Systematic Review and Meta-Analysis

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Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability, and negative affect: a systematic review and meta-analysis

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Abstract

Hypersensitivity due to central pain mechanisms can influence recovery and lead to worse clinical outcomes, but the ability of quantitative sensory testing (QST), an index of sensitisation, to predict outcomes in chronic musculoskeletal disorders remains unclear. We systematically reviewed the evidence for ability of QST to predict pain, disability, and negative affect using searches of CENTRAL, MEDLINE, EMBASE, AMED, CINAHL, and PubMed databases up to April 2018. Title screening, data extraction, and methodological quality assessments were performed independently by 2 reviewers. Associations were reported between baseline QST and outcomes using adjusted (β) and unadjusted (*r*) correlations. Of the 37 eligible studies (n = 3860 participants), 32 were prospective cohort studies and 5 randomised controlled trials. Pain was an outcome in 30 studies, disability in 11, and negative affect in 3. Meta-analysis revealed that baseline QST predicted musculoskeletal pain (mean $r = 0.31$, 95% confidence interval [CI]: 0.23-0.38, n = 1057 participants) and disability (mean $r = 0.30$, 95% CI: 0.19-0.40, n = 290 participants). Baseline modalities quantifying central mechanisms such as temporal summation and conditioned pain modulation were associated with follow-up pain (temporal summation: mean $r = 0.37$, 95% CI: 0.17-0.54; conditioned pain modulation: mean $r = 0.36$, 95% CI: 0.20-0.50), whereas baseline mechanical threshold modalities were predictive of follow-up disability (mean $r = 0.25$, 95% CI: 0.03-0.45). Quantitative sensory testing indices of pain hypersensitivity might help develop targeted interventions aiming to improve outcomes across a range of musculoskeletal conditions.

Keywords: Musculoskeletal pain, Pain sensitisation, Quantitative sensory testing, Systematic review, Outcome prediction

1. Introduction

Musculoskeletal disease is a worldwide phenomenon and one of the most frequent reasons for seeking health care assistance.[60] Pain is paramount in a range of symptoms associated with musculoskeletal pathology, which contributes to functional limitation.[80,102] The most prevalent musculoskeletal conditions that transition into chronicity include osteoarthritis (OA), low back pain (LBP) or neck pain, and rheumatoid arthritis.[11] Chronic pain may be initiated by musculoskeletal pathology, but is frequently also augmented by modulation of sensory inputs by the peripheral nervous system and central nervous system (CNS).[9,22,67,82,93]

Central sensitisation refers to neurophysiological processes that can occur throughout the CNS leading to changes in the spinal cord as well as in supraspinal centres such as the brainstem, the cerebral cortex, the thalamus, and the limbic system.[52] Central sensitisation is implicated in pain chronification, manifested by pain hypersensitivity (augmentation), and spread to sites beyond those directly affected by musculoskeletal pathology.[109] Sustained activation of peripheral nociceptive pathways due to musculoskeletal pathology (eg, trauma or inflammation) drives pain hypersensitivity,[31] which may be maintained by neuroplastic changes in the CNS.[76] Pain hypersensitivity is influenced by physical, genetic, psychological, and environmental factors.[79] Researchers have suggested that cognitive factors such as maladaptive beliefs (catastrophising, fear of movement, and expectations of treatment outcomes) might contribute to pain hypersensitivity.[101,113] Pain-specific cognitions such as catastrophisation influence endogenous pain modulation in healthy participants.[100] The presence of pain hypersensitivity complicates the clinical picture of chronic

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musculoskeletal conditions,[69] may cause or contribute to the transition from acute to chronic pain, and may be a barrier to achieving optimal treatment outcomes.[26,34,51]

Clinically important pain hypersensitivity is not present in all individuals with chronic pain,[90,109] contributing to heterogeneity in prognosis and treatment outcomes. It has been suggested that people with centrally driven pain hypersensitivity might better respond to education, exercise, and cognitive behavioural therapy than to treatments focusing on reducing nociceptive triggers alone.[53,65,66]

Detection and measurement of hypersensitivity is challenging in human research and clinical practice, and there is no consensus yet on the most appropriate tools for use in chronic musculoskeletal pain.[33,63] Identifying optimal indices of hypersensitivity is required to develop targeted treatment strategies that can improve patient outcomes. Self-report questionnaires may identify risk factors and symptoms that are commonly associated with central sensitisation.[3] Qualities of pain in people with central sensitisation, however, overlap substantially with pain qualities in people with predominant nociceptive pain mechanisms. Quantitative sensory testing (QST) is a psychophysical approach through which stimuli are applied under standardised testing protocols, and the participants' self-reported sensory experience is quantified.[38] Quantitative sensory testing can explore mechanisms responsible for the development or maintenance of local and widespread pain in musculoskeletal disorders.[20,74] Quantitative sensory testing uses simple tools for the assessment of the perception of touch, vibration, proprioception, and pinprick/blunt pressure sensitivity or sensitivity to cold or heat stimuli.[21] The various QST modalities can provide important information about pain mechanisms,[6,20] and can be used to quantify sensory alterations to healthy individuals and patients alike.[85] However, the exact neurophysiological mechanisms that underline QST responses are not yet fully established.

The predictive capacity of QST has been previously explored in nonmusculoskeletal pain states. Baseline sensory measurements have been associated with analgesic consumption in patients with chronic pancreatitis[73] and in healthy individuals with experimental pain,[29] with the clinical course of painful temporomandibular disorder,[89] and with tension-type headaches.[13] In musculoskeletal conditions, QST measures before surgery have been associated with acute postoperative outcomes[2,27,86,107]; however, the capacity of QST to predict long-term postoperative outcomes and outcomes in nonsurgical contexts has not been fully investigated. Potential influences from QST modality and musculoskeletal diagnosis, and prediction of different pain-related experiences, such as pain severity, reduced functional capacity (disability), anxiety, and depression (negative affect)[91] remain uncertain. A greater understanding of the role of pain hypersensitivity in prognosis and how QST might predict musculoskeletal outcomes should help better predict those who are most likely to gain benefit from treatments aiming to reduce ongoing pain, distress, or disability.

We used systematic literature review and meta-analysis to primarily determine the ability of QST to predict musculoskeletal outcomes in unadjusted analyses. In secondary analyses, we explored possible mechanisms underlying prediction by adjusting for other covariates and confounders.

2. Methods

The present systematic review adheres to an a priori but not publicly registered protocol.

2.1. Systematic literature search

A systematic online search was conducted in the following databases: CENTRAL, MEDLINE, EMBASE, AMED, CINAHL, and PubMed from 1948 until April 2018. In the absence of a previously standardised search strategy for QST and musculoskeletal conditions, a unique strategy (Appendix 1, available as supplemental digital content at http://links.lww.com/PAIN/A787) was based on previous systematic reviews. The QST elements of the search strategy were adapted from a systematic review on the utilisation of QST in painful OA,[98] and the musculoskeletal components were adapted from a systematic review on musculoskeletal intervention and imaging.[32] The search strategy was not limited to a specific study design to maximise the potential to retrieve relevant studies and because statistical association analysis can be frequently found in randomised controlled trials (RCTs) as well as in prospective cohort studies. A list of the search terms and their combinations that were used in the aforementioned databases is demonstrated in Appendix 1 (available as supplemental digital content at http://links.lww.com/PAIN/A787). Citation tracking from identified studies as well as from relevant reviews was also used to maximise the efficiency of the search strategy. No contact of authors to retrieve missing data was attempted.

2.2. Inclusion/exclusion criteria

We operationally defined QST as a method that attempts to measure, in a quantifiable way, responses to sensory stimuli applied on the skin with the aim to be used as an indicator of altered pain sensitivity. Studies that featured QST in their methodology were considered for inclusion in the systematic literature review only if they satisfied the criteria summarised in **Table 1**. All identified studies were downloaded and imported to

Table 1

Study eligibility criteria.

Inclusion criteria
1. Prospective studies that had recruited adult participants with any musculoskeletal condition and had used QST to predict a longitudinal outcome.
2. QST modalities used one or more of chemical, electrical, mechanical, and/or thermal stimuli applied to skin, muscle, or joint
3. Univariate, bivariate, or multivariate statistical relationship between QST and outcomes reported, or report data that allow such calculation.
4. QST protocol describes stimulus modality, anatomical site, and intensity.
5. Published in English language as an original research article in a peer-reviewed journal.
Exclusion criteria
1. Studies reporting only cross-sectional data.
2. Duplicate publication of data (follow-up analysis of already published data).
3. Books or book chapters, PhD theses or other dissertations, and abstracts of conference presentations.

QST, quantitative sensory testing.

EndNote X8 (Thomson Reuters) where the duplicates were removed. Two reviewers independently undertook the two-phase screening process. Phase one (V.G. and D.A.W.), was the evaluation of the titles and abstracts of the identified studies, whereas phase 2 (V.G. and K.A.-A.) consisted of full-text retrieval of all studies deemed eligible for inclusion at the end of phase one.

2.3. Data extraction

To increase reliability, 2 independent reviewers (V.G. and K.A.-A.) extracted the data from included studies using a bespoke spreadsheet. Data were extracted on study design, setting, sample selection, length of follow-up, musculoskeletal condition, affected joint or body part, diagnostic criteria, demographic data (mean age, sex and number of participants), pain severity at baseline and at follow-up, stimulus protocol, QST modalities and outcome measures, and the anatomical site of QST. Correlation coefficient (*r*), regression coefficient (β), odds ratios (ORs), area under the curve, and χ^2 values were collected along with their *P*-value, SD, SE and 95% confidence interval (CI). We adhered to suggestions by Hayden et al.[40] and, when data were extracted from a regression model, the prognostic factors that the derived value was adjusted for were also extracted (Appendix 2, available as supplemental digital content at http://links.lww.com/PAIN/A787). In all cases of disagreement on the extracted data or their interpretation, consensus was achieved through discussion, whenever necessary including all authors.

2.4. Quality and content assessment

The quality of included studies was appraised by the Quality In Prognosis Studies (QUIPS) Tool[41] for observational cohort studies as well as RCTs.

2.5. Data synthesis and analysis

Coding of the data was conducted by one reviewer (V.G.) and was validated by one coinvestigator (D.F.M.). Data from included studies were primarily categorised according to association values featured in the studies: *r*-correlation coefficients (unadjusted correlation) and β-coefficients (adjusted correlation). All extracted OR values were log-transformed to β-coefficients with the use of RevMan 5 (Review Manager. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and were therefore fitted in the adjusted correlation data cohort. Data were further subdivided according to the musculoskeletal outcome (pain, disability, and negative affect) measured in the study and, given sufficient data, separate meta-analysis was conducted for each outcome. When a study used a single outcome measure to observe more than one outcome (eg, pain and disability), then we categorised the data according to which outcome the tool was prioritising. If there was an equal weight on both outcomes, then we included the data on both subsets. In secondary, exploratory analyses, data were further subgrouped according to study design (RCT or prospective cohort) and QST modalities based on the type of stimulation such as mechanical (pressure/punctate detection or tolerance threshold with algometers, von Frey monofilaments, or pinpricks), thermal (cold–hot detection or pain thresholds), movement (pain provocation testing), and electrical (detection or pain thresholds). For the purposes of this review, we further subclassified QST modalities as "static" and "dynamic," with static modalities including pain detection and tolerance thresholds, and dynamic modalities investigating changes in certain mechanisms of pain processing with specialised stimulation (descending pain modulation, temporal and spatial summation).[6] All QST and outcome measurements were extracted at baseline and subsequent follow-ups. If different QST application sites were reported, data were extracted for all and grouped into local, distal, and remote to the affected joint sites. We defined as local site the primary area of clinical pain (knee, neck, low back, shoulder, elbow, and hip). Distal sites (eg, tibialis anterior in knee OA) were in the same limb as the musculoskeletal pathology, and distant sites were elsewhere in the body.

Forest and funnel plots were developed from pooled data of comparable studies by using a random-effects model of analysis in R (meta package, R Core Team 2017, Austria). To increase the sample size of the model and allow for more rigorous analysis, data were pooled for meta-analysis only where there were at least 3 eligible studies. When a single study reported both correlation and regression coefficients, both values were used in separate meta-analysis models. In cases where a single study reported more than one result from the same analytical approach (unadjusted correlation or adjusted correlation), the stronger association value was incorporated into the model.[48] If associations were of similar strength, the statistically significant value ($P < 0.05$) was preferred for analysis, usually indicating the larger numbers of participants. In situations where unadjusted and adjusted β-coefficient values were reported, we incorporated only the adjusted values in the models.[4] When multiple associations from the same study were statistically significant, we included the one related to the most clinically relevant aspect of the outcome (worst pain or pain with movement). Single studies that examined the relationship of QST and outcome in 2 different musculoskeletal conditions were subdivided into 2 separate studies for the purposes of statistical analysis and were included in the same model.

Pearson's *r* or Spearman's ρ were included in the same models and were z-transformed during the analysis to normalise the sampling distribution of unadjusted correlation (*r*) and decrease the bias of the average correlation.[17] Given the variability in study design, QST modalities, and follow-up outcome measures, statistics to test the null hypothesis of statistical validity (Cochran's Q test) and to quantify the percentage of variance attributable to study heterogeneity rather than chance (I^2 statistic) were calculated and reported for each forest plot.[47] Where statistically significant, heterogeneity was determined by an I^2 value with an associated *P*-value of <0.1. I^2 values of 25% were considered as low heterogeneity, of 50% as moderate, and of 75% as high.[47] As per study protocol, we a priori considered a cutoff I^2 value of 50% to perform subgroup analysis with subgroups defined based on methodological quality, QST application site (local vs distal or distant), musculoskeletal condition, QST protocol, and QST modality. Based on levels of heterogeneity and where there were sufficient data, further post hoc exploratory analyses were permitted. The post hoc analyses reported here explore relationships between baseline QST and follow-up pain according to different QST stimulus within specific modalities, site of clinical pain (axial or peripheral), study design, and studies that in their regression models had adjusted for baseline pain. Data were converted when necessary to ensure that higher numerical QST values reflected greater sensitivity.

To assess for publication bias, funnel plots were developed and to assess funnel plot asymmetry, Egger test was performed.[28] Judging overall risk of bias for each study is recommended where judgments can be made within a specific context such as developing clinical practice guidelines[46] or for undertaking sensitivity analyses.[42] The overall risk of bias for both study designs was determined to allow combined subgroup analyses according to levels of bias (high, moderate, and low). We

a priori set study confounding and appropriate statistical analysis as the most important domains for QUIPS.[41] The likely magnitude and direction of bias was considered for an overall judgement whenever there was a different measurement of bias between domains of the same tool.[46] All discrepancies were discussed between the 2 reviewers (V.G. and K.A.-A.), and the overall risk of bias was determined through consensus.

For interpretation purposes, the strength of any unadjusted association was considered little or zero, fair, moderate to good, and good to excellent when *r* values were between 0.00 and 0.25, 0.25 to 0.50, 0.50 to 0.75, and >0.75, respectively.[81]

The criteria for exclusion from the meta-analysis were the absence of unadjusted or adjusted correlation data. The present article was composed under the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[55]

3. Results

3.1. Characteristics of included studies

The study selection process is shown in **Figure 1** (37 studies), a summary of the study characteristics in **Table 2**, and an overview of study data in Appendix 3 and 4a, b, c (available as supplemental digital content at http://links.lww.com/PAIN/A787). Of the 37 studies that met the inclusion criteria, 32[1,10,16,19,23–25,35,37,49,54,56,57,59,62,70,75,77,78,83,94,95,97,99,104–106,108,110–112] were prospective cohort studies and 5 were RCTs.[5,18,43,50,61] The total number of participants was 3810, of whom 277 were in RCTs. Women comprised 58% of all participants, and the average age of participants in each study ranged from 36 to 72 years (**Table 2**). Interventions offered in the RCTs were non-steroidal anti-inflammatory drugs,[5] cervical and shoulder manipulation,[18] exercise therapy,[43] transcranial magnetic stimulation,[61] and a combination of analgesic medication, physiotherapy, education, and psychological support.[50] Knee OA was the most commonly studied condition (13/37 studies), and postoperative pain after thoracotomy, subacromial decompression, total hip replacement or total knee replacement, and abdominal surgery comprised the second commonest condition (8/37). The remaining studies focused on whiplash-associated disorders (WAD) (6/37), LBP (4/37), shoulder pain (3/37), epicondylitis (1/37), fibromyalgia (1/37), and anterior cruciate ligament tear (1/37).

Thirty-four studies reported data that could be included in meta-analysis; 22 studies reported correlation coefficients, and 24 studies reported β-coefficients or ORs. Two studies each reported on either 2 separate conditions (LBP and neck pain) or 2 interventions (total hip replacement and total knee replacement) and each provided data for their different populations that allowed fitting within a single meta-analysis model. All 37 identified studies demonstrated good methodological quality with most of them (25/37) displaying low risk of bias (Appendix 5, available as supplemental digital content at http://links.lww.com/PAIN/A787). Out of the 34 studies included in meta-analysis models, 24 were considered of low risk of bias and 10 of moderate risk (Appendix 5, available as supplemental digital content at http://links.lww.com/PAIN/A787).

3.2. Quantitative sensory testing modalities, outcomes, and test sites

The majority of the studies (30/37) reported on more than one QST modality. Mechanical pressure (assessed by various pressure algometers) was the most common stimulus (26/37), followed by cold (15/37), heat (14/37), and punctate (pinprick: 5/37, von Frey monofilaments 3/37) stimuli. Nearly all studies (32/37) reported pain detection and tolerance thresholds as a QST outcome. Conditioned pain modulation (CPM) (12/37), temporal summation (TS) (8/37), pain intensity (8/37), sensation detection threshold (6/37), and spatial summation (1/37) was each reported in a minority of studies. Most publications reported

Table 2

Summary of study characteristics.

	Cohort	RCT	All studies
No. Studies	32	5	37
No. Subjects	3583	277	3860
Mean age (y)	55	54	55
Female, %	56	72	58
Setting			
Hospital	6	2	8
Community	6	2	8
Unclear	20	1	21
Diagnosis			
OA	15	2	17
MSK injury	1	0	1
Whiplash	5	1	6
Neck pain	1	0	1
Low back pain	4	0	4
Fibromyalgia	0	1	1
Shoulder pain	3	1	4
Postoperative pain	3	0	3
Affected site			
Knee	15	2	17
Hip	1	0	1
Neck	6	1	7
Low back	4	0	4
Shoulder	3	1	4
Thorax	1	0	1
Abdominal area	2	0	2
Widespread body pain	0	1	1
MSK outcome measure			
Pain	26	4	30
Disability	10	1	11
Depression	2	0	2
Anxiety	1	0	1
QST stimulus modality*			
Mechanical			
Pressure	21	5	26
Punctate	8	0	8
Movement	1	0	1
Electrical	5	1	6
Thermal			
Heat	13	1	14
Cold	14	1	15
QST outcome measure*			
Pain detection threshold	28	4	32
Pain tolerance threshold	6	0	6
Sensation detection threshold	5	1	6
Pain intensity	8	0	8
Conditioned pain modulation	11	1	12
Temporal summation	5	3	8
Spatial summation	1	0	1
QST test sites*			
Affected joint	20	4	24
Distal to affected joint	10	3	13
Remote	20	3	23

* One study may involve more than one QST modality, outcome measure, and test site.
MSK, musculoskeletal; OA, osteoarthritis; RCT, randomised controlled trial; QST, quantitative sensory testing.

more than one anatomical site for QST assessment (Appendix 3, available as supplemental digital content at http://links.lww.com/PAIN/A787). The commonest were the site of clinical pain (24/37), followed equally by sites that were distal to (13) or remote from (13) the site of reported pain.

3.3. Reliability of quantitative sensory testing

Four studies[49,59,75,110,112] reported that QST applications were performed by the same individual but did not report test–retest reliability. One study[19] referenced a previous study to report QST reliability. Only 1 of the 37 studies[83] reported intraclass correlation coefficient for test–retest and interrater reliability with values 0.92 to 0.97 for mechanical pain sensitivity, 0.70 to 0.92 for heat pain threshold, and 0.87 to 0.97 for pressure pain detection threshold (PPT). In 2 studies,[5,54] assessments were conducted by multiple individuals but no intraclass correlation coefficient or interobserver variability was reported. One of the studies[54] reported that this as a methodological limitation.

3.4. Ability of quantitative sensory testing to predict outcomes in people with musculoskeletal conditions

Baseline QST demonstrated a statistically significant association with worse musculoskeletal-related outcomes (pain or disability) in 35 of the 37 studies (Appendix 3, available as supplemental digital content at http://links.lww.com/PAIN/A787). Presentation of associations varied between studies as Pearson's *r*, β-coefficients, ORs, area under the curve, and χ^2. Several studies[24,25,35,61,75,77,78,104,105,112] reported both correlation-coefficient and regression-coefficient values. Two studies[59,70] narratively reported (without presenting data) no observed correlation between baseline QST, measured using mechanical and thermal modalities (sensitivity and pain threshold) and follow-up pain. Five other studies used mechanical stimuli[5,49,78,112] or electrical stimuli,[99] but presented data only partially, favouring data that supported association.

Twenty-five studies reported regression analyses, of which 22 reported baseline factors used for statistical adjustment. Appendix 2 describes these 22 studies, their outcomes, and the factors they adjusted for (available as supplemental digital content at http://links.lww.com/PAIN/A787). Pain alone was the outcome in 13/22 and disability alone in 6/22. Both pain and disability were reported in 2/22, and disability and negative affect were reported together in 1/22. Fifteen studies reported baseline pain scores, of which 11 adjusted outcomes for baseline pain, and 4 for factors other than pain measured at baseline (pain catastrophising, depression, age, sex, ethnicity, analgesia requirement, pain duration, and genetic factors). Adjustment for baseline disability was reported in 3/9 of the studies reporting disability as an outcome. The single study that measured negative affect did not adjust for baseline negative affect.

3.5. Outcome prediction by baseline quantitative sensory testing (primary analysis)

3.5.1. Prediction of clinical pain by baseline quantitative sensory testing

Unadjusted (*r*) correlation data were available from 18 studies that permitted meta-analysis examining the ability of QST to predict follow-up pain. The pooled unadjusted *r* value among the included studies was 0.31 (95% CI: 0.23-0.38) (**Fig. 2**). I^2 calculations indicated 36% of heterogeneity ($P = 0.07$). Funnel plot for studies reporting unadjusted correlations were symmetrical, suggesting little or no bias (the Egger test = −1.0, $P = 0.32$) (**Fig. 3A**).

Subgroup analyses according to risk of bias showed that unadjusted correlations for studies with low ($r = 0.28$, 95% CI: 0.19-0.38; $I^2 = 53\%$, $P = 0.01$) and moderate ($r = 0.34$, 95% CI: 0.17-0.48; $I^2 = 0\%$, $P = 0.50$) risk of bias were similar to those reported in **Figure 2**.

Seven studies[25,43,49,61,78,103,110] reported unadjusted correlation data between baseline QST and change in pain as observed between 2 time points (baseline and follow-up). When pooled, they yielded an overall $r = 0.32$ (95% CI: 0.19-0.44) and heterogeneity of 29% ($P = 0.21$).

3.5.2. Prediction of disability by baseline quantitative sensory testing

Eleven studies[1,16,19,24,50,75,94,95,97,104,105] reported disability outcomes and most of these (7/11) included participants with WAD. Meta-analysis revealed a mean unadjusted correlation between baseline QST and disability outcome of 0.30 (95% CI: 0.19-0.40) (**Fig. 4**). I^2 calculations indicated heterogeneity of 0% ($P = 0.72$) for the unadjusted correlation subset. Funnel plot and the Egger test did not show significant asymmetry for the unadjusted data set (the Egger test = −0.10, $P = 0.93$) (Appendix 6, available as supplemental digital content at http://links.lww.com/PAIN/A787).

Subgroup analyses according to risk of bias showed that studies with low risk of bias yielded similar unadjusted correlation ($r = 0.30$, 95% CI: 0.18-0.41; $I^2 = 0\%$, $P = 0.51$) to the correlation reported in **Figure 4**. Meta-analysis of unadjusted correlation data from the small number of studies with moderate risk of bias was not feasible for disability.

3.5.3. Prediction of negative affect by baseline quantitative sensory testing

Three studies[35,94,104] examined whether QST can predict pain-related negative affect (depression or anxiety), of which 2 studies[35,94] reported statistically significant prediction of depression and posttraumatic stress disorder (Appendix 3, available as supplemental digital content at http://links.lww.com/PAIN/A787).

3.5.4. Effect of study design on outcome prediction by baseline quantitative sensory testing

Post hoc subgroup analyses for unadjusted correlations and heterogeneity were similar for cohort studies ($r = 0.31$, 95% CI: 0.24-0.38; $I^2 = 14\%$, $P = 0.30$) as for RCTs ($r = 0.27$, 95% CI: −0.02 to 0.52; $I^2 = 73\%$, $P = 0.01$), and therefore similar to the overall models presented in **Figure 2**.

3.5.5. Effect of quantitative sensory testing anatomical site on outcome prediction by baseline quantitative sensory testing

We tested the levels of association between QST application site (sites of pathology or remote) and pain. Subgroup analyses of unadjusted correlation data for application of QST at the site of pathology showed $r = 0.30$, 95% CI: 0.22-0.38; $I^2 = 43\%$, $P = 0.03$. Unadjusted correlation data for application of QST at a remote site showed $r = 0.19$, 95% CI: 0.07-0.30; $I^2 = 23\%$, $P = 0.27$. Pooling of distal site data for subgroup analysis was not feasible.

3.5.6. Effect of quantitative sensory testing modality on outcome prediction by baseline quantitative sensory testing

Multiple subgroups were analysed to examine whether specific QST modalities (or similar groups of those) could predict follow-up

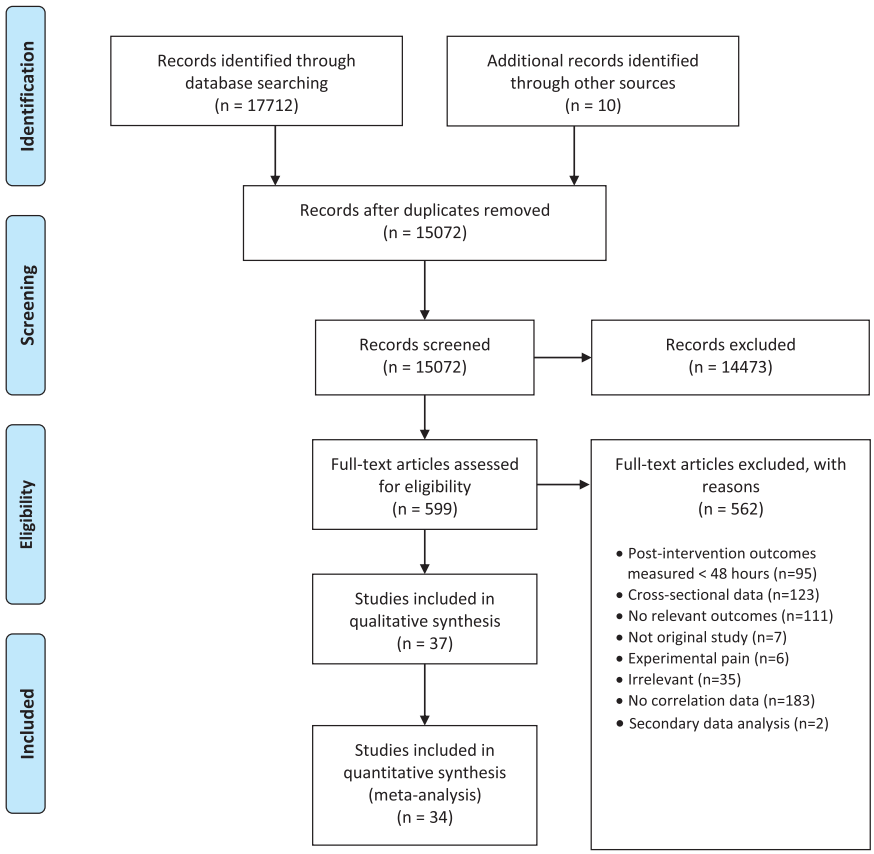

Figure 1. PRISMA flowchart of the study selection process.

pain or pain-related disability (**Table 3**). In terms of pain, the pooled unadjusted correlation results between static modalities such as pain detection threshold (mechanical, thermal, and electrical) and clinical pain outcomes were lower (0.20) than the 0.31 presented in **Figure 2** yielding a range from 0.14 to 0.20 and I^2 values of 0%. PPT demonstrated a pooled unadjusted correlation (*r*) of 0.20 (95% CI: 0.11-0.29) and heterogeneity of 0% ($P = 0.57$). Higher pooled unadjusted correlation values were given by TS (0.37, 95% CI: 0.17-0.54) and CPM alone (0.36, 95% CI: 0.20-0.50) and by a model including only dynamic modalities (CPM and TS) (0.38, 95% CI: 0.26-0.49) with displayed heterogeneity of 69% ($P = 0.02$), 43% ($P = 0.12$), and 53% ($P = 0.02$), respectively. Post hoc subgrouping of CPM according to conditioning stimulus (cold water immersion), and subgrouping of predictive capacity in axial (LBP and Neck pain) or peripheral (OA) pathologies yielded similar pooled unadjusted correlations as those presented in **Table 3**. Conditioned pain modulation–related post hoc subgroup analyses displayed either complete absence (0%) or nonstatistically significant ($P > 0.05$) heterogeneity. Pooling of TS data according to type of stimulus for post hoc subgroup analysis was not feasible. Insufficient data precluded also meta-analysis of unadjusted correlation values for disability outcomes.

3.6. Adjusted associations of musculoskeletal outcomes with baseline quantitative sensory testing (secondary analyses)

3.6.1. Association of clinical pain with baseline quantitative sensory testing

Adjusted (β) correlation data were also available from 18 studies that permitted meta-analysis examining the association of baseline QST with follow-up pain when other variables are taken into account. The pooled adjusted correlation among the included studies was 0.18 (95% CI: 0.11-0.25) out of which, in post hoc analysis, studies that adjusted for baseline pain (13/18) displayed a pooled adjusted correlation of 0.13 (95% CI: 0.06-0.20). I^2 calculations indicated 69% heterogeneity ($P < 0.01$) for the adjusted correlation data set and 72% ($P < 0.01$) for the subset that adjusted for baseline pain. Funnel plots for adjusted correlations deviated to the right (0.00-2.22) (the Egger test = 10.0, $P < 0.0001$) (**Fig. 3B**), indicating publication bias.

Subgroup analyses according to risk of bias showed that adjusted correlation for studies with low risk of bias were similar ($\beta = 0.12$, 95% CI: 0.06-0.18; $I^2 = 61\%$, $P < 0.01$) to those reported in **Figure 2** but higher ($\beta = 0.43$, 95% CI: 0.21-0.65; $I^2 = 32\%$, $P = 0.22$) for studies with moderate risk of bias.

3.6.2. Association of disability with baseline quantitative sensory testing

Meta-analysis revealed a mean adjusted correlation between baseline QST and disability outcome of 0.35 (95% CI: 0.21-0.49) with I^2 calculations yielding heterogeneity of 59% ($P = 0.01$) (**Fig. 4**). Funnel plot and the Egger test indicated significant asymmetry for the adjusted data set (the Egger test = 4.3, $P < 0.01$) (Appendix 6, available as supplemental digital content at http://links.lww.com/PAIN/A787).

Subgroup analyses according to risk of bias showed that studies with low risk of bias yielded similar pooled adjusted correlation ($\beta = 0.35$, 95% CI: 0.18-0.52; $I^2 = 64\%$, $P < 0.01$) to the correlation reported in **Figure 4**. Meta-analysis of adjusted correlation data from studies with moderate risk of bias was not feasible for disability.

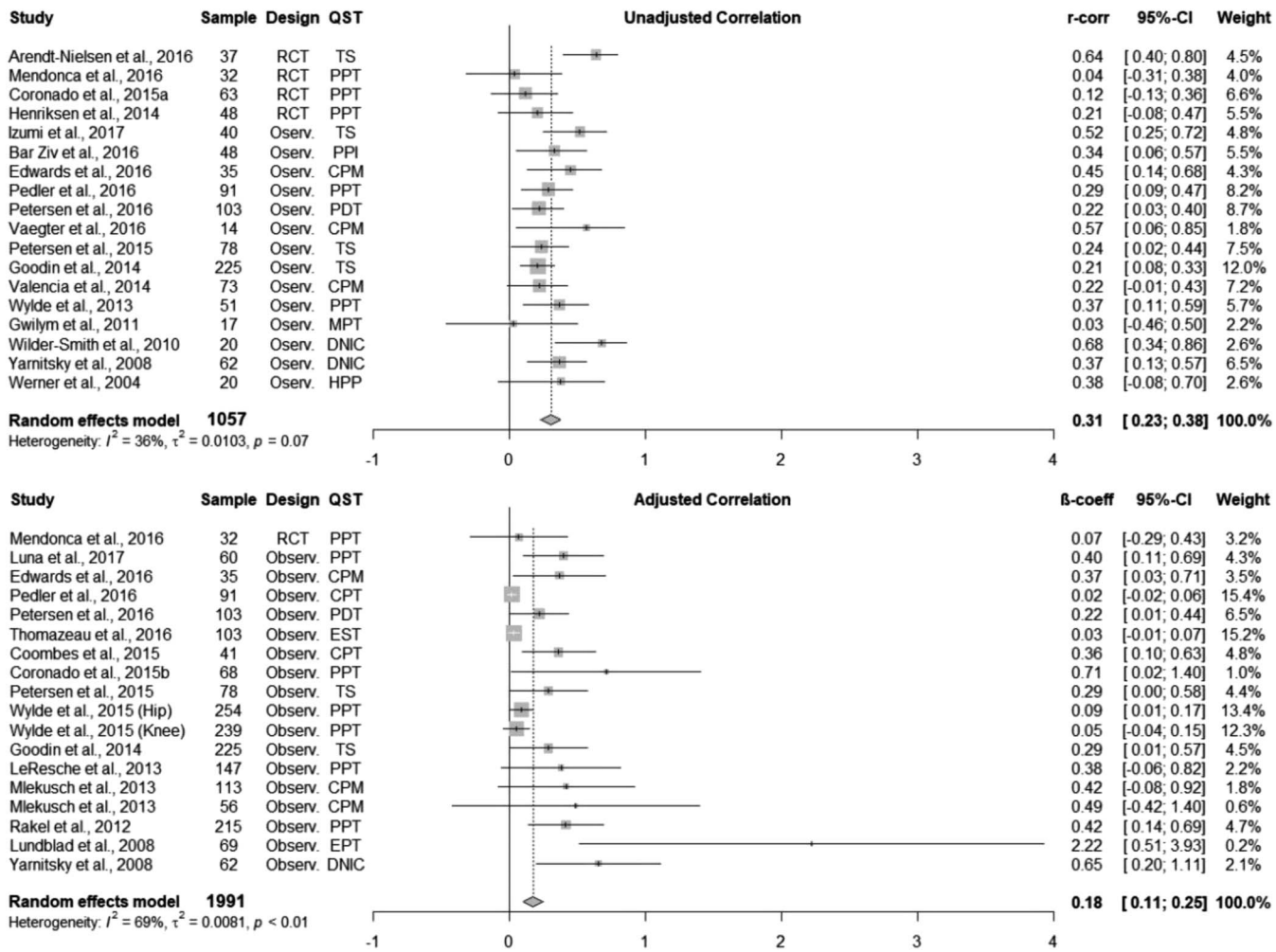

Figure 2. Forest plots showing the overall association (*r*-correlations and β-coefficients) between QST and follow-up pain. CI, confidence interval; CPM, conditioned pain modulation; CPT, cold pain detection threshold; DNIC, diffuse noxious inhibitory control; EPT, electrical pain threshold; EST, electrical sensation threshold; MEP, motor-evoked potentials; Observ., observational cohort study; PDT, pressure detection threshold; PPT, pain pressure detection threshold; QST, quantitative sensory testing; RCT, randomised controlled trial; TS, temporal summation. Forest plot showing the pooled unadjusted (0.31, 95% CI: 0.23-0.38) and adjusted correlation (0.18, 95% CI: 0.11-0.25) of QST modalities with musculoskeletal pain. The unadjusted correlation plot has been derived through the incorporation of correlation-coefficient data (Pearson's or Spearman's *r*) expressing a univariate association unadjusted by other factors, whereas the adjusted correlation plot has been derived through the incorporation of β-coefficient data from linear or logistic regressions expressing a multivariate association.

3.6.3. Effect of site of clinical pain on association with baseline quantitative sensory testing

Multiple subgroup analyses according to musculoskeletal condition revealed similar pooled adjusted correlation for OA (β = 0.30, 95% CI: 0.18-0.42; I^2 = 0%, P = 0.89), higher adjusted correlation for LBP (β = 0.46, 95% CI: 0.16-0.75; I^2 = 0%, P = 0.72), and lower adjusted correlation for postoperative pain (β = 0.13, 95% CI: 0.02-0.24; I^2 = 77%, P < 0.01). Meta-analysis of the subgroup of studies reporting an association between baseline QST and WAD-related disability indicated an adjusted correlation of 0.47 (95% CI: 0.18-0.76) and significant heterogeneity (I^2 = 74%, P < 0.01). Post hoc subgroup analysis was also performed to explore the degree of association between QST and clinical pain according to its anatomical site because adjusted correlation data were available both for peripheral joint and axial pain. Models for adjusted correlation were similar for peripheral joint pain (β = 0.22, 95% CI: 0.12-0.32) as for axial pain (β = 0.22, 95% CI: 0.00-0.43) and therefore similar to the overall models presented in **Figure 2**. Heterogeneity in the axial pain model (I^2 = 49%, P = 0.08) was slightly lower than for peripheral joints (I^2 = 73%, P = <0.01).

3.6.4. Effect of quantitative sensory testing modality on association with baseline quantitative sensory testing

Pooled adjusted correlation results between static modalities such as pain detection threshold (mechanical, thermal, and electrical) and clinical pain outcomes approximated the 0.20 presented in **Figure 2**, yielding a range from 0.13 to 0.17 and I^2 values from 68% to 74% (**Table 3**). PPT as a stand-alone modality demonstrated a pooled adjusted correlation (β) of 0.14 (95% CI: 0.05-0.23) and heterogeneity of 72% (P < 0.01). Pooled adjusted correlation values by CPM alone (0.35, 95% CI: 0.15-0.54) and by a model including only dynamic modalities (CPM and TS) (0.33, 95% CI: 0.19-0.47) yielded higher values than those in the overall models in **Figure 2**. Both analyses displayed heterogeneity of 0% (P = 0.41 and 0.80, respectively).

For studies reporting disability as the clinical outcome, subgroup analysis of thermal pain detection threshold modalities showed a pooled adjusted correlation of 0.37 (95% CI: 0.16-0.58), and the subset using cold as the thermal stimulus revealed pooled adjusted correlation for cold pain detection threshold of 0.48 (95% CI: 0.19-0.77). Both subgroups showed statistically

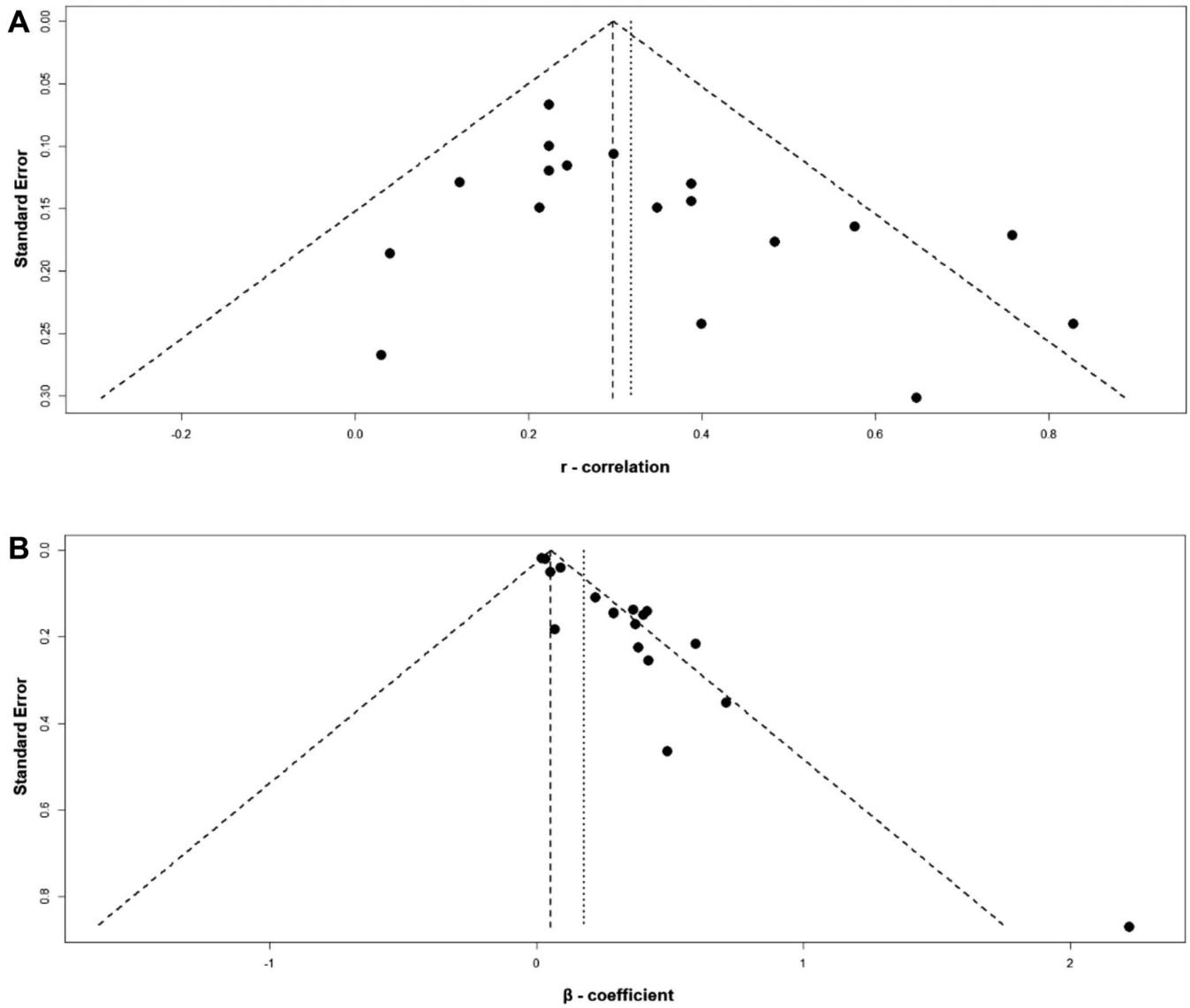

Figure 3. Funnel plots for QST studies (n = 18) examining the capacity of pain hypersensitivity (as measured by QST) to predict or associate with pain at follow-up depicting (A): unadjusted (*r*-correlation) data with little or no indication of publication bias due to their symmetrical presentation and (B): adjusted (β-coefficient) data with an indication of publication bias due to asymmetry. The axes on both graphs are different scales. QST, quantitative sensory testing.

significant heterogeneity ($P = <0.01$) with I^2 scores of 69% and 74%.

4. Discussion

This systematic review and meta-analysis demonstrates a predictive relationship between baseline QST, a measure of pain hypersensitivity, and musculoskeletal pain and disability at follow-up. This is demonstrated across multiple musculoskeletal conditions (OA, LBP, WAD, and postoperative pain) affecting different anatomical sites (knee, hip, low back, neck, and shoulder), and across different QST modalities and study contexts (cohort studies and RCTs). The results of this review show that pain hypersensitivity predicts prognosis. Quantitative sensory testing might help identify people who could most benefit from interventions aiming to improve pain and disability.

Previous systematic reviews have been less conclusive on the ability of QST to predict longitudinal outcomes in patients with peripheral musculoskeletal conditions, healthy volunteers, surgical patients, and patients with chronic pain.[36,72,86] The present systematic review extends these reports by demonstrating longitudinal prediction of several outcomes across a range of musculoskeletal conditions, and addressing through meta-analysis the limited power of individual studies. We found that QST might predict other outcomes beyond pain and disability such as depression in people with musculoskeletal pain. Depression and chronic pain may share similar brain activation pathways as shown by magnetic resonance imaging,[39,64,88] and shared mechanisms might explain shared predictive factors. Future studies might explore whether QST can predict additional outcomes such as ability to self-care or absenteeism/presenteeism. Our findings also indicate that prediction of poor outcomes by QST evidence of pain hypersensitivity is not disease specific, applying similarly to axial and nonaxial musculoskeletal pain. Quantitative sensory testing can also predict acute postoperative pain.[2,27,107]

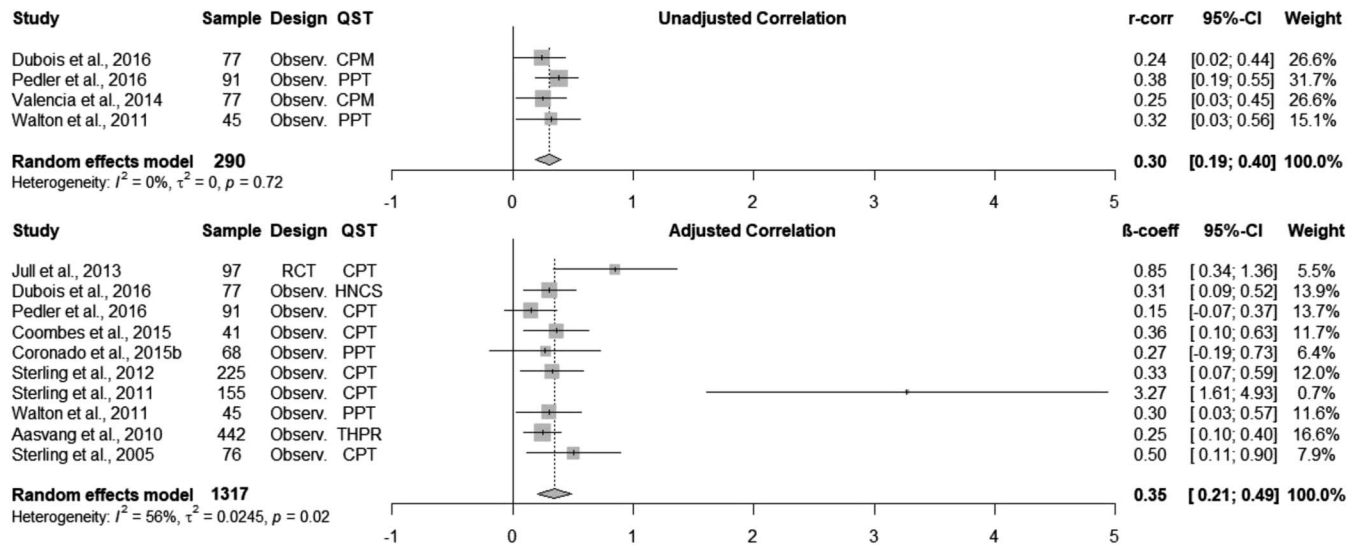

Figure 4. Forest plot showing the overall association (*r*-correlations and β-coefficients) between QST and follow-up disability in musculoskeletal conditions. CI, confidence interval; CPM, conditioned pain modulation; CPT, cold pain detection threshold; EPT, electrical pain threshold; HNCS, heterotopic noxious counterstimulation; Observ., observational cohort study; PPT, pain pressure threshold; QST, quantitative sensory testing; RCT, randomised controlled trial; THPR, tonic heat pain response. Forest plot showing the pooled unadjusted (0.30, 95% CI: 0.19-0.40) and adjusted correlation (0.35, 95% CI: 0.21-0.49) of QST modalities with musculoskeletal disability. The unadjusted correlation plot has been derived through the incorporation of correlation-coefficient data (Pearson's or Spearman's *r*) expressing a univariate association unadjusted by other factors, whereas the adjusted correlation plot has been derived through the incorporation of β-coefficient data from linear or logistic regressions expressing a multivariate association.

We did not find significant differences in outcome prediction by QST between data from cohort studies and those from RCTs, supporting generalisation of conclusions from our findings. Treatments received by participants might be similar between cohort studies and RCTs, and generalisation of our findings to other treatment contexts should be cautious. Future research might explore whether baseline QST evidence of hypersensitivity can predict *good* response to novel treatments that more effectively reverse hypersensitivity.

Our primary purpose was to investigate outcome prediction in people with musculoskeletal pain. Those destined to experience worse outcomes stand to gain more from effective interventions. Predictors of poor outcomes might also shed some light on mechanisms and potential targets for interventions aiming to improve outcome. Univariate prediction is important for identifying people at risk of poor outcome, but provides only very limited mechanistic understanding. Multiple regression provides greater insight into causal relationships by adjusting for other factors to reduce confounding[40,58] and bias.[41,44] Outcome prediction by QST seemed stronger in unadjusted than in adjusted correlation analyses, but the magnitude of these 2 values should not be

Table 3

Associations between QST modalities and pain or disability.

	QST modality	Clinical outcome	No. of studies	Sample size	Overall correlation	95% confidence intervals	I^2	I^2 *P*-value
Unadjusted correlation (*r*)	PDT (all)*	Pain	10	576	0.19	0.10 to 0.27	0%	0.75
	PDT (mechanical)	Pain	9	503	0.20	0.11 to 0.28	0%	0.73
	PDT (thermal)	Pain	5	298	0.16	0.04 to 0.27	0%	0.88
	PPT	Pain	7	466	0.20	0.11 to 0.29	0%	0.57
	HPT	Pain	4	207	0.14	0.00 to 0.27	0%	0.82
	CPM	Pain	6	282	0.36	0.20 to 0.50	43%	0.12
	TS	Pain	4	380	0.37	0.17 to 0.54	69%	0.02
	Dynamic mods†	Pain	9	943	0.38	0.26 to 0.49	53%	0.03
	PDT (all)	Disability	3	213	0.25	0.03 to 0.45	63%	0.07
Adjusted correlation (β)	PPT	Pain	11	1378	0.14	0.05 to 0.23	72%	<0.01
	CPT	Pain	3	279	0.14	−0.10 to 0.37	68%	0.04
	CPM	Pain	5	413	0.35	0.15 to 0.54	0%	0.41
	TS	Pain	3	450	0.26	0.08 to 0.44	0%	0.83
	Dynamic mods†	Pain	7	716	0.33	0.19 to 0.47	0%	0.80
	PDT (all)	Pain	13	1488	0.17	0.08 to 0.26	68%	<0.01
	PDT (thermal)	Pain	4	461	0.13	−0.01 to 0.30	74%	0.01
	PDT (all)	Disability	8	1195	0.35	0.16 to 0.55	63%	<0.01
	PDT (thermal)	Disability	7	1127	0.37	0.16 to 0.58	69%	<0.01
	CPT	Disability	6	685	0.48	0.19 to 0.77	74%	<0.01
	PPT	Disability	3	256	0.02	−0.01 to 0.05	86%	<0.01

* PDT (all) includes all pain detection threshold modalities such as pain pressure detection threshold, pain pressure tolerance threshold, electrical pain threshold, cold pain detection threshold, and heat pain detection threshold.
† Dynamic modalities include conditioning pain modulation and temporal summation data taken across studies and fit into the same model.
CPM, conditioned pain modulation; CPT, cold pain threshold; HPT, heat pain threshold; PDT, pain detection threshold; PPT, pain pressure detection threshold; QST, quantitative sensory testing; TS, temporal summation.

compared directly because they are measured through different scales. However, weaker associations in adjusted analyses might be expected in light of the cross-sectional associations between QST and outcome measures at baseline,[30,34,98] and the well-recognised prediction of an outcome measure by its baseline value. Significant outcome prediction by QST in adjusted analyses suggests a direct effect of pain hypersensitivity on musculoskeletal outcome.

Pain hypersensitivity has been identified in multiple reports of chronic pain conditions as an underlying pathophysiology[9,92,96] and has been associated with the development of additional symptoms, such as fatigue and mood disturbance,[3] that can further impact on prognosis.[12,109] Quantitative sensory testing can identify the presence of pain hypersensitivity in people with OA[30,98] and WAD.[34] Our findings that QST can predict clinical outcomes in people with musculoskeletal pain indicate that pain hypersensitivity could be investigated as a mechanism for worse prognosis. This is further supported by a recent study,[71] published after our database search end-date, showing that patients with knee OA and higher TS responded poorly to exercise programs.

Possible mechanisms by which pain hypersensitivity might lead to worse outcomes include alterations in pain processing, which can persist despite treatment.[7,8,96] Pain hypersensitivity might also pose a barrier to gaining benefit from current treatments, for example, by reducing treatment uptake or engagement.[15,51,91] Interventions targeting hypersensitivity might have benefit across a range of musculoskeletal conditions.

Various QST modalities have been designed to address different mechanisms of hypersensitivity, body regions, or medical conditions and therefore might differentially predict outcome. Pain hypersensitivity may be due to changes in the peripheral nervous system or CNS. Alterations in pain thresholds using deep stimuli, such as those used for pressure pain detection thresholds at sites local to musculoskeletal pathology, might predominantly reflect peripherally driven pain hypersensitivity. However, dynamic QST modalities such as CPM or TS were most strongly associated with musculoskeletal pain and disability, suggesting a possible role for centrally driven pain hypersensitivity.[6] Conditioned pain modulation reflects cerebral processes that are implicated in depressive or psychological disorders even in the absence of nociceptive drive.[7] Conditioned pain modulation might therefore be associated with psychological mechanisms contributing to chronic musculoskeletal pain. Thermal pain and pain in response to punctate stimulation are mediated by cutaneous nerves, rather than those localised within musculoskeletal tissues. We found that thermal modalities in general, and cold pain thresholds in particular, were associated with pain-related disability. Data leading to these conclusions were predominantly from studies of whiplash-related pain and disability,[34] and condition-specific injury mechanisms might be responsible for disturbances to the nervous system that differ between conditions. Further research might explore whether a contribution of thermal QST modalities to worst outcomes might also apply to other musculoskeletal diagnoses.

Centrally driven pain hypersensitivity has also been associated with reduced pain detection thresholds at sites remote from the site of pathology,[45,68,87] whereas increased sensitivity at the site of pathology might reflect peripheral sensitisation alone plus augmentation by central sensitisation.[98] Our findings that hypersensitivity at a remote site can predict worse musculoskeletal outcomes further support a contribution from central sensitisation. However, pain thresholds at the site of clinical pain also predicted outcomes, and a contribution of peripheral sensitisation to prognosis deserves further study.

Interpretation of our findings is subject to a number of limitations. Outcome prediction can be influenced by the type of therapeutic intervention that participants receive, and the effect of treatments on pain hypersensitivity cannot be determined from the available data. We found significant heterogeneity between studies in several of our subgroup analyses, suggesting that factors additional to those explored here might influence the ability of QST to predict musculoskeletal outcomes. Funnel plots displayed significant asymmetry suggesting possible publication bias, particularly for adjusted analyses. However, 26 of the 37 reports were judged to be of low risk of bias and the remaining studies of only moderate risk. Sensitivity analyses showed that the levels of bias did not have a significant effect on our main findings. Our search strategy was intentionally broad, but it remains possible that not all relevant studies have been identified. Small numbers of studies and participants limit our ability to exclude differences between some subgroups, and our use of a small number of studies in several analyses might limit generalisability. The current meta-analyses suggest relatively weak predictive ability[81] for QST, with correlations only sometimes and marginally above 0.30, a threshold considered to be clinically meaningful.[84] However, what consists a meaningful deviation from that threshold was not established, and analyses regarding the magnitude of those deviations were not performed. Inferences in relation to pooled predictive values must be drawn with caution. A systematic review with meta-analysis of cross-sectional studies[48] also indicated that pain detection thresholds might not present a clinically important correlation with pain or disability in spinal pain. However, the significant association even in adjusted analyses between QST and musculoskeletal outcomes might suggest underlying mechanisms and potential targets for intervention. Other prognostic factors, including psychological factors such as depression or anxiety[14] and maladaptive beliefs such as catastrophizing or fear avoidance,[26] might complement outcome prediction by QST.

Identifying which patients might be at particular risk of poor outcome is important to identify those who are most likely to benefit from treatment. Quantitative sensory testing modalities with stimuli applied at the site of clinical pain, dynamic modalities such as CPM and TS, and thermal pain detection thresholds seemed to have the greatest potential. PPTs have advantages of ease of application in clinical settings, low cost, and high user and patient acceptability. Further refinement of QST and adoption of standardised QST protocols are recommended. We noted important methodological variation between published studies, particularly reflected by the range of stimulus types used in dynamic modalities. Studies which used blunt pressure as a testing stimulus and hand immersion in cold water as a conditioning stimulus contributed most to evidence that CPM can predict musculoskeletal outcomes. However, available data did not enable us to draw robust conclusions on superiority between different stimulus types for TS. Additional confirmatory research is required in larger and more homogenous populations, inside and outside the musculoskeletal spectrum. Translation into clinical practice requires also feasibility in clinical contexts, acceptability to patients, and evidence that implementation improves patient outcomes. Future studies should aim to define reliability of specific QST approaches and establish clinically meaningful thresholds in specific pathologies to translate QST from a research tool into a clinical decision aid for musculoskeletal conditions.

In conclusion, we have shown that QST, an index of pain hypersensitivity, can predict worse musculoskeletal outcomes of pain, disability, and negative affect. Our findings are consistent with important contributions from hypersensitivity to outcome, and reducing pain hypersensitivity has potential to improve outcome for people with musculoskeletal conditions.

Conflict of interest statement

D.A. Walsh has undertaken paid consultancy to Pfizer Ltd and GSK Consumer Healthcare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A787.

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