ABSTRACT
Introduction Recent systematic reviews have identified many biopsychosocial factors associated with the development of chronic musculoskeletal pain (CMP). Despite often being specific to a particular musculoskeletal condition, findings are similar across systematic reviews. Research is needed to aggregate these findings to identify consistent factors across musculoskeletal disorders that are associated with the development of CMP. The objective of this study is to provide a meta-level synthesis of all biopsychosocial factors associated with the development of CMP.

Methods and analysis An umbrella review and meta-level narrative synthesis–meta-analysis has been designed informed by Joanna Briggs Institute and Cochrane guidance. This protocol is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-P. Sources will include Ovid Medline, Embase, Web of Science Core Collection, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, PsycINFO, CINAHL, PEDro, PROSPERO, Google Scholar and grey literature. Inclusion criteria: any systematic review which investigates biopsychosocial factors which may be associated with the development of CMP.

Results Dissemination All details on search strategy, inclusion and exclusion criteria, and data extraction will be specified. Quality of included papers will be assessed using the Joanna Briggs Institute Critical Appraisal Tool. Narrative synthesis will be presented in a table format and a systematic narrative synthesis will be completed. The outcome is musculoskeletal pain lasting beyond 3 months. Two independent reviewers will be involved in all stages; screening, selection, data extraction and risk of bias evaluation using the Joanna Briggs Institute Critical Appraisal Tool. A meta-level narrative synthesis will be conducted based on (a) factors associated with development of CMP, (b) the range of musculoskeletal disorders for which the same/similar findings have been established and (c) the quality of studies informing these findings. Where possible, meta-analysis will be performed. The Grading of Recommendations, Assessment, Development and Evaluation guidelines will be followed to determine the level of evidence for each biopsychosocial factor.

Ethics and dissemination This umbrella review does not require ethical approval. Findings will be presented at conferences and published in a peer reviewed journal. PROSPERO registration number CRD42020193081.
higher now—causing a loss over 30 million working days each year due to MSK conditions, creating a substantial financial and economic burden. MSK complaints also account for up to 30% of general practitioner consultations. A significant proportion of these likely being for the management of CMP with its estimated prevalence in the UK at 43%. CMP is also a huge burden internationally with low back pain identified as the single greatest cause of years lived with a disability, thus prompting the ICD to recently recognise CMP as a disease in its own right. Given the apparent difficulty in effectively managing CMP, and its increasing prevalence, a better understanding of CMP is needed.

To better understand CMP, there is a need to understand the factors which influence its development. The experience of MSK pain is biopsychosocial and therefore biological factors, such as the type and severity of MSK condition, do not equate to consistent experiences of pain among individuals. Rather, many individuals go on to develop CMP where others do not. This discrepancy has frequently been associated with the presence of many biopsychosocial factors such as catastrophised beliefs, lower socioeconomic status and fear of movement. Biopsychosocial factors, such as nociplastic mechanisms, and many biopsychosocial factors, are not specific to a particular MSK condition; synthesis of this evidence base may inform future research and management of CMP conditions as a whole.

Biomedical healthcare approaches tend to dominate the management of MSK conditions with biopsychosocial approaches often only considered once medical management has failed, as demonstrated by National Institute for Health and Care Excellence guidance for low back pain. However, existing systematic reviews often focus on biological, psychological or social factors individually or in relation to only one form or CMP, for example, low back pain. Given that nociceptive mechanisms, and many biopsychosocial factors, are not specific to a particular MSK condition, synthesis of this evidence base may inform future research and management of CMP conditions as a whole.

METHODS

Design and registration

This protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) (see online supplementary file A for completed PRISMA-P checklist). The methodology has been guided by the Joanna Briggs Institute Manual for Evidence Synthesis of Umbrella Reviews and the Cochrane handbook for the conduct of systematic reviews.

Patient and public involvement

The basis for the need and relevance of this umbrella review is based on the clinical interactions of the authors with previous and current patients with CMP. This includes members of the patient and public involvement and engagement group within the Centre of Precision Rehabilitation for Spinal Pain at the University of Birmingham. The group includes individuals with chronic spinal pain.

Eligibility criteria

The eligibility criteria were established using a modified PICOS statement (see table 1). ‘I’ was replaced with ‘E’ of CMP before it has been established. This provides a window of opportunity for healthcare services to deliver proactive biopsychosocial treatments with an aim of preventing development of CMP. This strategy works well for other chronic diseases such as heart disease and diabetes.

To address the growing prevalence and burden of CMP, it is timely to synthesise the existing literature to identify which biopsychosocial factors are associated with its development. Given the abundance of systematic reviews, an umbrella review will be most appropriate in achieving this.

AIM

To establish which biopsychosocial factors are associated with the development of CMP.

Table 1 PICOS statement

| Population | Individuals aged 18 and over who have experienced an MSK disorder. |
| Exposure   | Any biopsychosocial factors which may have influenced outcome, for example, patient reported higher levels of pain at onset. |
| Comparator | Those who have not been exposed to the biopsychosocial factor under investigation, for example, the comparator to those who report higher levels of pain at onset would be those who report lower levels of pain at onset. |
| Outcome    | Persistence in MSK pain beyond 3 months. This may be identified through any MSK pain-related outcome measure or through clinician diagnosis. |
| Study designs | Systematic reviews of prospective longitudinal design studies. |

MSK, musculoskeletal.
for exposure due to the epidemiological nature of the review.29

Inclusion criteria
Systematic reviews of observational studies with/without meta-analysis investigating factors associated with MSK pain lasting longer than 3 months.

Exclusion criteria
Systematic reviews which include interventionalal studies, for example, factors associated with successful surgery, populations with a high risk or evidence of poor tissue healing, for example, autoimmune disorders, injuries where tissue healing may be incomplete at 3 months, for example, fractures, draw body region-specific conclusions which are not generalisable to the wider CMP population, for example, a bony heel spur associated with chronic heel pain, pool data with non-MSK chronic pain populations, for example, cancer-related pain, potential systemic drivers of CMP, for example, spondyloarthropathy, do not include an appropriate comparator and systematic reviews where the full text is not available in the English language.

Information sources
A systematic search of electronic databases and grey literature will be conducted. Ovid MEDLINE, Ovid EMBASE, Web of Science Core Collection and Google Scholar will be searched as suggested by Bramer et al.30 who found this combination to be most effective for the retrieval of systematic reviews. In addition, the PEDro, CINAHL and Ovid PsycINFO databases will be searched as well as the Cochrane database for systematic reviews, the Database of Abstracts of Reviews of Effects and the PROSPERO register as all are particularly relevant for the subject of MSK pain and/or systematic reviews. There will be no limitation on search dates. Grey literature will be searched using the Canadian Agency for Drugs and Technologies in Health grey literature searching tool. To ensure literature saturation, we will also scan the reference lists of included studies or relevant reviews identified through the search.

Search strategy
The search strategy has been designed by the lead author (MD) with the assistance of coauthors (NRH, ABR and AS) and an experienced health sciences librarian with expertise of systematic review searching. The search strategy includes a validated search strategy for prognostic studies recommended by the Cochrane Prognosis Research Group.31 The initial search strategy was developed with Ovid MEDLINE using medical subject headings and text words and subsequently adapted to the syntax and subject headings of the other databases to be searched for this review. The search strategy has been peer reviewed by other members of the review team (NRH, ABR, AS and JM) to reduce the risk of search errors and ensure the highest retrieval of eligible studies.32 Please see online supplemental file B for the Ovid MEDLINE search strategy.

Screening and selection
A systematic search of databases using the search strategies will be conducted by two reviewers independently of each other (MD and JM). Titles and abstracts will be retrieved and stored using Microsoft EndNote X9.3.3, will be assessed based on the inclusion/exclusion criteria and allocated into one of two groups: potentially eligible or not eligible. Full-text sources for potentially eligible studies will then be sourced and discussed between both reviewers for confirmation of eligibility. Additional information to determine eligibility will be sought from study authors via email where necessary. Any disagreement of eligibility at this stage will be referred to a third reviewer (NRH). All reasons for excluding reviews will be recorded using a PRISMA flow chart. None of the reviewers will be blinded to the journal titles, study authors or institutions.

Data extraction
Two reviewers (MD and JM) will independently extract data. All data excluded will be agreed by both reviewers in discussion and any disagreement will be referred to a third reviewer (NRH). Where study data are unclear or missing, the corresponding author will be contacted via email for clarification or further information. A second and final email will be sent if no response has been received after 2 weeks. In the event of a non-response after a further 2 weeks, includable data will be extracted based on agreement between the two reviewers with any disagreement referred to a third reviewer. Data will be extracted using a bespoke and standardised proforma which has been piloted a priori (see online supplemental file C). Data extraction will, where possible, include quantitative data such as demographic information, ORs, relative risk ratios, size of effects and Pearson’s χ2 scores which will be stored on Microsoft Excel.

Data items
The data to be extracted are summarised in table 2. As per Joanna Briggs Umbrella Review guidance, data will not be collected from the original research studies but extracted from the included systematic reviews only.

Risk of bias assessment
Two reviewers (MD and JM) will independently perform risk of bias assessment of included systematic reviews using the Assessing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2) guidelines and checklist.33 AMSTAR-2 has been shown to be valid and reliable for the appraisal of systematic reviews34 35 and has been used in many high-quality healthcare Umbrella Reviews.36–38 AMSTAR-2 includes assessment of study eligibility criteria, identification and selection of studies, data collection methods, study appraisal methods and findings and synthesis methods. Overall confidence in the results of each systematic review will be rated as high, moderate, low or critically low.33 Any disagreements will be discussed
and referred to a third reviewer (NRH) for a conclusive decision. Reporting bias will be determined based on whether a protocol exists as a peer review publication or through registration with PROSPERO.

**Data synthesis**

Meta-analysis will be performed where two or more included reviews have reported on the same biopsychosocial factor and the data can be suitably pooled for statistical analysis. Statistical analysis will then be performed by computing OR using a random-effects model with a 95% CI. Pearson’s $\chi^2$ test will be used to assess statistical significance of heterogeneity between reviews. Publication bias will be assessed through the use of an inverted funnel plot. All statistical analysis will be conducted using IBM SPSS Statistics V.26 and Microsoft Excel.

Where meta-analysis is not possible, meta-level narrative synthesis will be performed in accordance with guidance by Popay et al (Guidance on the Conduct of Narrative Synthesis in Systematic Reviews. Results of an ESRC funded research project (unpublished report)) and The Cochrane Consumers and Communication Review Group. However, the first step of ‘developing a theory of how the intervention works’ will be removed due to the non-interventional nature of this umbrella review. Narrative synthesis will be structured around three domains: (a) the biological, psychological or social factors associated with the development of CMP, (b) the range of MSK disorders for which the same/similar findings have been established and (c) the risk of bias of the studies informing these findings. Using standardised templates, data will be extracted and presented in tabular format. Discussion will be orientated around similarities and differences between the findings of included studies, in line with our three domains. A detailed outline of methodological problems or biases will also be included, alongside an assessment of completeness and applicability.

**Confidence in cumulative evidence**

Umbrella reviews have been criticised for lack of consistent or appropriate methods in ascertaining the level of certainty of findings. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is a well-established tool which is commonly used for this purpose with systematic reviews and has been recommended for use with umbrella reviews. The GRADE approach has been adapted for the assessment of evidence of prognostic factors. GRADE enables evaluation of criteria rating down factors associated with the development of CMP (risk of bias (informed by AMSTAR-2), inconsistency, indirectness, imprecision and publication bias) and criteria of rating up factors associated with the development of CMP (dose–response, large effect or for the nature of plausible biases) to provide a statement of the overall level of evidence as high, moderate, low or very low for each biopsychosocial factor.

**DISCUSSION**

Traditionally, research of CMP has been orientated towards a particular chronic MSK condition rather than considering CMP as an overarching condition in itself. Rather, this umbrella review will consider CMP as a disease in its own right in line with the ICD and seeks to contribute to the body of evidence supporting a shift away from the over-medicalisation of CMP.

Physical assessment and imaging are typically utilised to determine physical ‘abnormalities’ with these ‘abnormalities’ then serving as the rationale for the diagnosis and treatment of a specific MSK condition. Treatments may include surgery, acupuncture, manual therapy, injections, pharmacology or surgery, among others, with the aim of ‘fixing’ the ‘abnormality’ and improving the MSK condition. However, research demonstrates that these ‘abnormalities’ are heavily prevalent in healthy populations with no history of MSK conditions. This raises concern for the validity of this form of diagnosis. In addition, a large multicentre randomised control trial also demonstrates that sham surgery is equally as effective as surgical intervention for shoulder pain, raising questions for the mechanisms of how effective interventions for MSK pain work. This same finding has also been found with sham surgery for knee, back and elbow pain as evidenced by a high-quality systematic review suggesting that the mechanisms of pain and successful intervention are similar, regardless of the type of MSK condition. Notably, the participants in these studies typically have had symptoms for longer than 3 months and therefore these findings are relevant to the CMP population.

The nociplastic mechanisms by which individuals experience CMP are thought to be contributed to by functional
and anatomical changes in the central nervous system.\textsuperscript{50–52} Reorganisation of brain activity takes place with reduced activation of the somatosensory cortex, which is usually highly active during nociception, and an increase in activity of the corticolimbic system, thus creating a shift from nociceptive to emotional circuits.\textsuperscript{30} These changes have been shown to be consistent across a range of MSK conditions.\textsuperscript{53–56} Furthermore, this persistent activity of the corticolimbic system is responsible for the development of many behavioural and psychological presentations,\textsuperscript{57} many of which have separately been identified as risk factors for the development of CMP, such as fear.\textsuperscript{6} It is further evidenced by the consistent biopsychosocial factors shown to be associated with development of CMP regardless of the type of MSK condition.\textsuperscript{16–18} For these reasons, and that CMP is considered a disease in its own right, this umbrella review recognises the need to aggregate the findings of systemic reviews on the biopsychosocial factors associated with the development of CMP, for all MSK conditions.

**AMENDMENTS**

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale for the change.

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**Contributors** MD conceived, designed and will coordinate the review; will collect, manage, analyse and interpret data. NRH, ABR and AS contributed to conception and design of the review and will provide general advice on the coordination of the review as well as collection, management, analysis and synthesis of data.

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