Oct;139(2):267–84. Available from:  
619 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2852643/>  
620
- 621 40. Cornelius M, Walker J, Pejisa M, Hand M, Campbell C, Haythornthwaite J, et al. (201)  
622 Presurgical Quantitative Sensory Testing predicts persistent postoperative pain in total knee  
623 replacement patients. *The Journal of Pain* [Internet]. 2015 [cited 2023 Sep 25];16(4):S26.  
624 Available from: <https://doi.org/10.1016/j.jpain.2015.01.116>  
625



- 626 41. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The  
627 PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *British*  
628 *Medical Journal*. 2021 Mar 29;372(71).  
629
- 630 42. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing Bias in  
631 *Studies of Prognostic Factors*. *Annals of Internal Medicine*. 2013 Feb 19;158(4):280.  
632
- 633 43. Wylde V, Palmer S, Learmonth ID, Dieppe P. The association between pre-operative pain  
634 sensitisation and chronic pain after knee replacement: an exploratory study. *Osteoarthritis*  
635 *and Cartilage*. 2013 Sep;21(9):1253–6.  
636
- 637 44. Dürsteler C, Salazar Y, Rodriguez U, Pelfort X, Verdié LP. Conditioned pain modulation  
638 predicts persistent pain after knee replacement surgery. *PAIN Reports*. 2021 Jan;6(1):e910.  
639
- 640 45. Georgopoulos V, Akin-Akinyosoye K, Zhang W, McWilliams DF, Hendrick P, Walsh DA.  
641 Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability,  
642 and negative affect: a systematic review and meta-analysis. *Pain*. 2019 Apr  
643 24;160(9):1920–32.  
644
- 645 46. Goldsmith R, Wright C, Bell SF, Rushton A. Cold hyperalgesia as a prognostic factor in  
646 whiplash associated disorders: A systematic review. *Manual Therapy*. 2012 Oct;17(5):402–  
647 10.  
648

- 649 47. Petersen KK, Vaegter HB, Stubhaug A, Wolff A, Scammell BE, Arendt-Nielsen L, et al.  
650 The predictive value of quantitative sensory testing. *Pain*. 2020 Jul 21; Publish Ahead of  
651 Print.  
652
- 653 48. Weaver KR, Griffioen MA, Klinedinst NJ, Galik E, Duarte AC, Colloca L, et al.  
654 Quantitative Sensory Testing Across Chronic Pain Conditions and Use in Special  
655 Populations. *Frontiers in Pain Research*. 2022 Jan 28;2.  
656
- 657 49. Wilder-Smith CH, Hill L, Dyer RA, Torr G, Coetzee and. Postoperative Sensitization and  
658 Pain After Cesarean Delivery and the Effects of Single IM Doses of Tramadol and  
659 Diclofenac Alone and in Combination. *Anesthesia & Analgesia*. 2003 Aug;97(2):526–33.  
660
- 661 50. Nielsen PR, Nørgaard L, Rasmussen LS, Kehlet H. Prediction of post-operative pain by an  
662 electrical pain stimulus. *Acta Anaesthesiologica Scandinavica*. 2007 May;51(5):582–6.  
663
- 664 51. Group CCPM. The Cochrane Collaboration Prognosis Methods Group, Review Tools.  
665 [Internet]. Cochrane.org. 2018. Available from:  
666 <https://methods.cochrane.org/prognosis/tools>  
667
- 668 52. Lunn TH, Gaarn-Larsen L, Kehlet H. Prediction of postoperative pain by preoperative pain  
669 response to heat stimulation in total knee replacement. *Pain*. 2013 Sep;154(9):1878–85.  
670

671 53. Strulov L, Zimmer EZ, Granot M, Tamir A, Jakobi P, Lowenstein L. Pain Catastrophizing,  
672 Response to Experimental Heat Stimuli, and Post–Cesarean Section Pain. *The Journal of*  
673 *Pain*. 2007 Mar;8(3):273–9.  
674

675 54. Aasvang Eske K, Gmaehle E, Hansen Jeanette B, Gmaehle B, Forman Julie L, Schwarz J,  
676 et al. Predictive Risk Factors for Persistent Postherniotomy Pain. *Anesthesiology*. 2010 Apr  
677 1;112(4):957–69.  
678

679 55. NHS England. NHS England waiting time statistics. [Internet]. 2024. Available from  
680 [https://www.england.nhs.uk/statistics/statistical-work-areas/rtt-waiting-times/rtt-data-](https://www.england.nhs.uk/statistics/statistical-work-areas/rtt-waiting-times/rtt-data-2023-24/)  
681 [2023-24/](https://www.england.nhs.uk/statistics/statistical-work-areas/rtt-waiting-times/rtt-data-2023-24/)  
682

683 56. National Joint Registry. Annual report [Internet]. Available from  
684 <https://www.njrcentre.org.uk/njr-annual-report-2022/>  
685

686 57. NHS England. National pay tariff [Internet].  
687 [https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-](https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/)  
688 [annexes-and-supporting-documents/](https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/)  
689  
690  
691  
692  
693  
694

695

696

697

698 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**)

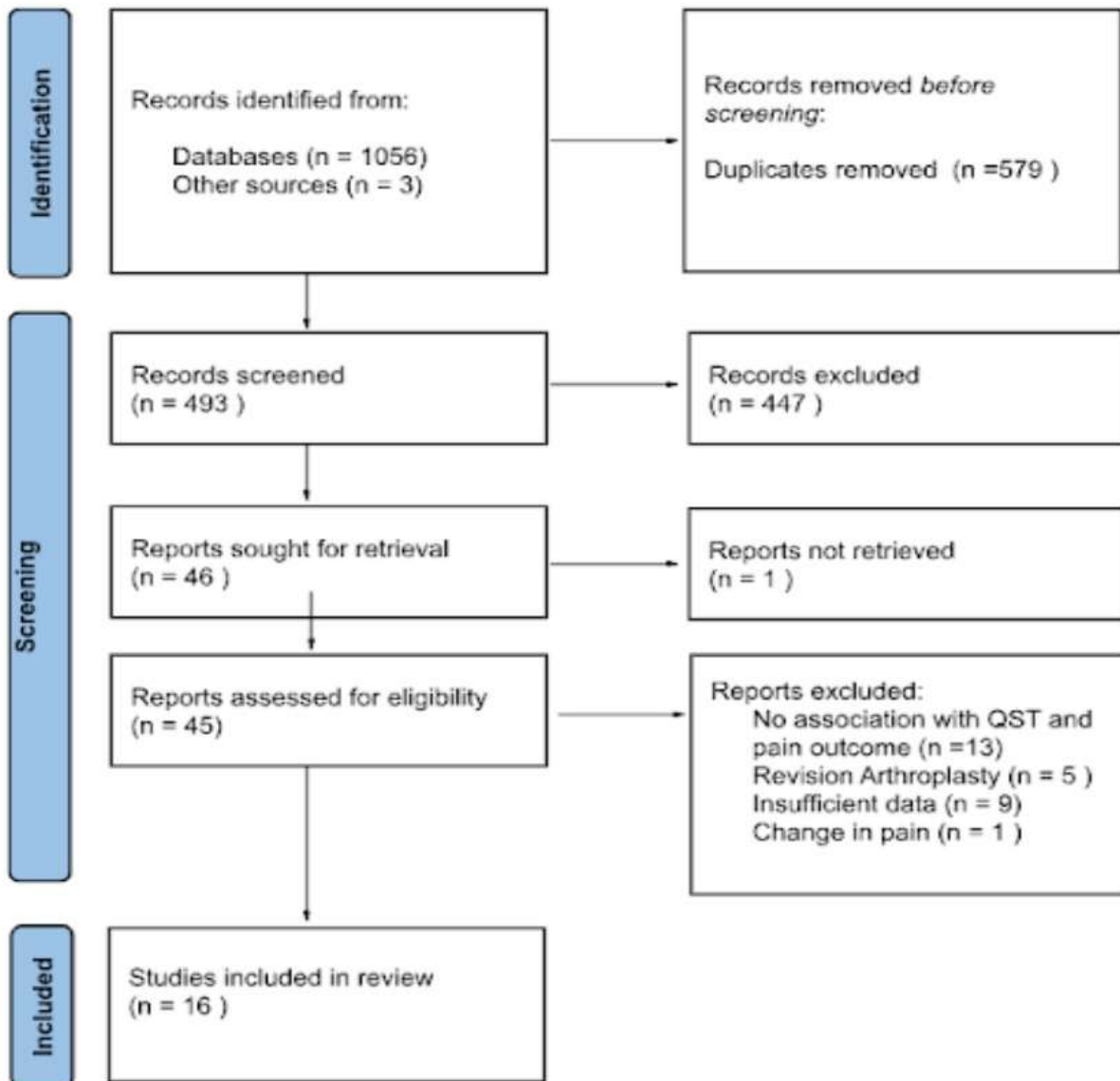
699  
700  
701  
702  
703  
704  
705  
706  
707

708

709

710 **Figure 2: PRISMA flowchart**

711



712

713

714

715

716

717

718 **Appendix: PRISMA 2020 Checklist**

719

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Pg. 1
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg. 2
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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



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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>OTHER INFORMATION</b>			
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

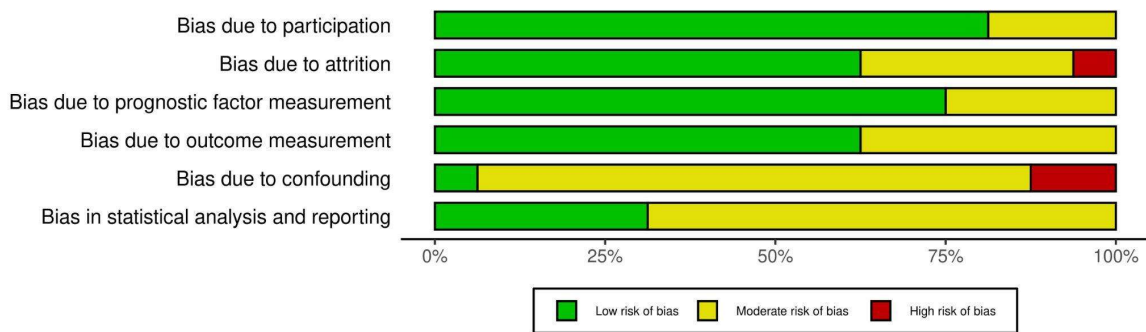
surgery" ) OR TITLE-ABS-KEY ( "total knee joint replacement" ) OR TITLE-ABS-KEY ( "total knee joint replacement surgery" ) OR TITLE-ABS-KEY ( "tri-compartmental knee replacement surgery" ) OR TITLE-ABS-KEY ( "tri-compartmental knee joint replacement" ) AND TITLE-ABS-KEY ( "quantitative sensory testing" ) 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	4	201 USA	Prospective cohort	193	68/128	61.68	MPT, HPT, and PPT	Patella	NRS	6 months
14	Wylde	3	201 United Kingdom	Prospective cohort	51	22/29	68	HPT and PPT	Volar forearm and medial knee	WOMAC	13 months
15	Lundblad	8	200 Sweden	Prospective cohort	69	34/35	68	EPT, EDT	Thumb and index finger	VAS	18 months
16	Martinez	7	200 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	<b>0.02</b>			
					Multivariate regression			<b>0.01</b>	0.04-0.29	0.34		
2	Dürsteler et al	2021	146	CPM	NRS	Pearson correlation	3 months	CPM	<b>0.004</b>			
							6 months (at rest)	CPM	<b>0.038</b>			
3	Larsen	2021	131	CPM, PTT and PPT	VAS	Multivariate linear regression	12 months	CPM	<b>0.04</b>		0.0324	-0.18

								PTT	<b>0.034</b>			-0.222
4	Leung	2021	232	PPT	WOMAC	Pearson correlation	6 months	PPT	0.068			
				PPT			12 months	PPT	<b>0.012</b>			
5	Kurien	2018	46	PPT, PDT, TSP, CPM	VAS	Pearson correlation	6 months	PPT	<b>0.039</b>			-0.262
								TSP	<b>0.01</b>			0.343
6	Petersen	2018	130	CDT, HPT, TSP, WDT	VAS	Pearson correlations	12 months	TSP	<b>0.013</b>			0.193
								KL	<b>0.027</b>			-0.168
								WDT	<b>0.012</b>			0.195
								HPT	<b>0.012</b>			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	<b>0.05</b>	-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)	<b>0.035</b>		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	<b>0.008</b>	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	<b>0.037</b>			0.24

								CPM	0.123			-0.176
								PPT	<b>0.008</b>			-0.051
						Univariate linear regression		TSP	<b>0.037</b>			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	<b>0.008</b>			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	<b>0.01</b>	1.69 to 50.07		
						Chi-squared test		EDT	<b>0.045</b>			
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 associations	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall Quality	Explanation
<i>Dynamic</i> <b>6/15 (40%)</b>									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	

<i>Mechanical</i> <b>6/13 (46%)</b>										High risk of bias in 2 bias domains
Mechanical Pain Threshold (MPT)	2	0/2	Observational studies	Serious	Not serious	Not Serious	Serious	Serious	Serious	⊕⊕○○ Low
Pressure Pain Threshold (PPT)	11	5/9	Observational studies	Very serious	Serious	Not Serious	Serious	Not serious	Not Serious	⊕⊕○○ Low
Cuff pressure tolerance threshold (cPTT)	3	1/2	Observational studies	Very serious	serious	Not Serious	Very serious	Serious	Serious	⊕○○○ Very low
<i>Thermal</i> <b>1/9 (11%)</b>										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	
Suprathresh old 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	Serious	Very serious	Serious	⊕○○○ Very low	
<i>Electrical</i> <b>2/2 (100%)</b>										All studies show high risk of bias in 2 bias domains
Electrical detection threshold (EDT)	1	1/1	Observational studies	Very serious	Not Serious	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
--	---	-----	--------------------------	-----------------	-------------	----------------	-----------------	-------------	------------------