Quantitative sensory testing and association with cervical spine radiculopathy disability: Systematic review.

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Contribution of paper.

- First systematic review investigating the association between quantitative sensory testing (QST) and disability in adults with cervical spine radiculopathy
- From four studies, there was no association between QST and disability
- There is a need to complete prospective studies investigating this relationship to enhance our understanding of this condition.

Abstract

Background

Cervical spine radiculopathy (CSR) is a complex clinical presentation that can have negative impacts on a person's physical and mental health and wellbeing and engagement with activities of daily living. Somatosensory phenotypes of CSR can be assessed through quantitative sensory testing (QST). However, to date no systematic review has been undertaken to determine the association between QST and disability in individuals with CSR. Accordingly, this present study sets out to investigate this.

Design

A systematic review was conducted including searches of PubMed (MEDLINE), EMBASE and CINHAL from inception to 22 March 2020. Quantitative studies investigating CSR populations with QST measurements and association with disability were included. One reviewer conducted the search strategy. Two reviewers independently assessed eligibility of all search results and completed methodological quality assessment using a modified Downs and Black checklist. Data were analysed narratively.

Results

Four studies were eligible for inclusion in the final review. The quality of these studies was high. There were no statistically significant associations between QST and disability among people with CSR.

Conclusions

This systematic review fulfilled the aim of investigating the association between QST and disability in people with CSR. From the four studies included for review, no study reported an association. Future research is required to standardise CSR diagnostic criteria. QST protocols and further prospective studies involving patients are likely to enhance our understanding of the clinical presentation of CSR. Key words

Cervical spine radiculopathy; Quantitative sensory testing; Disability; Systematic review

Cervical spine radiculopathy (CSR) prevalence values range between 1.2 to 5.8 per 1000 people and incidence rates range between 0.8 and 1.8 per 1,000 person-years [(1-5)]. CSR

is known to have negative impacts for individuals, families, societies and healthcare systems [6-8]. It has a complex clinical presentation with variable phenotype expression [9, 10], resulting in a substantial challenge for clinicians to assess and manage optimally [7, 11]. CSR is often associated with multiple overlapping co-morbidities including (but not limited too) psychosocial factors such as depression and anxiety symptoms [12-14], There is also an association between sedentary lifestyle, CSR and challenges performing daily activities [15, 16]. These factors may result in increased pain and disability for individuals. Disability, as defined by the International Classification of Functioning, Disability and Health (ICF), is an umbrella term for impairments (for example limb movement); activity limitations (for example walking) and/or participation restrictions (for example engagement in employment) [17]. Disability refers to the negative aspects of the interaction between an individual (with a health condition) and their contextual factors (environmental and personal) [17].

CSR is defined as a mechanical block to a spinal nerve or root through compression, or indirect interruption of nutrition or blood supply to a nerve axon or its root [18]. In clinical practice there is no definitive reference test to diagnose CSR [19, 20], nevertheless, clinicians will typically complete a detailed subjective assessment listening to the patient narrative around symptom description, location and possible psychosocial impacts to their activities of daily living [11, 21, 22]. Physical assessment can determine whether there is a loss of sensory, motor function and/or any activity impairments of disability, which may or may not be associated with complaints of pain by the individual [18]. Subjective sensations of paraesthesia, hyperaesthesia, dysaesthesia and/or allodynia, confirmed objectively by neurological examination, quantitative sensory testing (QST) and/or electrodiagnostic testing, occurring in the distribution of a spinal nerve are typical [22-25].

Identifying mechanism-based phenotypes of neuropathic pain states (including spinal radiculopathy) may optimise the diagnosis classification and subsequent management strategies [26-28]. There is evidence suggesting lower thresholds to thermal, mechanical and vibration detection for individuals with neuropathic pain presentations such as peripheral neuropathy (for example diabetes), carpal tunnel syndrome [29] and other spinal musculoskeletal disorders, for example cervical spine pain [30]. Furthermore, lower threshold to thermal and mechanical pain detection thresholds are also reported [31].

The complexity in the classification of pain is widely reported [32-37], which impacts the clinical assessment of pain conditions [32, 35, 38]. Clinical impressions (diagnosis) and prognosis formulation is based on signs and symptoms and, where available, the use of imaging and electrophysical testing (for example nerve conduction tests). However, this provides limited insight to a patient's underlying pain mechanisms, sensory experience, and daily activities participation. Identifying mechanism-based phenotypes in people with CSR may enhance the diagnosis classification and subsequently enrich our understanding of this complex presentation [26, 39-41]. QST provides enhanced understanding of sensory phenotypes of underlying pain mechanisms and is well validated [42-44]. This form of psychophysical testing procedure provides unique information about the functional status (hypo/hypersensitivity) of a person's somatosensory system. It is reported that hyper or hypo somatosensory function has associations with disability in musculoskeletal conditions (for example spinal pain) [45] and peripheral neuropathy presentations (for example carpal tunnel) [46]. This form of psychophysical testing has promising potential to improve CSR diagnosis (and other peripheral neuropathy presentations) by identifying specific mechanisms of pain and sensory experiences alongside our clinical reasoning frameworks [26, 44, 45]. To date, no systematic review has been conducted to investigate the possible association between disability and cervical spine radiculopathy. An enhanced understanding of the relationship between somatosensory function, sensitivity and disability could further support clinicians identifying phenotypic sub-groups, monitor symptom progression and subsequently enhance prognosis formulation. Accordingly, the primary aim of this review was to investigate the association between QST outcomes and disability in adults with CSR.

Methods

The systematic review was registered with PROSPERO review database (Ref: CRD42018103878). The PRISMA guidelines of reporting [47] were followed.

Search Strategy

One reviewer (MM) conducted the systematic search of electronic databases PubMed (MEDLINE), EMBASE and CINAHL from inception to March 22nd 2020. Figure 1 reports an example of the search strategy used in MEDLINE. Hand searches of reference lists and contacting lead authors of included articles was completed to determine if there were any pending article publications in this area or unpublished work identified. An unpublished (grey) literature search and trial registry search was completed (Search details available on request). The following databases were searched: OpenGrey, ClinicalTrials.gov, NIHR portfolio and WHO International Clinical Trials Registry Platform.

Eligibility Criteria

Studies were included if they met the following criteria:

a) Adult participants (over 18 years) with a diagnosis of CSR. Diagnosis was made by using a modified version of the International Association of Pain [20] radiculopathy and radicular pain classifications [23] detailed below (Figure 2).

b) Validated functional status or disability measure.

c) One or more components of the German Research Network on Neuropathic Pain (DFNS) QST testing protocol [42, 48]

d) Studies must be either case control, cross-sectional, or cohort study design

e) Published in English (or the availability of an English translation).

No restriction on the type of setting or publication date was applied to potential studies. Studies were excluded if the study population of CSR were related to systemic pathology, radiculitis, post-surgery, metabolic causes (for example diabetes, pre-diabetes), fracture, myelopathy or upper motor neurone pathology.

Study Identification

Based on the eligibility criteria, two reviewers independently assessed titles and abstracts of all search results (MM, MT). From this, full-text studies from potentially eligible studies were retrieved and independent assessment was completed by the same two reviewers. Final eligibility was based on a full-text assessment. Assessment of reliability (between-reviewer) for the eligibility criteria was performed for a random sample of 10 potentially eligible papers using a weighted Kappa statistic [49]. The between-reviewer agreement ranged from 90-100% across the criteria, with 90% (Kappa: 0.80) for overall agreement on eligibility of individual papers (available on request). Where there were any disagreements an experienced researcher (JV) acted as adjudicator. All disagreements were resolved through discussion and consensus between MM and MT.

Data Extraction

Data were extracted into a pre-defined data extraction table independently by two reviewers (MM, JV). Where there were any disagreements an experienced researcher acted as adjudicator (MT). Consensus was achieved on all data extraction points through discussion between MM and JV. Data extracted included: study characteristics, participants (number, age and gender), population setting, CSR definition, disability measure and QST components and outcomes. Corresponding authors were contacted to seek clarification or to request additional information on the data sets.

Quality Assessment

Two authors (MM, MT) independently assessed the quality of each included study using a modified Downs and Black checklist [36]. This tool is reported to be a valid and a reliable critical appraisal tool to assess methodological quality of non-randomised control studies [50], which was the predominant study design amongst our eligible papers. Any disagreement between reviewers in respect of study eligibility, data extraction or critical appraisal was firstly discussed between the two reviewers (MM and MT). If a consensus could not be reached a third reviewer (JV) acted as adjudicator.

Criterion 4, 8, 13 and 14 from the Downs and Black assessment tool were removed as our research question was not addressing interventions or their adverse effects. Criteria 15 was removed as the research question did not require blinding of assessors to an intervention. Item 19 was removed as compliance was not an objective of the research. Items 23 and 24 were removed from assessment of all studies as randomisation was not indicated in the study designs.

Data Analysis

Heterogeneity of the included studies was assessed by two reviewers (MM, JV) through examination of the data extraction table. This demonstrated heterogeneity with CSR diagnostic criteria, disability outcome measures and QST data presentation. It was therefore inappropriate to conduct a meta-analysis. Accordingly, a narrative (descriptive) analysis was performed.

Results

Search Strategy

One thousand nine hundred thirty-nine and 57 records were retrieved from the electronic data base and grey literature searching, respectively. One thousand eight hundred and thirty-four records were subsequently screened when duplicate records were removed. Thirty-two full text articles were retrieved and assessed for eligibility. A total of six studies met the inclusion criteria (Figure 3). However, one study was excluded as on further investigation the population did not match our inclusion criteria [51]. Two studies samples were recruited for concurrent studies [30, 52]. The characteristics and data collection methods were identical across both studies. Consequently, one [52] was excluded following discussion and agreement across all authors (MM, JV, MT). Accordingly, four studies were included for review [30, 31, 53, 54]

Study Characteristics

A total of 95 subjects were sampled across the included studies. The characteristics of the four included studies are presented in Table 1. Three studies were cross sectional design [31, 53, 54] and one study was an age matched cohort design [30]. One study sampled from primary practice through media advertisement (newspaper, social media) [53] and three studies from specific tertiary referral pain clinics through convenience sampling [30, 31, 54]. Two studies used the Neck Disability Index (NDI) [30, 53], one study used the Pain Disability Index (PDI) [54], and the Disability of Arm, Shoulder and Hand (DASH) was used by one study [31] to measure disability.

Quality Assessment (Risk of bias)

The scoring between the two reviewers of the included studies (Supplementary table 1) had an agreement rate of 92% (92/100). Disagreement on scores were with items 25 and 26 and final agreement was reached on all items after discussion.

Three studies scored 95% and one study scored (90%).

Definition of Cervical Spine Radiculopathy (CSR)

One study used self-reported pain and/or other sensory or motor dysfunction symptoms below the elbow to confirm radiculopathy [53]. Two studies combined clinical assessment findings (diminished/absent reflexes, myotomal weakness and/or sensory deficits to touch and vibration) and confirmed C6 or C7 nerve root compromise on imaging [30,31]. One study also used this criteria but a positive upper limb neurodynamic test was included in their confirmation of radiculopathy [31]. One study used self-reported cervical spine pain with radiating pain below the elbow [54].

Somatosensory phenotypes and pain sensitivity measurements

One study [30] used the standardised DFNS [42] Quantitative Sensory Testing (QST) protocol. The QST protocol included warm and cold detection thresholds (CDT,WDT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration detection threshold (VDT) and pressure pain threshold (PPT).

WDT, CDT and VDT were used across three other studies [31, 53, 54]. PPT was used in two additional studies [53, 54]. Warm and cold pain thresholds (WPT, CPT) were used in one further study [31]. Heat pain threshold (HPT), temporal summation of pain (TSP) and conditioned pain modulation (CPM) were used in one study [54].

Disability Measures

Two studies measured disability through the Neck Disability Index (NDI) [30,53]. Mean scores of 37.3 (SD 18.9) and 16.2 (SD 7.7) were reported for cervical radiculopathy groups from Chien et al (2008) [53] and Tampin et al (2012) [30] respectively. This represents *"complete"* [53] and *"moderate"* [30] disability classifications. One study reported a mean score of 42.1 (SD±4.7) with the Pain Disability Index (PDI) representing a *"high"* level of disability [54]. One study reported Disability of the Arm and Shoulder Questionnaire (DASH) mean scores of 30.4 (Inter Quartile Range, 25.3) [31] signifying a *"low"* level of disability among patients with CSR.

Primary analysis: Association between somatosensory function and/or pain sensitivity and disability.

Detection threshold

All studies completed cold detection threshold, warm detection threshold and vibration detection threshold measures in patients with CSR [30, 31, 53, 54]. There were no statistically significant associations between these detection threshold measures and disability outcome measures (NDI and DASH). Mechanical detection threshold was measured in one study, which reported no statistically significant associations between NDI disability measures [30].

Thermal hypo/hyperalgesia

Three studies measured cold pain threshold and heat pain threshold [30, 31, 53] and reported no statistically significant associations with NDI or DASH disability measures.

Mechanical hypo/hyperalgesia

Two studies completed pressure pain threshold measurements at local cervical spine sites [53, 54] and one study completed pressure pain threshold at distal sites in a *"dermatome zone"* ipsilaterally and at the same site contralaterally [30]. There were no statistically significant relationships between pressure pain threshold measurements and disability. One study measured conditioned pain modulation and temporal summation of pain and no statistically significant associations with disability scores were reported [54].

Warm detection threshold, cold detection threshold, pressure pain threshold and cold pain threshold and disability measurements are represented in supplementary figures 1-4.

DISCUSSION

This is the first systematic review of studies assessing the association of somatosensory phenotypes measured through QST and disability in adults with CSR. There were no statistically significant associations between QST and disability among patients with CSR.

Each study used variable diagnostic criteria for CSR, including a combination of sensory disturbances and/or motor weakness confirmed through electrophysical testing or manual muscle testing. One study utilised physical assessment techniques to confirm CSR among their sample. The variance may be attributed to the differences in diagnostic procedures and resources across global healthcare systems. It is advocated that clinicians continue to use robust patient centred clinical reasoning frameworks and use recommended guidelines to inform a CSR diagnosis [23, 28, 55].

Identifying somatosensory phenotypes through QST may enhance the CSR diagnosis classification and subsequently enrich our understanding of this complex presentation [26, 39-41]. QST methodologies are well validated [42-44], have encouraging potential to enhance entrapment neuropathy diagnosis [29] and can subsequently inform individualised treatment strategies by identifying subgroups of somatosensory phenotypes [56, 57]. Interestingly, each included study utilised different QST procedures to map somatosensory profiles, which may be attributed to the resources available and experience of conducting testing procedures such as DFNS [25]. The consistency of QST procedures across entrapment neuropathies such as CSR is strongly encouraged for future research protocols and clinical practice.

Contrasting the association of spinal pain without radiculopathy and disability, may support the contextualisation of this review's findings. A meta-analysis reported that the

relationship between pain threshold and pain-related disability among individuals with neck and low back pain was weak [58]. Pain threshold measures explained around 2% of the variance in disability and the modality of QST did not predict or inform the strength of relationship for both neck and low back pain [58]. However, these findings were based on pain intensity, perception and/or tolerance testing procedures. Further, the weakness in association may be attributed, in part, to evoked experimental pain testing not representing the same clinical pain construct for patients [58].

There are limitations of our systematic review. There were six studies that initially met our inclusion criteria. However, one study was not included as there was repetition of data. On further inspection, one more study did not meet the QST inclusion criteria, therefore four studies were included in the final review. First, our narrative (descriptive) analysis was based on four heterogenous studies (two from Australia, one from Denmark and one from Ireland) which limits the external validity across other geographical regions. Second, the measures of disability varied across the included studies and included NDI, DASH and PDI, therefore making a direct comparison across disability domains unfeasible. Greater consistency between the use of disability measures may have enhanced the analysis and improved external validity to clinical populations. The patient populations across the four studies varied in CSR diagnostic criteria and healthcare locations. Greater consistency and enhanced transparency of CSR diagnostic criteria may have improved the generalisability to clinical practice.

Furthermore, only one study recruited from primary practice which limits it application to clinicians working in this setting.

We also acknowledge that association between factors cannot, of itself, assume causation. The included studies were cross sectional in design where the exposure and outcome are simultaneously assessed, this can mean there is generally no evidence of a temporal relationship between exposure and outcome [59].

Additional research is necessary to advance our understanding of QST and its associations with disability in entrapment neuropathies such as CSR. The consistency of sensory testing protocols and CSR diagnostic criteria should be strongly encouraged among researchers and clinicians. Improving consistency will enhance diagnosis, care pathways and analysis of future reviews including updates to this review. Investigating CSR, QST and disability with patients from a range of primary healthcare settings and socioeconomic environments is necessary to enhance our understanding of how it impacts people from differing backgrounds. None of our included studies have investigated this impact and it may enhance clinical decision making if future studies measured health-related quality of life (for example EQ5D).

It is acknowledged that a full QST protocol is not routinely undertaken in a clinical setting. However, modified sensory testing assessments (for example light touch, pin prick and vibration detection) are used. Further research to enhance the clinical utility, reliability and cost of QST is ongoing and will enhance clinicians clinical reasoning decisions for this, and other, entrapment neuropathy. Future prospective cohort study designs assessing natural course and stability of QST and disability measurements will also provide valuable insights for clinicians managing this complex presentation and policy makers evaluating healthcare utilisation.

CONCLUSION

This systematic review fulfilled the primary aim of investigating the association between QST outcomes and disability in adults with CSR. From the four studies included, no study reported statistically significant associations. This may be attributed to the limited consistency between QST protocols and CSR diagnostic criteria found in these studies. Further research is recommended in standardising diagnosis classification criteria. In addition, research investigating the relationship between QST, pain sensitivity and disability is clearly indicated to further our understanding of this condition.

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Conflict of interests.

There are no conflicts of interest to disclose.

Ethical approval.

Not indicated for this systematic review.

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Figure 1 – MEDLINE search strategy - Completed on 22nd March 2020

Radiculopathy: Radiculopathy [MESH] OR Nerve* entrapment OR Radicular [MESH] OR Referred pain [MESH] OR Brachialgia [MESH] OR Cervicobrachial [MESH] OR Upper limb radiculopathy [MESH] OR Neck and arm pain [MESH] OR nerve truck [free text] or spinal disease [MESH]

AND

Disabilities of the Arm Shoulder and Hand [MESH] OR patient specific functional scale [MESH] OR Northwick Park pain questionnaire [MESH] OR Neck disability index [MESH] OR SF-36 OR Oswestry [MESH] OR Roland morris OR disability [MESH] OR function [MESH]

AND

warm detection OR pain tolerance OR cold pain OR heat pain OR temporal summation OR thermal pain OR peripheral sensitization OR central sensitization OR pressure pain OR hypesthesia OR hyperesthesia OR hyperalgesia OR psychophysics OR sensory threshold OR sensory detection OR thermal detection OR thermal threshold OR cold detection OR heat detection OR pain detection OR pain threshold OR sensitivity OR Quantitative sensory test OR QST OR Quantitative sensory. [NB. All free text terms]

Figure 2. Modified Radiculopathy Diagnostic Criteria

Definite CSR Diagnosis - Either (i) or (ii)

(i) Acute denervation with EMG studies or sensory changes in dermatomal distribution

AND

Weakness, atrophy or fasciculation in a myotomal distribution and Unilateral diminished deep tendon reflexes

(ii) Abnormal myelography, CT or MRI correlating with radiculopathy with neck pain or combined neck and arm pain

OR

Paraesthesia, hyperaesthesia or dysaesthesia in a nerve root distribution or muscle weakness in a myotomal distribution or atrophy

Probable CSR Diagnosis - Either (iii), (iv) or (v)

(iii) Neck pain, neck and arm pain, paraesthesia, hyperaesthesia or dysaesthesia in a nerve root distribution or muscle weakness in a myotomal distribution or atrophy

with

Sensory changes in dermatomal distribution or muscle weakness in a myotomal distribution or atrophy or fasciculation in a myotomal distribution or unilateral diminished deep tendon reflexes

(iv) Neck pain, neck and arm pain, paraesthesia, hyperaesthesia or dysaesthesia in a nerve root distribution or muscle weakness in a myotomal distribution or atrophy

with

Abnormal myelography, CT or MRI correlating with radiculopathy

(v) Neck pain or neck and arm pain with two from:

(v-i) Sensory changes in dermatomal distribution

(v-ii) Muscle weakness in a myotomal distribution or atrophy

(v-iii) Fasciculation in a myotomal distribution

(v-iv) Unilateral diminished deep tendon reflexes KEY

Reporting: *"Yes=1," "No=0"*

1. Is the hypothesis /aim /objective of the study clearly described?

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?

3. Are the characteristics of the patients / samples included in the study clearly described?

* 4. Are the interventions of interest clearly described? NB NA to all included studies

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

"Yes=2," "Partially=1," "No=0"

6. Are the main findings of the study clearly described?

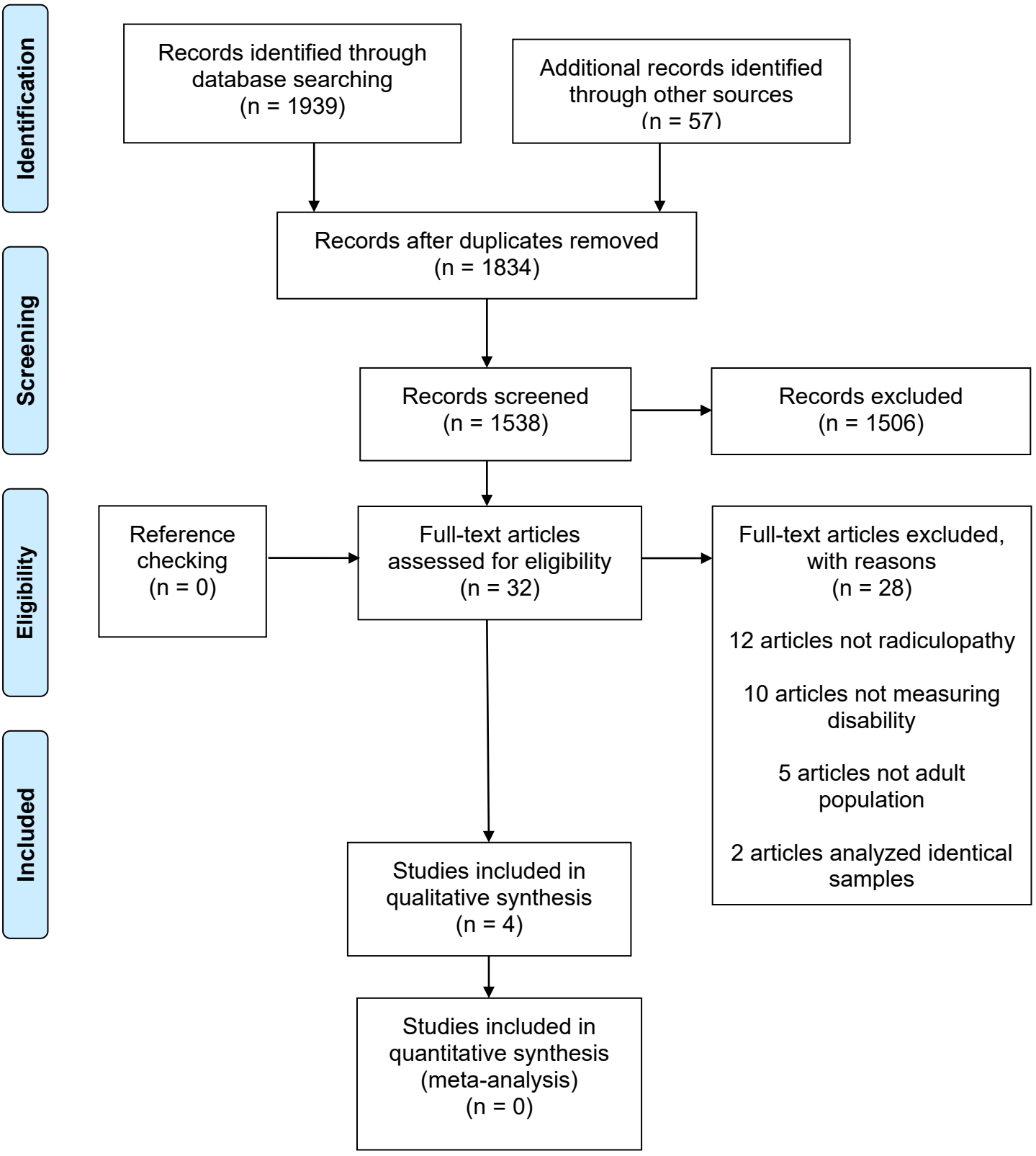
7. Does the study provide estimates of the random variability in the data for the main outcomes?

* 8. Have all important adverse events that may be a consequence of the intervention been reported? NB NA to all included studies

9. Have the characteristics of patients lost to follow-up been described?

10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

Study / Question	1	2	3	5	6	7	9	10	11	12	15	16	17	18	20	21	22	25	26	27	Total Score (%)
Tampin (2012) (30)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	**19/20 (95%)**
Vaegter (2017) (54)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	**19/20 (95%)**
Moloney (2013) (31)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	**18/20 (90%)**
Chien (2008) (53)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	**19/20 (95%)**


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1939)
Additional records identified through other sources (n = 57)
Records after duplicates removed (n = 1834)
Records screened (n = 1538)
Records excluded (n = 1506)
Reference checking (n = 0)
Full-text articles assessed for eligibility (n = 32)
Full-text articles excluded, with reasons (n = 28)
12 articles not radiculopathy
10 articles not measuring disability
5 articles not adult population
2 articles analyzed identical samples
Studies included in qualitative synthesis (n = 4)
Studies included in quantitative synthesis (meta-analysis) (n = 0)

External validity: *"Yes=1," "No=0," "Unable to determine=0"*

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

KEY

Reporting:"Yes=1,""No=0"

1. Is the hypothesis /aim /objective of the study clearly described?

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?

3. Are the characteristics of the patients / samples included in the study clearly described?

* 4. Are the interventions of interest clearly described? NB NA to all included studies

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

"Yes=2,""Partially=1,""No=0"

6. Are the main findings of the study clearly described?

7. Does the study provide estimates of the random variability in the data for the main outcomes?

* 8. Have all important adverse events that may be a consequence of the intervention been reported? NB NA to all included studies

9. Have the characteristics of patients lost to follow-up been described?

10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

External validity:"Yes=1,""No=0,""Unable to determine=0"

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

* 13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? NB NA to all included studies

Internal validity - bias: *"Yes=1," "No=0," "Unable to determine=0"*

* 14. Was an attempt made to blind study subjects to the intervention they have received? NB NA to all included studies

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

16. If any of the results of the study were based on *"data dredging"* was this made clear?

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

18. Were the statistical tests used to assess the main outcomes appropriate?

* 19. Was compliance with the intervention/s reliable? NB NA to all included studies

20. Were the main outcome measures used accurate (valid and reliable)?

Internal validity - confounding (selection bias): *"Yes=1," "No=0," "Unable to determine=0"*

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control

studies) recruited over the same period of time?

* 23. Were study subjects randomized to intervention groups? NB NA to all included studies

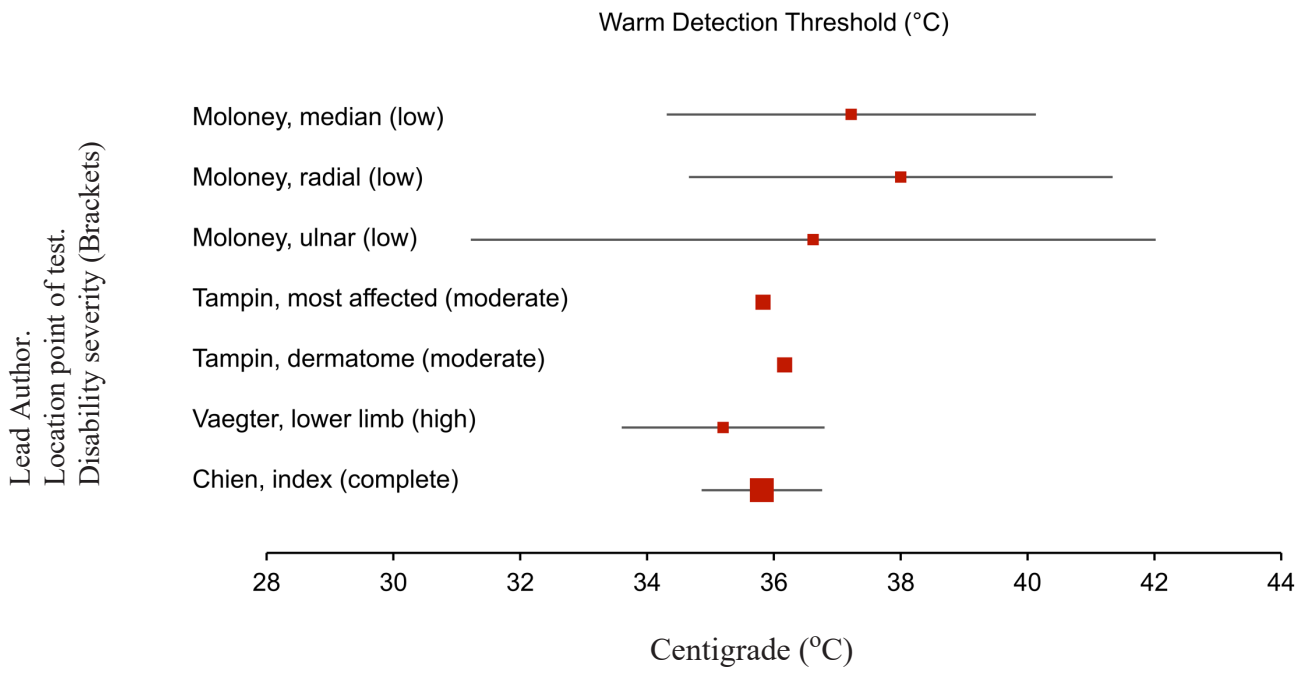
* 24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? NB NA to all included studies

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

26. Were losses of patients to follow-up taken into account?

27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

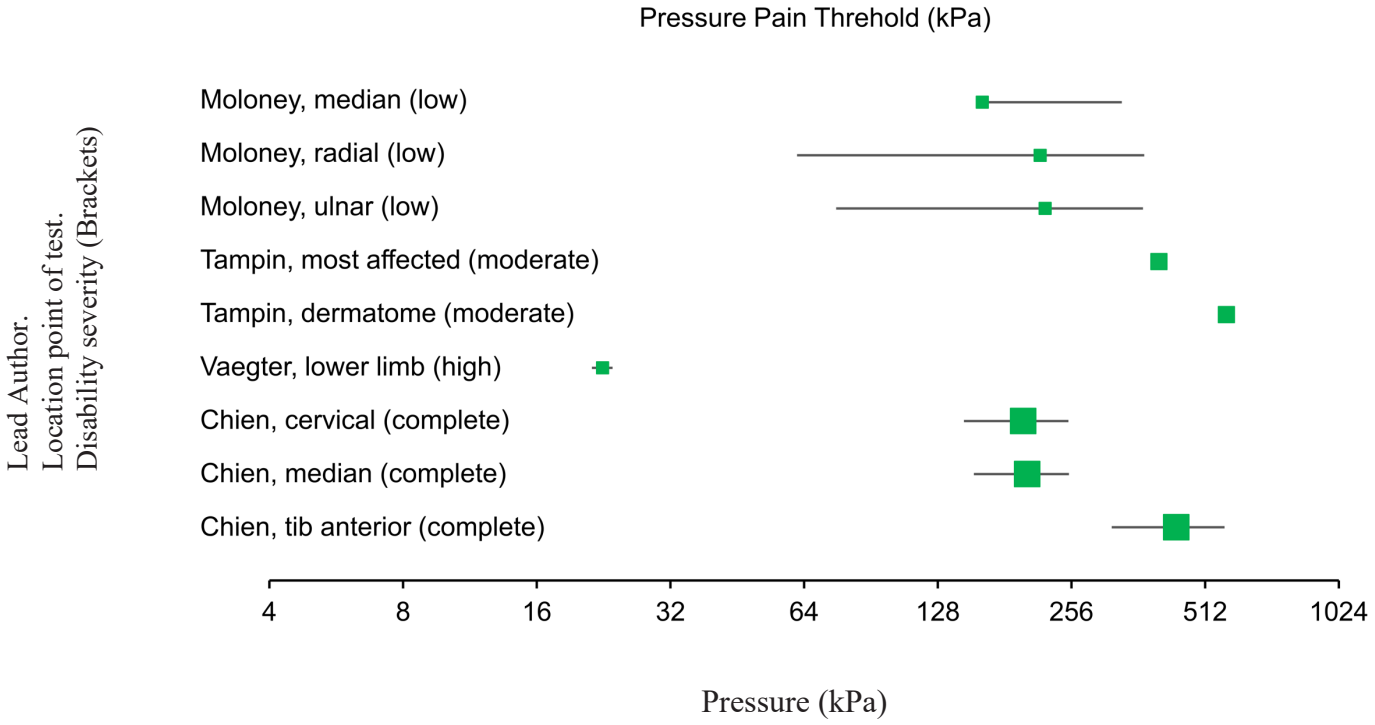
Supplementary figure 1



Centigrade (oC)

Forest plot showing point estimates and inter quartile ranges (IQR) between mean Warm Detection Threshold and disability with interquartile ranges for participants with cervical spine radiculopathy. 'Low', 'Moderate', 'High' and 'Complete' relate to the disability severity of participants with cervical spine radiculopathy in each included study. The size of the centre point corresponds to the sample size within the study.

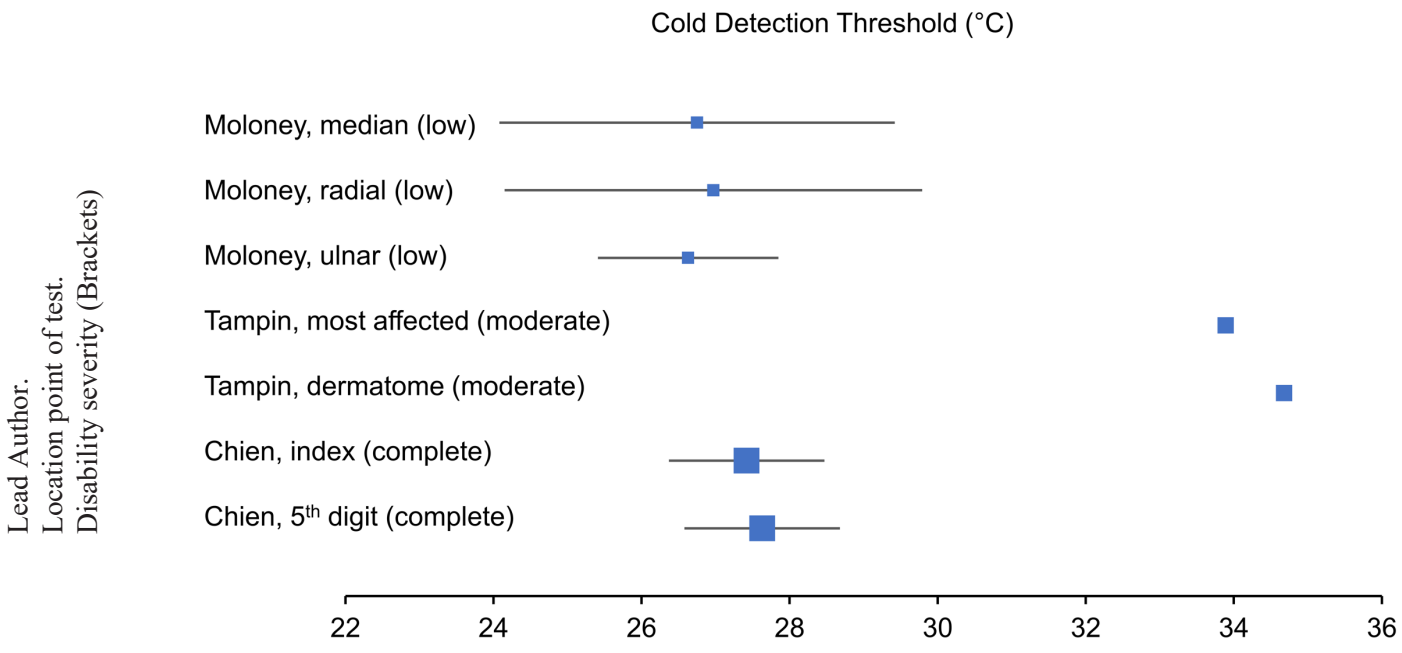
Supplementary figure 2



Pressure (kPa)

Forest plot showing point estimates and inter quartile ranges (IQR) between mean Pressure Pain Threshold and disability with interquartile ranges for participants with cervical spine radiculopathy. 'Low', 'Moderate', 'High' and 'Complete' relate to the disability severity of participants with cervical spine radiculopathy in each included study. The size of the centre point corresponds to the sample size within the study.

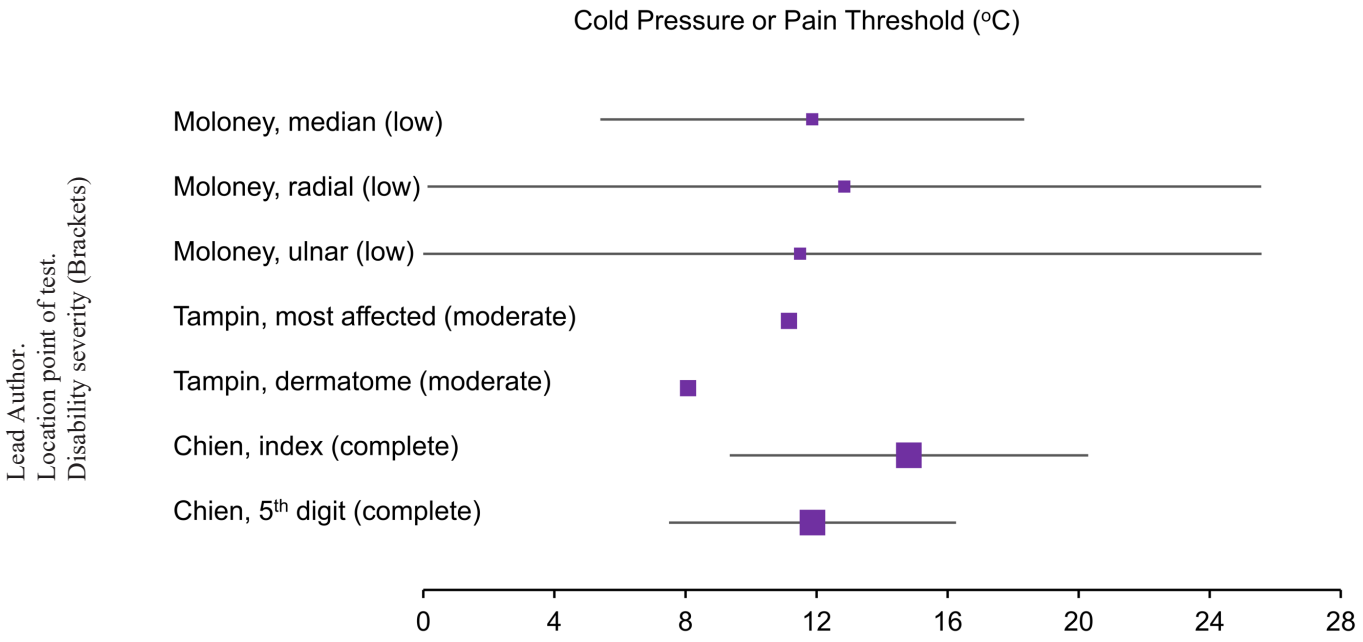
Supplementary figure 3



Centigrade (oC)

Forest plot showing point estimates and inter quartile ranges (IQR) between mean Cold Detection Threshold and disability with interquartile ranges for participants with cervical spine radiculopathy. 'Low', 'Moderate', 'High' and 'Complete' relate to the disability severity of participants with cervical spine radiculopathy in each included study. The size of the centre point corresponds to the sample size within the study.

Supplementary figure 4



Centigrade (oC)

Forest plot showing point estimates and inter quartile ranges (IQR) between mean Cold Pressure or Pain Threshold and disability with interquartile ranges for participants with cervical spine radiculopathy. 'Low', 'Moderate', 'High' and 'Complete' relate to the disability severity of participants with cervical spine radiculopathy in each included study. The size of the centre point corresponds to the sample size within the study.