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LONGITUDINAL CHANGES AND ASSOCIATIONS BETWEEN QUANTITATIVE SENSORY TESTING AND PSYCHOLOGICAL FACTORS IN WHIPLASH-ASSOCIATED DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSES-BASED DATA SYNTHESIS

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ABSTRACT

Whiplash-Associated Disorders (WAD) represent a multifactorial condition often accompanied by altered nociceptive processing and psychological factors. This systematic review on acute and chronic WAD aimed to investigate the relationship between Quantitative Sensory Testing (QST) and psychological factors and quantify whether their trajectories over time follows a similar pattern to disability levels. Eight databases were searched until October 2022. When two prospective studies examined the same QST or psychological variable, data synthesis was performed with random-effects meta-analysis by pooling within-group standardized mean differences from baseline to 3-, 6-, and 12-month follow-ups. From 5,754 studies, 49 comprising 3,825 WAD participants were eligible for the review and 14 for the data synthesis. Altered nociceptive processing in acute and chronic WAD, alongside worse scores on psychological factors, were identified. However, correlations between QST and psychological factors were heterogeneous and inconsistent. Furthermore, disability levels, some QST measures, and psychological factors followed general positive improvement over time, although there were differences in magnitude and temporal changes. These results may indicate that altered psychological factors and increased local pain sensitivity could play an important role in both acute and chronic WAD, although this does not exclude the potential influence of factors not explored in this review.

PERSPECTIVE

Acute WAD show improvements in levels of disability and psychological factors before significant improvements in nociceptive processing are evident. Facilitated nociceptive processing might not be as important as psychological factors in chronic WAD-related disability, which indicates that chronic and acute WAD should not be considered the same entity although there are similarities. Nonetheless, pressure pain thresholds in the neck might be the most appropriate measure to monitor WAD progression.

INTRODUCTION

Persistent spinal pain is the leading cause of years lived with disability worldwide.[1] One musculoskeletal health condition that has proven to be a particular challenge is whiplash-associated disorders (WAD), with a high societal and economic burden on individuals[2] and healthcare systems.[3] One year after whiplash trauma, half of those with acute WAD continue to report disability and pain.[4,5]

After acute whiplash, the neck region is commonly perceived as painful and more sensitive which may be explained by peripheral sensitization as a consequence of tissue injury and inflammation.[6] This response to whiplash injury, although painful is a normal response that subsides within the first months after injury for most cases.[7] However, for those who transition to chronic WAD, research over the last decades has shown manifestations of widespread nociceptive sensitization and increased psychological burden.[8] WAD is now understood as a complex and multifactorial condition,[9] in which altered nociceptive processing and psychological factors play important roles in disability and prognosis.[10,11] In this context, Quantitative Sensory Testing (QST) comprises different psychophysical measures that provide information on the functioning of sensory pathways and nociceptive processing.[12] QST measures are usually classified as static QST when involving threshold determination (e.g., detection, pain, or tolerance thresholds) or dynamic QST when assessing pain modulation at a central level (e.g., conditioned pain modulation or temporal summation).[13] Psychological factors, such as pain-related beliefs, avoidance behaviour, pain catastrophizing, kinesiophobia, anxiety, depression, and posttraumatic stress symptoms, are considered to play an important role in the onset and progression of musculoskeletal pain.[14]

High levels of psychological distress and facilitated nociceptive processing have been observed in individuals in both acute and chronic stages of WAD.[9] However, how

these factors develop and inter-relate over time from the acute injury stage to either recovery or the development of chronic pain and disability is not clear.[15] These data are needed to describe WAD recovery comprehensively. Selecting the most appropriate parameters to monitor in both a clinical and research setting may aid the future development of effective strategies to reduce WAD chronification. Given that disability is considered a comprehensive indicator of WAD recovery,[16] it is warranted to investigate whether the course of QST measures and psychological factors is related to the trajectory of disability. Considering the large amount of scientific WAD-related literature produced in the last years, it seems appropriate to conduct a systematic review and data synthesis to illuminate the relationships between temporal changes in QST and psychological factors and thereby aiding the continuous work towards optimizing rehabilitation strategies (e.g., better personalized treatments) for WAD.

Separately for acute and chronic WAD, the primary aim of this systematic review and data synthesis was to cross-sectionally investigate and estimate the relationship between QST measures and psychological factors. Furthermore, a secondary aim was to quantify the trajectories over time of QST measures and psychological factors and describe whether they follow a similar pattern to disability levels.

METHODS

Study design and registration

This systematic review and data synthesis was conducted following the PRISMA statement[17] and registered with PROSPERO (CRD42016051599).

Study eligibility criteria for the systematic review

Type of studies: Cross-sectional-, case-control-, cohort -studies, and controlled clinical trials evaluating QST alongside psychological variables in participants with WAD were included if full-text available and published in a peer-reviewed journal in English or Spanish languages.

Type of participants: Studies of adults (i.e., ≥18 years old) with acute (≤3 months post-whiplash trauma) or chronic (>3 months post-whiplash trauma) WAD, without considering the specific cause of the whiplash trauma (e.g., motor vehicle accident, sports injury or sudden fall). Mixed populations with composite data were excluded unless data could be obtained for the separate populations.

Type of outcome measures: Studies assessing QST measures and psychological factors measured by standardized and valid methods were included. When multiple studies used the same sample, the publication that provided the most information was included.

Data sources and searches

Eight databases (PubMed, Web of Science, Cochrane, Rehabilitation & Sports Medicine Source, SPORTDiscus with Full Text, APA PsycArticles, PEDro, and Scopus) were searched from inception to 1 October 2022. The search was conducted using four independent blocks referring to the population of interest (WAD), the outcome variables (QST measurements and psychological factors), and the study type (experimental and observational studies). A block related to potential interventions was not included in the search strategy as this review did not intend to assess the effect of any particular treatment. The search strategy of each database is provided in *Supplementary material A*.

In order to identify additional records, a detailed review of the bibliographic references included in the reviewed full-text articles was performed.

Selection of studies

Study selection was conducted independently by two researchers (PBL and MOL). In case of disagreement, a consensus was sought by involving a third researcher (VDG). After screening of study titles and abstracts for potential inclusion, studies identified as potentially relevant were collected for full-text screening and final decision of inclusion or exclusion for review.

Data extraction

Data extraction from the included studies was performed by two authors (PBL and MOL). Study characteristics and outcome data of interest included study design, number of participants, socio-demographic characteristics, QST measures (QST modality and body location), questionnaires related to psychological factors, disability, and other variables measured in each study, such as range of movement or pain visual analog scale. In addition, main results, including correlation or association findings between QST and psychological factors, were extracted when possible.

Risk of bias assessment

Two researchers (PBL and MOL) independently examined the methodological quality of the studies, and in case of disagreement, a third decisive opinion was considered (VDG). For risk of bias assessment, appropriate scales were chosen according to study designs.

The Newcastle-Ottawa scale was used for cross-sectional, case-control, and cohort studies.[18] This scale evaluates seven to eight items categorized into three criteria

(selection, comparability, and exposure or outcome) with a maximum score is 9 (10 in cross-sectional studies). Articles scoring at least 7 were considered of "high quality", a score of 4-6 was considered of "fair quality", and less than 4 was considered of "poor quality". Due to the observational nature of this review, the Newcastle-Ottawa scale for cohort studies was also used to evaluate controlled clinical trials.

Deviations from the PROSPERO protocol

In addition to the pre-registered databases, Scopus, Rehabilitation & Sports Medicine Source, SPORTDiscus, APA PsycArticles, and PEDro databases were also searched to identify any potential missing literature from the search in the initially proposed databases.

The study set out to conduct a synthesis of correlations between QST measures and psychological factors. However, due to the heterogeneity of the QST and psychological variables assessed in the included studies, it was not possible to synthetize correlation coefficients of these variables for neither acute nor chronic WAD. Instead, standardized mean differences of QST measures and psychological factor scores from prospective studies were synthesized in order to qualitatively describe their trajectory over time. In addition, to increase clinical relevance, an analysis of disability was also included. To improve the data reliability, only high-quality studies were included in this data synthesis (i.e., excluding fair- and poor-quality studies).

The PEDro scale was replaced by the Newcastle-Ottawa scale for assessing the risk of bias for prospective cohort studies as the aim of the current study was to describe the trajectory of specific outcome measures over time rather than evaluating treatment effectiveness.

Study eligibility criteria for the data synthesis

Studies that met the selection criteria for the systematic review regarding the type of participants and outcome measures along with a prospective design including repeated measures of QST and psychological variables across a follow-up period were selected for inclusion in the data synthesis. In addition, if available, WAD subgroups within each study were considered as independent cohorts (e.g., treatment arms in clinical trials or subgroups stratified by disability levels in observational studies). Finally, only high-quality studies (i.e., ≥7 in the Newcastle-Ottawa scale) were considered for the data synthesis to increase robustness.

Data synthesis

Differentiations were made between studies addressing acute or chronic WAD when presenting and interpreting the results in the current study. When possible, the mean and standard deviation at baseline and follow-up endpoints from prospective studies (≤3-, 6-, or ≥12-months follow-up) were extracted for QST assessments, psychological factors, and disability scores. For acute WAD, the baseline assessment was considered to be between the period of the whiplash trauma and the start of any potential intervention. For chronic WAD, the baseline assessment was considered the assessment prior to any type of intervention to establish the participants' starting point. If the data were not reported directly in an article, three attempts were made to contact the study authors via email, requesting them to provide the data. If unsuccessful, the median and interquartile range, when available, was extracted and transformed into mean and standard deviation.[19]

When a minimum of two independent cohorts examined the same QST measure or psychological factor, standardized mean differences estimated by Hedges' g were calculated (i.e., the result of subtracting the baseline mean minus the follow-up mean,

divided by the averaged standard deviation weighted by sample size)[20] and pooled with a random-effects meta-analysis following a restricted maximum-likelihood estimation.[21] For ease of interpretation, irrespective of the parameter being assessed, improvements (i.e., lower disability, increased tolerance to noxious stimuli before they become painful, or improved scores in questionnaires assessing psychological factors) were expressed as positive Hedges' *g*. In contrast, a worsening was expressed as negative Hedges' *g*. Absolute value of Hedges' *g* was considered small ($g \geq 0.20$ & <0.50), medium ($g \geq 0.50$ & <0.80) or large ($g \geq 0.80$).[22] Heterogeneity between studies' results was investigated using I^2 statistics with values >50% indicating substantial heterogeneity across studies.[23] Publication bias was examined by using funnel plots and Egger's tests.[24] All analyses were completed using STATA v.16.1 (*StataCorp, College Station, Texas 77845, USA*), and alpha was set at $P<0.05$.

RESULTS

Study Selection

The selection process of the articles is summarized in Figure 1. After removing duplicates, 5,754 records were found. One-hundred and forty-two full-text articles were screened as potential eligible studies resulting in 49 studies being included in the review. The list of records excluded after full-text screening is presented in *Supplementary material B.* No additional records were found within the bibliographic references of the reviewed full-text articles.

Study Characteristics

Table 1 presents the main characteristics of the included articles in this systematic review comprising a total of 3,825 WAD participants (66% female). Seventeen studies included

acute WAD participants,[7,25-40] while 31 studies included chronic WAD participants.[41-71] Fourteen out of 21 studies including follow-ups after a baseline assessment performed repeated assessments of both QST measures and psychological factors.[7,25-28,30,36,37,39,47,54,57,67,69] Further information of selected articles is presented in *Supplementary material C*.

Risk of bias assessment

The total Newcastle-Ottawa score is presented for each study in Table 1. In addition, tables showing the methodological quality assessment results of the retrieved studies by using the Newcastle-Ottawa scale, as well as further details of the risk of bias assessment for each study design, are presented in *Supplementary material D.*

From the 25 case-control studies, 9 studies (36%)were considered to be of high quality,[25,26,37,42,44,55,59,62,71] 11 studies (44%) of fair quality,[7,33,41,43,46,50,58,61,63,70,72] and 5 studies (20%)of poor quality.[29,45,52,60,65]

From the 7 cross-sectional studies, 5 (71%) were considered to be of high quality,[32,48,49,51,56] and 2 studies (29%) of fair quality.[38,64]

From the 7 identified cohort studies, all assessing acute WAD participants, 5 (71%) were considered to be of high quality,[30,31,34-36] and 2 (29%) of fair quality.[28,40]

From the 10 clinical trials, 5 trials (50%) were considered to be of high quality,[27,53,54,66,67] and 5 trials (50%) of fair quality.[39,47,57,68,69]

Quantitative Sensory Testing

All studies evaluated at least one static QST measures (e.g., pressure pain thresholds (PPT), cold pain threshold (CPT), heat pain thresholds (HPT), pressure pain tolerance (PPTol)), while 12 studies (24%) also evaluated dynamic QST measures (e.g.,

conditioned pain modulation (CPM), temporal summation of pain, exercise-induced hypoalgesia).

For studies reporting PPT, 11 out of 13 (85%) of chronic WAD studies[41-44,52,55,59,61,63,65,70] and 3 out of 3 (100%) of acute WAD studies[26,33,37] found lower PPTs in the neck region in WAD participants compared to controls. Among them, only 2 studies did not find differences in a remote PPT leg site in WAD participants compared to controls.[26,52] Regarding prospective studies, 5 out of 7 (71%) in chronic WAD[47,57,67-69] and 7 out of 8 (88%) in acute WAD[26,28,33,36,37,39,40] found an improvement in PPTs over a 3- to 12-month period.

For thermal pain thresholds (i.e., CPT or HPT), 8 out of 9 (89%) of chronic WAD studies[42,43,58,59,61,63,65,70] and 3 out of 3 (100%) of acute WAD studies[33,36,37] found an increased pain sensitivity in WAD participants compared to controls (i.e., CPT at higher temperatures or HPT at lower temperatures). For prospective studies, 2 out of 4 (50%) on chronic WAD[47,67] showed improved CPT and/or HPT at 6 months. However, 5 out of 5 (100%) prospective acute WAD studies[7,27,33,36,37] found no changes in CPT or HPT over time.

For dynamic QST measures, about 50% of chronic WAD studies found a decreased CPM,[44,60,72] higher temporal summation,[41,45,62] or impaired exercise-induced hypoalgesia;[61,62] while for acute WAD studies, 2 out of 2 (100%) found decreased CPM compared to controls.[26,72] The only study presenting repeated-measures of CPM on chronic WAD found an improvement in the CPM just after treatment,[68] which is was not the case for the only prospective study on acute WAD, where no changes was observed over a 6-months follow-up.[26]

Psychological factors

All studies evaluated psychological factors (e.g., posttraumatic stress symptoms, pain catastrophizing, fear-avoidance beliefs, depression, anxiety) via use of questionnaires. A detailed explanation of specific questionnaires for each construct is presented in *Supplementary Material E*.

Almost all (>92%) chronic WAD studies[44,46,49,50,53,58,60-63,65,66,70-72] and 100% of acute WAD studies[25-27,36,43,72] reported worse levels of pain catastrophizing, kinesiophobia, posttraumatic stress symptoms, psychological distress, depression, anxiety, and/or stress symptoms in WAD participants compared to reference values or controls. Furthermore, all prospective studies in chronic-[47,53,67,69] and acute WAD[26,27,37,39,43] found improved levels of psychological factors over time.

Relationship between QST and psychological factors

Only 6 studies (12%) reported correlations between QST measures and psychological factors in chronic[59,65,70,71] and acute WAD participants,[30,32] while no studies provided any correlation or association results between changes in these variables. The pairs of specific QST measures and psychological factors evaluated simultaneously in two or more studies are presented in *Supplementary Material F*.

Small to moderate correlations between different QST measures and psychological factors were found both in chronic WAD (Table 2A) and acute WAD (Table 2B) studies, demonstrating that on some occasions, increased pain sensitivity was related to higher levels of psychological distress or altered cognitions. Specifically for chronic WAD studies, Sterling et al. found moderate positive correlations between CPT at the cervical spine and Pain Catastrophizing Scale scores.[65] Likewise, Wallin et al. reported positive correlations between CPT at the cervical spine and anxiety, depression, stress, catastrophizing, pain self-efficacy, and fear-avoidance beliefs.[70] Additionally, they

reported negative correlations between PPT and HPT at the cervical spine and anxiety, depression, stress, catastrophizing, pain self-efficacy, and fear-avoidance beliefs.[70] Furthermore, Lenoir et al. found moderate negative correlations between electrical pain thresholds at the median nerve and scores in the magnification subscale of the Pain Catastrophizing Scale and the Pain Anxiety Symptoms Scale.[71] In contrast, Scott et al. found no correlation between Sort-Form State-Trait Anxiety Inventory scores and any QST measure (PPT, CPT, HPT, or punctate hyperalgesia).[59]

For acute WAD, Rivest et al. found a moderate positive correlation between Pain Catastrophizing Scale scores and CPT at the cervical spine and a moderate negative correlation between catastrophizing thoughts and PPT at the cervical spine in a male subsample.[32] Similarly, Pedler et al. reported positive correlations between CPT at the cervical spine and kinesiophobia, pain coping, and posttraumatic stress disorder symptoms, while the same psychological factors were negatively correlated with PPT at the cervical spine.[30]

Data synthesis

From 21 prospective studies, 9 high-quality prospective studies were included in the meta-analyses for the data synthesis,[7,25-27,30,36,37,54,67] accounting for 14 individual cohorts. Five studies were excluded due to being rated as fair-quality[28,39,47,57,69] and 7 due to not reporting results of repeated measurements.[29,31,33-35,40,53] During this process, 5 authors were contacted to retrieve additional information that could not be extracted from a total of 9 articles. Three out of these 5 authors provided additional data corresponding to 6 articles.

Figure 2 (chronic WAD cohorts) and figure 3 (acute WAD cohorts) synthesize the pooled Hedges' *g* for levels of disability, QST measures, and psychological factors at 3-, 6-, and 12-months post-whiplash trauma compared to baseline. Individual forest plots for

each variable and I^2 values at each time point can be found in supplementary materials for both chronic WAD (*Supplementary material G*: Figures 1a-1g) and acute WAD (*Supplementary material G*: Figures 2a-2k) cohorts. *Supplementary material H* contains individual funnel plots for each variable.

Two high-quality studies accounting for 4 individual cohorts and including 250 chronic WAD participants performed follow-ups of QST and psychological factors.[54,67] The pooled Hedges' *g*of disability levels since baseline showed small to moderate improvement in disability at 3-months (g=0.50; P<0.01), 6-months (g=0.46; P<0.01), and 12-months (g=0.55; P<0.01) (Figure 2a). For QST measures (Figure 2b), only PPT at the neck region showed small improvements at 3-months (g=0.27; P<0.01), 6-months (g=0.26; P=0.02), and 12-months (g=0.28; P<0.01); while there were no significant effects (P<0.11) at any time point for PPT at the leg or CPT at the neck regions. Regarding psychological factors (Figure 2c), a small to moderate improvement in the Pain Catastrophizing Scale scores were found at 3-months (g=0.46; P<0.01), 6-months (g=0.45; P<0.01), and 12-months (g=0.59; P<0.01); and a small improvement in the Posttraumatic Diagnostic Scale scores were found at 3-months (g=0.21; P=0.02), 6-months (g=0.26; P<0.01), and 12-months (g=0.33; P<0.01). Heterogeneity was low for all variables (i.e., I^2 values <50%). No publication bias was detected after examining funnel plots and Egger's tests.

Seven high-quality studies accounting for 4 individual cohorts and including 394 acute WAD participants performed follow-ups of QST measures and psychological factors.[7,25-27,30,36,37] The pooled Hedges' *g* of disability levels since baseline showed large improvements in disability at 3 months (g=0.95; P<0.01), 6 months (g=1.33; P<0.01), and 12 months (g=1.24; P<0.01) (Figure 3a). For QST measures (Figure 3b), pooled data showed a small improvement of PPT in the neck region at 3-months (g=0.36; P<0.01)

and 6-months (g=0.42; P<0.01) and a large increase at 12-months (g=0.89; P<0.01). However, PPT in the leg region only showed a small improvement at 6-months (g=0.20; P=0.05) that was not maintained at 12-months (g=0.15; P=0.15). For thermal thresholds, both CPT and HPT in the neck region showed a small improvement at 12-months (CPT: g=0.32, HPT: g=0.39; P<0.05). Regarding psychological factors (Figure 3c), a moderate to large improvements in the Impact Event Scale scores, the Global Health Questionnaire-28, the Tampa Scale of Kinesiophobia, and the Pictorial Fear of Activities Scale- Cervical Spine were found at 3-months (IES: g=0.75, GHQ-28: g=0.68, TSK: g=0.54, PFActS-C: g=0.58; P<0.01), 6-months (IES: g=0.73, GHQ-28: g=0.82, TSK: g=0.69, PFActS-C: g=0.76; P<0.05), and 12-months (IES: g=0.90, GHQ-28: g=0.89, TSK: g=0.53, PFActS-C: g=0.72; P<0.01). I^2 values indicated substantial heterogeneity across studies for the NDI and the TSK at 3-months (NDI: I^2=64%; TSK: I^2=59%) and 6-months (NDI: I^2=79%; TSK: I^2=81%). No publication bias was detected after examining funnel plots and Egger's tests.

DISCUSSION

This systematic review included 49 studies, comprising 1,493 chronic and 2,332 acute WAD participants, that investigated QST measures alongside psychological factors. Data synthesis of 9 studies (comprising 4 chronic and 9 acute independent WAD cohorts) indicated that despite chronicity, levels of disability, some QST measures, and psychological factors of participants with WAD showed an overall positive change over time. Nevertheless, these variables do not follow the exact same trajectory over time, as they differ in temporality and magnitude, while psychological factors outweigh altered nociception in explaining disability in chronic WAD. Chronic WAD participants displayed a small to moderate improvement in levels of disability and psychological

factors at 3-months compared to baseline. Furthermore, these improvements were sustained at 6- and 12-months. In contrast, acute WAD participants showed a large reduction in disability levels and a moderate to a large improvement in psychological factors at 3-months that slightly continued improving at 6- and 12-months. However, for QST measures in acute WAD, only a small improvement for PPT in the neck region was found at 3-months together with larger increases in the long term (>12 months). Additionally, PPT measured in the leg region and thermal pain thresholds (i.e., CPT and HPT) in the neck region revealed a small improvement at 6-months and 12-months in participants with acute WAD.

Relationship between QST and psychological factors

The objective of this review was to quantitatively assess the relationship between QST measures and psychological factors through a meta-analysis. However, despite the large number of studies on the subject, only 5 conducted correlational analyses between QST and psychological variables.[30,32,59,65,70] Unfortunately, none of those studies considered the same variables and therefore, could not be included in meta-analyses. Additionally, no prospective study explored the relationship between changes in QST and psychological factors. However, Kamper et al. reported a negative correlation between changes in neck pain and PPT over the neck,[28] which indicated that a reduction in the neck pain intensity was associated with an increase in neck PPT (i.e., decreased sensitivity). Such association could indicate that the recovery experienced by the proportion of acute WAD cases during the first months after the whiplash trauma may reflect the natural course of recovery and tissue healing,[26,37] but this would not be the case for those WAD cases with persistent pain, where pain sensitivity remained altered.

There is compelling evidence that chronic musculoskeletal conditions such as low back, knee, or non-specific neck pain, are often accompanied by facilitated nociceptive processing (e.g., reduced PPT) and psychological distress (e.g., pain catastrophizing, posttraumatic stress symptoms).[73-75] A recent meta-analysis evaluating the relationship between QST measures and psychological factors in people with peripheral joint pain, found that PPT is the only QST measure that is consistently associated with psychological factors such as pain catastrophizing and depression.[76]. In our review, 3 studies in chronic-[65,70,71] and 2 in acute WAD[30,32] found moderate correlations between low pain thresholds (high thresholds in case of cold-based stimuli, e.g., CPT) and levels of psychological distress. However, these results were inconsistent. Scott et al. found no correlation between PPT, CPT, or HPT and anxiety;[59] and Lenoir et al. found no correlation between temporal summation or CPM and posttraumatic stress symptoms, pain catastrophizing, or anxiety responses to pain.[71] Similarly, Rivest et al. found no correlation between PPT and CPT and catastrophizing thoughts in a subgroup of women with acute WAD.[32] Overall, these findings indicate that the coexistence of psychological factors and a facilitated nociceptive system are common in those with WAD, although such a relationship may not be linear. Considering the impracticality of using in-depth QST in clinical practice, self-reported questionnaires such as the Central Sensitization Inventory (CSI) were developed as a clinical proxy for assessing facilitated nociception. However, a recent meta-analysis has shown that the CSI weakly correlates (at best) with QST measures. Instead, CSI strongly correlates with psychological factors;[77] therefore, it could be used to assess cognitive and emotional components in WAD.[51]

Acute WAD versus Chronic WAD versus healthy controls

The present findings showed significant baseline differences in all variables between acute WAD participants and healthy controls in almost all studies, supporting the tenet that altered nociceptive processing and increased psychological distress is present soon after a whiplash trauma.[9,37,78] However, due to the paucity of studies that have investigated participants for preexisting alterations in nociceptive processing and psychological factors, it is not possible to determine if this may have influenced the results of the previous studies on whiplash. In contrast to the findings for acute WAD, the results for chronic WAD were not consistent across QST measures inferring the heterogenous presence of altered nociceptive processing in this population. In other words, while all chronic WAD studies revealed significantly worse scores in all psychological variables for WAD participants compared with healthy controls, only some static QST measures such as PPT or CPT showed consistent between-group differences.[42,43,58,59,61,65] As opposed to acute cases, these findings in chronic WAD participants could potentially indicate that psychological factors might outweigh altered nociceptive processing in explaining the persistence of pain and disability.[79,80] After all, chronic WAD cases represent a subsample of people with an originally acute WAD who have developed persistent pain and disability and high levels of psychological distress over time.[34] However, this discrepancy between chronic and acute WAD for QST variables may be partially attributed to the heterogeneous characteristics of chronic WAD samples. Inclusion criteria for chronic WAD studies were mainly based on reported pain and disability for more than 3 months and meeting the Quebec Task Force criteria for Grades I-III.[81] Despite Grade II, (pain, stiffness, or increased tenderness in the cervical region and musculoskeletal signs such as reduced range of motion or tender points on palpation)[81], being predominantly used as an inclusion criterion, this classification has been the subject of debate due to its lack of discriminative ability.[82] Additionally, data

synthesis of acute WAD studies shows that improvements in disability, QST measures, and psychological factors continue to occur beyond 3 and 6 months.[25,26,37,39] Therefore, these observed long-term improvements may exert an additive or a confounding effect in controlled clinical trials with chronic WAD, which would call into question whether WAD studies should recruit and combine data from participants who had experienced a whiplash trauma 3 months and several years ago. At least, it is reasonable to consider symptom duration as a potential confounder and introduce it as a covariate in the statistical analyses of chronic WAD studies, as several studies have already done regarding age and sex.[31,34,36,56]

Interestingly, data synthesis of acute WAD studies demonstrated that PPT measured in the neck region appears to improve earlier and more significantly than PPT in the leg and thermal pain thresholds in the neck region. Remote body regions normalizing their sensitivity to noxious stimulation later than the neck region could indicate that altered nociceptive processing in the nervous system might be influenced or maintained by factors different from those strictly related to tissue healing.[26,37] For example, posttraumatic stress symptoms are commonly reported by whiplash injured patients ,[83,84] and are associated with persistent neck pain.[85] It has been suggested that psychological factors acting as persistent stressors during the acute phase could contribute to a widespread hypersensitivity to noxious stimuli via immune-mediated pro-inflammatory mechanisms.[86,87] Another proposed hypothesis is that the initial inflammatory response in the neck tissues resolves first,[6] leaving central mechanisms as the primary driver of widespread hyperalgesia after this.

Methodological quality

To improve the robustness of the current findings, the data synthesis was based on high-quality prospective studies, but this unfortunately also decreased the number of prospective studies that could be included. Nonetheless, although most of the studies in the systematic review were considered fair to high quality, there were systematic biases that may lead to a distortion of interpretation and generalizability of results.[88] Moreover, almost all selected observational studies did not present the flow of screened participants from the start of the study. Information on the participant flow would allow for determining to what extent the selected samples are representative of the WAD population as a whole and ensure that self-selection bias is not occurring in a particular sub-sample of people with WAD.

Future observational studies in WAD population should follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations,[89] paying particular attention to reporting sample size calculations, presenting clear selection criteria for the WAD population, specifying the methods and locations of recruitment, and reporting the participant selection process, including reasons for non-participation. Case-control studies should perform matching, at least by sex and age, clearly presenting the criteria by which a control is considered a healthy participant; and blind assessors concerning group allocation. Prospective studies should establish a follow-up period sufficiently long to allow for changes not inherent to the measurement error of the instruments.

Limitations

It was not possible to perform meta-analyses of correlational analyses, and this is a limitation of our review. Furthermore, the current results only represented studies assessing QST measures and psychological factors simultaneously. This was also the case for the results regarding the course of disability. Taken together, these results should be interpreted with caution as they cannot account for potential studies that did not simultaneously assess both QST measures and psychological factors. Second, although this review did not aim to analyze the effects of any interventions, the variety and heterogeneity of treatments used (i.e., controlled intervention in clinical trials or unconstrained intervention in prospective non-controlled studies) may have influenced the trajectory of the QST measures or psychological factors over time. However, the lack of substantial heterogeneity across studies (i.e., I^2 values <50%) suggests that similar trajectories were followed by WAD participants despite the different treatment options used in the included studies. Nevertheless, substantial heterogeneity was found in levels of disability for acute WAD, which could be explained by the larger standardized mean differences found in two small studies.[26,39] Finally, some assessment procedures, such as the brachial plexus provocation test (BPPT) or the nociceptive flexion reflex (NFR), were considered as "other variables" in the current review, whereas another recent review on WAD included them as QST variables.[90] Despite the BPPT and NFR might be useful for assessing participants in the clinical setting,[91,92] these tests do not comply with using a calibrated stimulus and measuring the subjective perception of thresholds, which are characteristics of QST.[93]

Conclusion

This systematic review revealed a paucity of studies investigating correlations between QST measures and psychological factors in participants with WAD. Nevertheless, based on cross-sectional assessments, it can be concluded that facilitated nociceptive processing occurs alongside increased psychological distress (e.g., catastrophizing, or kinesiophobia) in both acute and chronic WAD compared to healthy controls. However, some QST measures do not provide highly consistent results in chronic WAD, which might be due to the considerable heterogeneity of chronic WAD samples. Furthermore, levels of disability, QST measures, and psychological factors showed a general positive change over time in both acute and chronic WAD, although they differ in temporality and magnitude. Finally, given that QST measures are more consistently affected in acute WAD, facilitated nociceptive processing might not be as important as psychological factors in chronic WAD, which indicates that chronic and acute WAD should not be considered the same entity.

Disclosures

The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

FIGURE 1. PRISMA Flow diagram describing the literature search procedure.

FIGURE 2. Summary plot of Hedges' g of variables pooled in the data synthesis for the cohorts with chronic whiplash-associated disorders. Error bars represent the confidence interval at 95% of Hedges' g. Positive values represent improvements in the investigated variable (e.g., lower disability, increased tolerance to noxious stimuli, or lower scores in questionnaires assessing psychological factors) from baseline values. Hedges' g: small ($\geq$ 0.2 g <0.5), medium ($\geq$ 0.5 g <0.8) or large (g $\geq$ 0.8).

FIGURE 3. Summary plot of Hedges' g of variables pooled in the data synthesis for the cohorts with acute whiplash-associated disorders. Error bars represent the confidence interval at 95% of Hedges' g. Positive effect sizes values represent improvements in the investigated variable (e.g., lower disability, increased tolerance to noxious stimuli, or lower scores in questionnaires assessing psychological factors) from baseline values. Hedges' g: small ($\geq$ 0.2 g <0.5), medium ($\geq$ 0.5 g <0.8) or large (g $\geq$ 0.8).

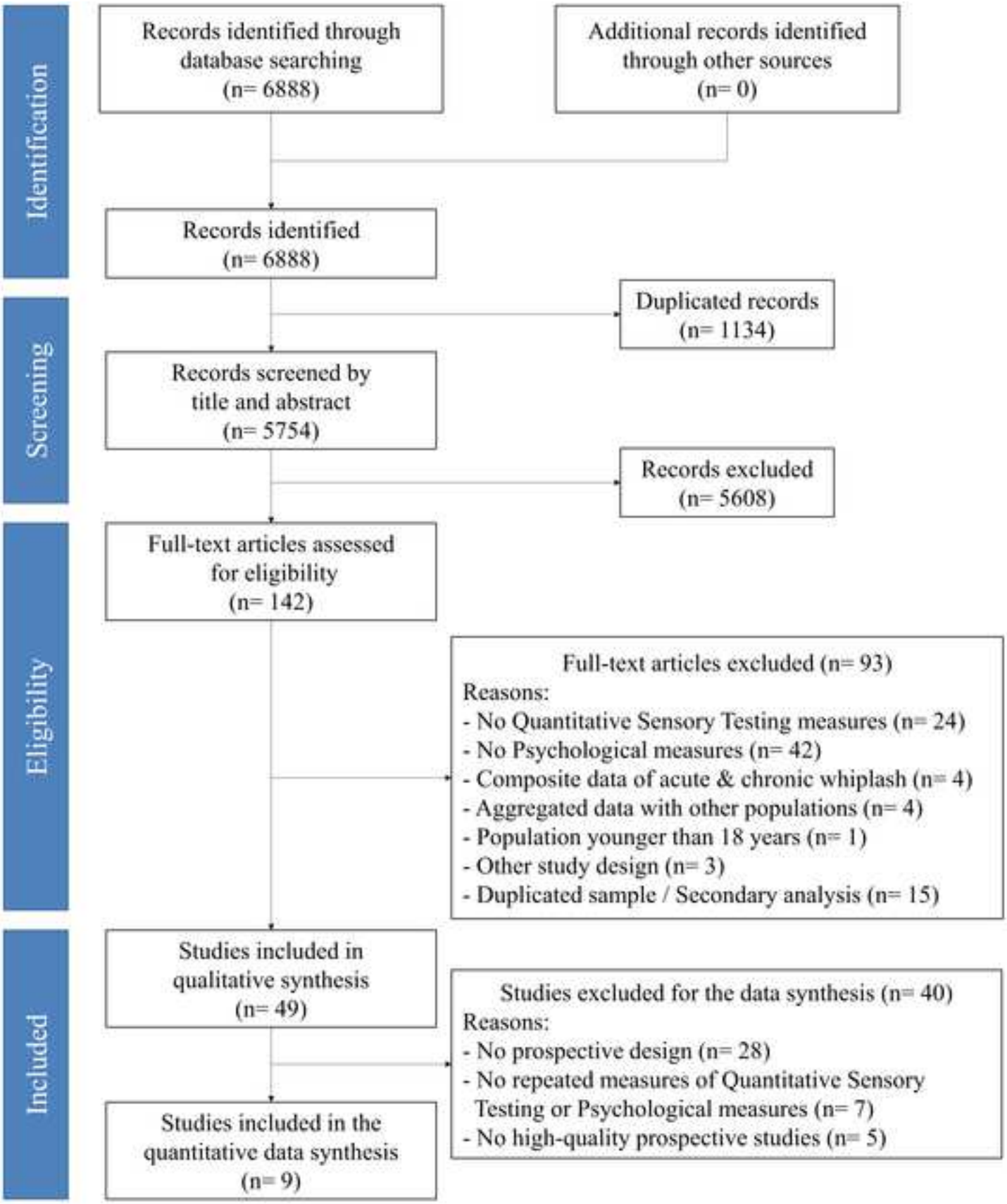
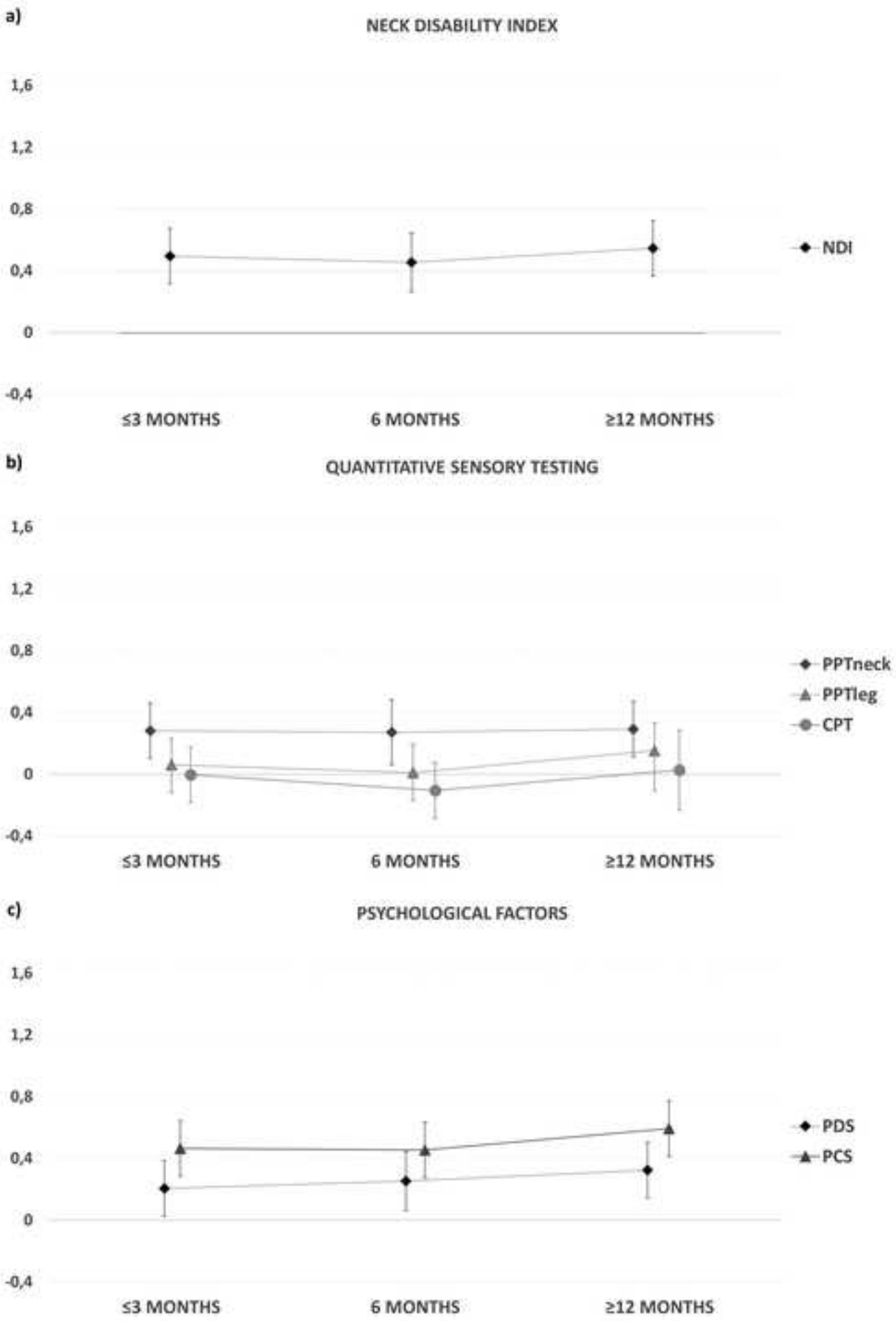


Figure_2_revised

Click here to access/download;Figure;Figure 2_R1.tif



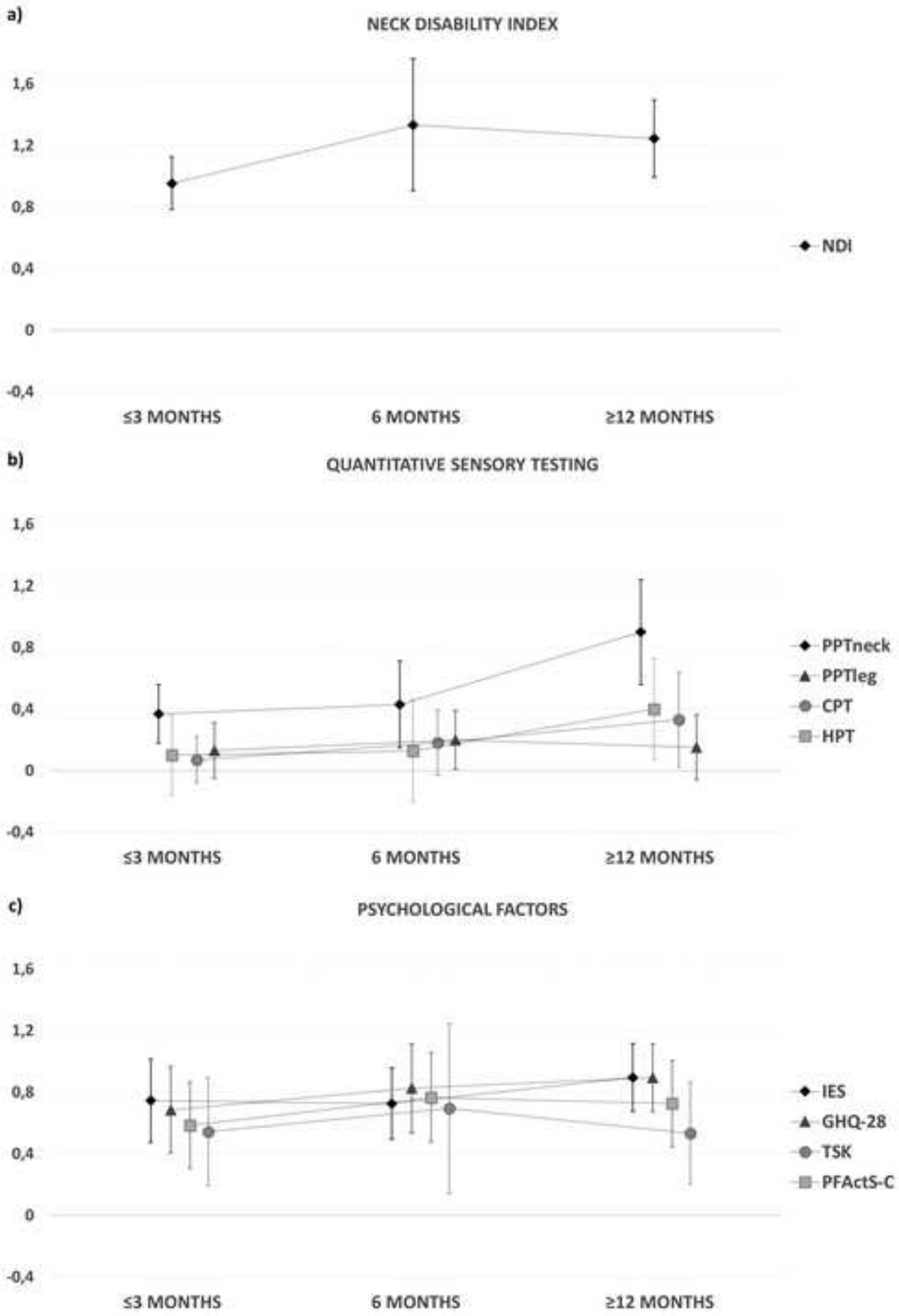


TABLE 1. Summary of studies included in the systematic review.

Study	Design	Grade	WAD cases (N, sex, age)	QST measures	Psychological factors	Results: QST measures & Psychological factors	N-O
A) CHRONIC WAD STUDIES							
Banic, 2004[2]	Case-control (single assessment)	n/a	n=27; 70% f; 39 (34-48) yr	PPT, PPTol, EPT, TS.	SCL-90-R	▪PPT, PPTol, TS: ↑ ▪EPT: ≈ ▪SCL-90-R: ↑	4
Chien, 2008[6]	Case-control (single assessment)	II	n=50; 78% f; 37.2 (±10.4) yr	PPT, CPT, VT, WDT, CDT, EDT.	SCL-90-R	▪PPT, CPT, VT, WDT, EDT: ↑ ▪CDT: ≈ ▪SCL-90-R: ↑	8
Chien, 2009[7]	Case-control (single assessment)	II	n=31; 81% f; 35.3 (±10.7) yr	PPT, HPT, CPT, VT, WDT, CDT, EDT, EPT.	SCL-90-R	▪PPT, CPT, VT, WDT, CDT, EDT, EPT: ↑ ▪HPT: ≈ ▪SCL-90-R: ↑	6
Coppieters, 2017[12]	Case-control (single assessment)	II	n=31; 100% f; 35.3 (±10.8) yr	PPT, CPM.	PCS, PVAQ	▪PPT, CPM: ↑ ▪PCS, PVAQ: ↑	7
Curatolo, 2001[14]	Case-control (single assessment)	n/a	n=14; 57% f; 48 (35-54) yr	HPTol, EPT, TS.	SCL-90-R	▪EPT, TS: ↑ ▪HPTol: ≈ ▪SCL-90-R: ↑	2
De Kooning, 2017[16]	Case-Control (single assessment)	I-III	n=30; 67% f; 42.2 (±10.7) yr	PPT.	PCS, IES	PPT: n/a ▪PCS: ↑ ▪IES: n/a	6
Dunne, 2012[18]	Clinical trial (repeated measures 3 & 6 mo)	II-III	n=26; 50% f; 32.5 (±7.1) yr	PPT, CPT, HPT.	PDS, IES-R, DASS, TSK	▪PPT, CPT, HPT: ↗ ▪PDS, IES-R, DASS, TSK: ↗	6
Elliott, 2009[20]	Cross-sectional	II	n=79; 100% f; 29.7 (±7.7) yr	PPT, CPT, HPT.	TSK, GHQ-28, IES	n/a	7
Farrell, 2020a[22]	Cross-sectional	II	n=41; 61% f; 39.6 (±11.0) yr	PPT, CPT.	PCS, PDS	n/a	7
Farrell, 2020b[23]	Case-control (single assessment)	II	n = 24; 67% f; 49 (15) yr	PPT, CDT, CPT, WDT, HPT, TSL, MDT, MPS, MPT, TS, VDT.	PCS, DASS, IES-R	▪CDT, WDT, TSL, HPT, MDT: ↑ ▪CPT, MPT, MPS, TS, VDT, PPT: ≈ ▪PCS, DASS: ↑	5

Study	Design	Grade	WAD cases (N, sex, age)	QST measures	Psychological factors	Results: QST measures & Psychological factors	N-O
						▪IES: n/a	
Hendriks, 2020[24]	Cross-sectional	n/a	n = 125; 57% f; 40.2 (±11.3) yr	PPT, TS.	SCL-90-R, 4DSQ, IES, TSK	n/a	7
Herren-Gerber, 2004[26]	Case-control (single assessment)	n/a	n=15; 67% f; 32 (27-47) yr	PPT, PPTol.	PRSIQ, PRBCQ	▪PPT, PPTol: ↑ ▪PRSIQ, PRBCS: ↑	3
Jull, 2007[29]	Clinical trial (repeated measures 10 wk)	II	n=71; 72% f; 39.7 (±11.1) yr	PPT, CPT.	GHQ-28, TSK, IES	▪PPT, CPT: ↗ GHQ-28, TSK, IES: ↗	7
Lenoir, 2022[34]	Case-control (single assessment)	II-III	n = 72; 71% f; 41.6 (±10.6) yr	EDT, EPT, TS, CPM.	PCS, IES-R, PASS	▪EPT: ↑ ▪EDT, TS, CPM: ≈ ▪PCS, IES-R, PASS: ↑	7
Michaleff, 2014[44]	Clinical trial (repeated measures 14 wk, 6 & 12 mo)	II-III	n=85; 57% f; 42.6 (±12.3) yr	PPT, CPT.	PDS, PCS	▪PPT, CPT: ↗ PDS, PCS: ↗	8
Olivegren, 1999[48]	Case-control (single assessment)	II-III	n = 22; 73% f; 37 (22-66) yr	PPT, PPTol.	MACL	▪PPT: ↑ ▪PPTol: ≈ ▪MACL: ≈	8
Pedler, 2013[54]	Cross-sectional	I-II	n = 64, 55% f; 44.7 (±12.6) yr	PPT, CPT.	PDS	n/a	7
Prushansky, 2006[56]	Clinical trial (repeated measures 16 & 44 wk)	II-III	n=40; 56% f; 41.7 (±11.8) yr	PPT.	SCL-90-R	▪PPT: ↗ ▪SCL-90-R: ↗	4
Raak, 2006[57]	Case-control (single assessment)	n/a	n=17; 94% f; 50.8 (±11.3) yr	▪CDT, WDT, CPT, HPT.	PCS	▪CDT, CPT, HPT: ↑ ▪WDT: ≈ ▪PCS: ↑	4
Scott, 2005[65]	Case-control (single assessment)	II	n=30; 17 (57%) f; 41.6 (±10) yr	PPT, HPT, CPT, punctate hyperalgesia.	SF-STAI	▪PPT, HPT, CPT: ↑ ▪Punctate hyperalgesia: ≈ ▪SF-STAI: ≈	7
Serrano-Muñoz, 2019[66]	Case-control (single assessment)	I-III	n=20; 73% f; 39.9 (±3.5) yr	▪THPI, CPM.	PCS	▪CPM: ↑ ▪THIP: ≈	3

Study	Design	Grade	WAD cases (N, sex, age)	QST measures	Psychological factors	Results: QST measures & Psychological factors	N-O
						▪PCS: ↑	
Smith, 2013[70]	Case-control (single assessment)	II	n=90; 64% f 45.1 (±10.7) yr	PPT, CPT, HPT.	GHQ-28, PDS, PCS	▪ PPT, CPT, HPT: ↑ ▪GHQ-28: ↑ ▪PDS, PCS: n/a.	4
Smith, 2017[68]	Case-control (single assessment)	II	n=21; 55% f; 44.5 (±10.5) yr	PPT, CPT, HPT, CPTP, CPM, EIH.	PCS, TSK, PDS	▪PPT, CPT, CPTP: ↑ ▪HPT, CPM, EIH: ≈ ▪TSK: ↑ ▪PCS: ≈ PDS: n/a	5
Smith, 2020[69]	Case-control (single assessment)	II	n=40; 70% f; 37.3 (±13.6) yr	PPT, CPTP, CPM, TS, EIH.	PCL-5, PCS, TSK	▪TS, EIH: ↑ ▪PPT, CPM: ≈ •PCL-5, PCS, TSK: n/a	7
Sterling, 2008[78]	Case control (single assessment)	II	n=30; 77% f 37 (23-58) yr	PPT, CPT, HPT.	GHQ-28, PCS	▪PPT, CPT: ↑ ▪HPT: ≈. ▪GHQ-28, PCS: ↑	3
Sterling, 2010b[83]	Clinical trial (repeated measures pre- post session)	II-III	n=39; 69% f 40.5 (±13.7) yr	▪PPT, CPT.	GHQ-28	▪PPT, CPT, HTP: ≈ ▪GHQ-28: n/a	7
Sterling, 2015[84]	Clinical trial (repeated measures 12 wk, 6 & 12 mo)	II	n=80; 68% f; 41.6 (±11.7) yr	▪PPT, CPT.	PDS, PCS	▪PPT, CPT: ↗ ▪PDS, PCS: ↗	8
Sterling, 2016[75]	Cross-sectional	II	n=21; 71% f; 44.4 (±11.1) yr	▪PPT, CPT, HPT.	PCS, TSK, PDS	n/a	6
Tobbackx, 2013[85]	Crossover trial (repeated measures pre- post session)	II	n=39; 72% f; 40.1 (±7.1) yr	PPT, TS, CPM.	PCS, TSK	▪PPT, TS, CPM: ↗ ▪PCS, TSK: n/a	6
Van Osterwijck, 2011[86]	Clinical trial (repeated measures 1, 2 & 3 wk)	I-II	n=6; 83% f; 35.7 (±7.3) yr	PPT.	TSK, PCS, PCI	▪PPT: ↗ ▪TSK, PCI: ↗ ▪PCS: n/a	5

Study	Design	Grade	WAD cases (N, sex, age)	QST measures	Psychological factors	Results: QST measures & Psychological factors	N-O
Wallin, 2012[89]	Case-control (single assessment)	II-III	n=28; 100% f; 40.1 (±7.1) yr	PPT, CPT, CDT, HPT, WDT.	PCS, HADS, PASS, ASI, PSEQ, GSES, IES, FABQ	▪PPT, CDT, WDT, CPT, HPT: ↑ ▪PCS, HADS, PASS, ASI, PSEQ, GSES, IES: ↑	6
Daenen, 2014[15]	Case-control (single assessment)	I-III	n=35; 74% f; 43.8 (±9.6) yr	PPT, CPM.	IES, PCS, PVAQ, BDI	▪PPT: n/a. ▪TS: ↑ ▪CPM: ≈ ▪PCS, PVAQ, BDI: ↑ ▪IES: ≈	6
B) ACUTE WAD STUDIES							
Andersen, 2022[1]	Cohort (repeated measures 1, 3, 6 & 12 mo)	I-III	n=747; 64% f; 34.8 (±11.4) yr	▪PPT, PPTol.	IES	▪PPT, PPTol: ↗ ▪IES: n/a	6
Chien, 2010b[8]	Case-control (repeated measures 3 & 6 mo)	II	n=52; 62% f; 36.3 (±13.1) yr;	PPT, HPT, CPT, VT, WDT, CDT, EDT.	IES, GHQ-28	▪PPT, CPT: n/a. ▪VT, WDT, CDT, EDT: ↑ & ↗ ▪GHQ-28: ↑ (change over time: n/a) ▪IES: ↗ (differences with controls: n/a)	8
Christensen, 2021[9]	Case-control (repeated measures 3, 5 wk, & 6 mo)	II	n=22; 64% f; 30.6 (±7.4) yr	PPT, PPTol, CPM, STPS.	PCS, TSK, BDI	▪PPT, PPTol: ↑ & ↗ ▪CPM, STPS: ↑ & ≈ ▪PCS, TSK, BDI: ↑ & ↗	7
Jull, 2013[28]	Clinical trial (repeated measures 11 wk, 6 & 12 mo)	II	n=101; 58% f; 35.6 (±12.4) yr	PPT, CPT, HPT.	IES, PFActS-C, GHQ-28	▪PPT, CPT: ≈ ▪HPT: n/a ▪IES, PFActS-C, GHQ-28: ↗	9
Kamper, 2011[30]	Cohort (repeated measures 1 & 3 mo)	I-III	n=100; 72% f; 40.1 (±13.3) yr	PPT.	DASS, CSQ-C, TSK	▪PPT: ↗ ▪DASS, TSK, CSQ-C: n/a	5
Kasch, 2011[31]	Case-control (repeated measures 1, 3, 6, & 12 mo)	I-III	n = 141; n/a; n/a	PPT, PPTol, CPTP.	MBHI, SCL-90-R	n/a (change over time, differences with controls)	3

Study	Design	Grade	WAD cases (N, sex, age)	QST measures	Psychological factors	Results: QST measures & Psychological factors	N-O
Pedler, 2016[53]	Cohort (repeated measures 6 wk & 3 mo)	I-III	n=103; 72% f; 39.7 (±13.9) yr	PPT, CPT.	TSK, PFActS-C, CSQ-C, PDS	n/a (change over time)	8
Ritchie, 2013[61]	Cohort (repeated measures 1, 3, 6, & 12 mo)	I-III	n=262; n/a; 37.1 (±14.2) yr	CPT.	PDS	n/a (change over time)	7
Rivest, 2010[63]	Cross-sectional	I-III	n = 37; 57% f; 32.7 (±16.8) yr	PPT, CPT.	PCS	n/a	8
Sterling, 2003[80]	Case control (repeated measures 1, 2, 6, & 12 mo)	II-III	n=76; 70% f; 34.2 (±11.8) yr	PPT, CPT, HPT.	GHQ-28	▪PPT, CPT, HPT: ↑ & ↗ ▪GHQ-28: ↑ & ↗	7
Sterling, 2006[79]	Cohort (repeated measures 2-3 yr)	II-III	n=65; 71% f 35.5 (±11.8) yr	PPT, CPT, HPT.	GHQ-28, TSK, IES	▪PPT, CPT, HPT: ↑ & ↗ ▪GHQ-28, TSK, IES: ↑ (change over time: n/a)	8
Sterling, 2009[82]	Cross-sectional	I-III	n=85; 62% f; 36.3 (±12.7) yr	PPT, CPT.	GHQ-28	n/a	6
Sterling, 2010a[73]	Case control (repeated measures 3 wk, 3 & 6 mo)	II-III	n=62; 58% f; 35.5 (±12.9) yr	PPT, CPT.	GHQ-28, IES	▪PPT: ↑ & ↗ ▪CPT: ↑ & ≈ ▪GHQ-28, IES: n/a	6
Sterling, 2011[76]	Cohort (repeated measures 1, 2, 6, & 12 mo)	I-III	n=155; 63% f; 36.9 (±12.8) yr	PPT, CPT.	PDS	n/a	7
Sterling, 2012[77]	Cohort (repeated measures 3 wk & 12 mo)	I-III	n=286; 63% f; 35.3 (±13.1) yr	CPT.	IES	n/a	8

Study	Design	Grade	WAD cases (N, sex, age)	QST measures	Psychological factors	Results: QST measures & Psychological factors	N-O
Sterling, 2013[74]	Case-control (repeated measures 3 wk &3 mo)	II-III	n=58; 74% f; 37.9 (±8.6) yr	PPT, CPT, HPT.	PDS, CSQ-C	▪PPT, CPT, HPT: ↑ & ≈ ▪PDS, CSQ-C: ↑ & ≈	5
Wiangkham, 2019[92]	Clinical trial (repeated measures 3 mo)	II	n=28; 32% f; 35.7 (14.3) yr	PPT.	IES, FABQ	▪PPT: ↗ ▪IES, FABQ: ↗.	6
Daenen, 2014[15]	Case-control (single assessment)	I-III	n=30; 47% f; 43.3 (±11.0) yr	▪PPT, CPM.	IES, PCS, PVAQ, BDI	▪PPT: n/a. ▪TS: ↑ ▪CPM: ≈ ▪PCS, PVAQ, BDI: ↑ ▪IES: ≈	6

General abbreviations: WAD: Whiplash Associated Disorders; f: female; mo: months; wk: weeks; yr, years; n/a: no available; N-O: Newcastle-Ottawa (Total score of 7 ≥ stars: "high quality"; 4-6 stars: "fair quality"; 3 ≤ stars "poor quality"); ↑: greater pain sensitivity and psychological distress or altered cognitions compared to a control group; ↗: improvements over time compared to the baseline assessment in terms of a reduced pain sensitivity or lower levels of psychological factors; ≈: no differences with controls or change over time compared to the baseline assessment.

Psychological factors (Psycho factors) → 4DSQ: Four-Dimensional Symptom Questionnaire; ASI: Anxiety Sensitivity Index; BDI: Beck Depression Inventory; CSQ-C: Coping Strategy Questionnaire C; DASS: Depression Anxiety and Stress Scale; FABQ: Fear-Avoidance Beliefs Questionnaire; GHQ-28: General Health Questionnaire 28; HADS: Hospital Anxiety and Depression Scale; IES: Impact of Events Scale; IES-R: Impact of Events Scale Revised; MOCL: Mood Adjective Check List; MBHI: Millon Behavioral Health Inventory; PASS: Pain Anxiety Symptoms Scale; PCI: Pain Coping Inventory; PCS: Pain Catastrophizing Scale; PCL-5: Posttraumatic Stress Diagnostic Checklist 5; PDS: Posttraumatic Stress Diagnostic Scale; PFActS-C: Pictorial Fear of Activities Scale- Cervical Spine; PRBCQ: Pain-Related Beliefs of Control Questionnaire; PRSIQ: Pain-Related Self-Instructions Questionnaire; PSEQ: Pain Self-Efficacy Scale; PVAQ: Pain Vigilance Awareness Questionnaire; SCL-90-R: Symptom Check List-90, revised version; SF-STAI: Sort-Form State-Trait Anxiety Inventory; TSK: Tampa Scale of Kinesiophobia.

Quantitative sensory testing (QST) → CDT: Cold Detection Threshold; CPM: Conditioned Pain Modulation; CPT: Cold Pain Threshold; CPTP: Cold Pressor Test Pain; EDT: Electrical Detection Threshold; EIH: Exercise-Induced Hypoalgesia; EPT: Electrical Pain Threshold; ER: Electrocutaneous Ratio; HPT: Heat Pain Threshold; HPTol: Heat Pain Tolerance; MDT: Mechanical Detection Threshold; MPS: Mechanical Pain Sensitivity; MPT: Mechanical Pain Threshold; PPT: Pressure

Study	Design	Grade	WAD cases (N, sex, age)	QST measures	Psychological factors	Results: QST measures & Psychological factors	N-O

Pain Threshold; PPTol: Pressure Pain Tolerance; STPS: Supra-Threshold Pain Stimulation; THPI: Tonic Heat Pain Intensity; TS: Temporal Summation; TSL: Thermal Sensory Limen; VDT: Vibration Disappearance Threshold; VT: Vibration Threshold; WDT: Warm Detection Threshold.

TABLE 2. Characteristics and findings of chronic and acute whiplash associated disorders (WAD) studies examining correlations between QST measurements and psychological factors.

Study	N-O	N	QST measures	Psychological factors	Significative correlations
A) CHRONIC WAD					
Sterling, 2008[78]	3	30	PPT, CPT, HPT.	GHQ-28, PCS	PCS & CPT (r=0.51, P=0.01)
Wallin, 2012[89]	6	28	PPT, CPT, CDT, HPT, WDT.	PCS, HADS, PASS, ASI, PSEQ, IES, FABQ	Significant intercorrelations (R^2=0.36) between QST measures and the psychological variables.
Lenoir, 2022[34]	7	72	EDT, EPT, TS, CPM.	PCS, IES-R, PASS	EPT & PCS (r=−0.33; P<0.01) EPT & PASS (r=−0.33; P<0.01)
Scott, 2005[65]	7	30	PPT, HPT, CPT	SF-STAI	n.s.
B) ACUTE WAD					
Pedler, 2016[53]	8	103	PPT, CPT.	TSK, CSQ-C, PFActS-C, PDS	CPT & CSQ-C (r=0.28; P<0.01) CPT & PDS (r=0.25; P<0.01) CPT & TSK (r=0.21; P<0.01) CPT & PFAct-S-C (r=0.20; P<0.01) PPT & CSQ-C (r=0.31; P<0.01) PPT & PDS (r=0.29; P<0.01) PPT & TSK (r=0.25; P<0.01) PPT & PFAct-S-C (r=0.24; P<0.01)
Rivest, 2010[63]	8	37	PPT, CPT.	PCS	*All sample:* CPT & PCS (r=0.46, p<0.01) *Male subsample:* PPT & PCS (r=-0.56, p>0.05)

N-O: Newcastle-Ottawa (7 ≥ stars: "high quality"; 4-6 stars: "fair quality"; 3 ≤ stars "poor quality"). **Psychological factors →** ASI: Anxiety Sensitivity Index; CSQ-C: Coping Strategy Questionnaire C; FABQ: Fear-Avoidance Beliefs Questionnaire; GHQ-28: General Health Questionnaire 28; HADS: Hospital Anxiety and Depression Scale; IES: Impact of Events Scale; IES-R: Impact of Events Scale Revised; PASS: Pain Anxiety Symptoms Scale; PCS: Pain Catastrophizing Scale; PDS: Posttraumatic Stress Diagnostic Scale; PFActS-C: Pictorial Fear of Activities Scale- Cervical Spine; PSEQ: Pain Self-Efficacy Scale; SF-STAI: Sort-Form State-Trait Anxiety Inventory; TSK: Tampa Scale of Kinesiophobia; **Quantitative sensory testing (QST) →** CDT: Cold Detection Threshold; CPM: Conditioned Pain Modulation; CPT: Cold Pain Threshold; EDT: Electrical Detection Threshold; EPT: Electrical Pain Threshold; HPT: Heat Pain Threshold; PPT: Pressure Pain Threshold; TS: Temporal Summation; WDT: Warm Detection Threshold.

SUPPLEMENTARY MATERIAL A. Search strategy and procedure in each database.

Database	***PUBMED***
Procedure	Combining the search strategy with the Boolean Operator: AND.
Search strategy:	1st October 2022
Population	(WAD[TIAB] *OR* Whiplash[TIAB] *OR* Whiplash Injuries[MH] *OR* Whiplash associated disorder*[TIAB])
Outcome Measures	(Analgesia[MH:noexp] *OR* Algometry[TIAB] *OR* Allodynia[TIAB] *OR* Altered nociceptive processing[TIAB] *OR* Altered central pain processing[TIAB] *OR* Altered central processing[TIAB] *OR* Altered pain processing[TIAB] *OR* Bottom up[TIAB] *OR* Capsaicin[MH] *OR* Central hyperexcitability[TIAB] *OR* Central hypersensitivity[TIAB] *OR* Central nervous system sensitization[MH] *OR* Central sensitization*[TIAB] *OR* Central sensitisation*[TIAB] *OR* Central pain[TIAB] *OR* Chronic pain[MH] *OR* Cognitive-emotional sensitization[TIAB] *OR* Cognitive-emotional sensitisation[TIAB] *OR* Cold detection[TIAB] *OR* Cold pain[TIAB] *OR* Conditioned pain modulation[TIAB] *OR* Counterirritant effect[TIAB] *OR* CPM[TIAB] *OR* Detection threshold*[TIAB] *OR* Diffuse noxious inhibitory control[MH] *OR* DNIC[TIAB] *OR* Heat detection[TIAB] *OR* Heat pain[TIAB] *OR* Heterotopic facilitation[TIAB] *OR* Hyperalgesia[TIAB] *OR* Saline Solution, Hypertonic[MH] *OR* Hyperpathia[TIAB] *OR* Hyperesthesi*[TIAB] *OR* Hypersensitivity[MH:noexp] *OR* Hypesthesia[TIAB] *OR* Hypoalgesia[TIAB] *OR* Hypoesthesia*[TIAB] *OR* Ischemic pain[TIAB] *OR* Mechanical pain[TIAB] *OR* Nociceptors[MH] *OR* Pain modulation[TIAB] *OR* Pain pathophysiology[TIAB] *OR* Pain perception[MH] *OR* Pain physiopathology[TIAB] *OR* Pain processing[TIAB] *OR* Pain sensitisation[TIAB] *OR* Pain sensitization[TIAB] *OR* Pain tolerance[TIAB] *OR* Peripheral sensitisation[TIAB] *OR* Peripheral sensitization[TIAB] *OR* Pinprick test[TIAB] *OR* Pressure pain threshold[TIAB] *OR* Pressure pain tolerance[TIAB] *OR* Quantitative pain[TIAB] *OR* Quantitative sensory test*[TIAB] *OR* QST[TIAB] *OR* Pain, referred[MH] *OR* Second pain[TIAB] *OR* Sensitivity[TIAB] *OR* Sensory hypersensitivity[TIAB] *OR* Sensory profil*[TIAB] *OR* Sensory test*[TIAB] *OR* Sensory thresholds[MH] *OR* Somatosensory disorders[MH] *OR* Somatosensory profil*[TIAB] *OR* Spatial summation[TIAB] *OR* Postsynaptic Potential Summation[MH] *OR* Suprathreshold stimulation[TIAB] *OR* Tactile acuity[TIAB] *OR* Tactile detection Threshold[TIAB] *OR* Temporal summation[TIAB] *OR* Thermal pain[TIAB] *OR* Tolerance threshold[TIAB] *OR* Two-point discrimination[TIAB] *OR* Top down[TIAB] *OR* Vibration detection[TIAB] *OR* Warm detection[TIAB] *OR* Warm pain[TIAB] *OR* Wind up[TIAB] *OR* widespread hyperalgesia[TIAB])

	(Biopsychosocial[TIAB] *OR* Psycholog*[TIAB] *OR* Psychosocial[TIAB] *OR* Strategies[TIAB] *OR* Model[TIAB] *OR* Acceptance[TIAB] *OR* CPAQ[TIAB] *OR* Adherence[TIAB] *OR* Affect*[TIAB] *OR* Anxiety[TIAB] *OR* ASI[TIAB] *OR* STAI[TIAB] *OR* prime-MD[TIAB] *OR* Attitude*[TIAB] *OR* SOPA[TIAB] *OR* Avoidance[TIAB] *OR* Behavio*[TIAB] *OR* FSR[TIAB] *OR* Belief*[TIAB] *OR* PBPI[TIAB] *OR* BPI[TIAB] *OR* Catastrophizing[TIAB] *OR* Catastrophising[TIAB] *OR* PCS[TIAB] *OR* Cognition*[TIAB] *OR* Control[TIAB] *OR* Coping[TIAB] *OR* Cpci[TIAB] *OR* CSQ[TIAB] *OR* Depression[TIAB] *OR* PHQ-9[TIAB] *OR* MADRS[TIAB] *OR* CDMI[TIAB] *OR* BDI-II[TIAB] *OR* CES-D[TIAB] *OR* GHQ-28[TIAB] *OR* MDS[TIAB] *OR* MDI[TIAB] *OR* HADS[TIAB] *OR* MHI[TIAB] *OR* DASS-21[TIAB] *OR* Distress[TIAB] *OR* Emotional state*[TIAB] *OR* Endurance[TIAB] *OR* Expectation*[TIAB] *OR* Fear*[TIAB] *OR* CBSQ[TIAB] *OR* TSK[TIAB] *OR* FABQ[TIAB] *OR* FOPQ[TIAB] *OR* PFActS-C[TIAB] *OR* Helplessness[TIAB] *OR* Hypervigilance[TIAB] *OR* Inactivity[TIAB] *OR* Interference*[TIAB] *OR* Improvement[TIAB] *OR* Isolation[TIAB] *OR* Limit*[TIAB] *OR* Locus of control[TIAB] *OR* Major life events[TIAB] *OR* Mood*[TIAB] *OR* PASS[TIAB] *OR* Motivation*[TIAB] *OR* Perceived[TIAB] *OR* Perception*[TIAB] *OR* IPQ-R[TIAB] *OR* Personality[TIAB] *OR* Readiness to change[TIAB] *OR* Recovery[TIAB] *OR* Self-efficacy[TIAB] *OR* MPRCQ[TIAB] *OR* Satisfaction[TIAB] *OR* Solicitude[TIAB] *OR* Somatic[TIAB] *OR* Somatization[TIAB] *OR* Stress[TIAB] *OR* Stressful[TIAB] *OR* Support[TIAB] *OR* Thought suppression[TIAB] *OR* Transformation[TIAB] *OR* Quality of Life[TIAB] *OR* Vitality[TIAB] *OR* Well being[TIAB] *OR* Willingness[TIAB] *OR* Worry[TIAB] *OR* PSWQ[TIAB] *OR* Compensation[TIAB] *OR* Social[TIAB] *OR* MSSS[TIAB] *OR* CPI[TIAB] *OR* MSPSS[TIAB] *OR* Job*[TIAB] *OR* Job absen*[TIAB] *OR* Work*[TIAB] *OR* Activity[TIAB] *OR* Disability[TIAB] *OR* Function*[TIAB] *OR* Insomnia[TIAB] *OR* Sleep[TIAB] *OR* MOOS[TIAB] *OR* PSQI[TIAB])
Study type	(Case-Control Studies[TIAB] *OR* Cohort Studies[TIAB] *OR* Cross-Sectional Studies[TIAB] *OR* Observational Study[pt] *OR* Randomized Controlled Trial[pt] *OR* Controlled Clinical Trial[pt])
Filters	*Language:* English or Spanish *Species:* Humans

Number of items retrieved	**3139**

Database	***Web of Science***
Procedure	Advanced search in Web of Science – All databases. Combining the search strategy with the Boolean Operator: AND.
Search strategy:	1st October 2022
Population	TS=(WAD *OR* Whiplash *OR* Whiplash Injur* *OR* Whiplash associated disorder*)
Outcome Measures	TS=(Analgesia *OR* Algometry *OR* Allodynia *OR* Altered nociceptive processing *OR* Altered central pain processing *OR* Altered central processing *OR* Altered pain processing *OR* Bottom up *OR* Capsaicin *OR* Central hyperexcitability *OR* Central hypersensitivity *OR* Central sensitization* *OR* Central sensitisation* *OR* Central pain *OR* Chronic pain *OR* Cognitive-emotional sensitization *OR* Cognitive-emotional sensitization *OR* Cold detection *OR* Cold pain *OR* Conditioned pain modulation *OR* Counterirritant effect *OR* CPM *OR* Detection threshold* *OR* Diffuse noxious inhibitory control *OR* DNIC *OR* Heat detection *OR* Heat pain *OR* Heterotopic facilitation *OR* Hyperalgesia *OR* Hypertonic Saline Solution *OR* Hyperpathia *OR* Hyperesthesi* *OR* Hypersensitivity *OR* Hypesthesia *OR* Hypoalgesia *OR* Hypoesthesia* *OR* Ischemic pain *OR* Mechanical pain *OR* Nocicept* *OR* Pain modulation *OR* Pain pathophysiology *OR* Pain perception *OR* Pain physiopathology *OR* Pain processing *OR* Pain sensitization *OR* Pain sensitisation *OR* Pain tolerance *OR* Peripheral sensitisation *OR* Peripheral sensitization *OR* Pinprick test *OR* Pressure pain threshold *OR* Pressure pain tolerance *OR* Quantitative pain *OR* Quantitative sensory test* *OR* QST *OR* Referred Pain *OR* Second pain *OR* Sensitivity *OR* Sensory hypersensitivity *OR* Sensory profil* *OR* Sensory test* *OR* Sensory thresholds *OR* Somatosensory disorders *OR* Somatosensory profil* *OR* Spatial summation *OR* Postsynaptic Potential Summation *OR* Suprathreshold stimulation *OR* Tactile acuity *OR* Tactile detection Threshold *OR* Temporal summation *OR* Thermal pain *OR* Tolerance threshold *OR* Two-point discrimination *OR* Top down *OR* Vibration detection *OR* Warm detection *OR* Warm pain *OR* Wind up *OR* widespread hyperalgesia) TS=(Biopsychosocial *OR* Psycholog* *OR* Psychosocial *OR* Strategies *OR* Model *OR* Acceptance *OR* CPAQ *OR* Adherence *OR* Affect* *OR* Anxiety *OR* ASI *OR* STAI *OR* prime-MD *OR* Attitude* *OR* SOPA *OR* Avoidance *OR* Behavio* *OR* FSR *OR* Belief* *OR* PBPI *OR* BPI *OR* Catastrophizing *OR* Catastrophising *OR* PCS *OR* Cognition* *OR* Control *OR* Coping *OR* Cpci *OR* CSQ *OR* Depression *OR* PHQ-9 *OR* MADRS *OR* CDMI *OR* BDI-II *OR* CES-D *OR* GHQ-28 *OR* MDS *OR* MDI *OR* HADS *OR* MHI *OR* DASS-21 *OR* Distress *OR* Emotional state* *OR* Endurance *OR* Expectation* *OR* Fear* *OR* CBSQ *OR* TSK *OR* FABQ *OR* FOPQ *OR* PFActS-C *OR* Helplessness *OR* Hypervigilance *OR* Inactivity *OR* Interference* *OR* Improvement *OR*

	Isolation *OR* Limit* *OR* Locus of control *OR* Major life events *OR* Mood* *OR* PASS *OR* Motivation* *OR* Perceived *OR* Perception* *OR* IPQ-R *OR* Personality *OR* Readiness to change *OR* Recovery *OR* Self-efficacy *OR* MPRCQ *OR* Satisfaction *OR* Solicitude *OR* Somatic *OR* Somatization *OR* Stress *OR* Stressful *OR* Support *OR* Thought suppression *OR* Transformation *OR* Quality of Life *OR* Vitality *OR* Well being *OR* Willingness *OR* Worry *OR* PSWQ *OR* Compensation *OR* Social *OR* MSSS *OR* CPI *OR* MSPSS *OR* Job* *OR* Job absen* *OR* Work* *OR* Activity *OR* Disability *OR* Function* *OR* Insomnia *OR* Sleep *OR* MOOS *OR* PSQI)
Study type	TS=(Case-Control Studies *OR* Cohort Studies *OR* Cross-Sectional Studies *OR* Observational Study *OR* Randomized Controlled Trial *OR* Controlled Clinical Trial)
Filters	*Language:* English or Spanish

Number of items retrieved	**976**

Database	***COCHRANE***
Procedure	Individual search of blocks 1#, 2#, 3#, 4#,and 5#. Combined search: 1# AND 2# AND 3# AND (4# OR 5#).
Search strategy:	1st October 2022
Population	1#: (WAD OR Whiplash OR Whiplash Injur* OR Whiplash associated disorder*):ti,ab,kw
Outcome Measures	2#: (Analgesia OR Algometry OR Allodynia OR Altered nociceptive processing OR Altered central pain processing OR Altered central processing OR Altered pain processing OR Bottom up OR Capsaicin OR Central hyperexcitability OR Central hypersensitivity OR Central sensitization* OR Central sensitisation* OR Central pain OR Chronic pain OR Cognitive-emotional sensitization OR Cognitive-emotional sensitization OR Cold detection OR Cold pain OR Conditioned pain modulation OR Counterirritant effect OR CPM OR Detection threshold* OR Diffuse noxious inhibitory control OR DNIC OR Heat detection OR Heat pain OR Heterotopic facilitation OR Hyperalgesia OR Hypertonic Saline Solution OR Hyperpathia OR Hyperesthesi* OR Hypersensitivity OR Hypesthesia OR Hypoalgesia OR Hypoesthesia* OR Ischemic pain OR Mechanical pain OR Nocicept* OR Pain modulation OR Pain pathophysiology OR Pain perception OR Pain physiopathology OR Pain processing OR Pain sensitization OR Pain sensitisation OR Pain tolerance OR Peripheral sensitisation OR Peripheral sensitization OR Pinprick test OR Pressure pain threshold OR Pressure pain tolerance OR Quantitative pain OR Quantitative sensory test* OR QST OR Referred pain OR Second pain OR Sensitivity OR Sensory hypersensitivity OR Sensory profil* OR Sensory test* OR Sensory thresholds OR Somatosensory disorders OR Somatosensory profil* OR Spatial summation OR Postsynaptic Potential Summation OR Suprathreshold stimulation OR Tactile acuity OR Tactile detection Threshold OR Temporal summation OR Thermal pain OR Tolerance threshold OR Two-point discrimination OR Top down OR Vibration detection OR Warm detection OR Warm pain OR Wind up OR widespread hyperalgesia):ti,ab,kw 3#: (Biopsychosocial OR Psycholog* OR Psychosocial OR Strategies OR Model OR Acceptance OR CPAQ OR Adherence OR Affect* OR Anxiety OR ASI OR STAI OR prime-MD OR Attitude* OR SOPA OR Avoidance OR Behavio* OR FSR OR Belief* OR PBPI OR BPI OR Catastrophizing OR Catastrophising OR PCS OR Cognition* OR Control OR Coping OR Cpci OR CSQ OR Depression OR PHQ-9 OR MADRS OR CDMI OR BDI-II OR CES-D OR GHQ-28 OR MDS OR MDI OR HADS OR MHI OR DASS-21 OR Distress OR Emotional

	state* OR Endurance OR Expectation* OR Fear* OR CBSQ OR TSK OR FABQ OR FOPQ OR PFActS-C OR Helplessness OR Hypervigilance OR Inactivity OR Interference* OR Improvement OR Isolation OR Limit* OR Locus of control OR Major life events OR Mood* OR PASS OR Motivation* OR Perceived OR Perception* OR IPQ-R OR Personality OR Readiness to change OR Recovery OR Self-efficacy OR MPRCQ OR Satisfaction OR Solicitude OR Somatic OR Somatization OR Stress OR Stressful OR Support OR Thought suppression OR Transformation OR Quality of Life OR Vitality OR Well being OR Willingness OR Worry OR PSWQ OR Compensation OR Social OR MSSS OR CPI OR MSPSS OR Job* OR Job absen* OR Work* OR Activity OR Disability OR Function* OR Insomnia OR Sleep OR MOOS OR PSQI):ti,ab,kw
Study type	4#: (Case-Control Studies OR Cohort Studies OR Cross-Sectional Studies):ti,ab,kw 5#: (Observational Study OR Randomized Controlled Trial OR Controlled Clinical Trial):pt
Filters	*Content type:* Trials

Number of items retrieved	**64**

Database	***SCOPUS***
Procedure	Advanced document search. Combining the search strategy with the Boolean Operator: AND.
Search strategy:	1st October 2022
Population	TITLE-ABS-KEY(WAD OR Whiplash OR "Whiplash Injur*" OR "Whiplash associated disorder*")
Outcome Measures	TITLE-ABS-KEY(Analgesia OR Algometry OR Allodynia OR "Altered nociceptive processing" OR "Altered central pain processing" OR "Altered central processing" OR "Altered pain processing" OR "Bottom up" OR Capsaicin OR "Central hyperexcitability" OR "Central hypersensitivity" OR "Central sensitization*" OR "Central sensitisation*" OR "Central pain" OR "Chronic pain" OR "Cognitive-emotional sensitization" OR "Cognitive-emotional sensitisation" OR "Cold detection" OR "Cold pain" OR "Conditioned pain modulation" OR "Counterirritant effect" OR CPM OR "Detection threshold*" OR "Diffuse noxious inhibitory control" OR DNIC OR "Heat detection" OR "Heat pain" OR "Heterotopic facilitation" OR Hyperalgesia OR "Hypertonic Saline Solution" OR Hyperpathia OR Hyperesthesi* OR Hypersensitivity OR Hypesthesia OR Hypoalgesia OR Hypoesthesia* OR "Ischemic pain" OR "Mechanical pain" OR Nocicept* OR "Pain modulation" OR "Pain pathophysiology" OR "Pain perception" OR "Pain physiopathology" OR "Pain processing" OR "Pain sensitization" OR "Pain sensitisation" OR "Pain tolerance" OR "Peripheral sensitization" OR "Peripheral sensitisation" OR "Pinprick test" OR "Pressure pain threshold" OR "Pressure pain tolerance" OR "Quantitative pain" OR "Quantitative sensory test*" OR QST OR "Referred Pain" OR "Second pain" OR "Sensitivity" OR "Sensory hypersensitivity" OR "Sensory profil*" OR "Sensory test*" OR "Sensory thresholds" OR "Somatosensory disorders" OR "Somatosensory profil*" OR "Spatial summation" OR "Postsynaptic Potential Summation" OR "Suprathreshold stimulation" OR "Tactile acuity" OR "Tactile detection Threshold" OR "Temporal summation" OR "Thermal pain" OR "Tolerance threshold" OR "Two-point discrimination" OR "Top down" OR "Vibration detection" OR "Warm detection" OR "Warm pain" OR "Wind up" OR "Widespread hyperalgesia") TITLE-ABS-KEY(Biopsychosocial OR Psycholog* OR Psychosocial OR Strategies OR Model OR Acceptance OR "CPAQ" OR Adherence OR Affect* OR Anxiety OR "ASI" OR "STAI" OR "prime-MD" OR Attitude* OR "SOPA" OR Avoidance OR Behavio* OR "FSR" OR Belief* OR "PBPI" OR "BPI" OR Catastrophizing OR Catastrophising OR "PCS" OR Cognition* OR Control OR Coping OR "Cpci" OR "CSQ" OR Depression OR "PHQ-9" OR "MADRS" OR "CDMI" OR "BDI-II" OR "CES-D" OR "GHQ-28" OR "MDS" OR "MDI" OR

	"HADS" OR "MHI" OR "DASS-21" OR Distress OR "Emotional state*" OR Endurance OR Expectation* OR Fear* OR "CBSQ" OR "TSK" OR "FABQ" OR "FOPQ" OR "PFActS-C" OR Helplessness OR Hypervigilance OR Inactivity OR Interference* OR Improvement OR Isolation OR Limit* OR "Locus of control" OR "Major life events" OR Mood* OR "PASS" OR Motivation* OR Perceived OR Perception* OR "IPQ-R" OR Personality OR "Readiness to change" OR Recovery OR "Self-efficacy" OR "MPRCQ" OR Satisfaction OR Solicitude OR Somatic OR Somatization OR Stress OR Stressful OR Support OR "Thought suppression" OR Transformation OR "Quality of Life" OR Vitality OR "Well being" OR Willingness OR Worry OR "PSWQ" OR Compensation OR Social OR "MSSS" OR "CPI" OR "MSPSS" OR Job* OR "Job absen*" OR Work* OR Activity OR Disability OR Function* OR Insomnia OR Sleep OR "MOOS" OR "PSQI")
Study type	TITLE-ABS-KEY("Case-Control" OR "Cohort" OR "Cross-Sectional" OR "Controlled Trial" OR "Clinical Trial" OR Observational OR Experimental OR Prospective)
Filters	*Language:* English or Spanish

Number of items retrieved	**462**

Database	***Rehabilitation & Sports Medicine Source,*** ***SPORTDiscus with Full Text,*** ***APA PsycArticles*** ***(through EBSCOhost)***
Procedure	Advanced Search. Combining the search strategy (all text) with the Boolean Operator: AND.
Search strategy:	1st October 2022
Population	WAD OR Whiplash OR "Whiplash Injur*" OR "Whiplash associated disorder*"
Outcome Measures	Analgesia OR Algometry OR Allodynia OR "Altered nociceptive processing" OR "Altered central pain processing" OR "Altered central processing" OR "Altered pain processing" OR "Bottom up" OR Capsaicin OR "Central hyperexcitability" OR "Central hypersensitivity" OR "Central sensitization*" OR "Central sensitisation*" OR "Central pain" OR "Chronic pain" OR "Cognitive-emotional sensitization" OR "Cognitive-emotional sensitisation" OR "Cold detection" OR "Cold pain" OR "Conditioned pain modulation" OR "Counterirritant effect" OR CPM OR "Detection threshold*" OR "Diffuse noxious inhibitory control" OR DNIC OR "Heat detection" OR "Heat pain" OR "Heterotopic facilitation" OR Hyperalgesia OR "Hypertonic Saline Solution" OR Hyperpathia OR Hyperesthesi* OR Hypersensitivity OR Hypesthesia OR Hypoalgesia OR Hypoesthesia* OR "Ischemic pain" OR "Mechanical pain" OR Nocicept* OR "Pain modulation" OR "Pain pathophysiology" OR "Pain perception" OR "Pain physiopathology" OR "Pain processing" OR "Pain sensitization" OR "Pain sensitisation" OR "Pain tolerance" OR "Peripheral sensitization" OR "Peripheral sensitisation" OR "Pinprick test" OR "Pressure pain threshold" OR "Pressure pain tolerance" OR "Quantitative pain" OR "Quantitative sensory test*" OR QST OR "Referred Pain" OR "Second pain" OR "Sensitivity" OR "Sensory hypersensitivity" OR "Sensory profil*" OR "Sensory test*" OR "Sensory thresholds" OR "Somatosensory disorders" OR "Somatosensory profil*" OR "Spatial summation" OR "Postsynaptic Potential Summation" OR "Suprathreshold stimulation" OR "Tactile acuity" OR "Tactile detection Threshold" OR "Temporal summation" OR "Thermal pain" OR "Tolerance threshold" OR "Two-point discrimination" OR "Top down" OR "Vibration detection" OR "Warm detection" OR "Warm pain" OR "Wind up" OR "Widespread hyperalgesia" --- Biopsychosocial OR Psycholog* OR Psychosocial OR Strategies OR Model OR Acceptance OR "CPAQ" OR Adherence OR Affect* OR Anxiety OR "ASI" OR "STAI" OR "prime-MD" OR Attitude* OR "SOPA" OR Avoidance OR Behavio* OR "FSR" OR Belief* OR

	"PBPI" OR "BPI" OR Catastrophizing OR Catastrophising OR "PCS" OR Cognition* OR Control OR Coping OR "Cpci" OR "CSQ" OR Depression OR "PHQ-9" OR "MADRS" OR "CDMI" OR "BDI-II" OR "CES-D" OR "GHQ-28" OR "MDS" OR "MDI" OR "HADS" OR "MHI" OR "DASS-21" OR Distress OR "Emotional state*" OR Endurance OR Expectation* OR Fear* OR "CBSQ" OR "TSK" OR "FABQ" OR "FOPQ" OR "PFActS-C" OR Helplessness OR Hypervigilance OR Inactivity OR Interference* OR Improvement OR Isolation OR Limit* OR "Locus of control" OR "Major life events" OR Mood* OR "PASS" OR Motivation* OR Perceived OR Perception* OR "IPQ-R" OR Personality OR "Readiness to change" OR Recovery OR "Self-efficacy" OR "MPRCQ" OR Satisfaction OR Solicitude OR Somatic OR Somatization OR Stress OR Stressful OR Support OR "Thought suppression" OR Transformation OR "Quality of Life" OR Vitality OR "Well being" OR Willingness OR Worry OR "PSWQ" OR Compensation OR Social OR "MSSS" OR "CPI" OR "MSPSS" OR Job* OR "Job absen*" OR Work* OR Activity OR Disability OR Function* OR Insomnia OR Sleep OR "MOOS" OR "PSQI"
Study type	"Case-Control" OR "Cohort" OR "Cross-Sectional" OR "Controlled Trial" OR "Clinical Trial" OR Observational OR Experimental OR Prospective
Filters	*Language:* English or Spanish

Number of items retrieved	**1973**
Rehabilitation & Sports Medicine Source	947
SPORTDiscus with Full Text	925
APA PsycArticles	102

Database	***PEDro***
Procedure	Advanced search. Individual searches, matching all search terms with the Boolean Operator: AND
Search strategy:	1st October 2022
Individual search (1)	Abstract & Title: - Topic: Whiplash Method: Clinical trial
Individual search (2)	Abstract & Title: Whiplash Topic: Chronic pain Method: Clinical trial
Individual search (3)	Abstract & Title: Whiplash Topic: [no appropriate value in this field] Method: Clinical trial
Filters	- *Not applicable* -

Number of items retrieved	**273**
Individual search (1)	138
Individual search (2)	133
Individual search (3)	2

SUPPLEMENTARY MATERIAL B. List of records excluded after full-text screening grouped by reasons.

1-24 → Does not include Quantitative Sensory Testing measures.

25-66 → Does not include Psychological measures.

67-70 → Composite data of chronic and acute whiplash-associated disorders.

71-74 → Aggregated data with other populations.

75 → Population younger than 18 years.

76-78 → Other study design (i.e., congress abstract, review article, letter).

79-93 → Duplicated sample.

1 Andersen, T. E. et al. Trauma-focused cognitive behavioural therapy and exercise for chronic whiplash with comorbid posttraumatic stress disorder: a randomised controlled trial. Pain 162, 1221-1232, doi:10.1097/j.pain.0000000000002117 (2021).

2 Andersen, T. E., Hansen, M., Ravn, S. L. & Vaegter, H. B. The association of probable PTSD at baseline and pain-related outcomes after chronic pain rehabilitation: A comparison of DSM-5 and ICD-11 criteria for PTSD. Eur. J. Pain 26, 709-718, doi:10.1002/ejp.1899 (2022).

3 Bunketorp, L., Lindh, M., Carlsson, J. & Stener-Victorin, E. The perception of pain and pain-related cognitions in subacute whiplash-associated disorders: its influence on prolonged disability. Disability and rehabilitation 28, 271-279, doi:10.1080/09638280500158323 (2006).

4 Bunketorp, L., Lindh, M., Carlsson, J. & Stener-Victorin, E. The effectiveness of a supervised physical training model tailored to the individual needs of patients with

whiplash-associated disorders - a randomized controlled trial. Clinical rehabilitation 20, 201-217, doi:10.1191/0269215506cr934oa (2006).

5 Côté, P. et al. Is a government-regulated rehabilitation guideline more effective than general practitioner education or preferred-provider rehabilitation in promoting recovery from acute whiplash-associated disorders? A pragmatic randomised controlled trial. BMJ open 9, e021283, doi:10.1136/bmjopen-2017-021283 (2019).

6 Falla, D. et al. Perceived pain extent is associated with disability, depression and self-efficacy in individuals with whiplash-associated disorders. European journal of pain (London, England) 20, 1490-1501, doi:10.1002/ejp.873 (2016).

7 Garcia Naranjo, J., Barroso Rosa, S., Loro Ferrer, J. F., Liminana Canal, J. M. & Suarez Hernandez, E. A novel approach in the treatment of acute whiplash syndrome: Ultrasound-guided needle percutaneous electrolysis. A randomized controlled trial. Journal of oral rehabilitation 103, 1229-1234, doi:10.1111/joor.12571 (2017).

8 Ickmans, K. et al. Exercise and Cognitive Functioning in People With Chronic Whiplash-Associated Disorders: A Controlled Laboratory Study. The Journal of orthopaedic and sports physical therapy 46, 87-95, doi:10.2519/jospt.2016.6060 (2016).

9 Landén Ludvigsson, M., Peterson, G., Widh, S. & Peolsson, A. Exercise, headache, and factors associated with headache in chronic whiplash: analysis of a randomized clinical trial. Medicine 98, e18130, doi:10.1097/MD.0000000000018130 (2019).

10 Liew, B. X. W. et al. Investigating the Causal Mechanisms of Symptom Recovery in Chronic Whiplash-associated Disorders Using Bayesian Networks. Clin. J. Pain 35, 647-655, doi:10.1097/ajp.0000000000000728 (2019).

11 Ludvigsson, M. L., Peterson, G. & Peolsson, A. The effect of three exercise approaches on health-related quality of life, and factors associated with its

improvement in chronic whiplash-associated disorders: analysis of a randomized controlled trial. Qual. Life Res. 28, 357-368, doi:10.1007/s11136-018-2004-3 (2019).

12 Ludvigsson, M. L., Peterson, G. & Peolsson, A. Neck-specific exercise for radiating pain and neurological deficits in chronic whiplash, a 1-year follow-up of a randomised clinical trial. Scientific reports 10, doi:10.1038/s41598-020-62722-4 (2020).

13 Mankovsky-Arnold, T., Wideman, T. H., Larivière, C. & Sullivan, M. J. Measures of spontaneous and movement-evoked pain are associated with disability in patients with whiplash injuries. The journal of pain : official journal of the American Pain Society 15, 967-975, doi:10.1016/j.jpain.2014.06.010 (2014).

14 Paré, C. et al. The Relationship Between Level of Catastrophizing and Mental Health Comorbidity in Individuals With Whiplash Injuries. The Clinical journal of pain 35, 880-886, doi:10.1097/ajp.0000000000000749 (2019).

15 Pedler, A. & Sterling, M. Assessing fear-avoidance beliefs in patients with whiplash-associated disorders: a comparison of 2 measures. The Clinical journal of pain 27, 502-507, doi:10.1097/AJP.0b013e31820d97b0 (2011).

16 Pedrero-Martin, Y. et al. Self-efficacy beliefs mediate the association between pain intensity and pain interference in acute/subacute whiplash-associated disorders. Eur. Spine J. 30, 1689-1698, doi:10.1007/s00586-021-06731-5 (2021).

17 Smith, A. D. et al. Cervical radiofrequency neurotomy reduces psychological features in individuals with chronic whiplash symptoms. Pain physician 17, 265-274 (2014).

18 Sterling, M., Jull, G., Vicenzino, B., Kenardy, J. & Darnell, R. Development of motor system dysfunction following whiplash injury. Pain 103, 65-73, doi:10.1016/s0304-3959(02)00420-7 (2003).

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SUPPLEMENTARY MATERIAL C. Additional and detailed information of the studies included in the systematic review.

1A. Chronic WAD studies.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Banic, 2004[2] Newcastle – Ottawa: 4 (fair quality)	Case-control (single assessment)	Chronic WAD (grade n/a)	n=27; 70% f; 39 (34-48) yr	▪PPT, PPTol: site of more severe pain (WAD); trapezius muscle (controls). ▪EPT: right sural nerve.	SCL-90-R	- & VAS pain, EMG responses to EPT, NEO-FFI	▪PPT and PPTol: lower in WAD than controls. ▪EPT: no differences between WAD and controls. ▪TS on EPT: lower in WAD than controls. ▪SCL-90-R: elevated scores in all dimensions in WAD compared to controls. No QST-PSF correlation data available.
		Control	n=29; 69% f; 46 (29-53) yr				
Chien, 2008b[6] Newcastle – Ottawa: 8 (high quality)	Case-control (single assessment)	Chronic WAD: >3 mo and <3 yr (grade II)	n=50; 78% f; 37.2 (±10.4) yr	▪PPT: cervical spine, median nerve, tibialis anterior muscle. ▪CPT: mid-cervical region, dorsum of the hand. ▪VT: hand areas innervated by C6/8 dermatomes. ▪WDT, CDT: hand areas innervated by C6/8 dermatomes. ▪EDT: sites innervated by C5/8, tibialis anterior muscle.	SCL-90-R	NDI & BPPT	▪PPT: lower in WAD than controls in all sites, and lower in tibialis anterior in WAD than cervical radiculopathy group. ▪CPT: decreased in WAD compared to controls in the cervical spine, decreased in WAD compared to controls and cervical radiculopathy group in the hand. ▪VT: higher in WAD than controls and cervical radiculopathy group. ▪WDT: higher in WAD than controls. ▪CDT: no differences between groups. ▪EDT: higher in WAD than controls except for the tibialis anterior muscle site. ▪SCL-90-R: higher scores for the Generalized Severity Index and for the somatization and depression subscales in in WAD and cervical radiculopathy groups compared to controls. No QST-PSF correlation data available.
		Cervical radiculopathy	n=38; 68% f; 50.0 (±11.4) yr				
		Control	n=31; 81% f; 31.4 (±8.9) yr				

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Chien, 2009[7] Newcastle – Ottawa: 6 (fair quality)	Case-control (single assessment)	Chronic WAD: >3 mo and <3 yr (grade II)	n=31; 81% f; 35.3 (±10.7) yr	▪PPT: cervical spine, median nerve, tibialis anterior muscle. ▪HPT, CPT: mid-cervical region, dorsum of the hand. ▪VT: hand areas innervated by C6/8 dermatomes. ▪WDT, CDT: hand areas innervated by C7/8 dermatomes. ▪EDT, EPT: tibialis anterior muscle, sites innervated by C5/8.	SCL-90-R	NDI & BPPT, SVR	▪PPT: lower in WAD than controls. ▪HPT: no differences between groups. ▪CPT: decreased in WAD compared to controls. ▪VT, WDT: higher in WAD than controls. ▪CDT: decreased in WAD than controls at the C7 dermatome but not C8. ▪EDT: increased in WAD compared to controls. ▪EPT, ER: decreased in WAD compared to controls. ▪SCL-90-R: higher scores for the Generalized Severity Index and for the somatization and depression subscales in WAD compared to control.
		Control	n=31; 81% f; 31.4 (±8.9) yr				
Coppieters, 2017a[12] Newcastle – Ottawa: 7 (high quality)	Case-control (single assessment)	Chronic WAD: >3 mo (grade II)	n=31; 100% f; 35.3 (±10.8) yr	▪PPT: middle trapezius and quadriceps muscles. ▪CPM: at quadriceps PPT point after 2 min of cold-water immersion.	PCS, PVAQ	NDI & NRS, MRI, mPDQ, TMT, CSI	▪PPT, CPM: lower in chronic WAD than controls. ▪PCS, PVAQ: higher scores in chronic WAD than controls. No QST-PSF correlation data available.
		Chronic Idiopathic Neck Pain	n=34; 100% f; 34.9 (±10.9) yr				
		Control	n=28; 100% f; 30.3 (±13.2) yr				
Curatolo, 2001[14] Newcastle – Ottawa: 2 (poor quality)	Case-control (single session with assessments before and after local anesthesia infiltration)	Chronic WAD (grade n/a)	n=14; 57% f; 48 (35-54) yr	▪EPT, HPTol: cervical dermatome and a lumbosacral dermatome of the same side.	SCL-90-R	- & VAS, NEO-FFI	▪EPT and TS: lower in WAD than controls. ▪HPTol: no differences between groups. ▪SCL-90-R: higher scores for the Generalized Severity Index and for the somatization, depression, obsession-compulsion, anxiety, hostility and paranoid ideation subscales in WAD. No QST-PSF correlation data available.
		Control	n=14; 50% f; 41 (35-43) yr				

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
De Kooning, 2017[16] Newcastle – Ottawa: 6 (fair quality)	Case-Control (single session with 6 conditions)	Chronic WAD: >3mo (grade I-III)	n=30 67% f 42.2 (±10.7) yr	▪PPT: upper trapezius muscle.	PCS, IES	NDI &	▪PPT: n/a. ▪PCS: higher scores in WAD than controls. ▪IES: n/a.
		Controls	n=34 68% f 44.6 (±13.9) yr			- -	No QST-PSF correlation data available.
Dunne, 2012[18] Newcastle – Ottawa: 6 (fair quality)	Randomized Controlled Trial (assessments at baseline, 3 mo and 6 mo)	Chronic WAD: >3 mo with PTSD (grade II-III) Treatment group (Cognitive-behavioral Therapy) Control Group (waitlist)	n=26; 50% f; 32.5 (±7.1) yr	▪PPT: cervical spine, medial nerve, and tibialis anterior muscle. ▪CPT and HPT: cervical spine.	PDS, IES-R, DASS, TSK	NDI & NRS, negative affect, blood pressure, SF-36	▪PPT, CPT, HPT: no differences between groups; the treatment group improve over time. ▪PDS, IES-R, DASS, TSK: greater reduction in the treatment group than in controls. No QST-PSF correlation data available.
Elliott, 2009[20] Newcastle – Ottawa: 7 (high quality)	Cross-sectional	Chronic WAD: >3 mo and <3 yr (grade II)	n=79; 100% f; 29.7 (±7.7) yr	▪PPT: cervical spine and tibialis anterior muscle. ▪CPT and HPT: cervical spine.	TSK, GHQ-28, IES	NDI, & DHI-sf CROM, CJPE, MRI, SF-36	•PPT, CPT, TSK, GHQ-28, and IES contributed to a small extent in explaining the variation in fatty infiltration in the cervical extensor musculature. No QST-PSF correlation data available.
Farrell, 2020a[22]	Cross-sectional	Chronic WAD: >3 mo (grade II)	n=41; 61% f; 39.6 (±11.0) yr	▪PPT: cervical spine, median nerve, and tibialis anterior muscle. ▪CPT: mid to lower cervical spine.	PCS, PDS	NDI & VAS,	▪PPT and CPT: n/a. ▪PCS: Seven of 40 (18%, one non-responder) had PCS scores considered clinically relevant (≥ 30).

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Newcastle – Ottawa: 7 (high quality)						CROM	▪PDS: Fifteen of 41 (37%) people in the WAD group had PDS total symptom severity scores classified as moderate, moderate–severe or severe (i.e., ≥ 11). No QST-PSF correlation data available.
Farrell, 2020b[23] Newcastle – Ottawa: 5 (fair quality)	Case-control (single assessment)	Chronic WAD: >3 mo (grade II) Control	n = 24; 67% f; 49 (15) yr n = 24; 67% f; 50 (17) yr	▪PPT: hand (thenar eminence). ▪CDT, CPT, WDT, HPT, TSL: second metacarpophalangeal). ▪MDT, MPS, MPT, TS: proximal phalanx indicis using pinprick. ▪VDT: head of the second metacarpal.	PCS, DASS, IES-R	NDI & NRS, body chart, s-LANSS, NPSI	▪CDT, WDT, TSL: elevated in WAD group compared to controls. ▪HPT: reduced in WAD group compared to controls. ▪MDT: higher in WAD group compared to controls. ▪CPT, MPT, MPS, TS, VDT, PPT: no differences between groups. ▪PCS and DASS: WAD group scored higher than controls. ▪IES-R: 5/23 (22%, one non-responder) had IES-R scores consistent with posttraumatic stress disorder. No QST-PSF correlation data available.
Hendriks, 2020[24] Newcastle – Ottawa: 8 (high quality)	Cross-sectional	Chronic WAD: >3 mo (grade n/a)	n = 125; 57% f; 40.2 (±11.3) yr	▪PPT: upper trapezius and quadriceps muscle. ▪TS: on the upper trapezius and the quadriceps muscle at a rate of one pulse per second.	4DSQ, SCL-90-R, IES, TSK	NDI & VAS, mPDQ, CSI, CIS20R, SF-36	•PPT, TS, and TSK showed a weak correlation with CSI. •IES showed a moderate correlation with CSI. •4DSQ and SCL-90-R showed a strong correlation with CSI. No QST-PSF correlation data available.
Herren-Gerber, 2004[26] Newcastle – Ottawa: 3 (poor quality)	Case-control (single assessment)	Chronic WAD: >4 mo (grade n/a) (before and 15 minutes after local bupivacaine infiltration)	n=15; 67% f; 32 (27-47) yr	▪PPT, PPTol: most painful point of the neck (in WAD), non-painful point of the neck (in controls), pulp of the ipsilateral second toe.	PRSIQ, PRBCQ	- & VAS, CFQ, NEO-FFI, FPI, WBS	▪PPT: lower in WAD than controls in the neck sites. PPTol: lower in WAD than controls in all sites. ▪PRSIQ: higher active coping score than catastrophizing score in WAD. ▪PRBCS: higher controllability than helplessness in WAD. No QST-PSF correlation data available.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
		Control (no local infiltration)	n=15; 67% f; Md 35 (25-43) yr				
Jull, 2007[29] Newcastle – Ottawa: 7 (high quality)	Randomized Controlled Trial (measures at baseline at 10 wk)	Chronic WAD: >3 mo and <2 yr (grade II) Multimodal physical therapy group	n=36; 64% f; 40.9 (±11.9) yr	▪PPT: median nerve and tibialis anterior muscle. ▪CPT: cervical region.	GHQ-28, TSK, IES	NPI & CROM, CCFT, VAS	▪PPT and CPT: The subject sub-classification with both widespread mechanical and cold hyperalgesia had least improvement and exited the trial with persisting moderate neck pain and disability. GHQ-28 and IES: no changes between groups. TSK: greater changes in self-management program group than in the multimodal physical therapy group.
		Self-management program group	n=35; 80% f; 38.4 (±10.4) yr				No QST-PSF correlation data available.
Lenoir, 2022[34] Newcastle – Ottawa: 7 (high quality)	Case-control (single assessment)	Chronic WAD: >3 mo (grade II-III)	n = 72; 71% f; 41.6 (±10.6) yr	▪EDT, EPT, TS: median and sural nerves. ▪CPM: median and sural nerves after cold-water immersion.	PCS, IES-R, PASS	NDI & NRS, body chart, CSI, IPQ-R, SF-36	▪EPT: lower in WAD group compared to controls. ▪EDT, TS, CPM: no differences between groups. ▪PCS, IES-R, PASS: WAD group scored higher than controls. -EPT left wrist & PCS-magnification (r=−0.332; P<0.01). -EPT left wrist & PASS-20 (r=−0.325; P<0.01). -EPT left ankle & PASS-20 (r=−0.330; P<0.01). -EPT right wrist & PASS-20 (r=−0.252; P<0.05).
		Control	n = 58; 76% f; 40.7 (±10.4) yr				
Michaleff, 2014[44] Newcastle – Ottawa: 8 (high quality)	Randomized Controlled Trial (measures at baseline, 14	Chronic WAD: ≥3 mo and <1 yr (grade II-III) Intervention (Exercise)	n=85; 57% f; 42.6 (±12.3) yr	▪PPT: cervical spine and tibialis anterior muscle. ▪CPT: over cervical spine.	PDS, PCS	NDI, WDQ, P-SFS & NRS,	No QST or PSF changes available. No QST-PSF correlation data available.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
	wk, 6 mo and 12 mo)	Controls (Advice)	n=85; 71% f; 43.1 (±12.7) yr			GPE, CROM, s-LANSS, SF-36	
Olivegren, 1999[48] Newcastle – Ottawa: 8 (high quality)	Case-control (single assessment)	Chronic WAD: >16 mo (grade II-III)	n = 22; 73% f; 37 (22-66) yr	▪PPT: extensor carpi radialis longus, deltoideus, biceps, levator scapulae, sternocleidomastoid, and trapezius muscles. ▪PPTol: distal phalanx of the second digit.	MACL	- & VAS, body chart, CROM, handgrip strength	▪PPT: lower in WAD than controls. ▪PPTol: no differences between groups. ▪MACL: no differences between groups. No QST-PSF correlation data available.
		Control	n = 30; 67% f; 32 (19-63) yr				
Pedler, 2013[54] Newcastle – Ottawa: 7 (high quality)	Cross-sectional	Chronic WAD: >3 mo and < 2yr (grade I-II)	n = 64, 55% f; 44.7 (±12.6) yr	▪PPT: cervical spine, median nerve, tibialis anterior muscle. ▪CPT: cervical spine.	PDS	NDI & VAS, laterality task	•Performance on the neck laterality task was significantly associated with PPT and CPT. No QST-PSF correlation data available.
Prushansky, 2006[56] Newcastle – Ottawa: 4 (fair quality)	Controlled clinical trial (baseline, 16 wk and 44 wk)	Chronic WAD: >6 mo (grade II-III)	n=40; 56% f; 41.7 (±11.8) yr	▪PPT: several sites of the cervical spine.	SCL-90-R	NDI & GPE, VAS, CROM, isometric strength	▪PPT: higher at 44 wk compared to baseline. ▪SCL-90-R: lower scores in the Positive Symptom Distress Index and the Global Severity Index at 44 wk compared to baseline. No QST-PSF correlation data available.
Raak, 2006[57] Newcastle – Ottawa: 4 (fair quality)	Case-control (single assessment)	Chronic WAD: > 2 yr (grade n/a)	n=17; 94% f; 50.8 (±11.3) yr	▪CDT, WDT, CPT, HPT: left hand thenar eminence, left shoulder over the middle of the trapezius muscle	PCS	- & Pain VAS, Pain	▪CDT: higher in WAD than controls in the thenar eminence. ▪WDT: no differences between groups. ▪CPT: higher in WAD than controls in the trapezius muscle. ▪HPT: lower in WAD than controls in the trapezius muscle.
		Control	n=18; 94% f; 44.8 (±10.2) yr				

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
						unpleasantness VAS, Quality of sleep VAS	▪PCS: higher values in helplessness in WAD than controls, no differences for rumination and magnification dimensions. No QST-PSF correlation data available.
Scott, 2005[65] Newcastle – Ottawa: 7 (high quality)	Case-control (single assessment)	Chronic WAD: ≥3 mo (grade II)	n=30; 17 (57%) f; 41.6 (±10) yr	▪PPT: cervical spine, median, radial, and ulnar nerves, and tibialis anterior muscle. ▪HPT and CPT: tibialis anterior, deltoid insertion, and cervical spine. ▪Punctate hyperalgesia: tibialis anterior, deltoid insertion, and cervical spine.	SF-STAI	NDI & VAS	▪PPT: lower in WAD than controls; lower at C5–C6 in WAD than idiopathic neck pain. ▪HPT: lower in WAD than control and idiopathic neck pain at all of tested sites. ▪CPT: higher in WAD than control and idiopathic neck pain at all of tested sites. ▪Punctate hyperalgesia: no differences between groups. ▪SF-STAI: no differences between groups. No significant correlation between SF-STAI scores and any sensory measure (r ranged from 0.01 to 0.28; p>0.09).
		Chronic idiopathic neck pain: ≥ 3 mo	n=20; 17 (85%) f; 32 (±11) yr				
		Control	n=20; 12 (60%) f; 31.25 (±10) yr				
Serrano-Muñoz, 2019[66] Newcastle – Ottawa: 3 (poor quality)	Case-control (single assessment)	Chronic WAD: >6mo and <3yr (grade I-III) (pain VAS ≥ 4)	n=15; 73% f; 39.7 (±3.1) yr	▪THPI: hand (thenar eminence). ▪CPM: immersion in cold water of the nondominant hand for 30 seconds.	PCS	NDI, BPI & DN4, NPSI, EQ-5D	▪THIP: no differences between groups. ▪CPM: CPM effect in control group was greater than the Chronic WAD (pain VAS ≥ 4) group. ▪PCS: Chronic WAD (pain VAS ≥ 4) reported higher levels than controls. No QST-PSF correlation data available.
		Chronic WAD: >6mo and <3yr (grade I-III) (pain VAS < 4)	n=5; 100% f; 40.8 (±4.6) yr				
		Control	n=15; 60% f; 40.5 (±3.4) yr				
Smith, 2013[70]	Case-control (single assessment)	Chronic WAD: >6 mo (grade II) WAD_R	n=58 69% f 44.9 (±11.1) yr	▪PPT: cervical spine, median nerve, and tibialis anterior muscle.	GHQ-28, PDS, PCS	NDI &	▪PPT: lower in both WAD groups than controls, no differences between the WAD groups. ▪CPT: higher in both WAD groups than controls, no differences between the WAD groups.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Newcastle – Ottawa: 4 (fair quality)		(responders to cervical facet joint double blockade)		▪CPT, HPT: mid cervical region.		CROM, BPPT, CCFT, VAS, s-LANSS, NFR threshold (electrical stimulus)	▪HPT: lower in both WAD groups than controls, no differences between the WAD groups. ▪GHQ-28: higher total scores in both WAD groups than controls, no differences between the WAD groups; greater proportion of WAD individuals with generalized psychological distress compared to controls, no differences between the WAD groups. ▪PDS: no differences between the WAD groups in the posttraumatic stress severity score and in the proportion of individuals fulfilling the criteria for posttraumatic stress disorder. ▪PCS: higher scores and proportion of participants with elevated pain catastrophizing scores in WAD_NR than in WAD_R. No QST-PSF correlation data available.
		Chronic WAD: >6 mo (grade II) WAD_NR (non-responders to cervical facet joint double blockade)	n=32 56% f 45.4 (±9.7) yr				
		Control	n=30 70% f 44.2 (±9.7) yr				
Smith, 2017[68] Newcastle – Ottawa: 5 (fair quality)	Case-control (single assessment)	Chronic WAD: >3 mo and <10 yr (grade II)	n=21; 55% f; 44.5 (±10.5) yr	▪PPT: cervical spine, and tibialis anterior muscle. ▪CPT, HPT: mid-cervical spine. ▪CPTP: dominant hand ▪CPM: HPT over mid-cervical spine after 30 s of CPTP ▪EIH isometric (3-min isometric wall squat): same as PPT ▪EIH aerobic (30-min bicycle): same as PPT	PCS, TSK, PDS	NDI & PAR-Q, RPE, heart rate, blood pressure	▪PPT: lower values in WAD than controls in both sites. ▪CPT: higher values in WAD than controls ▪HPT: No difference between groups. ▪CPTP: reduced tolerance time in WAD compared with controls. ▪CPM: No difference between groups. ▪EIH isometric: Both groups showed higher PPT values post-exercise; no differences between groups. ▪EIH aerobic: No differences within and between groups. ▪PCS: No difference between groups. ▪TSK: higher levels in WAD than controls. ▪PDS: low levels of posttraumatic stress symptoms. No QST-PSF correlation data available.
		Control	n=19; 74% f; 37.4 (±10.8) yr				
Smith, 2020[69]		Chronic WAD: >3 mo and <10	n=40; 70% f; 37.3 (±13.6) yr		PCS, TSK,	NDI	▪PPT: no differences between groups. ▪CPM: no differences between groups.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Newcastle – Ottawa: 7 (high quality)	Case-control (single assessment)	yr (grade II) Control	n=30; 78% f; 40.4 (±14.3) yr	▪PPT: cervical spine, tibialis anterior muscle and hand. ▪CPTP: right hand. ▪CPM: PPT over left tibialis anterior after cold water immersion. ▪TS: cervical spine and hand. ▪EIH isometric (3-min isometric wall squat): same as PPT. ▪EIH aerobic (30-min treadmill walking): same as PPT.	PCL-5	& VAS, IPAQ	▪TS: WAD reported higher pain ratings following both the single and repeated pinprick stimuli in both the hand and cervical spine regions. ▪EIH isometric and EIH aerobic: controls showed a greater increase in PPTs during or following aerobic and isometric exercise in the hand region, cervical spine, and tibialis anterior. No changes within the WAD group, indicating impaired EIH. •WAD demonstrated mild levels of posttraumatic stress (PCL-5 <33), kinesiophobia (TSK <40), and pain catastrophizing (PCS < 24). No QST-PSF correlation data available.
Sterling, 2008[78] Newcastle – Ottawa: 3 (poor quality)	Case control (single assessment)	Chronic WAD: ≥3 mo (grade II) Controls	n=30 77% f 37 (23-58) yr n=30 80% f 30 (20-48) yr	▪PPT: cervical spine, median nerve, and tibialis anterior muscle. ▪CPT, HPT: cervical spine.	GHQ-28, PCS	NDI & VAS, NFR threshold, NFR VAS	▪PPT: Chronic WAD showed lower values than controls. ▪CPT: Chronic WAD showed higher values than controls. ▪HPT: No difference between groups. ▪GHQ-28 and PCS: Chronic WAD showed higher scores than controls. -WAD group: PCS & CPT (r=0.51, P=0.01).
Sterling, 2010b[83] Newcastle – Ottawa: 8 (high quality)	Randomized Controlled Trial (measures pre- post one single treatment session)	Chronic WAD: ≥3 mo (grade II-III) Intervention (Spinal Manual Therapy) Controls (Manual contact)	n=22 64% f 41.5 (±14.0) yr n=17 77% f 39.1 (±13.2) yr	▪PPT: cervical spine, median nerve, and tibialis anterior muscle. ▪CPT: cervical spine.	GHQ-28	NDI & NFR threshold, NFR VAS	▪PPT: no changes within groups and no differences between groups at any site. ▪CPT and HTP: no changes within groups and no differences between groups. ▪GHQ-28:scores indicating presence of psychological distress. No QST-PSF correlation data available.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Sterling, 2015[84] Newcastle – Ottawa: 8 (high quality)	Randomized Controlled Trial (measures at baseline, 6 wk, 12 wk, 6 mo and 12 mo)	Chronic WAD: ≥3 mo and <2 yr (grade II) Intervention (dry-needling / exercise / advice)	n=40; 60% f; 41.5 (±11.1) yr	▪PPT: cervical spine, median nerve and tibialis anterior muscle. ▪CPT: cervical spine.	PDS, PCS	NDI, WDQ, P-SFS & GPE, NRS, CROM, s-LANSS, SF-36	▪PPT: dry-needling group showed higher values at 12 wk. ▪CPT: dry-needling group showed lower values at 6 wk and 6 mo. ▪PDS: dry-needling group showed lower values at 12 mo. ▪PCS: dry-needling group showed lower levels at 6 wk and 12 mo. No QST-PSF correlation data available.
		Controls (sham needling / exercise / advice)	n=40; 75% f; 41.7 (±12.3) yr				
Sterling, 2016[75] Newcastle – Ottawa: 6 (fair quality)	Cross-sectional	Chronic WAD: ≥3 mo (grade II)	n=21 71% f 44.4 (±11.1) yr	▪PPT: cervical spine and tibialis anterior muscle. ▪CPT and HPT: cervical spine.	PCS, TSK, PDS	NDI & VAS, biomarkers, fMRI	No QST or PSF results available. No QST-PSF correlation data available.
Tobbackx, 2013[85] Newcastle – Ottawa: 6 (fair quality)	Randomized Crossover trial	Chronic WAD: ≥6 mo (grade II) Interventions: (Acupuncture) vs (Relaxation)	n=39 72% f 40.1 (±7.1) yr	▪PPT: upper trapezius muscle and calf belly. ▪TS: similar to PPT. ▪CPM: occlusion cuff on the arm.	PCS, TSK	NDI & WAD Symptom list (VAS)	▪PPT: higher values after treatments, highest values after acupuncture compared with relaxation. ▪TS: higher values after treatments, but no differences between groups. ▪CPM: lower values after treatments, lowest values after acupuncture compared with relaxation. ▪PCS, TSK: n/a No QST-PSF correlation data available.
Van Osterwijck, 2011[86]	Controlled trial (baseline and 1, 2, 3 wk after	Chronic WAD: ≥12 mo (grade I-II) Intervention:	n=6 83% f 35.7 (±7.3) yr	▪PPT: hand, upper trapezius muscle, and calf belly.	TSK, PCS, PCI	NDI & NET VAS,	▪PPT: higher values at upper trapezius and calf after intervention. ▪TSK: lower levels after intervention. ▪PCI: lower punctuation at resting domain after intervention.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Newcastle – Ottawa: 5 (fair quality)	intervention follow-up)	Pain Neurophysiology education				BPPT VAS, WAD Symptom list (VAS)	▪PCS: n/a. No QST-PSF correlation data available.
Wallin, 2012[89] Newcastle – Ottawa: 6 (fair quality)	Case-control (single assessment)	Chronic WAD: > 2 yr (grade II-III) Controls	n=28 100% f 40.1 (±7.1) yr n=29 100% f 35.4 (±3.7) yr	▪PPT: upper trapezius and tibialis anterior muscles. ▪CPT, CDT, HPT and WDT: thenar eminence, upper trapezius, and tibialis muscles.	PCS, HADS, PASS, ASI, PSEQ, IES, FABQ	- & VAS	▪PPT: WAD showed lower values than controls at all sites. ▪CDT: WAD showed decreased values than controls over thenar eminence and bilaterally over upper trapezius. ▪WDT: WAD showed increased values than controls at right trapezius and left tibialis anterior. ▪CPT: WAD showed higher values than controls at all sites. ▪HPT: WAD showed lower values than controls at thenar eminence and bilaterally over upper trapezius. ▪PCS, HADS, PASS, ASI, PSEQ, GSES and IES: WAD showed worse outcomes than controls. Significant intercorrelations (R^2=0.36) between pain intensity variables, QST measures (especially CPT and HPT), 2 of the PPT variables and the psychological variables.

1B. Acute WAD studies.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Andersen, 2022[1] Newcastle – Ottawa: 6 (fair quality)	Cohort (measures: 1, 3, 6, and 12 mo post-whiplash trauma)	Acute WAD: <10 days (grade I-III) subclinical PTSD	n=362; 56% f; 34.4 (±11.2) yr	▪PPT: head and neck muscles, tibialis anterior, and finger ▪PPTol: left masseter, infraespinatus and tibialis anterior, and finger	IES	- & Pain distribution, VAS CROM	▪PPT and PPTol: lower in clinical and mid PTSD than subclinical PTSD at all time points. Higher values over time in all WAD groups. ▪IES: Changes no monitored over time. No QST-PSF correlation data available.
		Acute WAD: <10 days (grade I-III) mild PTSD	n=293; 71% f; 35.5 (±11.4) yr				
		Acute WAD: <10 days (grade I-III) clinical PTSD	n=92; 76% f; 34.6 (±12.7) yr				
Chien, 2010b[8] Newcastle – Ottawa: 8 (high quality)	Case-control (with follow-up)	Acute WAD: < 1 mo (grade II) (measures <1, 3 and 6 mo post-whiplash trauma)	n=52; 62% f; 36.3 (±13.1) yr; - High-risk n=17; 76% f; 35.8 (±14.1) yr; - Low-risk n=35; 80% f; 36.6 (±12.2) yr	▪PPT: cervical spine, median nerve, tibialis anterior muscle. ▪HPT, CPT: mid-cervical region, dorsum of the hand. ▪VT: hand areas innervated by C6/8 dermatomes. ▪WDT, CDT: hand areas innervated by C7/8 dermatomes. ▪EDT: tibialis anterior muscle, sites innervated by C5/8.	IES, GHQ-28 (only at baseline)	NDI & BPPT, VAS	▪PPT, CPT: n/a. ▪VT: higher in high-risk WAD than controls at 1; higher in high-risk WAD than low-risk WAD and controls at 3-6 mo. ▪WDT: no differences between groups at 1 mo; higher in high-risk WAD than low-risk WAD and controls 3-6 mo. ▪CDT: lower in high- and low-risk WAD groups than controls at 1mo; no differences between groups at 3-6 mo. ▪EDT: higher in high- and low-risk WAD groups than controls at 1 mo, higher in high-risk WAD than low-risk WAD and controls at 3 and 6 mo. ▪GHQ-28: scores above the normal threshold in both WAD groups with higher scores in the high risk WAD group. ▪IES: 48% of the WAD participants obtained scores of more than 26 (moderate or greater posttraumatic stress reaction), but no differences between WAD groups at 1 mo; total score improved in low risk WAD group at 3 and 6 mo compared to 1 mo, but not in high risk WAD group. No QST-PSF correlation data available.
		Control (3 measures separated by 1mo)	n=38; 28 (74%) f; 32.6 (±8.7) yr				

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Christensen, 2021[9] Newcastle – Ottawa: 7 (high quality)	Case-control (with follow-up)	Acute WAD: < 3 wk (grade II) (measures within 3 wk, 5 wk and 6 mo post-whiplash trauma)	n=22; 64% f; 30.6 (±7.4) yr	▪PPT: splenius, upper trapezius, and gastrocnemius muscles. ▪PPTol: inflatable pressure cuff on the arm. ▪CPM: splenius, upper trapezius, and gastrocnemius muscles. ▪STPS: infraspinatus muscle applying a pressure of 120% of PPT during 60 sec.	PCS, TSK, BDI	NDI & NRS, electronic body chart, MOS-Sleep	▪PPT: lower in WAD than controls at 3 wk in the neck region; lower in WAD group at 3 wk compared to 5 wk and 6 mo. ▪PPTol: lower in WAD than controls at all time points; lower in WAD group at 3 wk compared to 5 wk and 6 mo. ▪CPM: impaired response in WAD group compared to controls at all time points; no changes within the WAD group over time. ▪STPS: expanded pressure-induced referred pain areas in the WAD group compared with the control group at 3 wk and 6 mo.
		Control (3 measures with a period of 2 wk and 6 mo after the first assessment)	n=22; 64% f; 30.5 (±7.4) yr				▪PCS: higher scores in WAD group than controls at 3 wk; lower scores in WAD at 5 wk and 6 mo compared to 3 wk. ▪TSK: higher scores in WAD group than controls at all time points; lower scores in WAD at 5 wk and 6 mo compared to 3 wk. ▪BDI: higher scores in WAD group than controls at all time points; lower scores in WAD at 6 mo compared to 3 wk.
		Control	n=14; 50% f; 41 (35-43) yr				No QST-PSF correlation data available.
Jull, 2013[28] Newcastle – Ottawa: 9 (high quality)	Randomized Controlled Trial (measures at baseline, 11 wk, 6 mo and 12 mo)	Acute WAD: <2 wk (grade II) Intervention (Pragmatic intervention)	n=49; 61% f; 36.4 (±12.8) yr	▪PPT: cervical spine and tibialis anterior muscle. ▪CPT and HPT: over cervical region	IES, PFActS-C, GHQ-28	NPI & VAS, CROM, CJPE, CCFT, balance, SVR	▪PPT: no changes within groups and no differences between groups at any time. ▪CPT: no changes within groups and no differences between groups at any time. ▪HPT: no data available
		Controls (Usual care)	n=52; 56% f; 35.4 (±12.1) yr				▪IES, PFActS-C, GHQ-28: Lower levels in both groups at 11 wk but no differences between groups at any time. No QST-PSF correlation data available.
Kamper, 2011[30]	Cohort (two		n=100; 72% f; 40.1 (±13.3) yr		DASS, TSK,	- &	▪PPT: increase in cervical measure and no change in tibialis anterior measure.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Newcastle – Ottawa: 5 (fair quality)	assessments 1 and 3 mo post-whiplash trauma)	Acute WAD: <4 wk (grade I-III)		▪PPT: cervical spine and tibialis anterior muscle	CSQ-C	VAS	▪DASS, TSK, CSQ-C: n/a No QST-PSF correlation data available.
Kasch, 2011[31] Newcastle – Ottawa: 3 (poor quality)	Case-control (measures within 1 wk, 1, 3, 6, and 12 mo post-whiplash trauma)	Acute WAD: 1 wk (grade I-III)	n = 141	▪PPT, PPTol: hand and interphalangeal joint, and upper trapezius, masseter, temporal, infraspinatus, and sternocleidomastoid. ▪CPTP: dominant hand.	MBHI, SCL-90-R	CNFDS & MPQ, CROM, isometric strength	No QST or PSF changes available. No QST-PSF correlation data available.
		Acute ankle sprain	n = 40				
Pedler, 2016[53] Newcastle – Ottawa: 8 (high quality)	Cohort (measures: <6 wk and 3 mo post-whiplash trauma)	Acute WAD: <6wk (grade I-III)	n=103 74 (72%) f 39.7 (±13.9) yr	▪PPT: at cervical spine. ▪CPT: over mid to lower regions of the cervical spine.	TSK, PFActS-C, CSQ-C, PDS	NDI & VAS	No QST or PSF changes available -CPT & CSQ-C (r=0.282; P<0.01), -CPT & PDS (r=0.247; P<0.01), -CPT & TSK (r=0.212; P<0.01), -CPT & PFAct-S-C (r=0.201; P<0.01). -PPT & CSQ-C (r=0.305; P<0.01), -PPT & PDS (r=0.286; P<0.01), -PPT & TSK (r=0.251; P<0.01), -PPT & PFAct-S-C (r=0.240; P<0.01).
Ritchie, 2013[61] Newcastle – Ottawa: 7 (high quality)	Cohort (measures within less than 1, 3, 6, and 12 mo post-whiplash trauma)	Acute WAD: <4 wk (grade I-III)	n=262; 37.1 (±14.2) yr	▪CPT: Mid cervical spine	PDS	NDI & -	No QST or PSF changes available. No QST-PSF correlation data available.
Rivest, 2010[63]	Cross-sectional	Acute WAD: <5 wk (grade I-III)	n = 37, 57% f; 32.7 (±16.8) yr	▪PPT: cervical spine, tibialis anterior muscle.	PCS	NDI &	▪PPT: lower in women than in men. ▪CPT: no gender differences. ▪PCS: no gender differences.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Newcastle – Ottawa: 8 (high quality)				▪CPT: mid-cervical spine.		-	-All sample: CPT & PCS (r=0.46, p<0.01). -Male subsample: PPT C5 & PCS (r=-0.56, p>0.05).
Sterling, 2003[80] Newcastle – Ottawa: 7 (high quality)	Case control (measures: <1 mo, 2, 3, and 6 mo post-whiplash trauma)	Acute WAD: <3 wk (grade II-III) Recovered (<8%NDI 6mo)	n=29 48% f 31.9 (±12.9) yr	▪PPT: cervical spine, median, radial, and ulnar nerves, and tibialis anterior muscle. ▪CPT, HPT: mid-cervical region.	GHQ-28	NDI & VAS, BPPT, SVR	▪PPT: Moderate/severe WAD showed lower PPTs at all sites compared with other three groups. PPTs of moderate/severe WAD group did not change over the study period and remained less than all other groups at 6 mo. Recovered and mild WAD groups showed lower PPTs at the cervical spine than controls at entry into the study. ▪CPT: Moderate/severe WAD showed higher CPT than the other three groups at all time points. ▪HPT: Moderate/severe WAD showed lower HPT than the other three groups at all time points.
		Acute WAD: <3 wk (grade II-III) Mild (10-28%NDI 6mo)	n=30 77% f 34.3 (±12.5) yr				▪GHQ-28: Moderate/severe and mild WAD improved scores at 6mo.
		Acute WAD: <3 wk (grade II-III) Moderate/severe (≥30%NDI 6mo)	n=17 94% f 43.7 (±14.5) yr				No QST-PSF correlation data available.
		Controls	n=20; 160% f 40,1 (±13.6) yr				
Sterling, 2006[79] Newcastle – Ottawa: 8 (high quality)	Cohort (measures: 2-3 yr post-whiplash trauma)	Acute WAD: <3 wk (grade II-III) Recovered (<8%NDI 2yr)	n=26; 58% f 30.5 (±8.4) yr	▪PPT: cervical spine, median nerve, and tibialis anterior muscle. ▪CPT, HPT: cervical spine.	GHQ-28, TSK, IES	NDI & CROM, CJPE, EMG, BPPT, BPPT VAS, SVR	▪PPT: Moderate/severe WAD showed lower PPTs at all sites than mild and recovered WAD in all times. ▪CPT: Moderate/severe WAD showed higher CPTs than mild and recovered WAD in all times. ▪HPT: Moderate/severe WAD showed lower HPTs than mild and recovered WAD in all times.
		Mild (10-28%NDI 2yr)	n=25; 76% f 36.4 (±14.8) yr				▪GHQ-28, TSK, IES: Moderate/severe WAD showed higher values than mild and recovered WAD in all times.
		Moderate/severe (≥30%NDI 2yr)	n=14; 86% f 45.6 (±13.0) yr				No QST-PSF correlation data available.
Sterling, 2009[82]	Cross-sectional	Acute WAD: <4 wk	n=85 62% f	▪PPT: cervical spine, median nerve, and	GHQ-28	NDI	▪PPT: s-LANSS≥12 showed lower values over both C2 and C5 spinous processes.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Newcastle – Ottawa: 6 (fair quality)		(grade I-III) Analysis groups: s-LANSS≥12 s-LANSS<12	36.3 (±12.7) yr	tibialis anterior muscle. ▪CPT: mid to lower cervical spine.		& BPPT, VAS BPPT, s-LANSS	▪CPT: s-LANSS≥12 showed higher values. ▪GHQ-28: No differences between the groups. No QST-PSF correlation data available.
Sterling, 2010a[73] Newcastle – Ottawa: 6 (fair quality)	Case control (measures: <3 wk, 3, and 6 mo post-whiplash trauma)	Acute WAD: <3 wk (grade II-III) Recovered (<8%NDI 6mo)	n=25 60.8% f 31.9 (±12.9) yr	▪PPT: cervical spine, median nerve, and tibialis anterior muscle. ▪CPT: mid to lower cervical spine.	GHQ-28, IES	NDI & VAS, NFR threshold, NFR VAS	▪PPT: Moderate/severe WAD showed lower PPTs at all sites when compared with other three groups. PPTs of moderate/severe WAD group did not change over the study period and remained less than all other groups at 3 mo. Recovered and mild WAD groups showed lower PPTs at the cervical spine site (C5) than controls at entry into the study. ▪CPT: Moderate/severe WAD showed higher CPT than the other three groups at all time points. ▪GHQ-28, IES: n/a. No QST-PSF correlation data available.
		Mild (10-28%NDI 6mo)	n=17 47% f 37 (±11.8) yr				
		Moderate/severe (≥30%NDI 6mo)	n=20 65% f 40 (±13.9) yr				
		Controls	n=22 63.6% f 40 (±12.6) yr				
Sterling, 2011[76] Newcastle – Ottawa: 7 (high quality)	Cohort (measures: <1 mo, 3, 6, and 12 mo post-whiplash trauma)	Acute WAD: <1 mo (grade I-III)	n=155 63% f 36.9 (±12.8) yr	▪PPT: cervical spine and median nerve. ▪CPT: mid to low cervical spine.	PDS	NDI & VAS, SVR	No QST or PSF changes available. No QST-PSF correlation data available.
Sterling, 2012[77]	Cohort (measures <3wk and 12 mo post-	Acute WAD: <1mo (grade I-III)	n=286 63% f 35.3 (±13.1) yr	▪CPT: over the mid cervical spine.	IES	NDI & CROM	No QST or PSF changes available. No QST-PSF correlation data available.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Newcastle – Ottawa: 8 (high quality)	whiplash trauma)						
Sterling, 2013[74] Newcastle – Ottawa: 5 (fair quality)	Case-control (measures: <3 wk, and 3 mo post-whiplash trauma)	Acute WAD: <3 wk (grade II-III) Recovered-Mild (<28%NDI 3mo)	n=20 70% f 34.9 (±7.8) yr	▪PPT: cervical spine and tibialis anterior muscle. ▪CPT and HPT: over mid to lower regions of the cervical spine.	PDS, CSQ-C	NDI & VAS, MRI, muscle fatty infiltratation, inflammatory biomarkers, SF-36	▪PPT, CPT, HPT: No changes within WAD groups. ▪PDS, CSQ-C: No changes within WAD groups. No QST-PSF correlation data available.
		Moderate/severe (≥30%NDI 3mo)	n=20 75% f 39.5 (±9.5) yr				
		Controls	n=18 78% f 40.1 (±9.6) yr				
Wiangkham, 2019 [92] Newcastle – Ottawa: 6 (fair quality)	Randomized Controlled Trial (measures at baseline and 3 mo)	Acute WAD: <4 wk (grade II) [Standard physiotherapy]	n=20; 15% f; 34 (16) yr	▪PPT: levator scapulae and tibialis anterior muscles	IES, FABQ	NDI & VAS, CROM, EQ-5D	▪PPT: higher values in both group at 3 mo compared to baseline. ▪IES and FABQ: reduced scores in both group at 3 mo compared to baseline. No QST-PSF correlation data available.
		[Active Behavioral Physiotherapy Intervention]	n=8; 75% f; 50 (19) yr				

1C. Combined chronic and acute WAD studies.

Study	Design	Group	N, age, gender	QST location	Psycho factors	Disability & others	Results
Daenen, 2014[15] Newcastle – Ottawa: 6 (fair quality)	Case-control (single assessment)	Acute WAD: < 1 mo (grade I-III)	n=30; 47% f; 43.3 (±11.0) yr	▪PPT: right trapezius belly and right quadriceps belly. ▪CPM: occlusion cuff at the left upper arm.	IES, PCS, PVAQ, BDI	NDI & Bimanual Coordination Test	▪PPT: n/a. ▪TS: no differences between groups. ▪CPM: TS during the conditioning stimulus was significantly higher in chronic and acute WAD compared to controls, and higher in chronic WAD compared to acute WAD.
		Chronic WAD: > 3 mo (grade I-III)	n=35; 74% f; 43.8 (±9.6) yr				▪IES: no differences between WAD groups. ▪PCS, PVAQ: higher scores in acute and chronic WAD than controls. ▪BDI: higher scores in acute and chronic WAD than controls; higher scores in chronic WAD than acute WAD.
		Control	n=31; 24 (77%) f; 43.19 (±16.1) yr				No QST-PSF correlation data available.

General abbreviations: f: female; mo: months; n/a: no available; PTSD: Posttraumatic stress disorder; wk: weeks; WAD: Whiplash Associated Disorders; yr, years.

Psychological factors (Psycho factors) → 4DSQ: Four-Dimensional Symptom Questionnaire; ASI: Anxiety Sensitivity Index; BDI: Beck Depression Inventory; CSQ-C: Coping Strategy Questionnaire C; DASS: Depression Anxiety and Stress Scale; FABQ: Fear-Avoidance Beliefs Questionnaire; GHQ-28: General Health Questionnaire 28; HADS: Hospital Anxiety and Depression Scale; IES: Impact of Events Scale; IES-R: Impact of Events Scale Revised; MOCL: Mood Adjective Check List; MBHI: Millon Behavioral Health Inventory; PASS: Pain Anxiety Symptoms Scale; PCI: Pain Coping Inventory; PCS: Pain Catastrophizing Scale; PCL-5: Posttraumatic Stress Diagnostic Checklist 5; PDS: Posttraumatic Stress Diagnostic Scale; PFActS-C: Pictorial Fear of Activities Scale- Cervical Spine; PRBCQ: Pain-Related Beliefs of Control Questionnaire; PRSIQ: Pain-Related Self-Instructions Questionnaire; PSEQ: Pain Self-Efficacy Scale; PVAQ: Pain Vigilance Awareness Questionnaire; SCL-90-R: Symptom Check List-90, revised version; SF-STAI: Sort-Form State-Trait Anxiety Inventory; TSK: Tampa Scale of Kinesiophobia.

Quantitative sensory testing (QST) → CDT: Cold Detection Threshold; CPM: Conditioned Pain Modulation; CPT: Cold Pain Threshold; CPTP: Cold Pressor Test Pain; EDT: Electrical Detection Threshold; EIH: Exercise-Induced Hypoalgesia; EPT: Electrical Pain Threshold; ER: Electrocutaneous Ratio; HPT: Heat Pain Threshold; HPTol: Heat Pain Tolerance; MDT: Mechanical Detection Threshold; MPS: Mechanical Pain Sensitivity; MPT: Mechanical Pain Threshold; PPT: Pressure Pain Threshold; PPTol: Pressure Pain Tolerance; STPS: Supra-Threshold Pain Stimulation; THPI: Tonic Heat Pain Intensity; TS: Temporal Summation; TSL: Thermal Sensory Limen; VDT: Vibration Disappearance Threshold; VT: Vibration Threshold; WDT: Warm Detection Threshold.

Disability & others → BPI: Brief Pain Inventory; BPPT: Brachial Plexus Provocation Test; CCFT: Cranio-Cervical Flexion Test; CFQ: Cognitive Failures Questionnaire; CIS20R: Checklist Individual Strength; CJPE: Cervical Joint Reposition Error; CNFDS: Copenhagen Neck Functional Disability Scale; CROM: Cervical Range of Motion; CSI: Central Sensitization Inventory; DHI-sf: Dizziness Handicap Inventory- short form; DN4: Douleur Neuropathique-4 items; EQ-5D: European Quality of life - 5 Dimensions; EMG: Electromyography; FPI: Freiburg Personality Inventory; GPE: Global Perceived Effect; GSES: General Self-Efficacy Scale; IPAQ: International Physical Activity Questionnaire; MOS-Sleep: Medical Outcomes Study Sleep Scale; MPQ: McGill Pain Questionnaire; MRI: Magnetic resonance imaging; fMRI: functional-MRI; NET: Neck Extension Test; NRS: Numeric Rating Scale; NDI; Neck Disability Index; NEO-FFI: Neuroticism, extraversion, openness—Five factor inventory; NFR: Nociceptive Flexion Reflex; NPI: Northwick Park Neck Pain Index; NPSI: Neuropathic Pain Symptom Inventory; PAR-Q: Physical Activity Readiness Questionnaire; mPDQ: modified Perceived Deficits Questionnaire; P-SFS: Patient-Specific Functional Scale; RPE: Rating of Perceived Exertion; SF-36: 36-Item Short Form Survey; s-LANSS: self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale; SVR: Sympathetic Vasoconstrictor Reflex; TMT: Trail Making Test; VAS: Visual Analogue Scale; WBS: Well-Being Scale; WDQ: Whiplash Disability Questionnaire.

SUPPLEMENTARY MATERIAL D. Further explanation of risk of bias assessment tools and detailed reasons of risk of bias in selected articles for each study design.

[see reference list in the main manuscript]

Risk of bias assessment tools

The Newcastle-Ottawa scale was used for cross-sectional, case-control, and prospective studies (i.e., cohort studies and clinical trials).[17] It is based on a star system and contains eight items for case-control or cohort studies, categorized into three groups: selection (0–4 stars), comparability (0–2 stars), and exposure or outcome (0–3 stars); and seven items for cross-sectional studies, categorized into the same three groups: selection (0–5 stars), comparability (0–2 stars), and exposure or outcome (0–3 stars).

Tables 1 to 4 present specific scores for each item evaluated in the included studies.

TABLE 1. Newcastle – Ottawa for cross-sectional studies.

Study	Selection	Comparability	Exposure	Total
Elliott, 2009 [20]	***	*	***	7
Farrell, 2020[a] [22]	****		***	7
Hendriks, 2020 [24]	*****		***	8
Pedler, 2013b [54]	****		***	7
Rivest, 2010 [63]	***	**	***	8
Sterling, 2009 [82]	***		***	6
Sterling, 2016 [75]	***		***	6

Stars (*) represent that a criterion is fulfilled. Selection ranges from 0 to 5 stars; Comparability ranges from 0 to 2 stars; Exposure ranges from 0 to 3 stars. Total score of 7 ≥ stars: “high quality”; 4-6 stars: “fair quality”; 3 ≤ stars “poor quality”.

TABLE 2. Newcastle – Ottawa for case-control studies.

Study	Selection	Comparability	Exposure	Total
Banic, 2004 [2]	*	**	*	4
Chien, 2008b [6]	****	**	**	8
Chien, 2009 [7]	****	*	*	6
Chien, 2010 [8]	****	**	**	8
Christensen, 2021 [9]	****	**	*	7
Coppieters, 2017[a] [12]	****	**	*	7
Curatolo, 2001 [14]	*		*	2
Daenen, 2014 [15]	****	*	*	6
De Kooning, 2017 [16]	****		**	6
Farrell, 2020[b] [23]	**	**	*	5
Herren-Gerber, 2004 [26]	*	**		3
Kasch, 2011 [31]	**		*	3
Lenoir, 2022[34]	****	**	*	7
Olivegren, 1999 [48]	***	**	***	8
Raak, 2006 [57]	**	*	*	4
Scott, 2005 [65]	****	**	*	7
Serrano-Munóz, 2019 [66]	**		*	3
Smith, 2013 [70]	***		*	4
Smith, 2017 [68]	***	*	*	5
Smith, 2020 [69]	****	**	*	7
Sterling, 2003 [80]	****	**	*	7
Sterling, 2008 [78]	*	*	*	3
Sterling, 2010[a] [73]	****	*	*	6
Sterling, 2013 [74]	****		*	5
Wallin, 2012 [89]	***	**	*	6

Stars (*) represent that a criterion is fulfilled. Selection ranges from 0 to 4 stars; Comparability ranges from 0 to 2 stars; Exposure ranges from 0 to 3 stars. Total score of 7 ≥ stars: “high quality”; 4-6 stars: “fair quality”; 3 ≤ stars “poor quality”.

TABLE 3. Newcastle – Ottawa for cohort studies.

Study	Selection	Comparability	Exposure	Total
Andersen, 2022 [1]	****		**	6
Kamper, 2011 [30]	***		**	5
Pedler, 2016 [53]	***	**	***	8
Ritchie, 2013 [61]	***	**	**	7
Sterling, 2006 [79]	***	**	***	8
Sterling, 2011 [76]	***	**	**	7
Sterling, 2012 [77]	****	*	***	8

Stars (*) represent that a criterion is fulfilled. Selection ranges from 0 to 4 stars; Comparability ranges from 0 to 2 stars; Exposure ranges from 0 to 3 stars. Total score of 7 ≥ stars: "high quality"; 4-6 stars: "fair quality"; 3 ≤ stars "poor quality".

TABLE 4. Newcastle – Ottawa for clinical trials.

Study	Selection	Comparability	Exposure	Total
Dunne, 2012 [18]	****		**	6
Jull, 2007 [29]	****		***	7
Jull, 2013 [28]	***		*	4
Michaleff, 2014 [44]	****	*	**	7
Prushansky, 2006 [56]	****		**	6
Sterling, 2010b [83]	***		**	5
Sterling, 2015 [84]	****	**	***	9
Tobbackx, 2013 [85]	****	*	***	8
Van Osterwijck, 2011 [86]	****	*	***	8
Wiangkham, 2019 [92]	***		***	6

Stars (*) represent that a criterion is fulfilled. Selection ranges from 0 to 4 stars; Comparability ranges from 0 to 2 stars; Exposure ranges from 0 to 3 stars. Total score of 7 ≥ stars: "high quality"; 4-6 stars: "fair quality"; 3 ≤ stars "poor quality".

SUPPLEMENTARY MATERIAL E. Clustering of studies by questionnaires assessing specific psychological factors constructs.

[see reference list in the main manuscript]

Psychological factors - Questionnaires

The Pain Catastrophizing Scale (PCS) was the most frequently used questionnaire with 20 studies (41%) reporting PCS-scores.[9,12,15,16,22,23,34,44,57,63,66,68-70,75,78,84-86,89] Thirteen studies (27%) included the Tampa Scale of Kinesiophobia (TSK)[9,18,20,24,29,30,53,68,69,75,79,85,86] to evaluate fear-avoidance beliefs, while another 4 studies (8%) evaluated the same construct by using the Pictorial Fear of Activities Scale-Cervical Spine (PFActS-C)[28,53] or the Fear-Avoidance Beliefs Questionnaire (FABQ).[89,92] Twelve studies (24%) evaluated the presence and severity of posttraumatic stress disorders with the Posttraumatic Stress Diagnostic Scale (PDS)[18,22,44,53,54,61,68,70,74-76,84] while 1 study (2%) used the Posttraumatic Stress Diagnostic Checklist-5 (PCL-5),[69] along with 16 studies (33%) using the Impact of Events Scale (IES)[1,8,15,16,18,20,24,28,29,77,79,89,92] or its revised version.[18,23,34] The General Health Questionnaire-28 (GHQ-28) was used in 11 studies (22%) to assess emotional distress.[8,20,28,29,70,73,74,78,79,82,83] Other emotional-related outcomes such as depression, anxiety, and/or stress symptoms were evaluated in other 10 studies (20%) by using the Depression Anxiety and Stress Scale (DASS),[18,23,30] the Beck Depression Inventory (BDI),[9,15] the Hospital Anxiety and Depression Scale (HADS),[89] the Four-Dimensional Symptom Questionnaire (4DSQ),[24], the Pain Anxiety Symptoms Scale (PASS),[34,89] or the Sort-Form State-Trait Anxiety Inventory (SF-STAI).[65] Additionally, 1 study (2%) investigated the fear of anxiety using the Anxiety Sensitivity Index (ASI).[89] Coping strategies were evaluated in 5 studies (10%) by using the Coping Strategy Questionnaire-

C (CSQ-C),[30,53,74] the Pain Coping Inventory (PCI),[86] or the Millon Behavioral Health Inventory (MBHI).[31] Attention to pain was evaluated in 2 studies (4%) with the Pain Vigilance Awareness Questionnaire (PVAQ),[12,15] while pain self-efficacy and mood was evaluated in other 2 studies (4%) by using the Pain Self-Efficacy Scale (PSEQ)[89] and the Mood Adjective Checklist (MOCL),[48] respectively. Finally, 8 studies (16%) included questionnaires evaluating multiple constructs covered above, the revised version of the Symptom Check List-90 (SCL-90-R) being used in 7 studies[2,6,7,14,24,31,56] and the Pain-Related Beliefs of Control (PRBCQ) and Pain-Related Self-Instructions Questionnaires (PRSIQ) in 1 study.[26]

SUPPLEMENTARY MATERIAL F. Pairs of specific QST measures and psychological factors evaluated simultaneously in two or more studies

TABLE 1. Number of studies that simultaneously evaluated a specific QST measure and psychological factors in WAD participants.

QST / **PF**	PPT	CPT	HPT	CPM	TS	CDT	WDT	EPT	EDT	PPTol	VT	EIH
PCS	17	11	7	7	3	3	3					2
TSK	13	7	5	4	2							2
PDS	11	12	5									
GHQ-28	11	11	7									
IES	12	9	4			2			2			
SCL-90-R	6	2			2	2	2	3	2	2	2	
DASS	3	2	2									
CSQ-C	3	2										
FABQ	2											
BDI	2			2								
IES-R	2	2	2									
PFActS-C	2	2										
PVAQ	2			2								

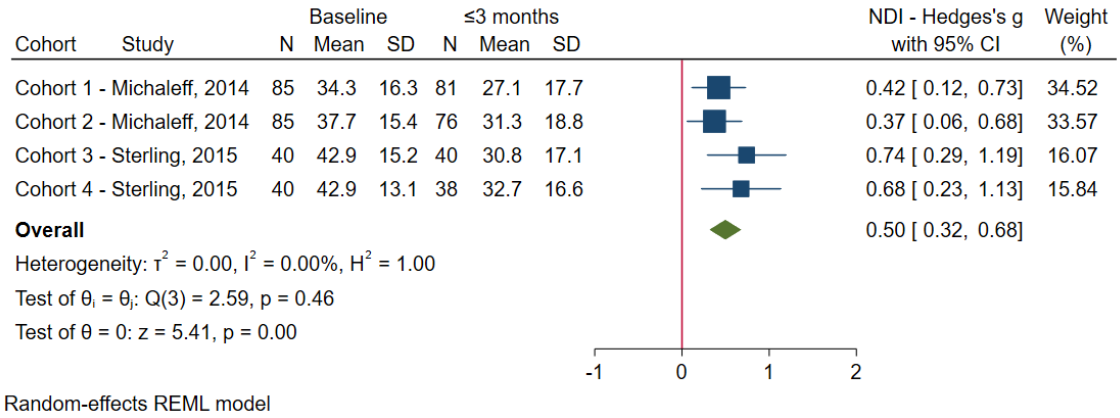
Psychological factors (PF) → BDI: Beck Depression Inventory; CSQ-C: Coping Strategy Questionnaire C; DASS: Depression Anxiety and Stress Scale; FABQ: Fear-Avoidance Beliefs Questionnaire; GHQ-28: General Health Questionnaire 28; IES: Impact of Events Scale; IES-R: Impact of Events Scale Revised; PCS: Pain Catastrophizing Scale; PDS: Posttraumatic Stress Diagnostic Scale; PFActS-C: Pictorial Fear of Activities Scale- Cervical Spine; PVAQ: Pain Vigilance Awareness Questionnaire; SCL-90-R: Symptom Check List-90, revised version; SF-STAI: Sort-Form State-Trait Anxiety Inventory; TSK: Tampa Scale of Kinesiophobia.

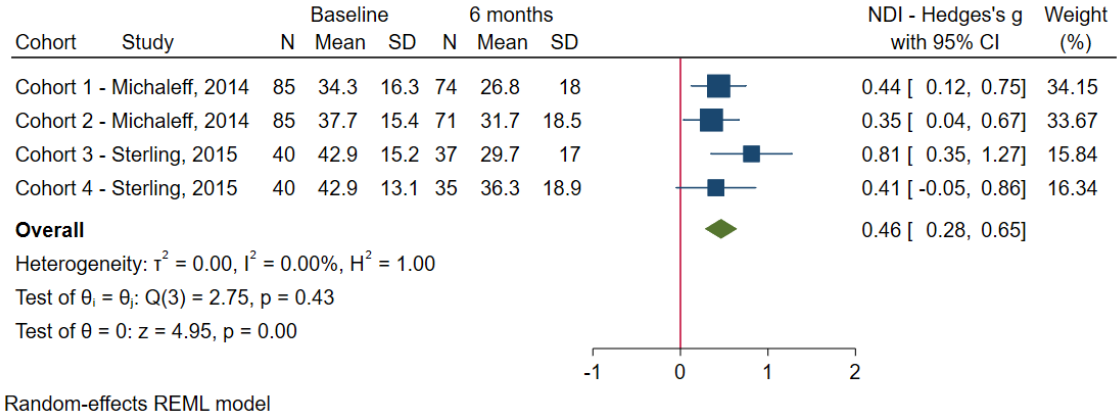
Quantitative sensory testing (QST) → CDT: Cold Detection Threshold; CPM: Conditioned Pain Modulation; CPT: Cold Pain Threshold; EDT: Electrical Detection Threshold; EIH: Exercise-Induced Hypoalgesia; EPT: Electrical Pain Threshold; HPT: Heat Pain Threshold; PPT: Pressure Pain Threshold; PPTol: Pressure Pain Tolerance; TS: Temporal Summation; VT: Vibration Threshold; WDT: Warm Detection Threshold.

SUPPLEMENTARY MATERIAL G. Individual Forest plots for each variable for chronic and acute WAD cohorts.

SUPPLEMENTARY FIGURE 1. Forest plots showing data synthesis of Hedges' *g* standardized mean difference within cohorts of chronic WAD studies assessing at baseline, ≤3 months, 6 months, and/or ≥12 months QST, psychological factors, and levels of disability. Cohort 1: Michaleff (2014) – Exercise cohort; Cohort 2: Michaleff (2014) – Advice cohort; Cohort 3: Sterling (2015) – Exercise plus dry-needling cohort; Cohort 4: Sterling (2015) – Exercise cohort; Cohort 7: Van Osterwijck (2011) – Pain neurophysiology education cohort. Hedges' *g*: small (≥ 0.2 g <0.5), medium (≥ 0.5 g <0.8) or large (g ≥ 0.8). Positive values represent a decrease/reduction from baseline values. Abbreviations: CPT: Cold Pain Threshold; NDI; Neck Disability Index; PCS: Pain Catastrophizing Scale; PDS: Posttraumatic Stress Diagnostic Scale; PPT: Pressure Pain Threshold.

FIGURE 1a. Chronic WAD NDI – Neck Disability Index.





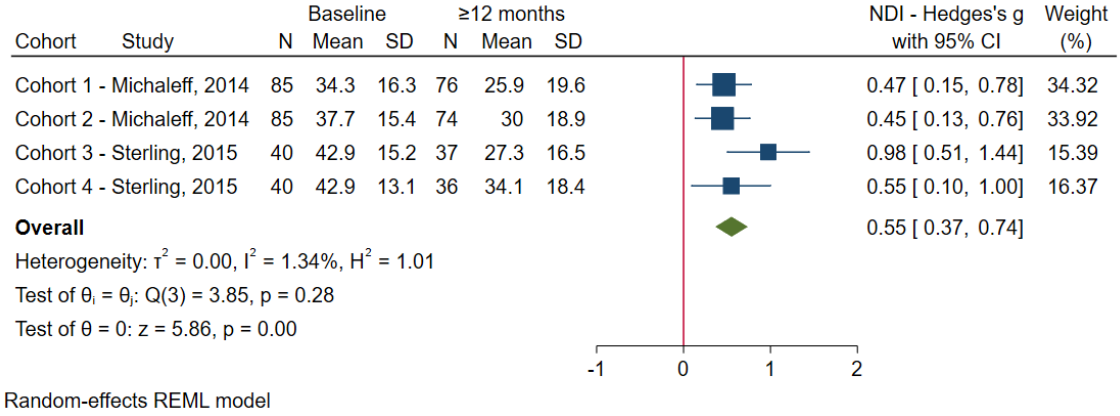


FIGURE 1b. Chronic WAD PPTneck – Pressure Pain Thresholds, neck region.

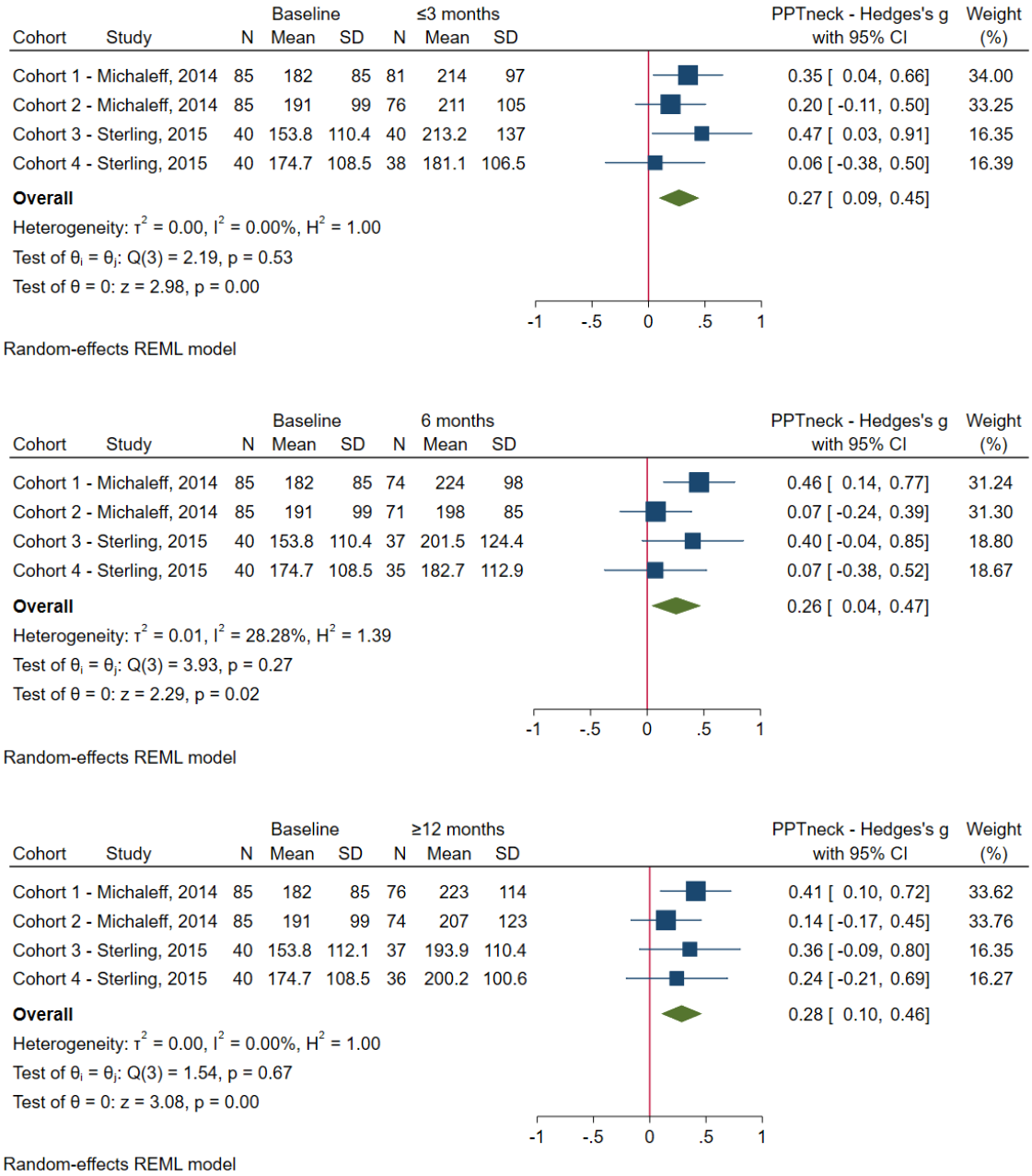


FIGURE 1c. Chronic WAD PPTleg – Pressure Pain Thresholds, leg region.

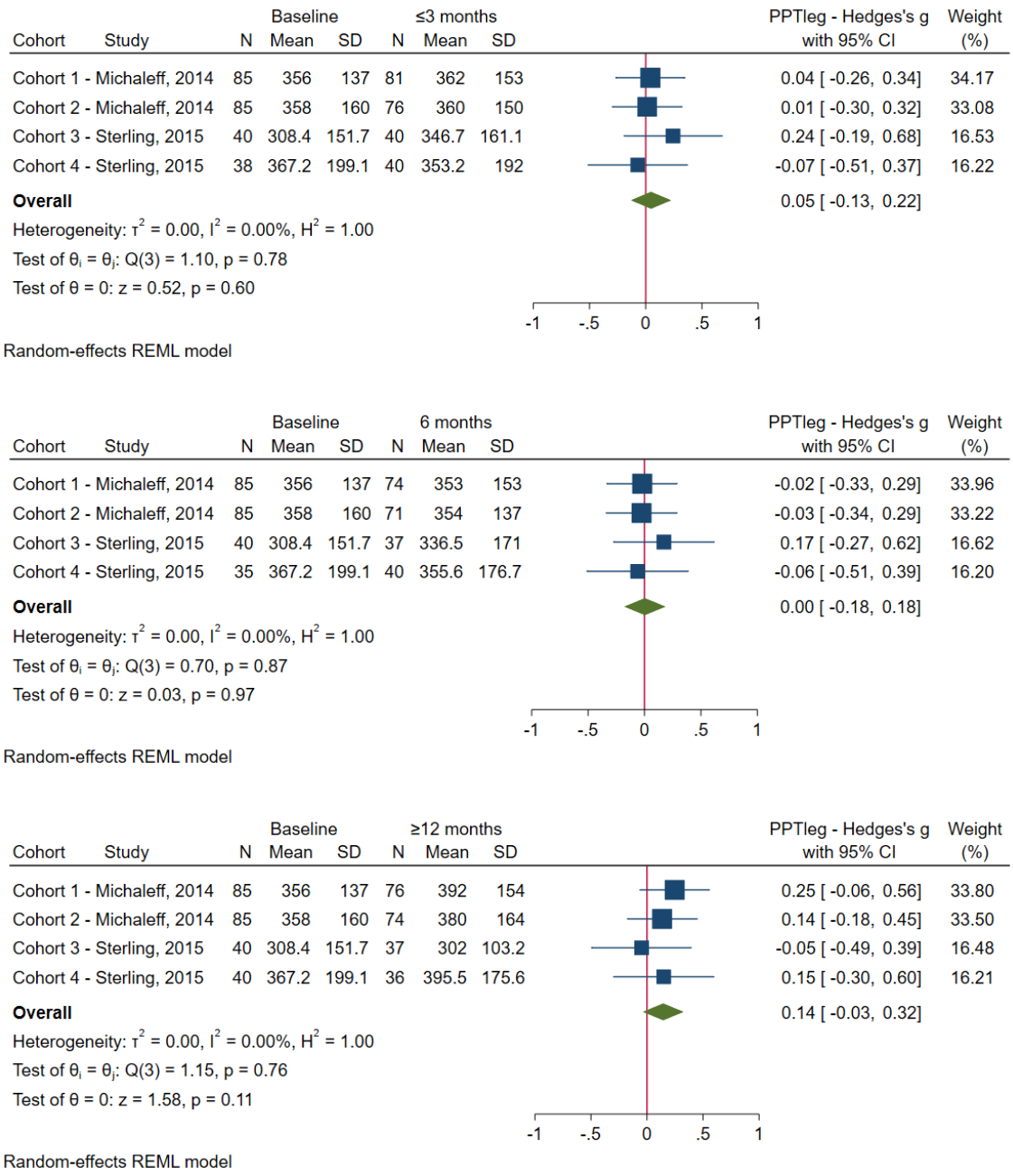
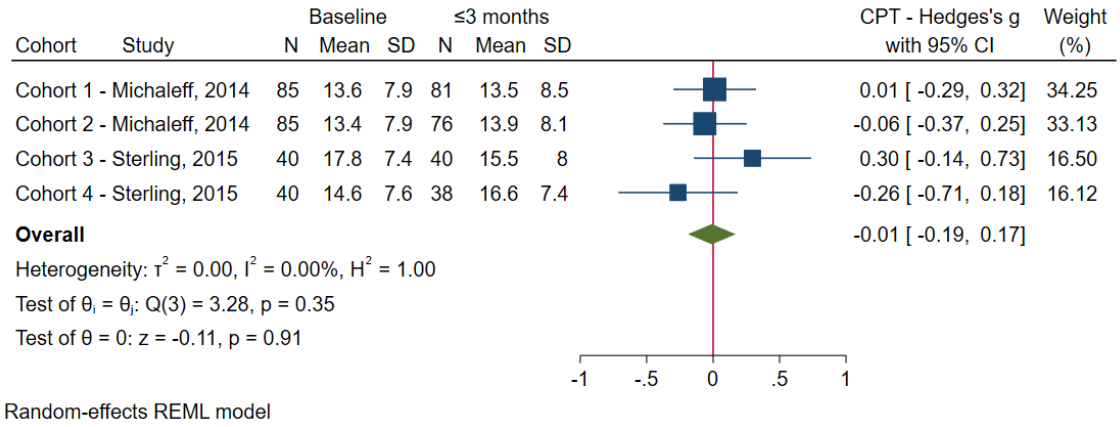
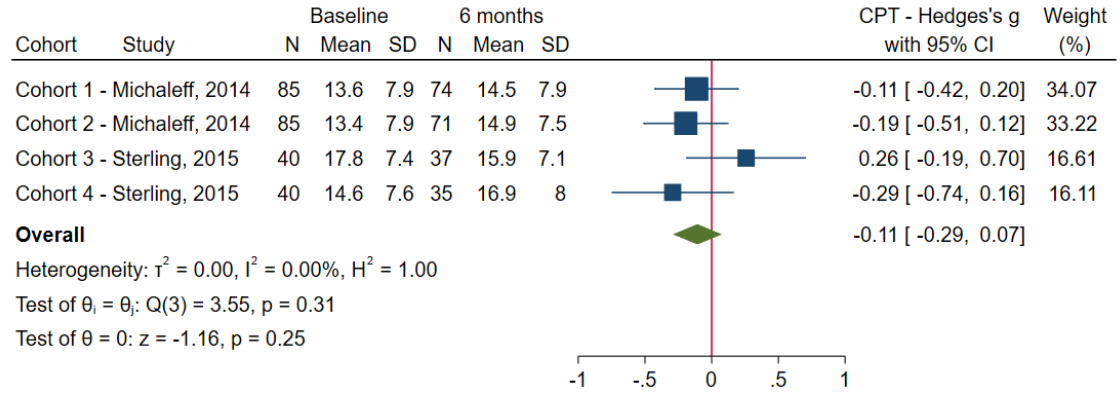


FIGURE 1d. Chronic WAD CPTneck – Cold Pain Thresholds, neck region.





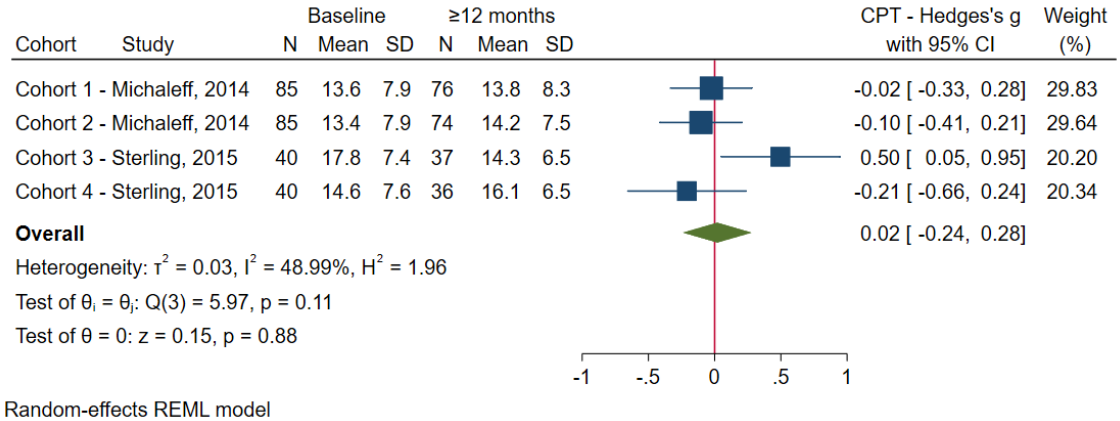
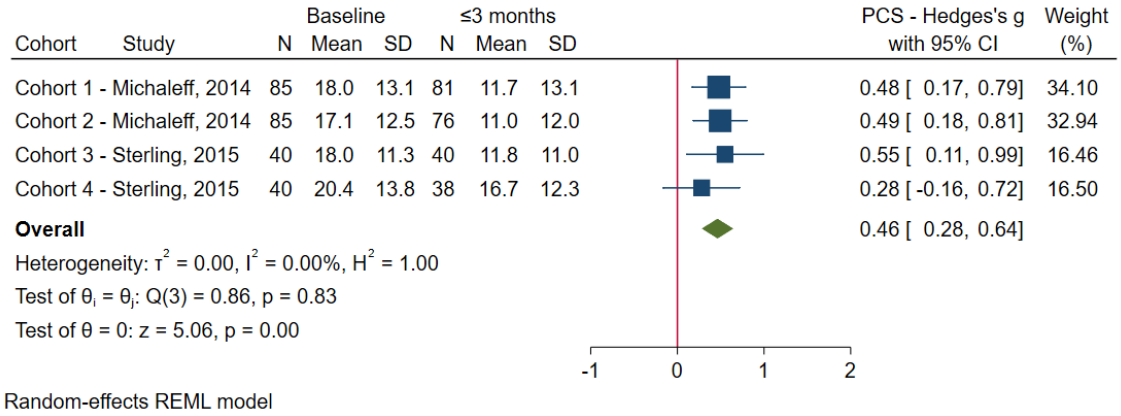
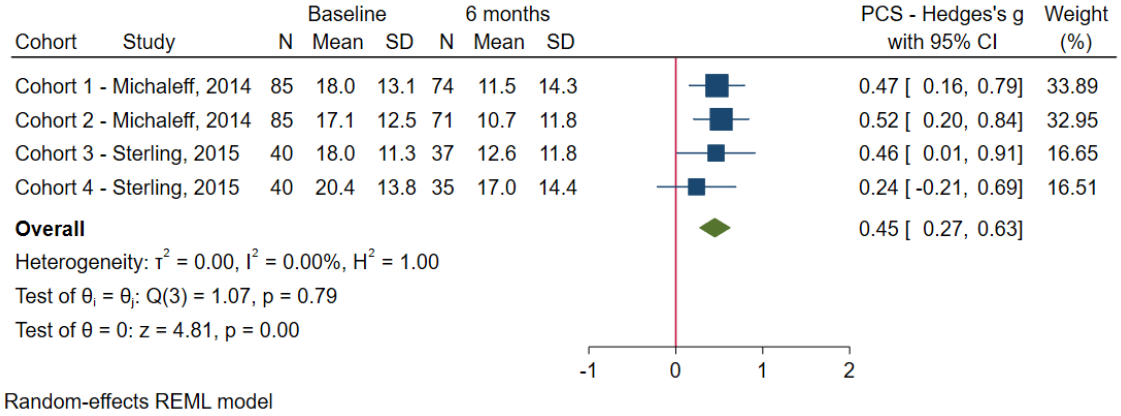


FIGURE 1e. Chronic WAD PCS – Pain Catastrophizing Scale.





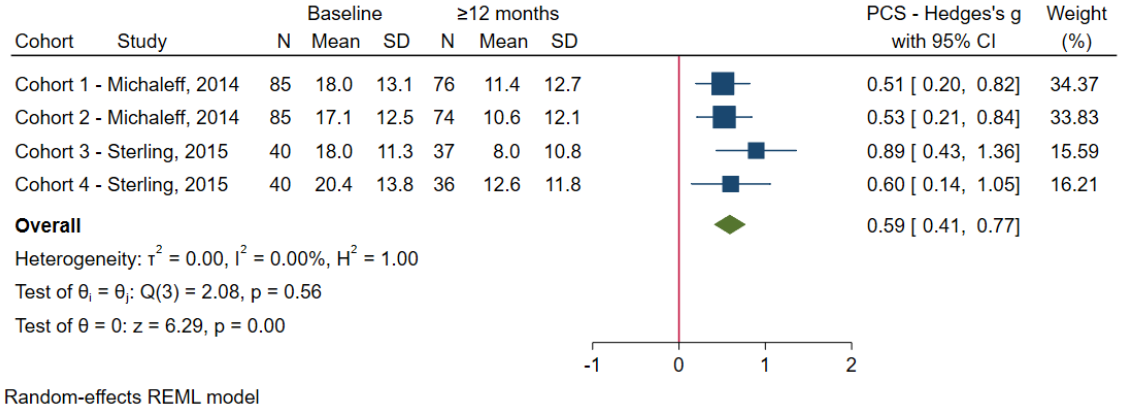
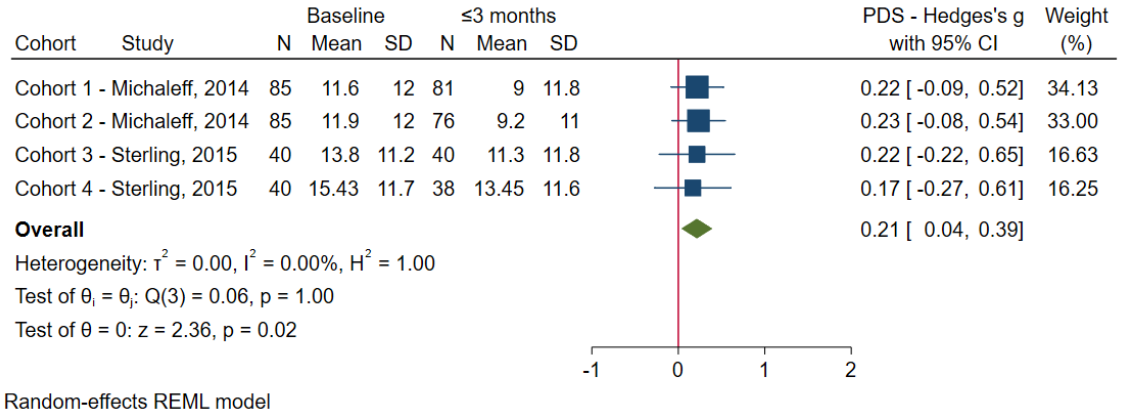
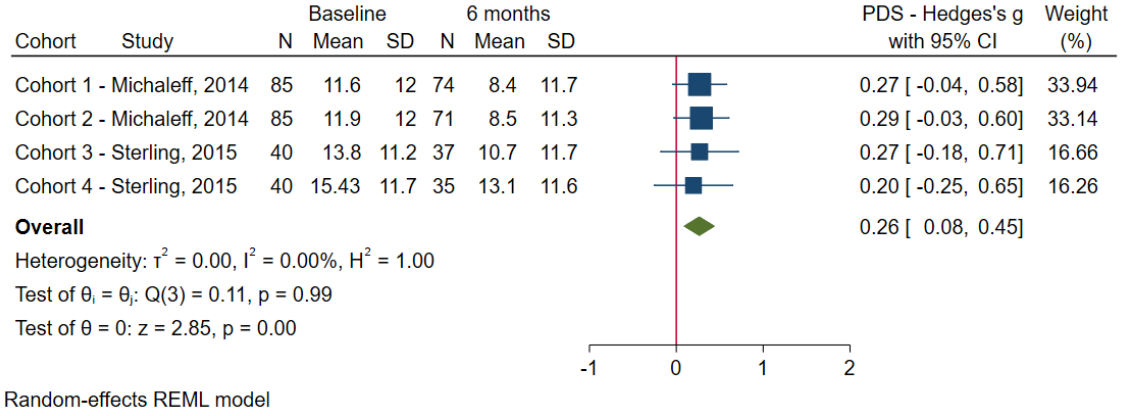
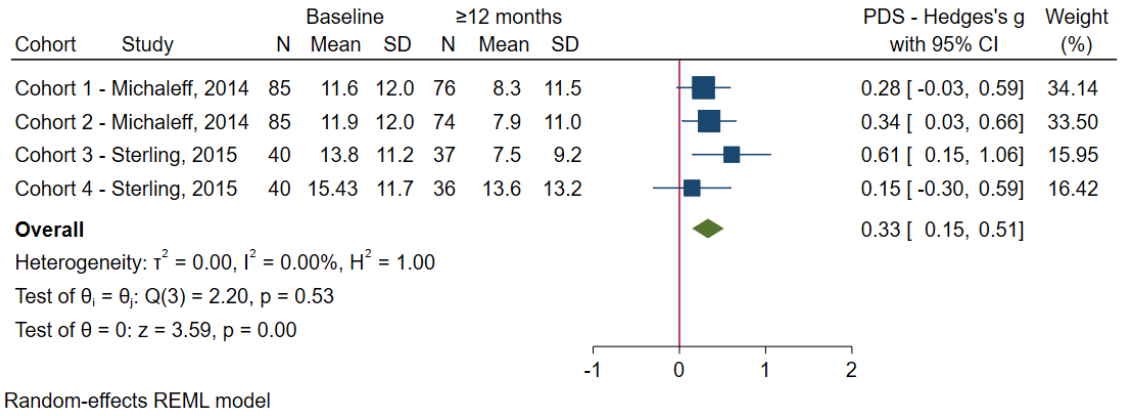


FIGURE 1f. Chronic WAD PDS – Post-traumatic Stress Diagnostic Scale.

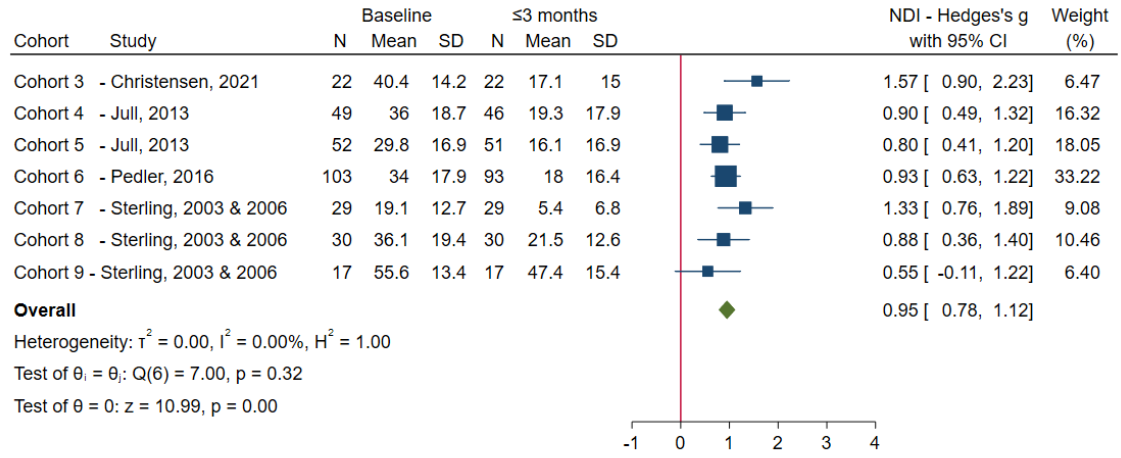


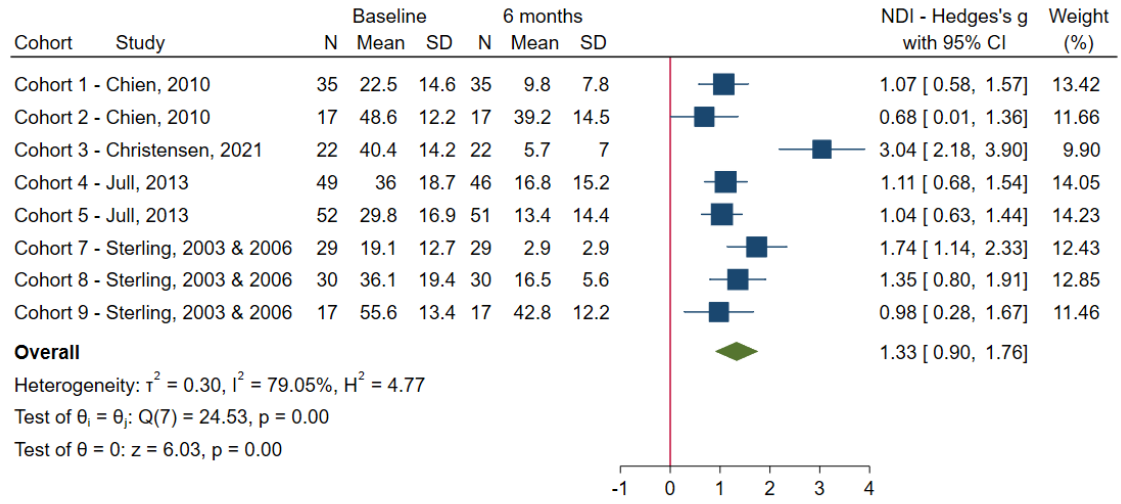




SUPPLEMENTARY FIGURE 2. Forest plots showing data synthesis of Hedges' *g* standardized mean difference within cohorts of acute WAD studies assessing at baseline, ≤3 months, 6 months, and/or ≥12 months QST, psychological factors, and levels of disability. Cohort 1: Chien (2010) – Low risk of poor recovery cohort; Cohort 2: Chien (2010) – High risk of poor recovery cohort; Cohort 3: Christensen (2021) – Unique cohort; Cohort 4: Jull (2013) – Pragmatic intervention cohort; Cohort 5: Jull (2013) – Usual care cohort; Cohort 6: Pedler (2016) – Unique cohort; Cohort 7: Sterling (2003&2006) – 6 to 24 month recovered cohort; Cohort 8: Sterling (2003&2006) – 6 to 24 month mild disability cohort; Cohort 9: Sterling (2003&2006) – 6 to 24 month moderate-severe disability cohort; Cohort 10: Sterling (2013) – Unique cohort. Hedges' *g*: small (≥ 0.2 g <0.5), medium (≥ 0.5 g <0.8) or large (g ≥ 0.8). Positive values represent a decrease/reduction from baseline values. Abbreviations: CPT: Cold Pain Threshold; GHQ-28: General Health Questionnaire 28; HPT: Heat Pain Threshold; IES: Impact of Events Scale; NDI; Neck Disability Index; PCS: Pain Catastrophizing Scale; PFActS-C: Pictorial Fear of Activities Scale- Cervical Spine; PPT: Pressure Pain Threshold; TSK: Tampa Scale of Kinesiophobia.

FIGURE 2a. Acute WAD NDI – Neck Disability Index.





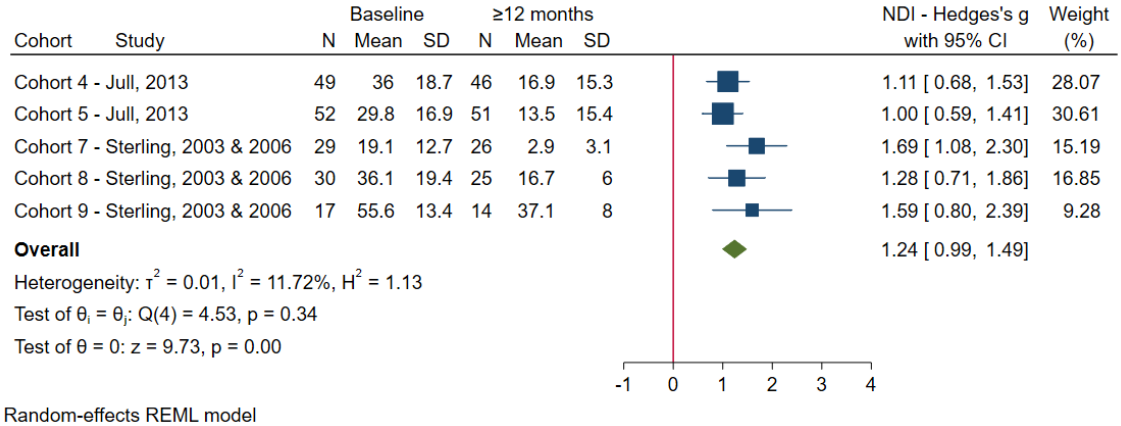


FIGURE 2b. Acute WAD PPTneck – Pressure Pain Thresholds, neck region.

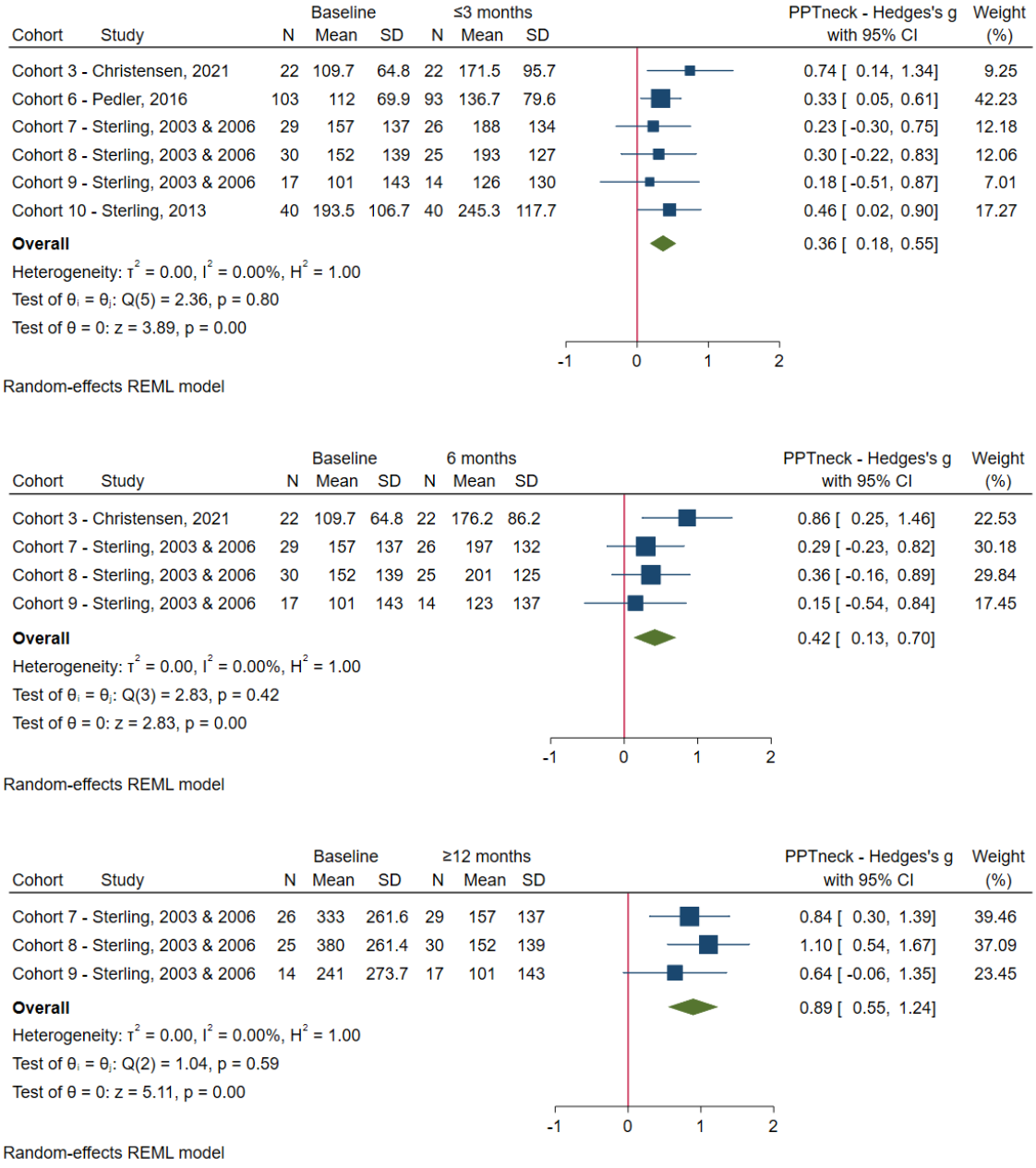
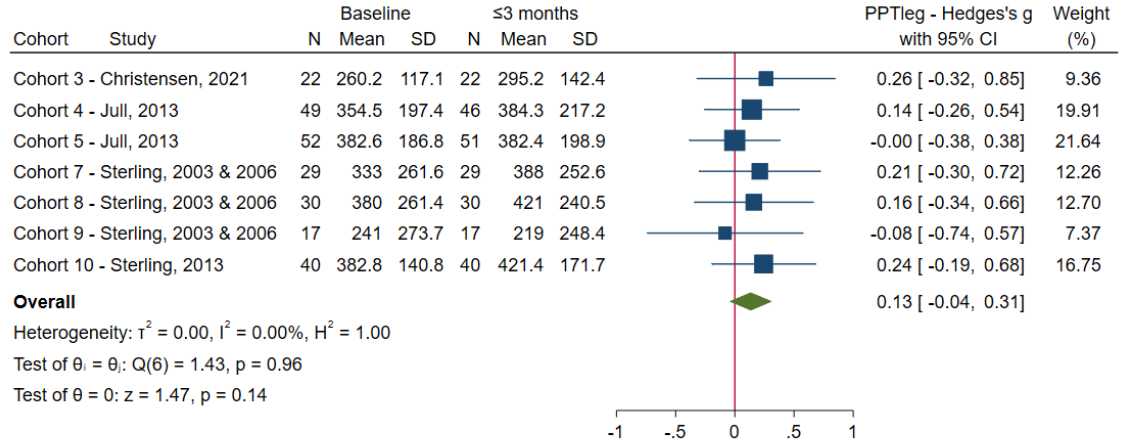
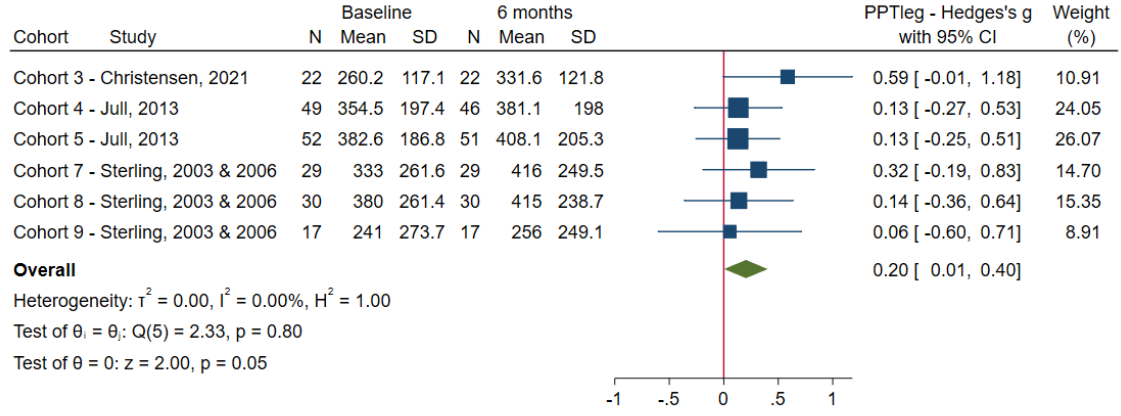


FIGURE 2c. Acute WAD PPTleg – Pressure Pain Thresholds, leg region.





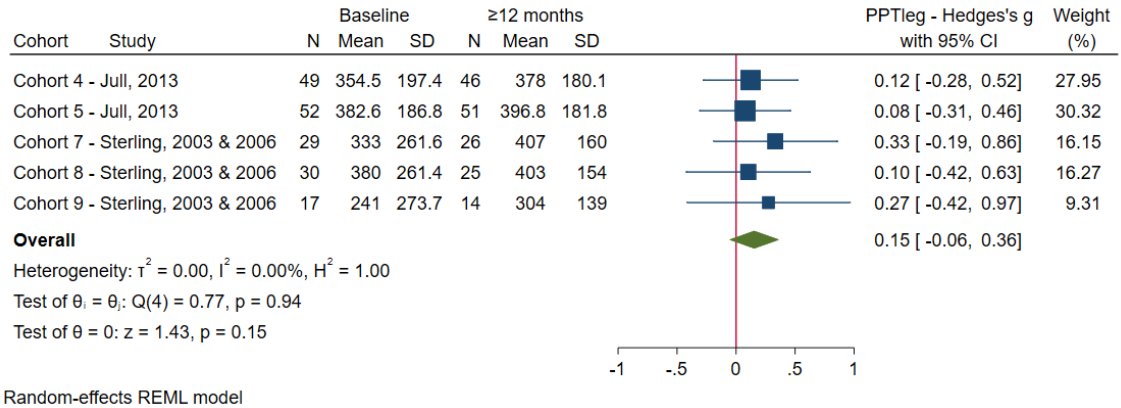
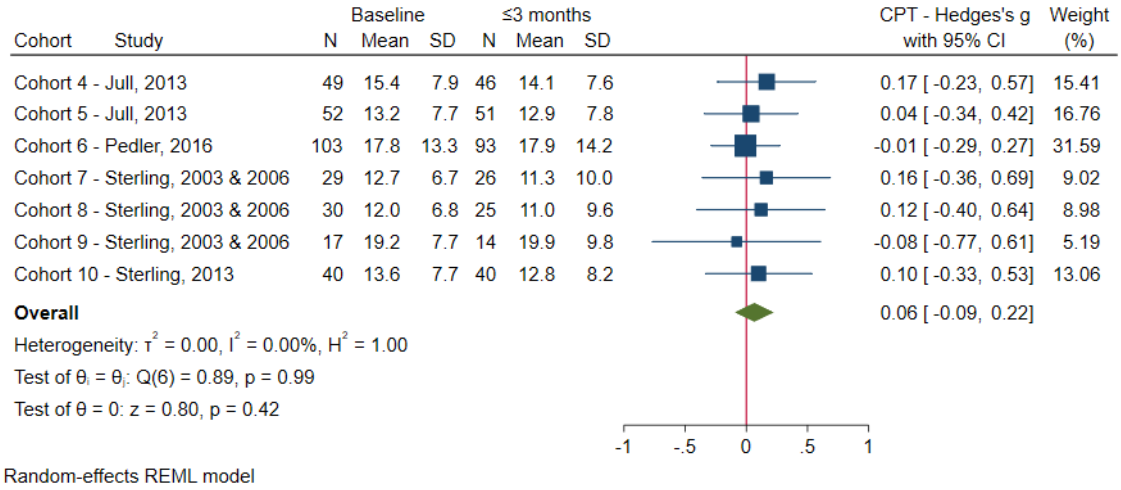
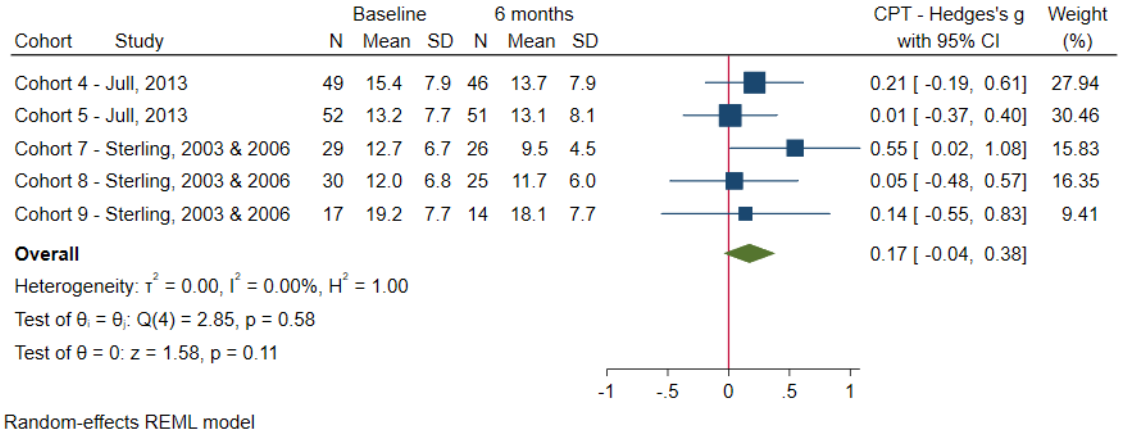


FIGURE 2d. Acute WAD CPTneck – Cold Pain Thresholds, neck region.





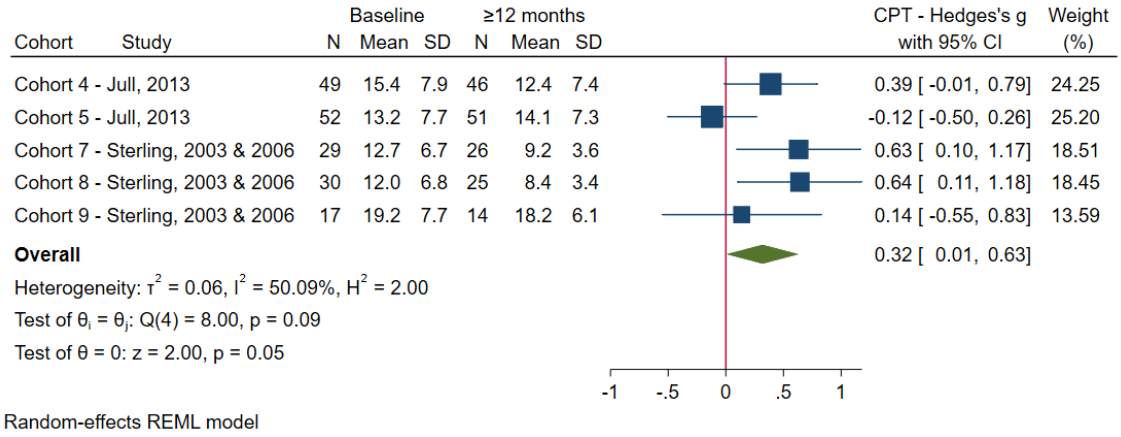
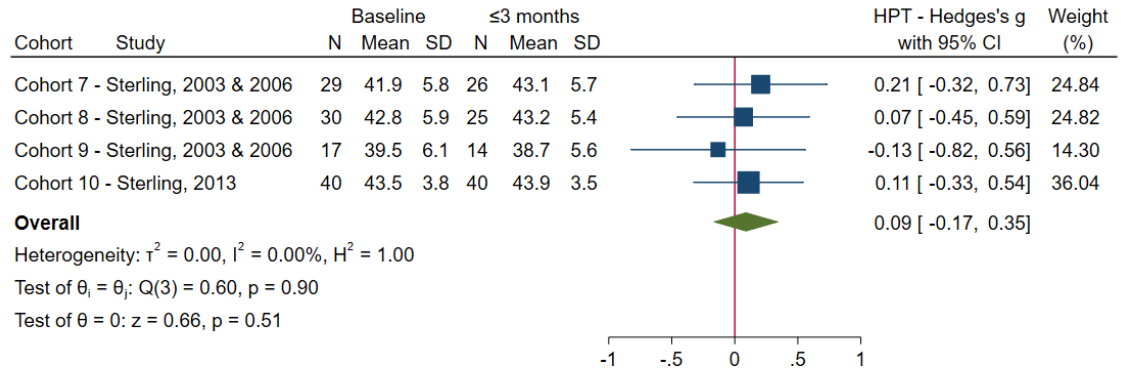
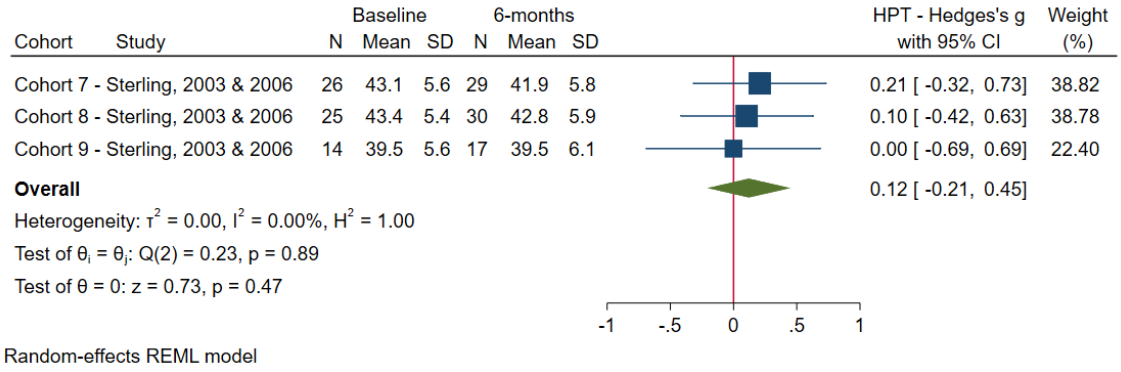


FIGURE 2e. Acute WAD HPTneck – Heat Pain Thresholds, neck region.





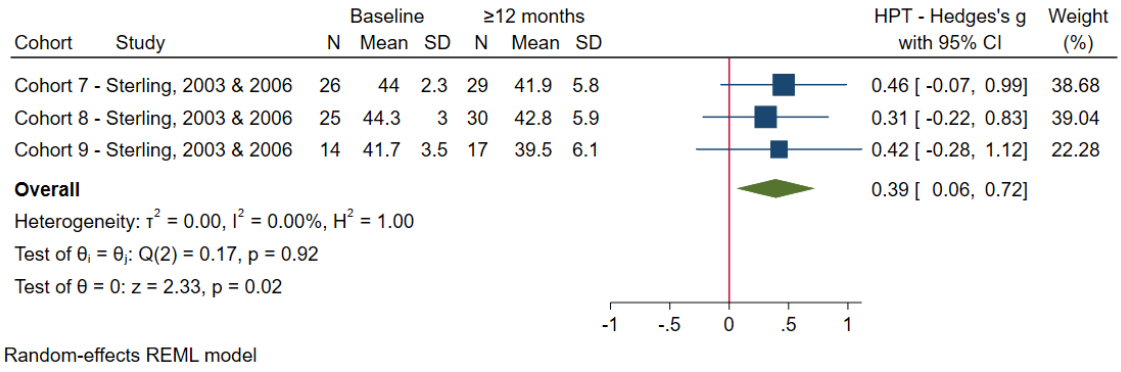
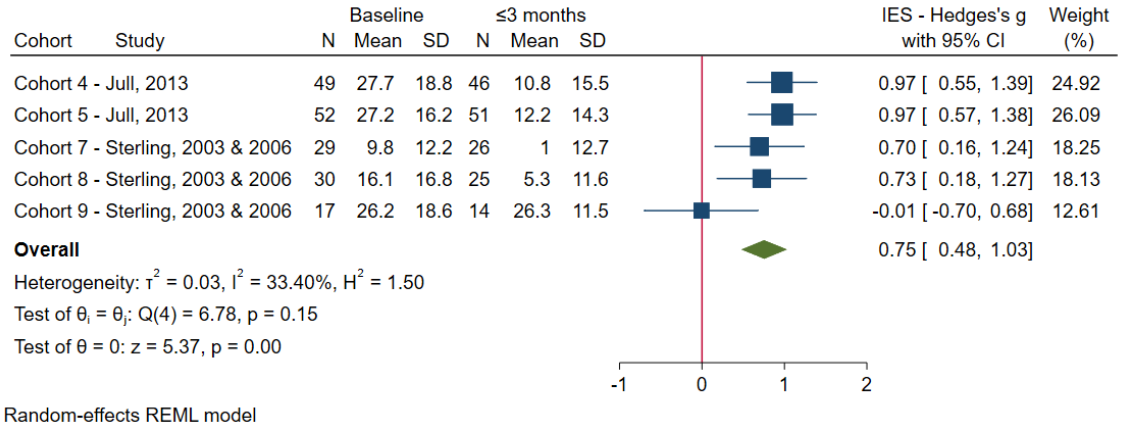
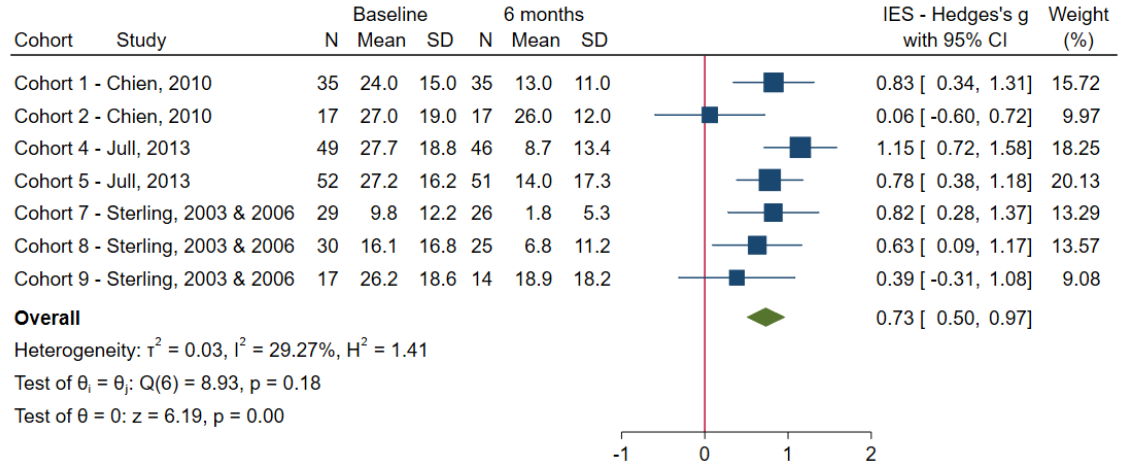


FIGURE 2f. Acute WAD IES – Impact Event Scale.





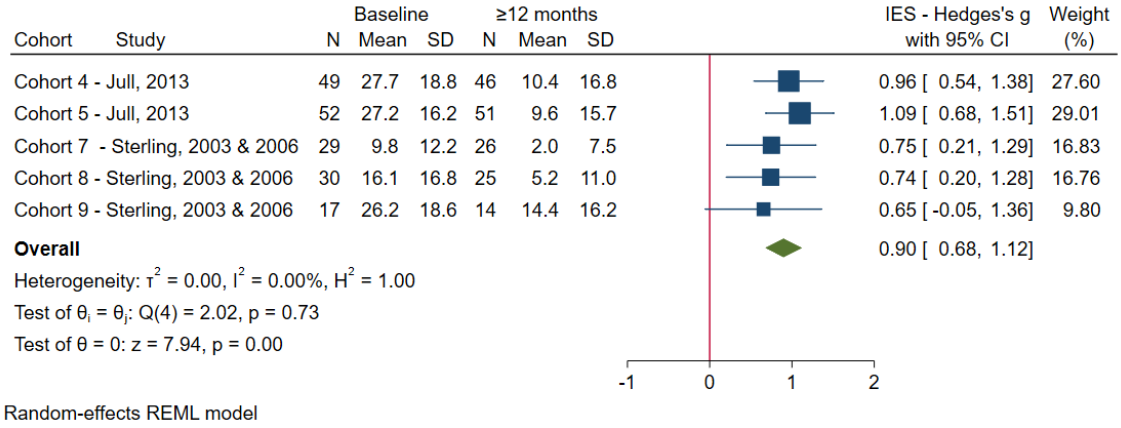
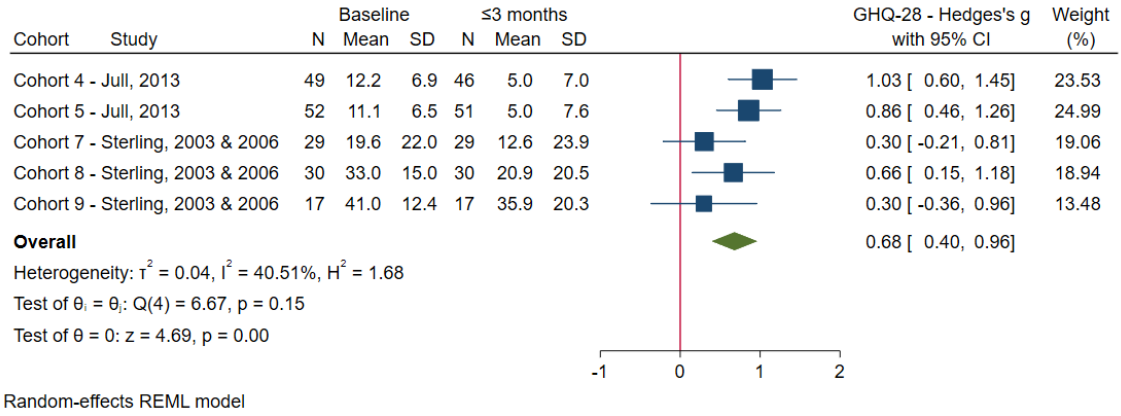
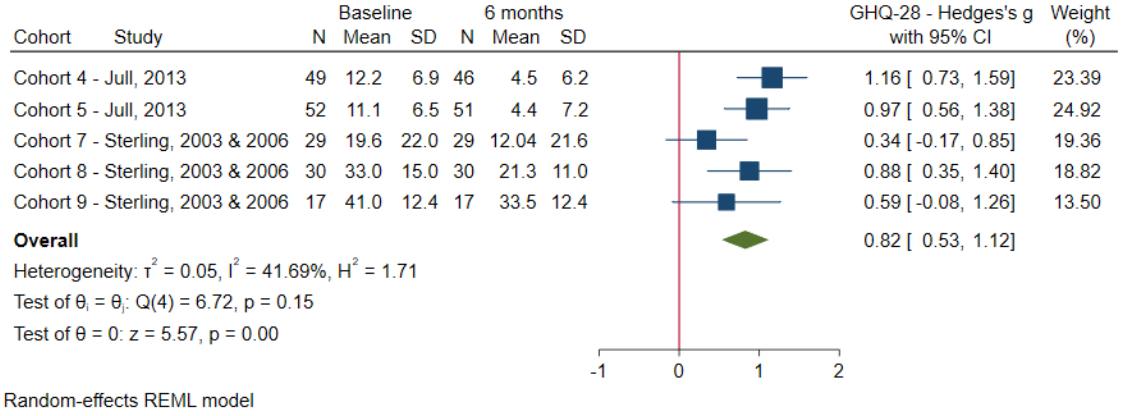


FIGURE 2g. Acute WAD GHQ-28 – Global Health Questionnaire.





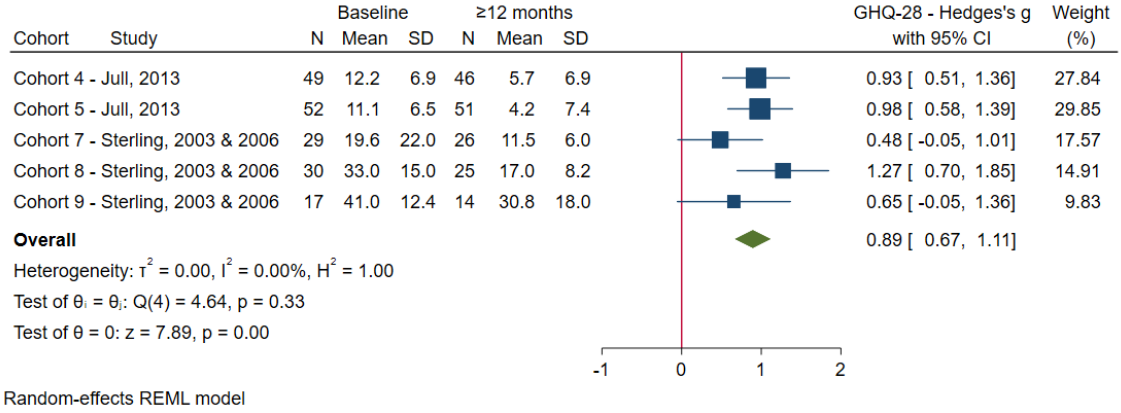
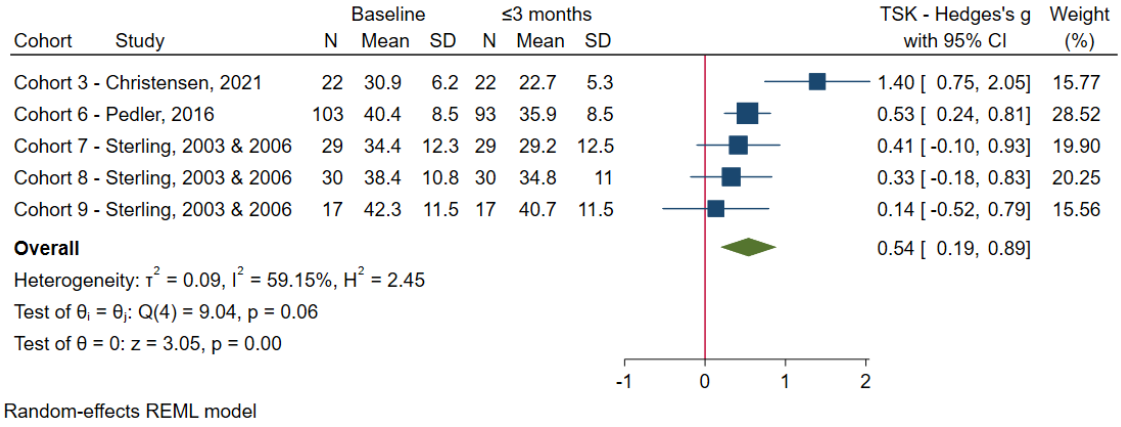
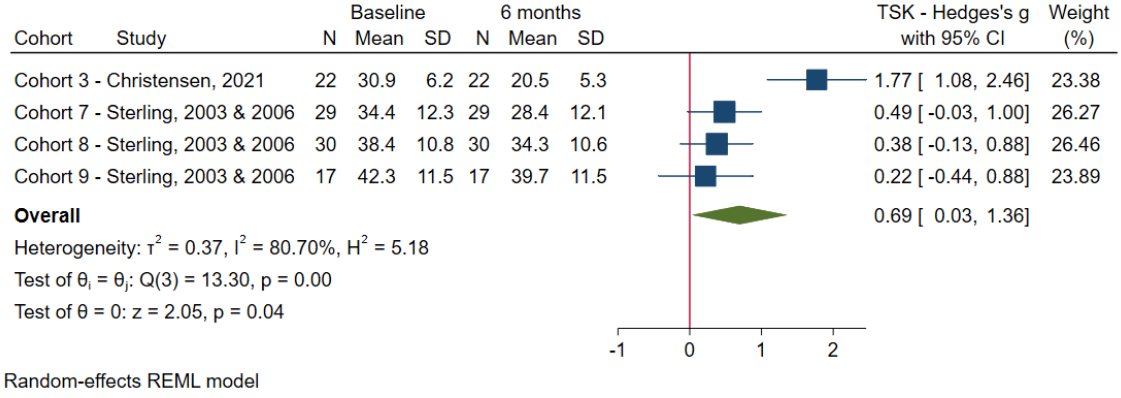


FIGURE 2h. Acute WAD TSK – Tampa Scale of Kinesiophobia.





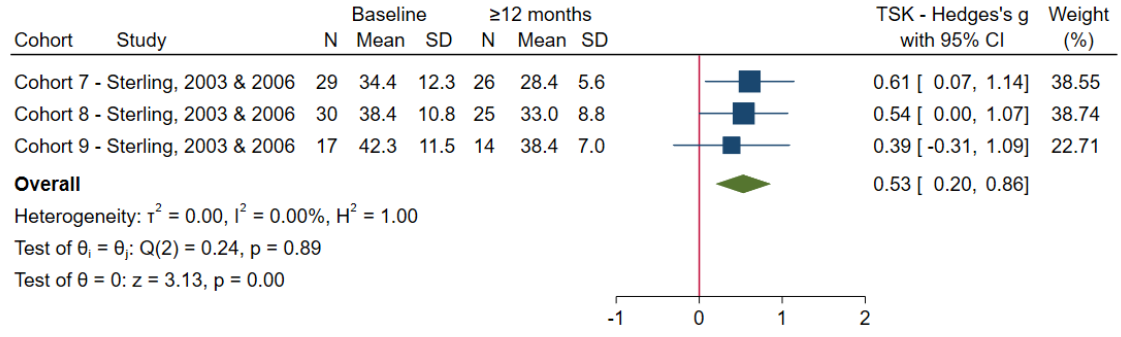
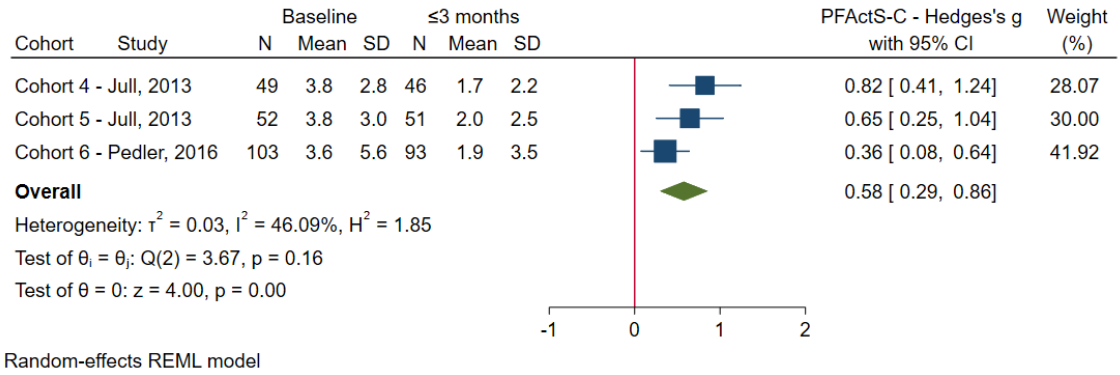
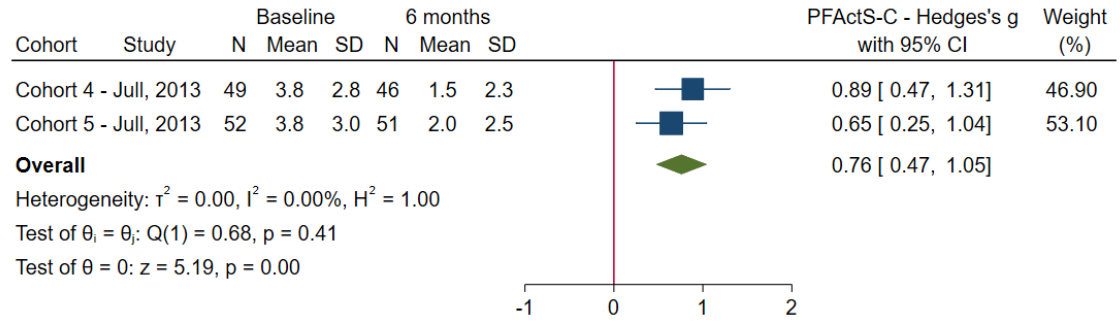


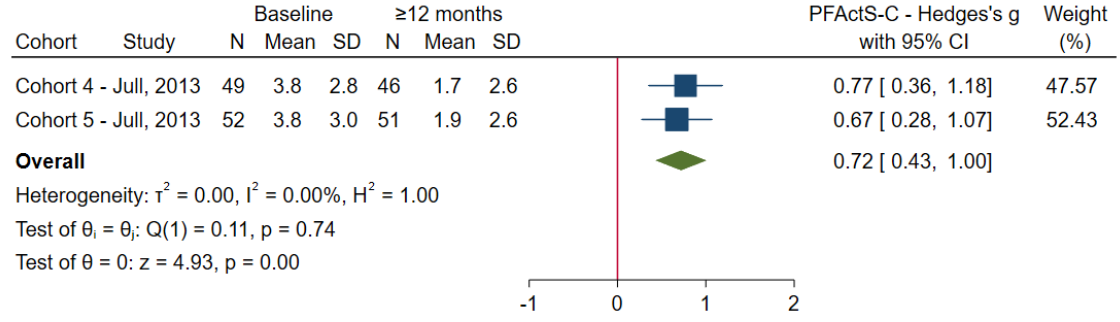
FIGURE 2i. Acute WAD PFActS-C– Pictorial Fear of Activity Scale-Cervical.



Random-effects REML model



Random-effects REML model

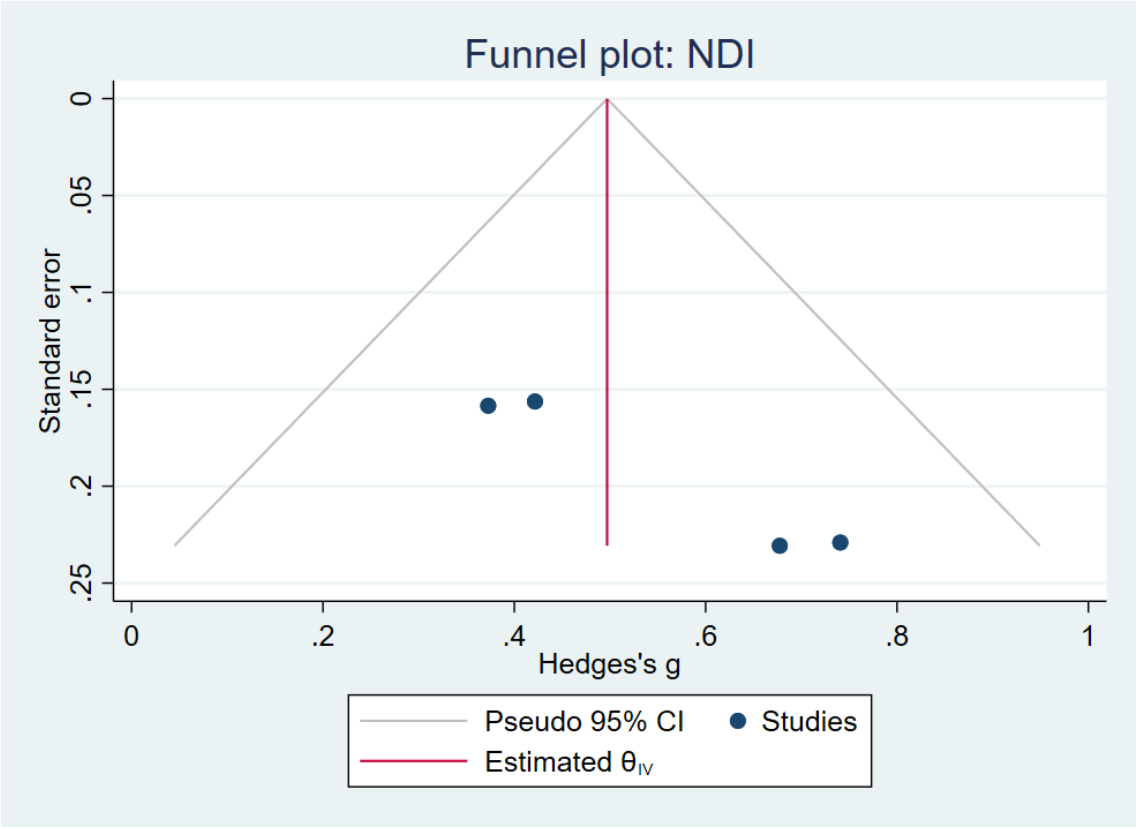


Random-effects REML model

SUPPLEMENTARY MATERIAL H. Funnel plots and Egger's tests for each variable for chronic and acute WAD cohorts.

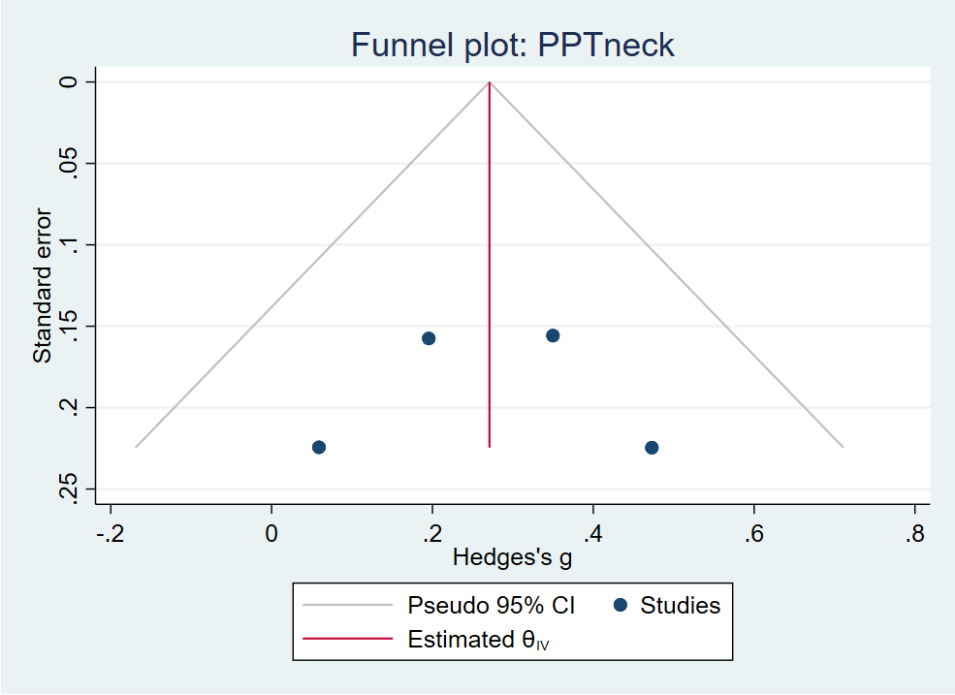
SUPPLEMENTARY FIGURE 1. Funnel plots and Egger's test assessing publication bias within cohorts of chronic WAD studies. Abbreviations: CPT: Cold Pain Threshold; NDI; Neck Disability Index; PCS: Pain Catastrophizing Scale; PDS: Posttraumatic Stress Diagnostic Scale; PPT: Pressure Pain Threshold.

FIGURE 1a. Chronic WAD NDI – Neck Disability Index.



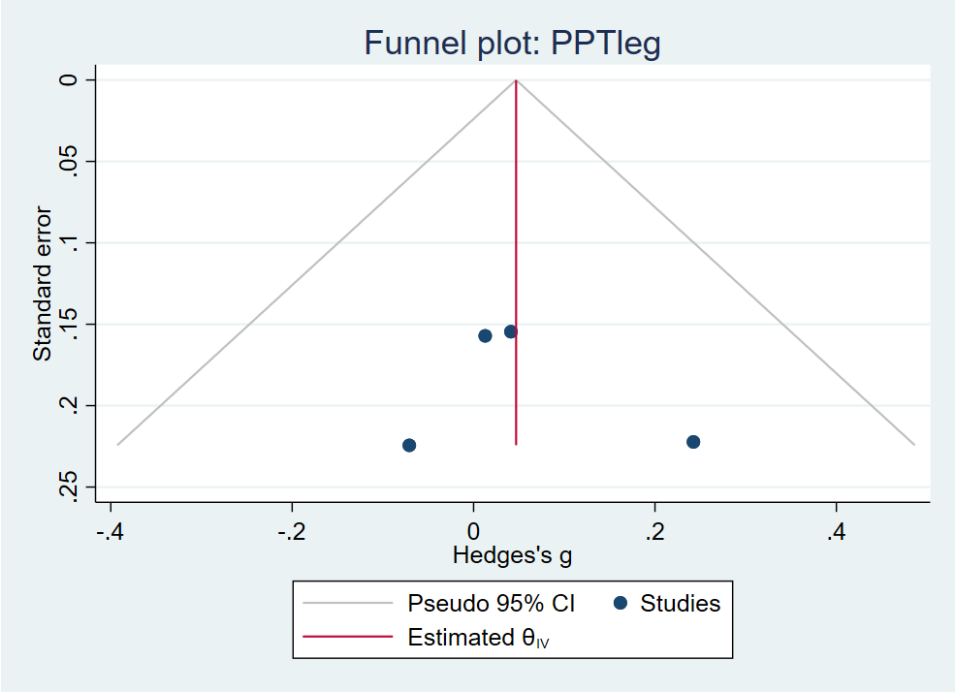
Egger's test: P= 0.1157

FIGURE 1b. Chronic WAD PPTneck – Pressure Pain Thresholds, neck region.



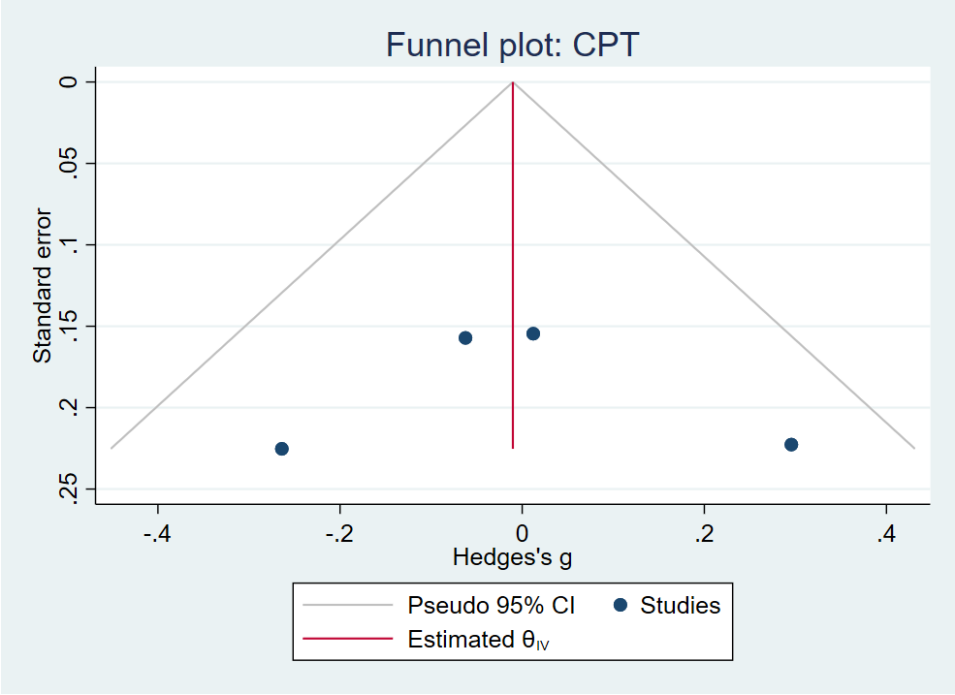
Egger's test: P= 0.9576

FIGURE 1c. Chronic WAD PPTleg – Pressure Pain Thresholds, leg region.



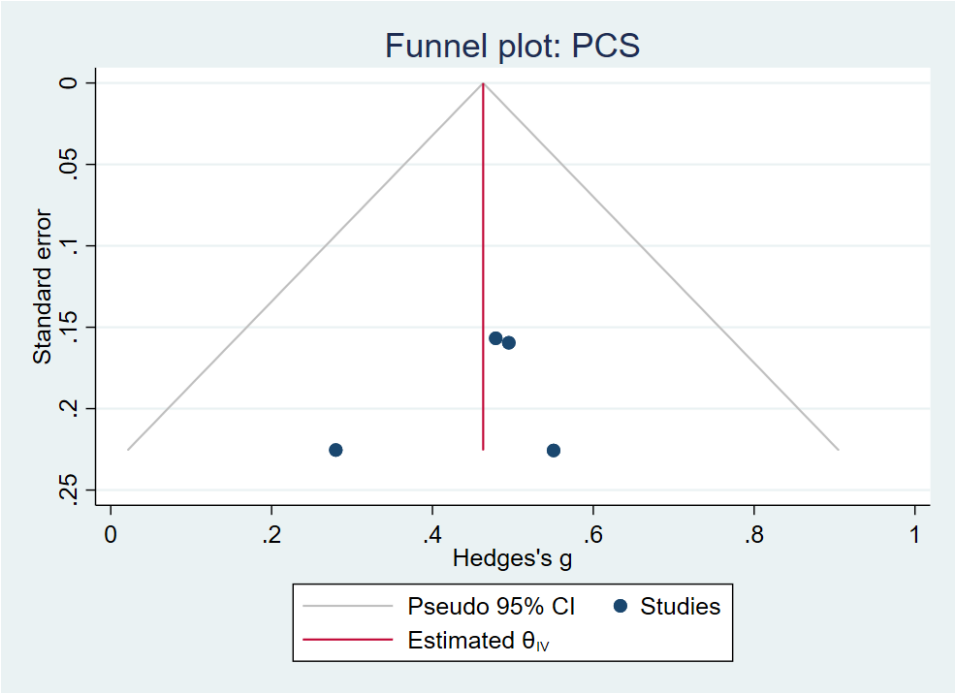
Egger's test: P= 0.7729

FIGURE 1d. Chronic WAD CPTneck – Cold Pain Thresholds, neck region.



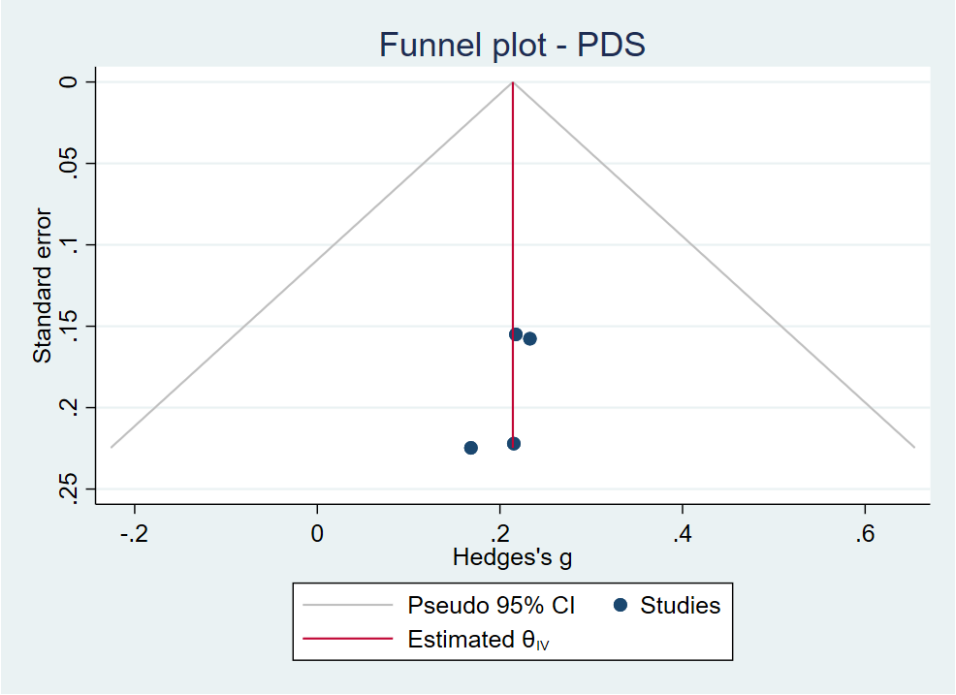
Egger's test: P= 0.8805

FIGURE 1e. Chronic WAD PCS – Pain Catastrophizing Scale.



Egger's test: P= 0.7168

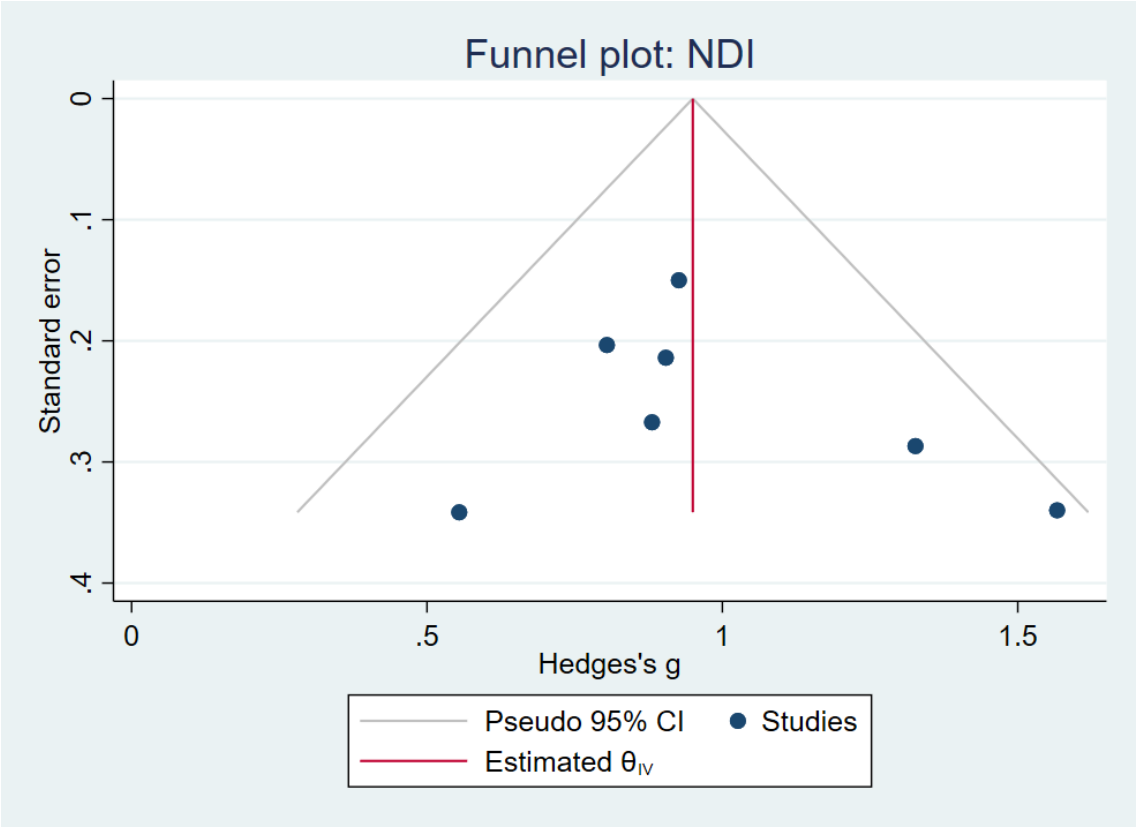
FIGURE 1f. Chronic WAD PDS – Post-traumatic Stress Diagnostic Scale.



Egger's test: P= 0.8633

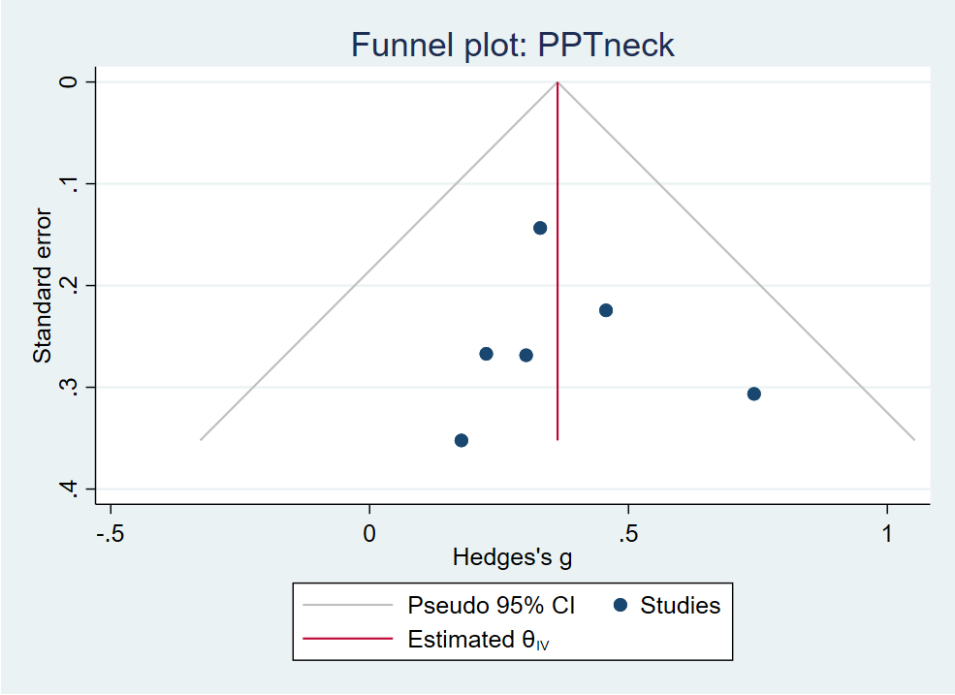
SUPPLEMENTARY FIGURE 2. Funnel plots and Egger's test assessing publication bias within cohorts of acute WAD studies. Abbreviations: CPT: Cold Pain Threshold; GHQ-28: General Health Questionnaire 28; HPT: Heat Pain Threshold; IES: Impact of Events Scale; NDI; Neck Disability Index; PCS: Pain Catastrophizing Scale; PFActS-C: Pictorial Fear of Activities Scale- Cervical Spine; PPT: Pressure Pain Threshold; TSK: Tampa Scale of Kinesiophobia.

FIGURE 2a. Acute WAD NDI – Neck Disability Index.



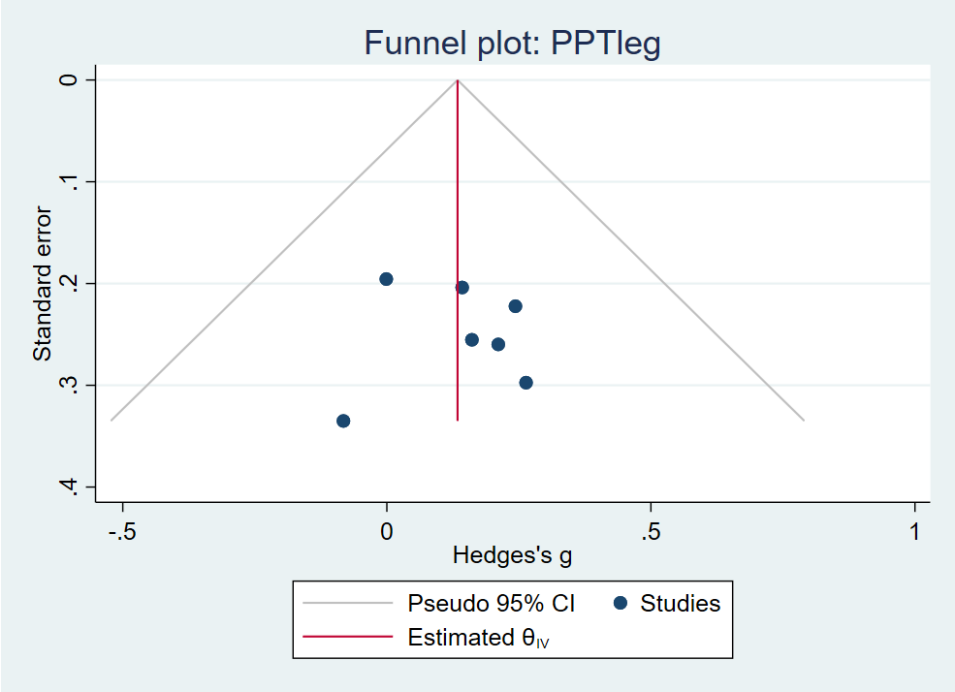
Egger's test: P= 0.4036

FIGURE 2b. Acute WAD PPTneck – Pressure Pain Thresholds, neck region.



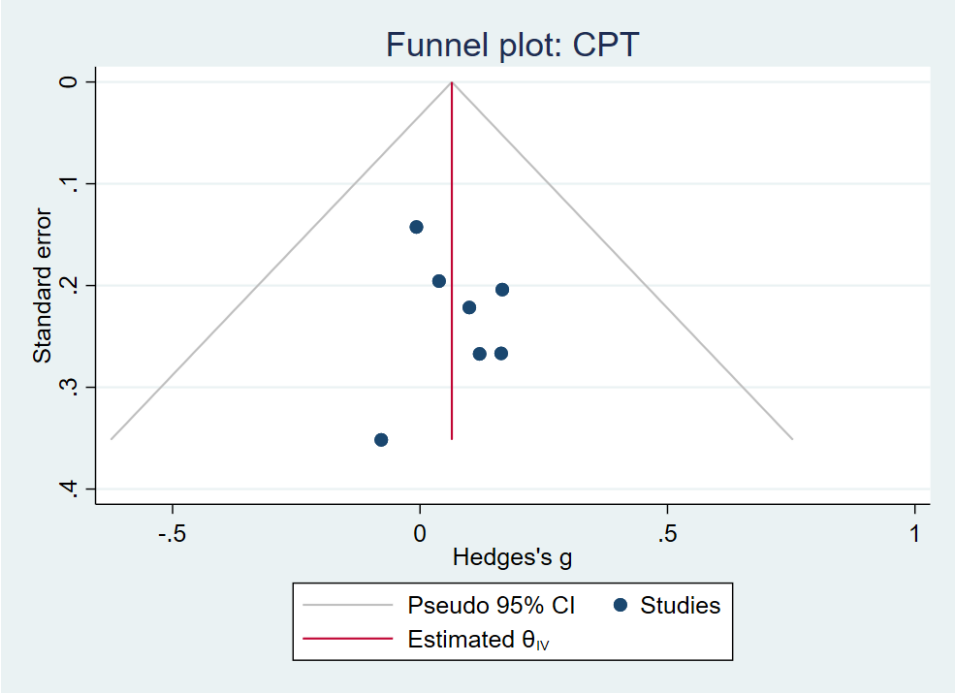
Egger's test: P= 0.8398

FIGURE 2c. Acute WAD PPTleg – Pressure Pain Thresholds, leg region.



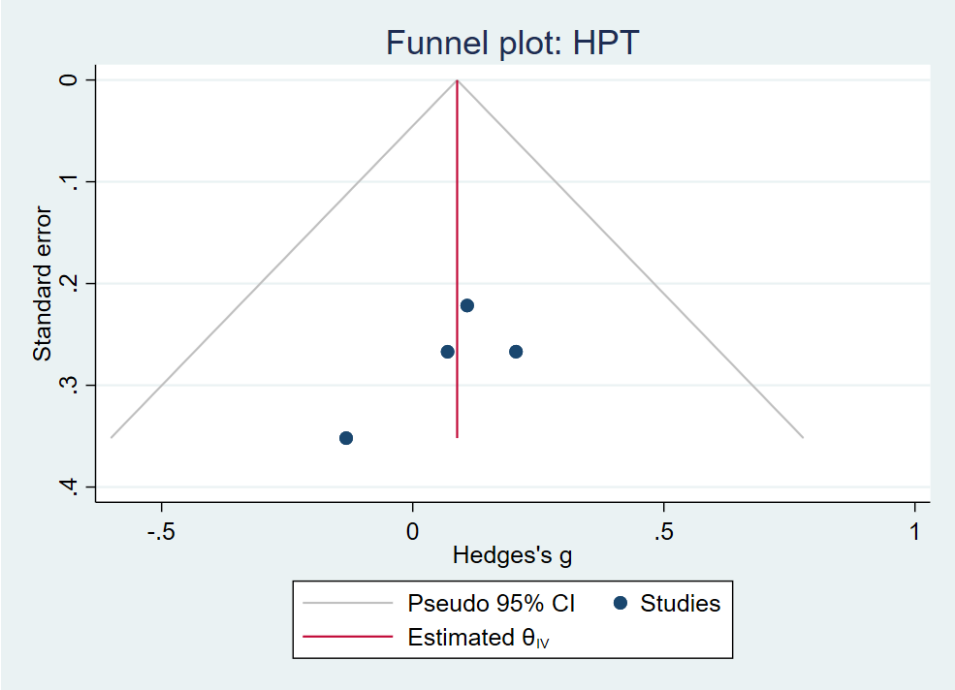
Egger's test: P= 0.9314

FIGURE 2d. Acute WAD CPTneck – Cold Pain Thresholds, neck region.



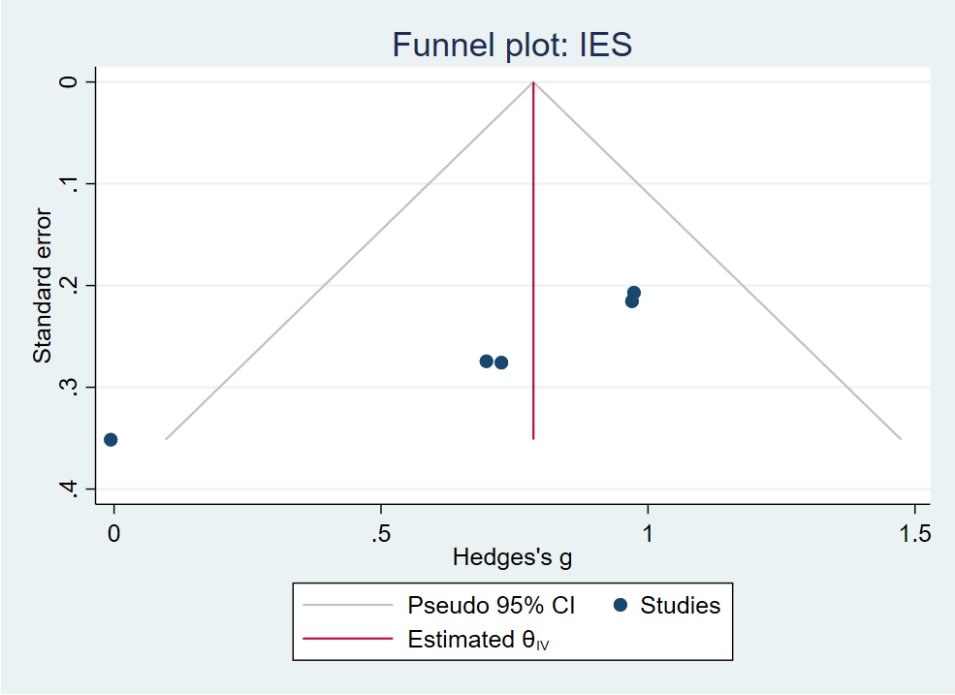
Egger's test: P= 0.7708

FIGURE 2e. Acute WAD HPTneck – Heat Pain Thresholds, neck region.



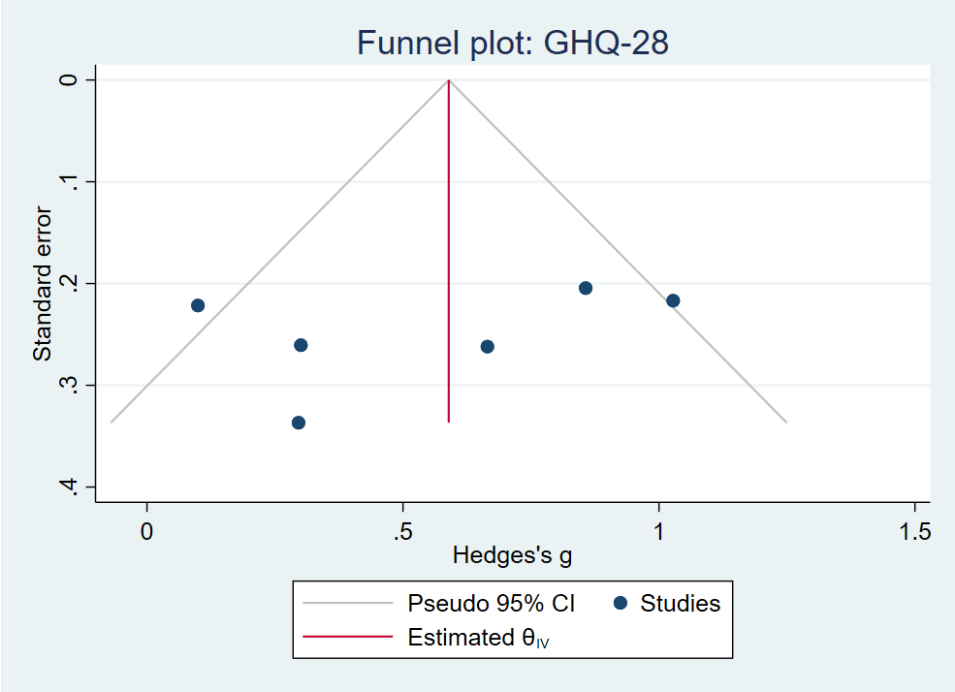
Egger's test: P= 0.5892

FIGURE 2f. Acute WAD IES – Impact Event Scale.



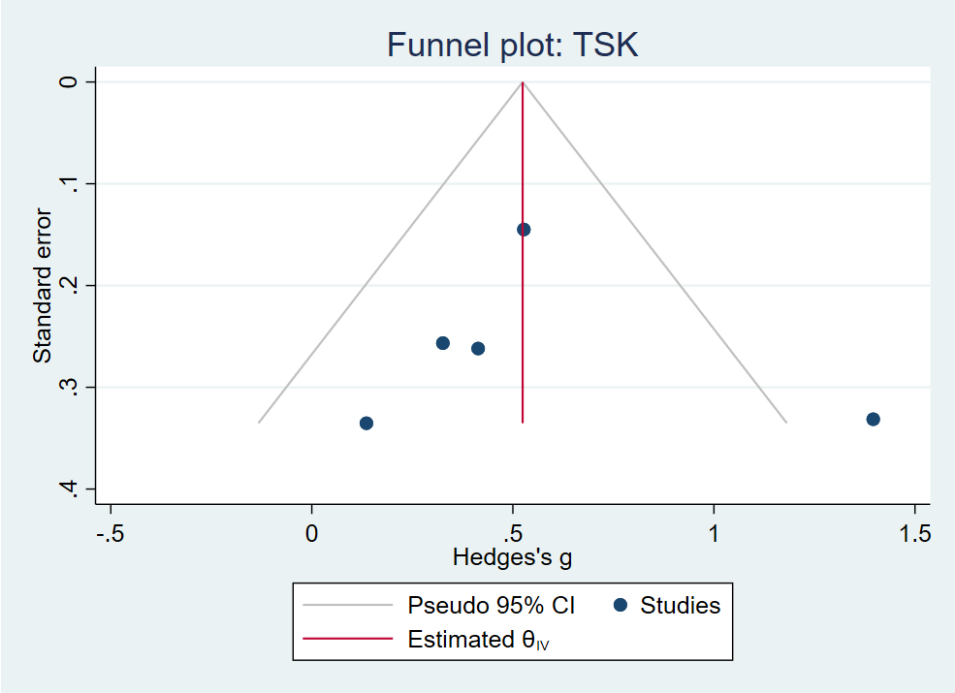
Egger's test: P= 0.0124

FIGURE 2g. Acute WAD GHQ-28 – Global Health Questionnaire.



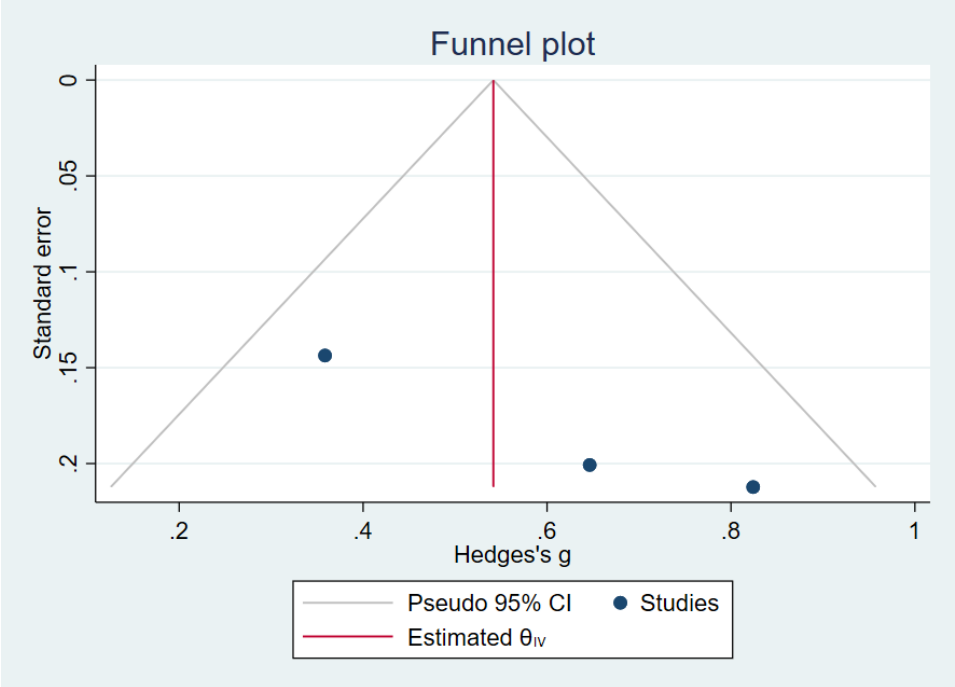
Egger's test: P= 0.0370

FIGURE 2h. Acute WAD TSK – Tampa Scale of Kinesiophobia.



Egger's test: P= 0.7136

FIGURE 2i. Acute WAD PFActS-C– Pictorial Fear of Activity Scale-Cervical.



Egger's test: P= 0.0603

Review paper for Journal of Pain

LONGITUDINAL CHANGES AND ASSOCIATIONS BETWEEN QUANTITATIVE SENSORY TESTING AND PSYCHOLOGICAL FACTORS IN WHIPLASH-ASSOCIATED DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSES-BASED DATA SYNTHESIS

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Running title: Pain mechanisms and psychological factors in WAD.

Keywords: whiplash-associated disorders; neck pain; chronic pain; acute pain; pain mechanisms; psychosocial factors.

ABSTRACT

Whiplash-Associated Disorders (WAD) represent a multifactorial condition often accompanied by altered nociceptive processing and psychological factors. This systematic review on acute and chronic WAD aimed to investigate the relationship between Quantitative Sensory Testing (QST) and psychological factors and quantify whether their trajectories over time follows a similar pattern to disability levels. Eight databases were searched until October 2022. When two prospective studies examined the same QST or psychological variable, data synthesis was performed with random-effects meta-analysis by pooling within-group standardized mean differences from baseline to 3-, 6-, and 12-month follow-ups. From 5,754 studies, 49 comprising 3,825 WAD participants were eligible for the review and 14 for the data synthesis. Altered nociceptive processing in acute and chronic WAD, alongside worse scores on psychological factors, were identified. However, correlations between QST and psychological factors were heterogeneous and inconsistent. Furthermore, disability levels, some QST measures, and psychological factors followed general positive improvement over time, although there were differences in magnitude and temporal changes. These results may indicate that altered psychological factors and increased local pain sensitivity could play an important role in both acute and chronic WAD, although this does not exclude the potential influence of factors not explored in this review.

PERSPECTIVE

Acute WAD show improvements in levels of disability and psychological factors before significant improvements in nociceptive processing are evident. Facilitated nociceptive processing might not be as important as psychological factors in chronic WAD-related disability, which indicates that chronic and acute WAD should not be considered the same entity although there are similarities. Nonetheless, pressure pain thresholds in the neck might be the most appropriate measure to monitor WAD progression.

INTRODUCTION

Persistent spinal pain is the leading cause of years lived with disability worldwide.[1] One musculoskeletal health condition that has proven to be a particular challenge is whiplash-associated disorders (WAD), with a high societal and economic burden on individuals[2] and healthcare systems.[3] One year after whiplash trauma, half of those with acute WAD continue to report disability and pain.[4,5]

After acute whiplash, the neck region is commonly perceived as painful and more sensitive which may be explained by peripheral sensitization as a consequence of tissue injury and inflammation.[6] This response to whiplash injury, although painful is a normal response that subsides within the first months after injury for most cases.[7] However, for those who transition to chronic WAD, research over the last decades has shown manifestations of widespread nociceptive sensitization and increased psychological burden.[8] WAD is now understood as a complex and multifactorial condition,[9] in which altered nociceptive processing and psychological factors play important roles in disability and prognosis.[10,11] In this context, Quantitative Sensory Testing (QST) comprises different psychophysical measures that provide information on the functioning of sensory pathways and nociceptive processing.[12] QST measures are usually classified as static QST when involving threshold determination (e.g., detection, pain, or tolerance thresholds) or dynamic QST when assessing pain modulation at a central level (e.g., conditioned pain modulation or temporal summation).[13] Psychological factors, such as pain-related beliefs, avoidance behaviour, pain catastrophizing, kinesiophobia, anxiety, depression, and posttraumatic stress symptoms, are considered to play an important role in the onset and progression of musculoskeletal pain.[14]

High levels of psychological distress and facilitated nociceptive processing have been observed in individuals in both acute and chronic stages of WAD.[9] However, how

these factors develop and inter-relate over time from the acute injury stage to either recovery or the development of chronic pain and disability is not clear.[15] These data are needed to describe WAD recovery comprehensively. Selecting the most appropriate parameters to monitor in both a clinical and research setting may aid the future development of effective strategies to reduce WAD chronification. Given that disability is considered a comprehensive indicator of WAD recovery,[16] it is warranted to investigate whether the course of QST measures and psychological factors is related to the trajectory of disability. Considering the large amount of scientific WAD-related literature produced in the last years, it seems appropriate to conduct a systematic review and data synthesis to illuminate the relationships between temporal changes in QST and psychological factors and thereby aiding the continuous work towards optimizing rehabilitation strategies (e.g., better personalized treatments) for WAD.

Separately for acute and chronic WAD, the primary aim of this systematic review and data synthesis was to cross-sectionally investigate and estimate the relationship between QST measures and psychological factors. Furthermore, a secondary aim was to quantify the trajectories over time of QST measures and psychological factors and describe whether they follow a similar pattern to disability levels.

METHODS

Study design and registration

This systematic review and data synthesis was conducted following the PRISMA statement[17] and registered with PROSPERO (CRD42016051599).

Study eligibility criteria for the systematic review

Type of studies: Cross-sectional-, case-control-, cohort -studies, and controlled clinical trials evaluating QST alongside psychological variables in participants with WAD were included if full-text available and published in a peer-reviewed journal in English or Spanish languages.

Type of participants: Studies of adults (i.e., ≥18 years old) with acute (≤3 months post-whiplash trauma) or chronic (>3 months post-whiplash trauma) WAD, without considering the specific cause of the whiplash trauma (e.g., motor vehicle accident, sports injury or sudden fall). Mixed populations with composite data were excluded unless data could be obtained for the separate populations.

Type of outcome measures: Studies assessing QST measures and psychological factors measured by standardized and valid methods were included. When multiple studies used the same sample, the publication that provided the most information was included.

Data sources and searches

Eight databases (PubMed, Web of Science, Cochrane, Rehabilitation & Sports Medicine Source, SPORTDiscus with Full Text, APA PsycArticles, PEDro, and Scopus) were searched from inception to 1 October 2022. The search was conducted using four independent blocks referring to the population of interest (WAD), the outcome variables (QST measurements and psychological factors), and the study type (experimental and observational studies). A block related to potential interventions was not included in the search strategy as this review did not intend to assess the effect of any particular treatment. The search strategy of each database is provided in *Supplementary material A*.

In order to identify additional records, a detailed review of the bibliographic references included in the reviewed full-text articles was performed.

Selection of studies

Study selection was conducted independently by two researchers (PBL and MOL). In case of disagreement, a consensus was sought by involving a third researcher (VDG). After screening of study titles and abstracts for potential inclusion, studies identified as potentially relevant were collected for full-text screening and final decision of inclusion or exclusion for review.

Data extraction

Data extraction from the included studies was performed by two authors (PBL and MOL). Study characteristics and outcome data of interest included study design, number of participants, socio-demographic characteristics, QST measures (QST modality and body location), questionnaires related to psychological factors, disability, and other variables measured in each study, such as range of movement or pain visual analog scale. In addition, main results, including correlation or association findings between QST and psychological factors, were extracted when possible.

Risk of bias assessment

Two researchers (PBL and MOL) independently examined the methodological quality of the studies, and in case of disagreement, a third decisive opinion was considered (VDG). For risk of bias assessment, appropriate scales were chosen according to study designs.

The Newcastle-Ottawa scale was used for cross-sectional, case-control, and cohort studies.[18] This scale evaluates seven to eight items categorized into three criteria

(selection, comparability, and exposure or outcome) with a maximum score is 9 (10 in cross-sectional studies). Articles scoring at least 7 were considered of "high quality", a score of 4-6 was considered of "fair quality", and less than 4 was considered of "poor quality". Due to the observational nature of this review, the Newcastle-Ottawa scale for cohort studies was also used to evaluate controlled clinical trials.

Deviations from the PROSPERO protocol

In addition to the pre-registered databases, Scopus, Rehabilitation & Sports Medicine Source, SPORTDiscus, APA PsycArticles, and PEDro databases were also searched to identify any potential missing literature from the search in the initially proposed databases.

The study set out to conduct a synthesis of correlations between QST measures and psychological factors. However, due to the heterogeneity of the QST and psychological variables assessed in the included studies, it was not possible to synthetize correlation coefficients of these variables for neither acute nor chronic WAD. Instead, standardized mean differences of QST measures and psychological factor scores from prospective studies were synthesized in order to qualitatively describe their trajectory over time. In addition, to increase clinical relevance, an analysis of disability was also included. To improve the data reliability, only high-quality studies were included in this data synthesis (i.e., excluding fair- and poor-quality studies).

The PEDro scale was replaced by the Newcastle-Ottawa scale for assessing the risk of bias for prospective cohort studies as the aim of the current study was to describe the trajectory of specific outcome measures over time rather than evaluating treatment effectiveness.

Study eligibility criteria for the data synthesis

Studies that met the selection criteria for the systematic review regarding the type of participants and outcome measures along with a prospective design including repeated measures of QST and psychological variables across a follow-up period were selected for inclusion in the data synthesis. In addition, if available, WAD subgroups within each study were considered as independent cohorts (e.g., treatment arms in clinical trials or subgroups stratified by disability levels in observational studies). Finally, only high-quality studies (i.e., ≥7 in the Newcastle-Ottawa scale) were considered for the data synthesis to increase robustness.

Data synthesis

Differentiations were made between studies addressing acute or chronic WAD when presenting and interpreting the results in the current study. When possible, the mean and standard deviation at baseline and follow-up endpoints from prospective studies (≤3-, 6-, or ≥12-months follow-up) were extracted for QST assessments, psychological factors, and disability scores. For acute WAD, the baseline assessment was considered to be between the period of the whiplash trauma and the start of any potential intervention. For chronic WAD, the baseline assessment was considered the assessment prior to any type of intervention to establish the participants' starting point. If the data were not reported directly in an article, three attempts were made to contact the study authors via email, requesting them to provide the data. If unsuccessful, the median and interquartile range, when available, was extracted and transformed into mean and standard deviation.[19]

When a minimum of two independent cohorts examined the same QST measure or psychological factor, standardized mean differences estimated by Hedges' g were calculated (i.e., the result of subtracting the baseline mean minus the follow-up mean,

divided by the averaged standard deviation weighted by sample size)[20] and pooled with a random-effects meta-analysis following a restricted maximum-likelihood estimation.[21] For ease of interpretation, irrespective of the parameter being assessed, improvements (i.e., lower disability, increased tolerance to noxious stimuli before they become painful, or improved scores in questionnaires assessing psychological factors) were expressed as positive Hedges' *g*. In contrast, a worsening was expressed as negative Hedges' *g*. Absolute value of Hedges' *g* was considered small ($g \geq 0.20$ & <0.50), medium ($g \geq 0.50$ & <0.80) or large ($g \geq 0.80$).[22] Heterogeneity between studies' results was investigated using I^2 statistics with values >50% indicating substantial heterogeneity across studies.[23] Publication bias was examined by using funnel plots and Egger's tests.[24] All analyses were completed using STATA v.16.1 (*StataCorp, College Station, Texas 77845, USA*), and alpha was set at $P<0.05$.

RESULTS

Study Selection

The selection process of the articles is summarized in Figure 1. After removing duplicates, 5,754 records were found. One-hundred and forty-two full-text articles were screened as potential eligible studies resulting in 49 studies being included in the review. The list of records excluded after full-text screening is presented in *Supplementary material B.* No additional records were found within the bibliographic references of the reviewed full-text articles.

Study Characteristics

Table 1 presents the main characteristics of the included articles in this systematic review comprising a total of 3,825 WAD participants (66% female). Seventeen studies included

acute WAD participants,[7,25-40] while 31 studies included chronic WAD participants.[41-71] Fourteen out of 21 studies including follow-ups after a baseline assessment performed repeated assessments of both QST measures and psychological factors.[7,25-28,30,36,37,39,47,54,57,67,69] Further information of selected articles is presented in *Supplementary material C*.

Risk of bias assessment

The total Newcastle-Ottawa score is presented for each study in Table 1. In addition, tables showing the methodological quality assessment results of the retrieved studies by using the Newcastle-Ottawa scale, as well as further details of the risk of bias assessment for each study design, are presented in *Supplementary material D.*

From the 25 case-control studies, 9 studies (36%)were considered to be of high quality,[25,26,37,42,44,55,59,62,71] 11 studies (44%) of fair quality,[7,33,41,43,46,50,58,61,63,70,72] and 5 studies (20%)of poor quality.[29,45,52,60,65]

From the 7 cross-sectional studies, 5 (71%) were considered to be of high quality,[32,48,49,51,56] and 2 studies (29%) of fair quality.[38,64]

From the 7 identified cohort studies, all assessing acute WAD participants, 5 (71%) were considered to be of high quality,[30,31,34-36] and 2 (29%) of fair quality.[28,40]

From the 10 clinical trials, 5 trials (50%) were considered to be of high quality,[27,53,54,66,67] and 5 trials (50%) of fair quality.[39,47,57,68,69]

Quantitative Sensory Testing

All studies evaluated at least one static QST measures (e.g., pressure pain thresholds (PPT), cold pain threshold (CPT), heat pain thresholds (HPT), pressure pain tolerance (PPTol)), while 12 studies (24%) also evaluated dynamic QST measures (e.g.,

conditioned pain modulation (CPM), temporal summation of pain, exercise-induced hypoalgesia).

For studies reporting PPT, 11 out of 13 (85%) of chronic WAD studies[41-44,52,55,59,61,63,65,70] and 3 out of 3 (100%) of acute WAD studies[26,33,37] found lower PPTs in the neck region in WAD participants compared to controls. Among them, only 2 studies did not find differences in a remote PPT leg site in WAD participants compared to controls.[26,52] Regarding prospective studies, 5 out of 7 (71%) in chronic WAD[47,57,67-69] and 7 out of 8 (88%) in acute WAD[26,28,33,36,37,39,40] found an improvement in PPTs over a 3- to 12-month period.

For thermal pain thresholds (i.e., CPT or HPT), 8 out of 9 (89%) of chronic WAD studies[42,43,58,59,61,63,65,70] and 3 out of 3 (100%) of acute WAD studies[33,36,37] found an increased pain sensitivity in WAD participants compared to controls (i.e., CPT at higher temperatures or HPT at lower temperatures). For prospective studies, 2 out of 4 (50%) on chronic WAD[47,67] showed improved CPT and/or HPT at 6 months. However, 5 out of 5 (100%) prospective acute WAD studies[7,27,33,36,37] found no changes in CPT or HPT over time.

For dynamic QST measures, about 50% of chronic WAD studies found a decreased CPM,[44,60,72] higher temporal summation,[41,45,62] or impaired exercise-induced hypoalgesia;[61,62] while for acute WAD studies, 2 out of 2 (100%) found decreased CPM compared to controls.[26,72] The only study presenting repeated-measures of CPM on chronic WAD found an improvement in the CPM just after treatment,[68] which is was not the case for the only prospective study on acute WAD, where no changes was observed over a 6-months follow-up.[26]

Psychological factors

All studies evaluated psychological factors (e.g., posttraumatic stress symptoms, pain catastrophizing, fear-avoidance beliefs, depression, anxiety) via use of questionnaires. A detailed explanation of specific questionnaires for each construct is presented in *Supplementary Material E*.

Almost all (>92%) chronic WAD studies[44,46,49,50,53,58,60-63,65,66,70-72] and 100% of acute WAD studies[25-27,36,43,72] reported worse levels of pain catastrophizing, kinesiophobia, posttraumatic stress symptoms, psychological distress, depression, anxiety, and/or stress symptoms in WAD participants compared to reference values or controls. Furthermore, all prospective studies in chronic-[47,53,67,69] and acute WAD[26,27,37,39,43] found improved levels of psychological factors over time.

Relationship between QST and psychological factors

Only 6 studies (12%) reported correlations between QST measures and psychological factors in chronic[59,65,70,71] and acute WAD participants,[30,32] while no studies provided any correlation or association results between changes in these variables. The pairs of specific QST measures and psychological factors evaluated simultaneously in two or more studies are presented in *Supplementary Material F*.

Small to moderate correlations between different QST measures and psychological factors were found both in chronic WAD (Table 2A) and acute WAD (Table 2B) studies, demonstrating that on some occasions, increased pain sensitivity was related to higher levels of psychological distress or altered cognitions. Specifically for chronic WAD studies, Sterling et al. found moderate positive correlations between CPT at the cervical spine and Pain Catastrophizing Scale scores.[65] Likewise, Wallin et al. reported positive correlations between CPT at the cervical spine and anxiety, depression, stress, catastrophizing, pain self-efficacy, and fear-avoidance beliefs.[70] Additionally, they

reported negative correlations between PPT and HPT at the cervical spine and anxiety, depression, stress, catastrophizing, pain self-efficacy, and fear-avoidance beliefs.[70] Furthermore, Lenoir et al. found moderate negative correlations between electrical pain thresholds at the median nerve and scores in the magnification subscale of the Pain Catastrophizing Scale and the Pain Anxiety Symptoms Scale.[71] In contrast, Scott et al. found no correlation between Sort-Form State-Trait Anxiety Inventory scores and any QST measure (PPT, CPT, HPT, or punctate hyperalgesia).[59]

For acute WAD, Rivest et al. found a moderate positive correlation between Pain Catastrophizing Scale scores and CPT at the cervical spine and a moderate negative correlation between catastrophizing thoughts and PPT at the cervical spine in a male subsample.[32] Similarly, Pedler et al. reported positive correlations between CPT at the cervical spine and kinesiophobia, pain coping, and posttraumatic stress disorder symptoms, while the same psychological factors were negatively correlated with PPT at the cervical spine.[30]

Data synthesis

From 21 prospective studies, 9 high-quality prospective studies were included in the meta-analyses for the data synthesis,[7,25-27,30,36,37,54,67] accounting for 14 individual cohorts. Five studies were excluded due to being rated as fair-quality[28,39,47,57,69] and 7 due to not reporting results of repeated measurements.[29,31,33-35,40,53] During this process, 5 authors were contacted to retrieve additional information that could not be extracted from a total of 9 articles. Three out of these 5 authors provided additional data corresponding to 6 articles.

Figure 2 (chronic WAD cohorts) and figure 3 (acute WAD cohorts) synthesize the pooled Hedges' *g* for levels of disability, QST measures, and psychological factors at 3-, 6-, and 12-months post-whiplash trauma compared to baseline. Individual forest plots for

each variable and I^2 values at each time point can be found in supplementary materials for both chronic WAD (*Supplementary material G*: Figures 1a-1g) and acute WAD (*Supplementary material G*: Figures 2a-2k) cohorts. *Supplementary material H* contains individual funnel plots for each variable.

Two high-quality studies accounting for 4 individual cohorts and including 250 chronic WAD participants performed follow-ups of QST and psychological factors.[54,67] The pooled Hedges' *g*of disability levels since baseline showed small to moderate improvement in disability at 3-months (g=0.50; P<0.01), 6-months (g=0.46; P<0.01), and 12-months (g=0.55; P<0.01) (Figure 2a). For QST measures (Figure 2b), only PPT at the neck region showed small improvements at 3-months (g=0.27; P<0.01), 6-months (g=0.26; P=0.02), and 12-months (g=0.28; P<0.01); while there were no significant effects (P<0.11) at any time point for PPT at the leg or CPT at the neck regions. Regarding psychological factors (Figure 2c), a small to moderate improvement in the Pain Catastrophizing Scale scores were found at 3-months (g=0.46; P<0.01), 6-months (g=0.45; P<0.01), and 12-months (g=0.59; P<0.01); and a small improvement in the Posttraumatic Diagnostic Scale scores were found at 3-months (g=0.21; P=0.02), 6-months (g=0.26; P<0.01), and 12-months (g=0.33; P<0.01). Heterogeneity was low for all variables (i.e., I^2 values <50%). No publication bias was detected after examining funnel plots and Egger's tests.

Seven high-quality studies accounting for 4 individual cohorts and including 394 acute WAD participants performed follow-ups of QST measures and psychological factors.[7,25-27,30,36,37] The pooled Hedges' *g* of disability levels since baseline showed large improvements in disability at 3 months (g=0.95; P<0.01), 6 months (g=1.33; P<0.01), and 12 months (g=1.24; P<0.01) (Figure 3a). For QST measures (Figure 3b), pooled data showed a small improvement of PPT in the neck region at 3-months (g=0.36; P<0.01)

and 6-months (g=0.42; P<0.01) and a large increase at 12-months (g=0.89; P<0.01). However, PPT in the leg region only showed a small improvement at 6-months (g=0.20; P=0.05) that was not maintained at 12-months (g=0.15; P=0.15). For thermal thresholds, both CPT and HPT in the neck region showed a small improvement at 12-months (CPT: g=0.32, HPT: g=0.39; P<0.05). Regarding psychological factors (Figure 3c), a moderate to large improvements in the Impact Event Scale scores, the Global Health Questionnaire-28, the Tampa Scale of Kinesiophobia, and the Pictorial Fear of Activities Scale- Cervical Spine were found at 3-months (IES: g=0.75, GHQ-28: g=0.68, TSK: g=0.54, PFActS-C: g=0.58; P<0.01), 6-months (IES: g=0.73, GHQ-28: g=0.82, TSK: g=0.69, PFActS-C: g=0.76; P<0.05), and 12-months (IES: g=0.90, GHQ-28: g=0.89, TSK: g=0.53, PFActS-C: g=0.72; P<0.01). I^2 values indicated substantial heterogeneity across studies for the NDI and the TSK at 3-months (NDI: I^2=64%; TSK: I^2=59%) and 6-months (NDI: I^2=79%; TSK: I^2=81%). No publication bias was detected after examining funnel plots and Egger's tests.

DISCUSSION

This systematic review included 49 studies, comprising 1,493 chronic and 2,332 acute WAD participants, that investigated QST measures alongside psychological factors. Data synthesis of 9 studies (comprising 4 chronic and 9 acute independent WAD cohorts) indicated that despite chronicity, levels of disability, some QST measures, and psychological factors of participants with WAD showed an overall positive change over time. Nevertheless, these variables do not follow the exact same trajectory over time, as they differ in temporality and magnitude, while psychological factors outweigh altered nociception in explaining disability in chronic WAD. Chronic WAD participants displayed a small to moderate improvement in levels of disability and psychological

factors at 3-months compared to baseline. Furthermore, these improvements were sustained at 6- and 12-months. In contrast, acute WAD participants showed a large reduction in disability levels and a moderate to a large improvement in psychological factors at 3-months that slightly continued improving at 6- and 12-months. However, for QST measures in acute WAD, only a small improvement for PPT in the neck region was found at 3-months together with larger increases in the long term (>12 months). Additionally, PPT measured in the leg region and thermal pain thresholds (i.e., CPT and HPT) in the neck region revealed a small improvement at 6-months and 12-months in participants with acute WAD.

Relationship between QST and psychological factors

The objective of this review was to quantitatively assess the relationship between QST measures and psychological factors through a meta-analysis. However, despite the large number of studies on the subject, only 5 conducted correlational analyses between QST and psychological variables.[30,32,59,65,70] Unfortunately, none of those studies considered the same variables and therefore, could not be included in meta-analyses. Additionally, no prospective study explored the relationship between changes in QST and psychological factors. However, Kamper et al. reported a negative correlation between changes in neck pain and PPT over the neck,[28] which indicated that a reduction in the neck pain intensity was associated with an increase in neck PPT (i.e., decreased sensitivity). Such association could indicate that the recovery experienced by the proportion of acute WAD cases during the first months after the whiplash trauma may reflect the natural course of recovery and tissue healing,[26,37] but this would not be the case for those WAD cases with persistent pain, where pain sensitivity remained altered.

There is compelling evidence that chronic musculoskeletal conditions such as low back, knee, or non-specific neck pain, are often accompanied by facilitated nociceptive processing (e.g., reduced PPT) and psychological distress (e.g., pain catastrophizing, posttraumatic stress symptoms).[73-75] A recent meta-analysis evaluating the relationship between QST measures and psychological factors in people with peripheral joint pain, found that PPT is the only QST measure that is consistently associated with psychological factors such as pain catastrophizing and depression.[76]. In our review, 3 studies in chronic-[65,70,71] and 2 in acute WAD[30,32] found moderate correlations between low pain thresholds (high thresholds in case of cold-based stimuli, e.g., CPT) and levels of psychological distress. However, these results were inconsistent. Scott et al. found no correlation between PPT, CPT, or HPT and anxiety;[59] and Lenoir et al. found no correlation between temporal summation or CPM and posttraumatic stress symptoms, pain catastrophizing, or anxiety responses to pain.[71] Similarly, Rivest et al. found no correlation between PPT and CPT and catastrophizing thoughts in a subgroup of women with acute WAD.[32] Overall, these findings indicate that the coexistence of psychological factors and a facilitated nociceptive system are common in those with WAD, although such a relationship may not be linear. Considering the impracticality of using in-depth QST in clinical practice, self-reported questionnaires such as the Central Sensitization Inventory (CSI) were developed as a clinical proxy for assessing facilitated nociception. However, a recent meta-analysis has shown that the CSI weakly correlates (at best) with QST measures. Instead, CSI strongly correlates with psychological factors;[77] therefore, it could be used to assess cognitive and emotional components in WAD.[51]

Acute WAD versus Chronic WAD versus healthy controls

The present findings showed significant baseline differences in all variables between acute WAD participants and healthy controls in almost all studies, supporting the tenet that altered nociceptive processing and increased psychological distress is present soon after a whiplash trauma.[9,37,78] However, due to the paucity of studies that have investigated participants for preexisting alterations in nociceptive processing and psychological factors, it is not possible to determine if this may have influenced the results of the previous studies on whiplash. In contrast to the findings for acute WAD, the results for chronic WAD were not consistent across QST measures inferring the heterogenous presence of altered nociceptive processing in this population. In other words, while all chronic WAD studies revealed significantly worse scores in all psychological variables for WAD participants compared with healthy controls, only some static QST measures such as PPT or CPT showed consistent between-group differences.[42,43,58,59,61,65] As opposed to acute cases, these findings in chronic WAD participants could potentially indicate that psychological factors might outweigh altered nociceptive processing in explaining the persistence of pain and disability.[79,80] After all, chronic WAD cases represent a subsample of people with an originally acute WAD who have developed persistent pain and disability and high levels of psychological distress over time.[34] However, this discrepancy between chronic and acute WAD for QST variables may be partially attributed to the heterogeneous characteristics of chronic WAD samples. Inclusion criteria for chronic WAD studies were mainly based on reported pain and disability for more than 3 months and meeting the Quebec Task Force criteria for Grades I-III.[81] Despite Grade II, (pain, stiffness, or increased tenderness in the cervical region and musculoskeletal signs such as reduced range of motion or tender points on palpation)[81], being predominantly used as an inclusion criterion, this classification has been the subject of debate due to its lack of discriminative ability.[82] Additionally, data

synthesis of acute WAD studies shows that improvements in disability, QST measures, and psychological factors continue to occur beyond 3 and 6 months.[25,26,37,39] Therefore, these observed long-term improvements may exert an additive or a confounding effect in controlled clinical trials with chronic WAD, which would call into question whether WAD studies should recruit and combine data from participants who had experienced a whiplash trauma 3 months and several years ago. At least, it is reasonable to consider symptom duration as a potential confounder and introduce it as a covariate in the statistical analyses of chronic WAD studies, as several studies have already done regarding age and sex.[31,34,36,56]

Interestingly, data synthesis of acute WAD studies demonstrated that PPT measured in the neck region appears to improve earlier and more significantly than PPT in the leg and thermal pain thresholds in the neck region. Remote body regions normalizing their sensitivity to noxious stimulation later than the neck region could indicate that altered nociceptive processing in the nervous system might be influenced or maintained by factors different from those strictly related to tissue healing.[26,37] For example, posttraumatic stress symptoms are commonly reported by whiplash injured patients ,[83,84] and are associated with persistent neck pain.[85] It has been suggested that psychological factors acting as persistent stressors during the acute phase could contribute to a widespread hypersensitivity to noxious stimuli via immune-mediated pro-inflammatory mechanisms.[86,87] Another proposed hypothesis is that the initial inflammatory response in the neck tissues resolves first,[6] leaving central mechanisms as the primary driver of widespread hyperalgesia after this.

Methodological quality

To improve the robustness of the current findings, the data synthesis was based on high-quality prospective studies, but this unfortunately also decreased the number of prospective studies that could be included. Nonetheless, although most of the studies in the systematic review were considered fair to high quality, there were systematic biases that may lead to a distortion of interpretation and generalizability of results.[88] Moreover, almost all selected observational studies did not present the flow of screened participants from the start of the study. Information on the participant flow would allow for determining to what extent the selected samples are representative of the WAD population as a whole and ensure that self-selection bias is not occurring in a particular sub-sample of people with WAD.

Future observational studies in WAD population should follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations,[89] paying particular attention to reporting sample size calculations, presenting clear selection criteria for the WAD population, specifying the methods and locations of recruitment, and reporting the participant selection process, including reasons for non-participation. Case-control studies should perform matching, at least by sex and age, clearly presenting the criteria by which a control is considered a healthy participant; and blind assessors concerning group allocation. Prospective studies should establish a follow-up period sufficiently long to allow for changes not inherent to the measurement error of the instruments.

Limitations

It was not possible to perform meta-analyses of correlational analyses, and this is a limitation of our review. Furthermore, the current results only represented studies assessing QST measures and psychological factors simultaneously. This was also the case for the results regarding the course of disability. Taken together, these results should be interpreted with caution as they cannot account for potential studies that did not simultaneously assess both QST measures and psychological factors. Second, although this review did not aim to analyze the effects of any interventions, the variety and heterogeneity of treatments used (i.e., controlled intervention in clinical trials or unconstrained intervention in prospective non-controlled studies) may have influenced the trajectory of the QST measures or psychological factors over time. However, the lack of substantial heterogeneity across studies (i.e., I^2 values <50%) suggests that similar trajectories were followed by WAD participants despite the different treatment options used in the included studies. Nevertheless, substantial heterogeneity was found in levels of disability for acute WAD, which could be explained by the larger standardized mean differences found in two small studies.[26,39] Finally, some assessment procedures, such as the brachial plexus provocation test (BPPT) or the nociceptive flexion reflex (NFR), were considered as "other variables" in the current review, whereas another recent review on WAD included them as QST variables.[90] Despite the BPPT and NFR might be useful for assessing participants in the clinical setting,[91,92] these tests do not comply with using a calibrated stimulus and measuring the subjective perception of thresholds, which are characteristics of QST.[93]

Conclusion

This systematic review revealed a paucity of studies investigating correlations between QST measures and psychological factors in participants with WAD. Nevertheless, based on cross-sectional assessments, it can be concluded that facilitated nociceptive processing occurs alongside increased psychological distress (e.g., catastrophizing, or kinesiophobia) in both acute and chronic WAD compared to healthy controls. However, some QST measures do not provide highly consistent results in chronic WAD, which might be due to the considerable heterogeneity of chronic WAD samples. Furthermore, levels of disability, QST measures, and psychological factors showed a general positive change over time in both acute and chronic WAD, although they differ in temporality and magnitude. Finally, given that QST measures are more consistently affected in acute WAD, facilitated nociceptive processing might not be as important as psychological factors in chronic WAD, which indicates that chronic and acute WAD should not be considered the same entity.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

FIGURE 1. PRISMA Flow diagram describing the literature search procedure.

FIGURE 2. Summary plot of Hedges' g of variables pooled in the data synthesis for the cohorts with chronic whiplash-associated disorders. Error bars represent the confidence interval at 95% of Hedges' g. Positive values represent improvements in the investigated variable (e.g., lower disability, increased tolerance to noxious stimuli, or lower scores in questionnaires assessing psychological factors) from baseline values. Hedges' g: small ($\geq$ 0.2 g <0.5), medium ($\geq$ 0.5 g <0.8) or large (g $\geq$ 0.8).

FIGURE 3. Summary plot of Hedges' g of variables pooled in the data synthesis for the cohorts with acute whiplash-associated disorders. Error bars represent the confidence interval at 95% of Hedges' g. Positive effect sizes values represent improvements in the investigated variable (e.g., lower disability, increased tolerance to noxious stimuli, or lower scores in questionnaires assessing psychological factors) from baseline values. Hedges' g: small ($\geq$ 0.2 g <0.5), medium ($\geq$ 0.5 g <0.8) or large (g $\geq$ 0.8).

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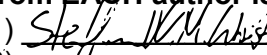
Signature (1)  Print Name: Steffan Wittrup McPhee Christensen Date: 18/11-2022
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Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-5
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.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl. A
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.	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.	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.	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.	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.	6-7
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.	7-8
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)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	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.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a 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.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Suppl. B
Study characteristics	17	Cite each included study and present its characteristics.	9-10 & Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10-11 & Suppl. C
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.	Suppl. E
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	17-18
	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.	Figure 2 & Figure 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	17-18
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	18-22
	23b	Discuss any limitations of the evidence included in the review.	23
	23c	Discuss any limitations of the review processes used.	23
	23d	Discuss implications of the results for practice, policy, and future research.	22-24
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	24
Competing interests	26	Declare any competing interests of review authors.	24
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.	-

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