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Title

The association between psychosocial factors and mental health symptoms to cervical spine pain with or without radiculopathy on health outcomes: systematic review protocol.

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Significance Statement:

This is a first systematic review protocol investigating the association of psychosocial factors and mental health symptoms and outcomes in adults with cervical spine pain with or without upper limb radiculopathy. The findings of this review are intended to enhance assessment and management decisions of clinicians and healthcare services for this complex and disabling condition.

Key Words:

Cervical spine pain; Cervical spine radiculopathy; Systematic review; Psychosocial; Mental health.

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Author Contributions:

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Introduction

Cervical spine pain is characterised as pain perceived anywhere in the posterior region of the cervical spine, from the superior nuchal line to the first thoracic spinous process [5]. Any lesion causing a mechanical compromise to a spinal nerve or its root can cause radiculopathy directly through compression or indirectly through the interruption of the blood supply or nutrition to a nerve axon or its root [44]. Cervical spine radiculopathy is identified as an objective loss of sensory and/or motor function as a result of conduction block to a spinal nerve or its root, this can occur with or without cervical spine pain [14]. People with CSp±R may also describe lancinating symptoms along narrow bands, which is similar but not identical to "dermatomal distribution", this is known as radicular pain [16, 40].

Cervical Spine Pain with or without radiculopathy (CSp±R) has significant negative impacts to a person's physical and mental health and wellbeing and is an enormous burden for individuals, families and societies [7, 11, 19]. The one year incidence of cervical spine pain ranges between 10.4% and 21.3% [20, 21] and Cervical spine radiculopathy prevalence values range between 1.1% to 6.3% [34, 37]. CSp±R is a leading cause of years lived with disability [30]. The global prevalence of cervical spine pain and years lived with disability has increased by 18.7% and 18.6% respectively over the last 10 years [30].

Multiple systematic reviews have established presence of psychological and/or mental health symptoms are associated with low back pain and negatively impact health outcomes and quality of life [33, 47]. This is not yet established for CSp±R and warrants further attention. Psychosocial factors encompass a wide range of characteristics such as patient's beliefs, emotions, behaviours, and family and workplace aspects [27]. Mental health symptoms or conditions are an extension of such factors. Examples of mental health conditions include major depressive disorders and anxiety. These conditions are among the leading causes of years lived with disability globally and less than a 10% positive improvement between 1990-2016 [30]. Stress, anxiety, depression and negative coping behaviours can adversely impact prognosis with musculoskeletal conditions such as low back pain [35], neck pain [39, 42], knee osteoarthritis [43, 49], carpal tunnel syndrome [18] and shoulder pain [8]. Psychosocial factors and/or mental health symptoms should be considered as part of a clinical reasoning framework to positively affect health outcomes and support prognosis [25].

Persistent pain and associative mental health symptoms are well established in low back pain [15, 32, 35]. Up to 20% of people with spinal pain, including CSp±R, will experience symptoms associated with depression and anxiety [3, 26]. Pain and disability associated with CSp±R limits a person's participation in social activities, working life and consequently negatively impacting quality of life [10, 31, 48]. Worryingly, there can be a devastating impact to a person's lived experience with CSp±R. People report their 'life is on hold', question their 'life purpose' and consider suicidal thoughts [36]. This potentially distressing association between CSp±R and

psychosocial factors or mental health symptoms requires enhanced attention from researchers, clinicians and healthcare services.

To date, no systematic review has examined the association between psychosocial factors and/or mental health symptoms in adults with CSp±R on health outcomes. A robust systematic review will enhance understanding and improve quality of healthcare services for these burdensome conditions. Therefore, our objective is to conduct a systematic review to assess the association between psychosocial factors and/or mental health symptoms and health outcomes in adults with CSp±R.

Methods

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [29] checklist guided the development and reporting of this review protocol. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [28] will be used on reporting the findings. The protocol for this systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020169497).

Eligibility criteria – Population

This systematic review will retrieve studies with samples of adults aged 18 years and over with CSp±R. It is anticipated that there will be variance in the definition of CSp±R across geographical location, clinical settings and from a historical standpoint. For example, The International Association of the Study of Pain [22] define cervical spine pain as pain perceived anywhere in the posterior region of the cervical spine, from the superior nuchal line to the first thoracic spinous process (Merskey and Bogduk, 1994). Whereas the Bone and Joint Decade 2000-2010 Task Force on Neck Pain describe cervical spine pain as the posterior neck region from the superior nuchal line to the spine of the scapula and the side region down to the superior border of the clavicle and the suprasternal notch [31].

Two reviewers will review all potentially eligible studies and a consensus decision will be sought on the CSp±R diagnosis. The CSp±R diagnosis criteria of all included studies will be described. From our previous work (Mansfield et al., *unpublished*) we anticipate a variance in cervical spine radiculopathy diagnostic criteria. Therefore this review we will take a pragmatic approach and include studies with *probable* or *definite* cervical spine radiculopathy diagnosis adapted from IASP and North American Spine Society [6, 22, 38] (**Figure 1**). Patients with CSp±R as a result of an upper motor neuron lesion, fracture, radiculitis, myelopathy, post-surgery, whiplash associated disorder (WAD), systemic pathology or metabolic diseases such as diabetes (including pre-diabetes) will be excluded.

Eligibility criteria - Exposure

Studies will be included if they assess psychosocial factors or mental health symptoms as an exposure. Studies must investigate one or more psychosocial or mental health symptoms (or condition). Psychosocial factors including cognitive (e.g. neuropsychological functioning), affective (e.g. distress, mood), behavioural (e.g. coping strategies), vocational (e.g. job satisfaction, self-perceived work ability) or interpersonal processes (e.g. social support) (Upton, 2013) will be considered. Mental health symptoms and conditions such as depressive symptoms, clinical depression, anxiety symptoms, perceived stress, personality, psychotic, traumatic and/or eating disorders will also be considered. Self-reported, objective standardised questionnaires (e.g. Beck Depression Index, Karasek's Job Control Questionnaire, GHQ-12) and/or psychosocial factors or mental health symptoms using dichotomous data ("yes/no") will be considered.

Eligibility criteria - Comparators

Studies will also be considered if the study population compares different severities of mental health symptoms or conditions or psychosocial factors. The "cut-off" values for mental health condition severity used in the included studies will be detailed in the data extraction tables.

Eligibility criteria - Outcome

Studies that include health outcomes informed by, but not limited to, core outcome domains for Outcome Measures in Rheumatology (OMERACT) for osteoarthritis [4], core outcome measurements for clinical trials with non-specific low back pain [9] and the Initiative on Methods Measurement and Pain Assessment in Clinical Trials for pain [12] will be considered. These domains are not designed specifically for CSp±R but intend to guide this review's data collection and analysis in the absence of a core health outcome set for CSp±R. The domains included for this review will include, pain for example Visual Analogue Scale (VAS), Numeric Pain Rating Scale (NPRS) [24]; disability such as Neck disability Index (NDI) [45], Disability of Arm and Shoulder Index (DASH) [2], International Physical Activity Questionnaire (IPAQ) [17]; Health Status for example 36-item Short Form Survey (SF-36) [23], 12 item Short Form Survey (SF-12) [46]. Health care utilisation such as clinician visits, spinal imaging, hospital length of stay will also be reviewed. The outcomes at different follow up periods for study inclusion (e.g. 1 month, 3 months, 6 months) will be reviewed. We will contact lead authors for missing or incomplete data to inform

analysis. Where data is incomplete or missing the authorship will take a pragmatic decision based on data available and whether to include for narrative review. A list of studies with missing or incomplete data sets will be listed as an appendix on publication.

Study characteristics

Studies must meet the population, exposure, comparator and outcome criteria to be included. Studies must be in the English language (or can be translated to English) and be either case control, cross-sectional, or cohort study design. No restriction on publication date will be applied. All articles suitable for inclusion will be referenced in the final manuscript. Studies will be excluded if they are animal or cadaveric studies, commentaries, editorials, single case study, reports or laboratory data, books or book chapters, letters, conference posters or proceedings that do not have full methodology and data sets available on request, lecture slides, study protocols, social media postings (including blogs) or online learning material (e.g. massive online learning sites, videos).

Information sources

The search strategy will be primarily developed by one author (MM) and reviewed by all corresponding authors to reach agreement and consensus. The draft search strategy is presented in **Figure 2**. A systematic search of electronic databases EMBASE, CINAHL, MEDLINE (PubMed) from inception to April 2020 will be completed by one reviewer (NS). The full PubMed search strategy will be made available as a supplementary file on dissemination. EndNote (X9.2 for MacOS) will be the reference manager software to store records, identify and remove duplicates. All included studies will undergo reference checking. When formal study inclusion has taken place, we will agree on "expert" authors in the field to contact by email requesting any pending articles and/or missing data. An unpublished (grey) literature search and trial registry will also be completed (e.g. WHO.It, ZETOC, British library higher education thesis deposits).

Data collection - Study selection

Results of the search strategy will be uploaded into Microsoft Excel spreadsheet. This will be securely remote-stored for all authors to access. Two reviewers will independently review, check titles and abstracts and document decisions on which of the studies should be included. A third reviewer will independently review decisions made by the two reviewers. The third reviewer will adjudicate any disagreements and discussion to reach final consensus.

An assessment of reliability will take place between MM and NS of 10% potentially eligible articles for full text order using a weighted Kappa statistic. The between

reviewer agreement data will be available in the final manuscript for the overall agreement. Following the title and abstract screening, potential eligible articles will be ordered full text. MM and NS will independently review full text articles against the inclusion criteria. Independent decisions on the inclusion criteria will be stored in table format and will be made available on request. MM and NS will reach consensus through discussion, where consensus cannot be reached a third author (MT) will act as an adjudicator.

Data collection – Data collection and extraction

Data extraction forms will be designed by the lead author (MM). This form will be reviewed and agreed by all authors part of this review. Two authors (MM and TS) will independently extract data from the included studies. Two authors (MM and TS) will meet to discuss the data extracted, any disagreements and reach consensus. If consensus cannot be achieved, a third author (MT) will be consulted and will act as adjudicator. Data extracted will include lead author and date of publication; study design; study demographics (country, sample size, age range or mean, gender ratio); definition of exposure; definition of comparator; outcome measure description; Risk estimates (Risk ratios, Hazard ratios, Odds ratio and/or mean differences including 95% Confidence Intervals (CI) where available or can be calculated post-hoc).

Methodological quality

Two authors (MM, NS) will independently assess the quality of each included study using a Newcastle-Ottawa Quality Scale (NOS) Assessment quality appraisal tool [41]. This appraisal tool is recommended by the Cochrane Handbook for Systematic Review. The NOS checklist assesses quality of articles across 3 domains: selection of the studies groups; comparability of the groups and control for cofounding factors; and exposure. MM and NS will discuss quality appraisal disagreements to reach consensus. MM and NS will independently determine whether outcomes are very low, low, moderate or high certainty based on the Grading of Recommendations, Assessment, Development and Evaluations [1]. GRADE will facilitate understanding outcomes quality and transparent grading of certainty in the included studies [1]. GRADE has five domains assessing the certainty of evidence: Risk of bias; Imprecision; Inconsistency; Indirectness; Publication bias.

Synthesis

Two authors (MM, TS) will assess included papers from a clinical perspective (e.g. diagnosis, variability in population characteristics) and study methodology to determine whether studies could be pooled together for synthesis. Where indicated, statistical heterogeneity assessments will be completed. If there is significant clinical heterogeneity, studies will be described narratively. For example, patient populations, clinical diagnosis. When there is minimal or no clinical heterogeneity, a random effects meta-analysis will be undertaken to compare the prevalence, odds or the risk of different psychosocial and mental health risk factors in CSp±R.

Additionally, statistical heterogeneity testing will be completed through the inconsistency value (I^2) and Cochran Q statistic. It is anticipated that there will variability on assessment across included studies therefore a random-effect model will be adopted. A calculation of publication bias will be conducted using a Galbraith plot [13]. Data analysis will follow guidelines in the Cochrane handbook (Section 9.4.5). We will complete an inverse-variance random-effects method by assessing the standardised mean difference and present with 95% confidence intervals and forest plots

Mixed sample populations are anticipated. An analysis of studies with cervical spine pain and radiculopathy will be completed as an additional sub-group analysis. Additionally, we will stratify results by duration of CSp±R (acute <3 months in duration and persistent ≥ 3 months in duration). Point of estimates (Risk ratio, hazard ratio and odds ratio) will also be analysed separately. A further sub-analysis on cervical spine radiculopathy *probable* and *definite* diagnostic criteria and their association with psychosocial and/or mental health factors will be completed. Furthermore, analyses will be conducted separately for cohort and case-control studies, and for unadjusted associations. Sensitivity analysis will be completed by an analysis of the study quality (risk of bias).

Discussion

This will be a first systematic review investigating the association between psychosocial factors or mental health symptoms in adults with CSp±R. It will a comprehensive synthesis review with the aim to enhance understanding of the association of psychosocial factors and CSp±R on health outcomes.

It is acknowledged that there will be limitations to this review. First, there are no core outcome sets for CSp±R which may mean a variability of measurements used to assess outcomes in the literature. We have recognised this and have identified closely related core outcome sets for osteoarthritis, chronic pain and low back pain to inform our analysis. Furthermore, we will compete sub-group analyses as detailed above. Second, there is no universally accepted diagnostic criteria for cervical spine radiculopathy. Therefore we have adopted an approach reflecting contemporary clinical practice to moderate radiculopathy diagnostic variance. A strength of our review will be including studies with standardised validated health outcome questionnaires. However, questionnaires may not be generalisable across all healthcare settings globally. This will be discussed narratively in our analysis.

We are expecting that the topic theme, methodology and results will have interest for a wide range of audiences. We will submit the final piece of work to an international multi-disciplinary, peer reviewed journal (e.g. *PAIN Reports, PAIN*) with open access. We aim to present findings at an international health science conference (e.g. International Association of the Study of Pain, World Conference of Physical Therapists). The findings will also form part of the knowledge exchange and

research informed teaching strategies with health and social care students in our affiliated university posts and associated clinical departments. All authors have a social media presence freely available to the general public. We plan to detail plain English findings through this medium (e.g. Twitter).

In summary, our findings will have relevance to patients, healthcare clinicians, researchers and policy makers. Enhancing our understanding of how psychosocial factors and/or mental health symptoms are associated with health outcomes in people with CSp±R will support the formulation of prognosis and collaborative management decisions. The review will identify gaps in research, thereby informing future experimental and observational study design. The results will also support the guidance of healthcare resources and aim to enhance overall health outcomes for patients.

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