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Role of post-trauma stress symptoms in the development of chronic musculoskeletal pain and disability: a protocol for a systematic review

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ABSTRACT

Introduction Post-traumatic stress symptoms (PTSS), pain and disability frequently co-occur following traumatic injuries. Although the coexistence of these symptoms is common, the relation between these symptoms and the impact on longer-term outcome remains poorly understood. This systematic review aims to determine the role of PTSS on the development of chronic pain and/or pain-related disability following musculoskeletal trauma.

Methods/analysis This protocol is developed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol. The review will include studies that recruited individuals aged ≥16 years sustaining any traumatic event that resulted in one or more musculoskeletal injuries and where a recognised measure for the presence of PTSS symptoms, pain and disability using either validated questionnaires or symptom checklists was employed. The following citation databases MEDLINE, PsycINFO, EMBASE, CINAHL, ZETOC, Web of Science, PubMed and Google Scholar, as well as reference lists from key journals and grey literature, will be searched from inception to 31 November 2021. Two independent reviewers will search, screen studies, extract data and assess risk of bias. The relationship of PTSS, pain and pain-related disability by injury type and severity will be estimated with 95% CI. If possible, study results will be pooled into a meta-analysis. However, if heterogeneity between studies is high, data analyses will be presented descriptively. The overall quality of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation guidelines.

Ethics and dissemination Ethical approval will not be required for this systematic review since only data from existing studies will be used. This review is expected to provide a better understanding of the factors associated with PTSS, pain and pain-related disability following musculoskeletal trauma, and help with the development of targeted therapeutic interventions. Results of this review will be disseminated in peer-reviewed publications and via national and international conferences.

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Strengths and limitations of this study

- ► To the best of our knowledge, this will be the first systematic review to explore the role of post-traumatic stress symptoms in the development of persistent pain and disability following musculoskeletal trauma.
- ► A wide range of medical databases and grey literature will be used to identify potential studies for inclusion.
- ► Two independent reviewers will be involved in conducting the study selection, data extraction and quality assessment.
- ► A broad search strategy and robust quality assessment criteria will be used to appraise and evaluate existing literature.
- ► Potential limitations are likely to be study heterogeneity, high risk of bias, imprecision and low number of studies, which may prevent meta-analysis from being performed.

BACKGROUND

Traumatic injuries account for 11% of the global disease burden; in 2015, an estimated 973 million people sustained injuries requiring healthcare, from which there were 4.7 million deaths.[1] Musculoskeletal injuries are now the second most common cause of years lived with disability and long-term pain worldwide.[2] Rates of disability associated with musculoskeletal trauma rose an estimated 45% between 1990 and 2010 and this figure is likely to continue rising.[3] In the UK, between 40 000 and 90 000 people are involved in a traumatic accident each year;[4 5] of these, 50% will have sustained a musculoskeletal injury.[4] An estimated 20 000 cases of major trauma are reported each year in England alone, resulting in over 5000 deaths and many permanent disabilities needing long-term care.[4] The estimated loss of economic output in 2010 as a result of major trauma in the UK was between £3.3 and £3.7 billion.[4] Musculoskeletal trauma is defined as traumatic injury to musculoskeletal structures including: bones, joints,

ligaments, tendons and muscles that surround these structures.[6]

Post-traumatic stress symptoms (PTSS) includes symptoms associated with post-traumatic stress disorder (PTSD), which can be diagnosed 1 month following a traumatic event[7] and acute stress disorder (ASD), which can be diagnosed within 1 month of a traumatic event.[8] Several studies have identified PTSS as an important factor in the development of chronic pain and disability following traumatic injuries.[9–11] However, the relationship between PTSS and the development of chronic pain and disability remains poorly understood. Reasons for this include PTSS diagnostic criteria, screening tools used to assess PTSS, study sample size and location of pain, all of which differ considerably between studies.

For example, two studies[12 13] have examined the prevalence of PTSS in patients with chronic pain accepted for pain rehabilitation in three Scandinavian hospital across Finland, Denmark and Sweden, using the core clusters of PTSS as outlined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria to ascertain diagnosis. In the first study, 23% of patients assessed for pain in Finland and Denmark fulfilled the DSM-IV criteria for PTSS, whereas in the second study, 29% of patients admitted for pain rehabilitation in Sweden reported PTSS at a level qualifying for a PTSD diagnosis. Furthermore, two systematic reviews[14 15] reported prevalence rates of PTSD between 11.7% and 19.1% among patients with chronic pain. Similarly, variation in chronic pain prevalence rate (range 30%–66%) have been reported in individuals with PTSD but research has mainly been carried out with war veterans.[16 17] A handful of studies have examined the role of PTSS in the development of chronic pain and pain related disability. But because of differences in sample size/study population, methods and the PTSS criteria used for diagnosis, estimates of pain and disability in individuals with PTSS vary considerably between studies. This warrants a thorough empirical examination of the role of PTSS and its impact on the development of pain and disability. A better understanding of this relationship should enable more targeted treatment. Therefore, the aim of this systematic review is to describe the literature investigating the role of PTSS in the development of chronic pain and disability following musculoskeletal trauma.

METHODS

This systematic review protocol has been developed according to the guidelines for conducting prognostic reviews proposed by Moons *et al*[18] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)[19] (online supplemental file 1). Prior to publication, an update of the search will be performed to be able to present the latest results.

The research question is: does PTSS have a role in the development of chronic pain and or disability following musculoskeletal trauma? In order to answer this question, ascertaining the role of PTSS (exposure) and outcome (chronic pain and or disability) will be sought. Only prospective observational cohort studies will be included, where PTSS is measured at baseline (exposure, within 3 months of a traumatic event) and patients followed up for the development of chronic pain and/or disability (outcome).

Eligibility criteria

Population

This review will include studies that recruited individuals aged ≥16 years sustaining any physically traumatic event that was reported to result in at least one musculoskeletal injury. Musculoskeletal injuries will be defined as damage to any bones, joints, ligaments (including intervertebral discs), tendons, muscles and the skin that surrounds these structures.[6] Common physically traumatic events are road traffic accidents (including whiplash injuries), blunt-force trauma, falls, sports injuries, stab wounds, gunshot wounds and violence. A broad range of musculoskeletal injuries are therefore included in this review. In studies with heterogeneous populations, more than 90% of the sample (aged ≥16 years) must have sustained a musculoskeletal injury.[6] Studies focusing solely on patients with brain injury or studies that include burns or neurological injury such as spinal cord injuries will be excluded. In studies where musculoskeletal trauma and neurological injuries are reported together, musculoskeletal trauma results will be reported separately. In studies where a proportion of the population is less than 16 years old, the reported mean or median age (in years) and a description of the distribution (SD or IQR range) will be provided. If these are not reported, we will attempt to contact the authors for raw data so that these can be calculated.

Patient-reported outcome measures

This review will include longitudinal studies with a recorded measure of PTSS (exposure) at baseline (within 3 months of the traumatic event in which injuries were sustained). Eligible studies must also have measured pain and/or pain-related disability for at least 3 months following the traumatic event.[20] Extracted outcomes data will be categorised by the time since injury. This will include any of the following measures.

Post-traumatic stress symptoms

Studies will be included if they have used one or more validated instrument/s to measure PTSS at baseline, for example, Impact of Event Scale (original, revised and abbreviated versions),[21–23] Clinician Administered PTSD scale,[24] PTSD Checklist for DSM-4 (PCL,),[25] PTSD Checklist for DSM-5 (PCL-5),[26] the Post-Traumatic Stress Diagnostic Scale[27] or the ASD Scale.[28]

Pain and disability

Studies will be included if they include at least one quantitative measure of pain at one or more follow-ups of

3 months or later, for example, self-reported pain intensity, such as from a Visual Analogue Scale[29] or the Numerical Rating Scale;[30] the short form-36 (SF36)[31] and SF12[32] and the Euro QOL five dimensional questionnaire,[33] the McGill pain questionnaire[34] or the Short Form McGill pain questionnaire,[35] designed to measure the quality and intensity of pain in adults; the Graded Chronic Pain Scale,[36] suitable for measuring chronic pain severity pain at any site; site-specific measures such as the Roland-Morris Disability Questionnaire,[37] the Oswestry Disability Index,[38] the Neck Disability Index[39] or the Western Ontario McMaster Universities Osteoarthritis Index,[40] measuring functional and physical disability related to pain at a particular anatomical location; or other pain-related score that assess function or disability status.

Study design

This systematic review will include only prospective observational studies and record linkage studies (data linkage from longitudinal surveys). Included studies will be published in either peer-reviewed scientific journals, Cochrane libraries or in the grey literature. Only articles published in English will be considered eligible.

Exclusion criteria

Single case studies, retrospective observational studies and randomised controlled trials will be excluded. Review articles, letters, editorials, conference proceedings and studies with only abstracts (ie, no available full text) will also be excluded.

Search strategy

The following citation databases MEDLINE (OVID), PsycINFO (OVID), EMBASE (OVID), CINAHL, ZETOC, PROSPERO, Web of Science, PubMed and Google Scholar as well as key journals and grey literature will be searched from inception to 31 November 2021. A search strategy has been developed to retrieve relevant articles, using the following key terms and Medical Subject Heading (MeSH): post-traumatic stress symptoms* (and all associated diagnoses and research terms), acute stress disorder* (ASD), pain* and disability*. A detailed Medline search strategy can be found in online supplemental file 2. Varying combinations of search terms will be used to identify all relevant studies. Existing strings from databases such as the Cochrane library will be searched for additional search terms as appropriate. Reference lists from recent review articles and from eligible manuscripts, identified by the above searches will be handsearched.

Preparing for eligibility screening

Before eligibility screening commences, search results identified by the outlined databases will be assembled into a digital library and organised by searched database using Endnote V.X9 (Clarivate Analytics) reference management software. Any identified duplicate articles will be identified and removed at this stage.

Table 1 Eligibility criteria

Study design	► Prospective observational cohort study. ► Record linkage study (data linkage from longitudinal surveys).
Study characteristics	► Study identified via electronic database search, grey literature, research archive or reference lists of eligible studies. ► Full text article available.
Participants	► Experienced musculoskeletal trauma within 3 months of the baseline assessment. ► >90% of participants are adults (aged ≥16 years).
Measures	► Post-traumatic stress symptoms measured at baseline (no more than 3 months post-trauma). ► Self-reported pain and/or disability measured at 3 months and/or longer following baseline.

Study selection

Two reviewers (FJ and DE) will independently screen and identify potential studies for inclusion by scrutinising titles and abstracts within the digital library. Both reviewers will then select articles for full-text screening and independently apply eligibility criteria to select appropriate articles for inclusion in the review. A third reviewer (DF) will arbitrate any disagreement over study eligibility and resolve through discussion. An inclusion criteria checklist (table 1) has been developed, based on study eligibility criteria, to ensure that studies are classified and interpreted appropriately. A PRISMA-P flow diagram will be provided to describe included and excluded studies along with reasons for exclusions.

Data extraction

Data from the included studies will be extracted independently by two reviewers (FJ and DE). Any disagreement over the eligibility of a study will be resolved through discussions with a third reviewer (DF). For missing data, attempts will be made to contact study authors at least twice by email and/or phone to gain further information. If corresponding authors fail to respond to our requests and the missing data negates the eligibility of a study, it will be removed from the review. Data presented only in graph/figures will be extracted and analysed where possible using software tool such as Web Plot Digitizer.[41] This process of extracting from figures will be conducted by only one reviewer (FJ). An adapted version of the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist[18] will be used to create a standardised data extraction form (spreadsheet) to manage the data extraction process. This form will be developed iteratively, being first pilot-tested on five eligible papers by each of the two reviewers (FJ and DE) independently. The standardised data extraction spreadsheet will contain header specific

to the review purpose to ensure all the relevant data are extracted, consistent with the inclusion criteria of this review. A third reviewer will check a random subset of the data extracted from the included studies to ensure that data have been extracted consistently without any deviation. Although the CHARMS checklist was developed primarily for reviews of prediction model studies, it can also be used to define and frame key data items to be extracted from each study for this review. The following data items will be extracted from each study: authors and year of publication, study location, study design, participants characteristics, outcomes of interest (self-reported pain and/or disability), predictor variables or symptom measurements, sample size, length of follow-up, items associated with risk of bias, summary statistics and methods for statistical analysis.

Quality assessment

Two reviewers (FJ and DE) will independently carry out quality assessment of each of the retained articles to assess bias. Differences in opinion will be resolved by further discussion/consensus or by involving a third reviewer (DF). Risk of bias and study quality of the retained articles will be assessed using the Quality In Prognostic Studies (QUIPS) tool.[42] The QUIPS risk of bias tool was developed for prognostic factor review questions and has demonstrated acceptable inter-rater reliability.[42] It consists of six domains assessing potential biases in prognostic studies: study participation, study attrition, prognostic factor measurement, confounding factors, outcome measurement and statistical analysis and reporting.[43] Each risk of bias domain is independently rated as 'low', 'moderate' or 'high' according to responses to prompting questions and consensus judgement from at least two reviewers.[42] The overall classification of the risk of bias of individual studies is defined as low risk of bias if all six domains are rated as low-to-moderate risk, while studies classified as high risk of bias if ≥1 domain assessed as a high risk of bias. Risk of bias ratings will be compared between the two reviewers. A narrative summary of study quality will be provided separately in a table. A critical appraisal describing the impact and overall impression of the quality of each retained study on the results will be discussed. A sensitivity analysis will be conducted to assess the effect of including or excluding poor quality studies on the main findings.

Data analysis and synthesis

If appropriate, a quantitative synthesis of the pooled data from retained studies will be provided. Results from outcome measures will be extracted and combined where possible. Calculations will be performed using STATA V.17.0 (STATA). Standardised mean difference with accompanying 95% CIs and median, adjusted and unadjusted covariates, ORs or relative risk (RR) of pain and/or disability will be extracted, or if not reported will be calculated from data provided. If appropriate, adjusted and unadjusted outcome data will be grouped separately and pooled estimates of the OR/RR for pain and or disability will be calculated. Risk ratio measures with 95% CIs will be calculated for binary outcomes (eg, presence of pain) or standardise mean difference with accompanying 95% CI where continuous scales of measurements were used to identify pain or disability. Results will be pooled if the association between PTSS and the outcome of interest (pain and or disability) was presented by the same summary statistics (RR or OR) in at least two studies. OR and RR will be summarised separately if the outcome is binary (eg, presence of pain v/s no pain reported) whereas continuous outcome (eg, pain scores) will be combined using mean difference or standardised mean difference.

Subgroup analyses of the outcome data may be performed if studies report severity or type of musculoskeletal trauma separately. The level of heterogeneity across studies will be assessed using the Cochrane Q-test and the I^2 statistical test with 95% CI. An I^2 of 50% is considered a substantial level of heterogeneity.[44] Depending on the level of heterogeneity, both fixed and random effect models will be used as summary effect measures. The Mantel-Haenszel[45] method will be used for fixed effects model if tests of heterogeneity are not significant, or the DerSimonian and Laird[46] method will be used for random effects model if the true effect size cannot be assumed due to different study population, regions or assessment methods across studies. A minimum of two studies are generally considered sufficient to perform a meta-analysis.[47]

Heterogeneity assessment

Sources of heterogeneity will be explored statistically by univariate and multivariate meta-regression. The statistical significance of univariate meta-regression analyses will be determined at $p<0.05$ and will be performed, for example, for the following covariates: country, study setting, study design, diagnostic methods and sample size. Statistically significant predictors from univariate models will be included in a multivariate meta-regression model, and the statistical significance will be determined at $p<0.05$. Meta-regression will be performed in STATA using the 'metareg' command.[48]

Subgroup analysis

Depending on the level of heterogeneity between studies, subgroup analyses may be conducted to clarify the source of heterogeneity. High heterogeneity between the included studies is highly likely to occur. Potential sources of heterogeneity could arise from study design, source of participants, follow-up time and studies where some participants were diagnosed with PTSS and results reported separately. Subgroup analysis on study level characteristics will be conducted to avoid aggregation bias.

Sensitivity analysis

Separate sensitivity analyses may be conducted when assessing the methodological quality of the included

studies. The following assumptions will be considered: sampling strategy, adequate response rate and studies using both validated assessment measures and or standardised assessment tools. A further analysis will be conducted excluding any studies with high risk of bias.

Narrative synthesis

If the level of heterogeneity is high between studies and pooled analysis of the studies is not possible, a narrative summary of the outcome of the selected studies will be undertaken and presented in the final review.

Publication bias and overall quality of the evidence

In order to investigate publication bias and small sample bias, the inverted funnel plot technique and the Egger statistic will be used. To examine the magnitude of publication bias, the trim and fill method[49] will be used to estimate the number of hypothetical studies missing because of publication bias and imputes missing effects until the funnel plot is symmetrical. The STATA command metatrim[50] will be used to perform the non-parametric trim and fill method. The Grading of Recommendations Assessment, Development and Evaluation (GRADE)[51] framework will be used to assess the quality of evidence for each outcome of interest described above across studies. Consistent with GRADE, the quality of the summary evidence will be assessed as high, moderate, low or very low. We will evaluate imprecision, inconsistency, indirectness, risk of bias including publication bias. Applicability of the results based on the study population will also be rated when making judgement about the quality of evidence presented in the included studies.[51] The minimum number of studies recommended when examining publication bias is 10.[52]

Patient and public involvement statement

As there is no direct patient involvement in this study, patients and the public were not invited to contribute to the writing or editing of this systematic review protocol. The research question of this review was informed by the notable lack of relevant literature examining the association of patients with PTSS in the development of persistent musculoskeletal pain and disability.

DISCUSSION

To the best of our knowledge, this will be the first systematic review to present an in-depth synthesis of the available prospective evidence exploring the association between early PTSS and persistent pain and disability following musculoskeletal trauma. The strengths and limitations identified in the included studies will be presented and described in the review. Strengths of prospective observational data include large sample sizes, collection of detailed information on the risk exposure and outcome of interests, the potential to observe patients prospectively over an extended period. Some limitations of observational data include the quality of data extracted which may be limited or inadequate to allow data to be combined in a meta-analysis. A narrative summary of the study findings will be presented to overcome this issue if necessary.

Implications of results

This systematic review will provide a synthesis of the available literature exploring the role of PTSS and the development of persistent pain and disability in adults aged ≥16 years who have experienced musculoskeletal trauma. The results of this review have the potential to inform clinical practice by providing evidence of the importance of early assessment and may provide indicators for tailored treatment of patients experiencing PTSS following traumatic injuries. A better understanding of the effect of PTSS in the development of persistent musculoskeletal pain and disability should herald further research in the area of early intervention for those presenting with increased level of stress following a musculoskeletal injury.

Ethics and dissemination

This review does not require ethical approval as only existing published data available in scientific databases will be used. Findings of this systematic review will be presented for peer review in an appropriate journal. Any data generated from this systematic review will be made available from the corresponding author on reasonable request.

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Contributors All authors contributed to the focus of the systematic review topic. FJ drafted the initial protocol with guidance and feedback from DF and DE at all stages. All authors approved the final version for publication. DF is guarantor.

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