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What is known and what is still unknown within chronic musculoskeletal pain? A systematic evidence and gap map

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the areas with the lowest quality of evidence.²⁸ Similarly, these overviews can inform researchers and funders where more evidence is *not* needed.^{9,33} One of the areas where the amount of research has increased exponentially and overviews are needed is within the management of chronic musculoskeletal (MSK) pain.

Chronic MSK pain (defined as persistent pain for more than 3 months affecting the bone, joint, muscle, or related soft tissue) is ranked among the top 20 diseases contributing most to the global burden of disease.^{23,27,36,38} The broad definition of chronic MSK pain results in a heterogeneous group of patients with disorders ranging from low to very high in complexity. This results in a range of negative consequences for people living with chronic MSK pain as well as their families.^{6,22,24,35} The societal and healthcare burden of chronic MSK pain is enormous and amounts to 2% of the gross domestic product in European countries.² Despite large research investments within this field, we still lack effective management strategies that can provide long-term benefits for people living with chronic MSK pain.¹⁰

This large production of knowledge makes it difficult to keep up and understand where to focus research efforts (ie, where do we need more knowledge?) and where to focus implementation efforts (ie, where do we have knowledge on effective treatments that have not yet been implemented?). To accommodate this, EGMs have previously been used to provide policymakers with a shortcut of synthesised knowledge within a certain area (eg, treatments for pediatric chronic pain) and, furthermore, to support funding and research priorities.^{4,5,29,34}

By mapping the current evidence and appraising the literature, an EGM within chronic MSK pain is an important step in informing and improving future research. Therefore, this study aimed to create a contemporary EGM of systematic reviews of randomised control trials investigating the management of chronic MSK pain in adults.

2. Methods

This EGM is based on a systematic search of the literature and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines for systematic reviews.¹⁰ A study protocol was registered on the Open Science Framework in January 2021 (doi: <http://10.17605/OSF.IO/3TQXH>). Two revisions were made after the original registration. The first revision was made to clarify the data extraction outcomes and was specified to include outcomes not only restricted to pain (eg, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [IMMPACT] recommendations). The second revision was made only to include systematic reviews that were based on at least 3 relevant randomised control studies (RCTs). We followed the Campbell Collaboration for the methodology of EGMs by using a structure including the following steps³⁹: development of scope, in/exclusion criteria, systematic review of the literature, extraction of data, analysis, and visualization.^{17,28,33} Data will be available for further analysis by contacting the authors.

2.1. Deviations from protocol and preregistration

To accommodate the workload of the high number of included reviews for this EGM, 2 new authors were invited to join the research group (C.D. and M.K.B.). To reduce the number of included reviews, we changed the number of included RCTs needed for inclusion from a minimum of 2 to a minimum of 3 RCTs. We planned on complementing our literature search with citation tracking which was not deemed necessary because of the high number (more than 450) of included systematic reviews.

2.2. Eligibility criteria

Systematic reviews were eligible for inclusion if they met the following criteria:

- (1) Any type of peer-reviewed published systematic review concerning management of chronic MSK pain (ie, not including pelvic pain, chronic primary headache, or orofacial pain and chronic primary visceral pain);
- (2) Published in English;
- (3) Focused on adults or reported separate findings from adult studies;
- (4) Based on at least 3 randomised studies focusing on any intervention for chronic MSK pain (defined as pain lasting at least 3 months or longer or pain described as “chronic,” “recurrent,” or “persistent”); and
- (5) Reports on at least one outcome of chronic musculoskeletal pain formulated by the IMMPACT recommendations or quality of life, sleep, work-related outcomes, or economic factors.

We excluded studies which were not based on a systematic search and synthesis (eg, narrative reviews, scoping reviews, editorials, and cross-sectional studies); nonhuman research; studies focusing solely on children (younger than the age of 18); systematic reviews investigating chronic secondary musculoskeletal pain (ie, chronic pain in bones, joint, and tendons arising from an underlying disease classified elsewhere);²⁰ studies only focusing on chronic MSK pain diagnosis, assessment, or prevalence; and studies published more than 20 years ago. If multiple versions of the same systematic review were identified, we only included the most recently published version. During the process of generating data for this EGM, a new MSK pain condition appeared in the literature, ie, long-COVID (SARS-CoV-2) MSK pain.⁸ At this stage, it is not known if this is a condition which will persist for many years, and hence, long-COVID MSK pain was not included.

2.3. Search strategy

We developed a highly sensitive search together with an experienced research librarian. The literature search included medical subject headings (eg, MeSH in PubMed and Emtree in Embase) and text words related to chronic MSK pain (see search in appendix 1). We conducted the search in the following databases: Embase by OVID, Medline by PubMed, the Cochrane Library, and PsycINFO.

2.4. Study selection

All citations from the literature search were imported into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Duplicates were removed using Covidence and Endnote and through a manual screening. Citations were kept in Covidence, and the subsequent screening and data extraction were completed using Covidence. Three authors (K.D.L., M.N.C., and R.E.L.) independently screened the titles and abstracts of the reviews. A fourth author (M.S.R.) was available to resolve any conflicts. Full-text reviews were screened independently by 3 authors (K.D.L., M.N.C., and R.E.L.) to assess the final inclusion into the review. Disagreements were solved through consensus with a fourth author (M.S.R.).

2.5. Data collection

We extracted data using Covidence and used standardised data extraction forms. The senior author (M.S.R.) instructed K.D.L.,

C.D., M.K.B., and M.N.C. in extracting data, and several papers were piloted until consensus between all extracting authors and M.S.R. were reached. The items extracted from each study included title, main author, publication year, journal, country, population, primary objective, setting, inclusion/exclusion criteria, date of literature search, meta-analysis, types of included reviews, number of RCTs included, source of financial support, conflict of interest, type of intervention, control groups, outcomes, and timing of outcome assessments.

2.6. Risk of bias

The 16-item AMSTAR-2 critical appraisal tool was used to assess the included systematic reviews.³¹ The appraisal tool included 7 critical domains including preregistration of protocol, adequacy of the literature search, justification of excluded studies, risk of bias analysis from included studies, the appropriateness of meta-analysis methods (if used), the role of risk of bias in the interpretation of the results (including financial support and conflict of interest), and, finally, the impact of publication bias. Quality assessments were performed independently by K.D.L., C.D., and M.K.B. All papers were double checked for agreement by K.D.L. Disagreements were resolved at a consensus meeting with M.S.R. Each included systematic review was summarized using a quality rating as a reflective measure for the strength of the results obtained from the review. This score was established based on the criteria used in Birnie et al.⁴:

- (1) High: no or one noncritical weakness; the systematic review provided an accurate and comprehensive summary of the results of the available reviews that addressed the question of interest.
- (2) Moderate: more than one noncritical weakness; the systematic review had more than one weakness but no critical flaws. It may have provided an accurate summary of the results of the available reviews that were included in the review.
- (3) Low: one critical flaw with or without noncritical weaknesses; the systematic review had a critical flaw and may not have provided an accurate and comprehensive summary of the available reviews that addressed the question of interest.
- (4) Critically low: more than one critical flaw with or without noncritical weaknesses; the systematic review had more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available reviews.

2.7. Data synthesis

Findings from the systematic reviews were summarised through a narrative synthesis describing the settings, populations, interventions, controls, outcomes, and the timing of outcomes (See **Table 1** for

description). The findings were used to create a tabular view and pie charts of the evidence and potential gaps, which were used to establish *absolute gaps* (areas with little to no evidence) and *synthesis gaps* (areas with poor quality evidence). The population was categorised into the following pain categories: foot/ankle, knee, hip/groin, back (thoracic, lumbar, and sacral), neck, shoulder, elbow, wrist/hand, widespread pain (eg, fibromyalgia), complex regional pain syndrome, and other pain types. The specific diagnosis was registered if available. Intervention groups were categorised into the following: physical (eg, exercise, surgery, and needling), psychological (eg, cognitive behavioural therapy, acceptance, and commitment therapy), pharmacological (eg, paracetamol, nonsteroidal anti-inflammatory drugs, and gabapentin), education/advice, interdisciplinary, and other intervention groups, similar to terminology described by Birnie et al.⁴ Control groups were categorised into the following: physical, psychological, pharmacological, interdisciplinary, education/advice, inactive (eg, rest or wait-and-see), placebo/sham, or other control groups. Outcomes were categorised based on the IMMPACT recommendations into the following³⁷: pain, physical functioning, emotional functioning, participant ratings of improvement, satisfaction with treatment, symptoms, adverse events, and participant disposition (eg, adherence to the treatment regimen and reasons for premature withdrawal from the trial). Furthermore, measures of quality of life, work-related, sleep-related, and economic outcomes and others were added to the list of possible outcomes. Last, the timing of outcomes was categorised into the following: 0 to 3 months, 3 to 6 months, 6 to 12 months, and above 12 months. Source of funding and conflicts of interest were reported and extracted for the risk of bias assessment, but not otherwise used in the analysis.

3. Results

From the database searches, 5586 records were identified. Duplicates were removed ($n = 126$), leaving 5460 records for screening. Through title and abstract screening, 4299 records were excluded and 1161 records were available for full-text screening. Of these, 704 were deemed ineligible, leaving 457 unique reviews to be included for further data extraction and analysis (PRISMA flowchart can be seen in **Fig. 1**). Meta-analyses were used in 63% of the included reviews. For a detailed description of the included systematic reviews, see Appendix 2: Study characteristics. The overall EGM can be seen in **Figure 2**.

3.1. Setting

The included reviews contained several different settings. However, 58% ($n = 267$) of the included reviews lacked a clear description of the setting. The settings most often described were

Table 1
Description of population, intervention, control, outcomes and timing.

	Population	Intervention	Control	Outcomes	Timing
Description	Foot/ankle pain, knee pain, hip or groin pain, back pain, neck pain, shoulder pain, elbow, wrist or hand, widespread pain, complex regional pain syndrome, and other pain	Physical, psychological, pharmacological, education or advice, interdisciplinary, and others	Physical, psychological, pharmacological, interdisciplinary, education or advice, inactive, placebo or sham, and others	Pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, participant disposition, quality of life, work related, sleep related, economic outcomes, and others	0-3 mo, 3-6 mo, 6-12 mo, and +12 mo

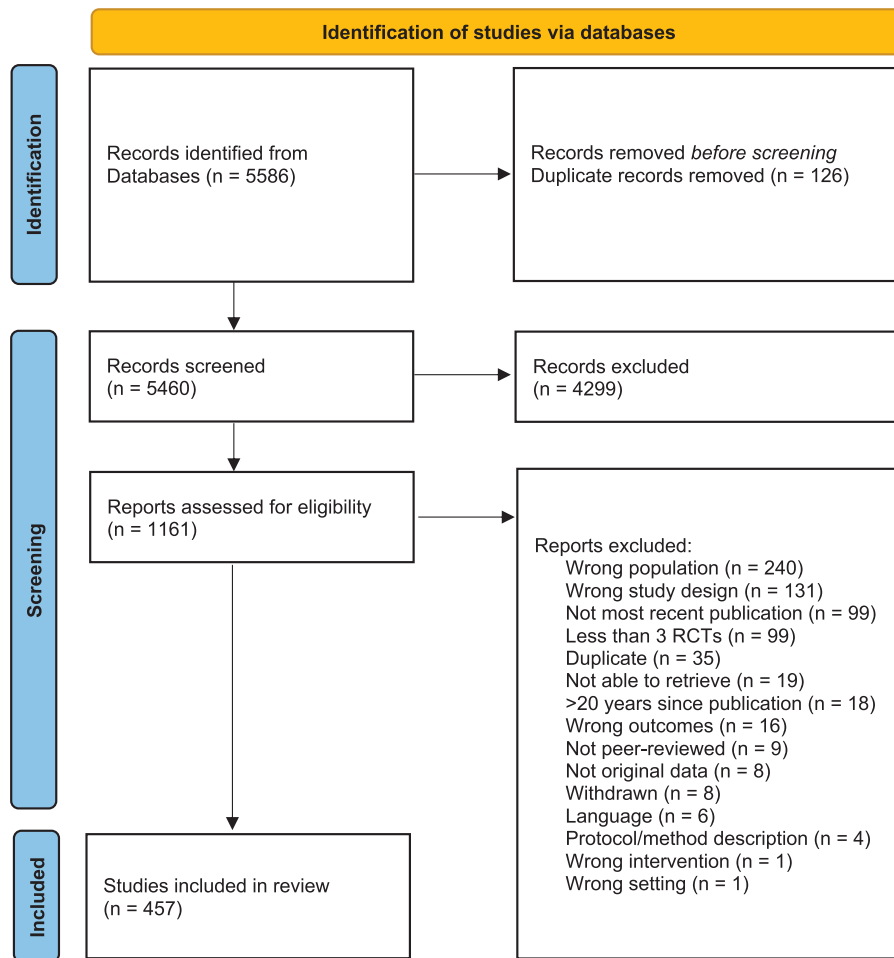


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart. PRISMA flowchart showing the screening and selection process for the systematic search with exclusion reasons provided. RCT, randomised clinical trial.

outpatient clinics (31%, $n = 142$), primary care (20%, $n = 94$), hospital (19%, $n = 85$), community (8%, $n = 34$), and, finally, 3% were categorised as other settings ($n = 14$) including specialised care centres, local clubs, and workplace.

3.2. Population

Back pain was the most frequently investigated painful condition with 55.5% ($n = 254$) followed by knee pain with 22% ($n = 101$), widespread pain with 17% ($n = 76$), neck pain with 14% ($n = 65$), foot or ankle pain with 8% ($n = 38$), shoulder pain with 8% ($n = 34$), hip pain with 5.5% ($n = 25$), elbow pain with 4% ($n = 20$), hand or wrist pain with 2% ($n = 8$), and complex regional pain syndrome with 1% ($n = 3$).

3.3. Interventions

The most frequently used intervention was physical intervention with 81% ($n = 372$) followed by education or advice with 20% ($n = 93$), pharmacological with 15% ($n = 73$), psychological with 11% ($n = 50$), others (eg, nutritional) with 4% ($n = 19$), and interdisciplinary with 3% ($n = 13$).

3.4. Control

The most frequently used control condition was physical intervention with 73% ($n = 334$) followed by placebo/sham with

61% ($n = 281$), education/advice with 34% ($n = 155$), inactive with 32% ($n = 145$), pharmacological with 21% ($n = 96$), psychological with 3% ($n = 14$), others (eg, nutritional) with 2% ($n = 15$), and interdisciplinary with 0.2% ($n = 1$).

3.5. Outcomes

The most frequently reported outcome measure was pain intensity with 97% ($n = 446$) followed by physical functioning with 87% ($n = 399$), quality of life with 39% ($n = 182$), emotional functioning with 27% ($n = 124$), symptoms and adverse events with 26% ($n = 121$), participants' rating of improvement with 22% ($n = 101$), others with 15% ($n = 70$), work related with 13% ($n = 64$), sleep related with 8% ($n = 38$), participant disposition with 5% ($n = 21$), and economic factors with 2% ($n = 9$). See outcomes used in individual studies (Appendix 3).

3.6. Timing of outcomes

For length of follow-up, most outcomes were reported between 0 and 3 months with 91% ($n = 416$), followed by 3 to 6 months with 75% ($n = 354$), 6 to 12 months with 60% ($n = 275$), and above 12 months with 28% ($n = 128$). See timing of outcomes used in individual studies (Appendix 3).

3.7. Quality assessment

Of the 457 reviews included, 41.4% were rated as critical low quality ($n = 188$), followed by 31.7% of low quality ($n = 145$), 10.3% were rated as moderate quality ($n = 47$), and, finally, 16.9% were rated as high quality ($n = 77$). The most common reason for being downgraded was not having a preregistered protocol, failing to describe the sources of funding in included reviews, and not providing a satisfactory explanation of the heterogeneity across included reviews. A full overview of the AMSTAR-2 quality rating can be seen in Appendix 2. Distribution of the evidence quality across interventions can be seen in Figure 3.

4. Discussion

This EGM with 457 unique systematic reviews found an overall low quality of systematic reviews pointing towards both synthesis gaps (areas with poor quality evidence) as well as absolute gaps (areas with little or no evidence). The absolute gaps were most clear for long-term outcomes (above 12 months) and non-pain-related outcomes (such as participant disposition). The most common interventions were physical (eg, exercise therapy), whereas the lowest number of systematic reviews investigated interdisciplinary care programs.

4.1. Explanation of findings

During the past 20 years, research has demonstrated that chronic MSK pain cannot be explained simply because of tissue damage.¹⁴ Despite this strong shift towards a multidimensional understanding of chronic MSK pain, a high proportion of interventions in the included systematic reviews had a biomedical focus (eg, exercises or pharmacological interventions), whereas multidisciplinary and psychological interventions had a very low representation. This is of concern as international organisations such as The International Association for the Study of Pain (IASP)

strongly advocate for a multidisciplinary approach to chronic pain management.¹² The interpretation of evidence is challenged by very heterogeneous control groups, whereas in pharmacological trials, placebo and sham groups are traditionally used. This is important as it controls for nonspecific effects, thus providing a better estimate of the true benefit of a drug. However, in the trials using physical interventions, the control groups were much more diverse, including other surgeries, exercise types, manual therapy, and various forms of acupuncture. This is a challenge when comparing the different treatment classes included in our EGM. Most of the included systematic reviews used short follow-up periods (0–3 months), and only a small number used long-term follow-up (+12 months). Research has highlighted that most people living with chronic MSK pain conditions experience fluctuating and recurrent pain, highlighting the need to measure the long-term effects of treatment.^{1,20} The lack of systematic reviews including long-term follow-up above 12 months may also be due to the challenge in retaining people in trials for more than a year, thus reducing the number of original trials suitable for such analyses.

4.2. Outcomes

Unsurprisingly, pain and physical functioning were the most used outcomes in almost all included systematic reviews. Despite the IMMPACT core outcome set having existed since 2003, only the minority of systematic reviews included emotional functioning, participant ratings of global improvement, symptoms, adverse events, and participant disposition. Chronic MSK patients have high healthcare use, lower work ability, and low quality of life. Therefore, it is surprising that only 2% of the included systematic reviews assessed the economic impact of the interventions being examined. As the healthcare resources are limited, it is of the utmost importance to understand the cost effectiveness of the interventions as this is pivotal knowledge before implementing new treatments into routine clinical care. Similarly, it is important



Figure 2. Mapping interventions for chronic musculoskeletal pain. Evidence and gap map showing interventions for chronic musculoskeletal pain overall. Types of interventions are listed within the rows, and IMMPACT outcome domains are listed in the columns. The size of the circles indicates a higher or lower number of systematic reviews. The number in circles indicates the number of systematic reviews identified. A lack of systematic reviews of any quality results in missing circles in the corresponding fields. IMMPACT, initiative on methods, measurement, and pain assessment in clinical trials.

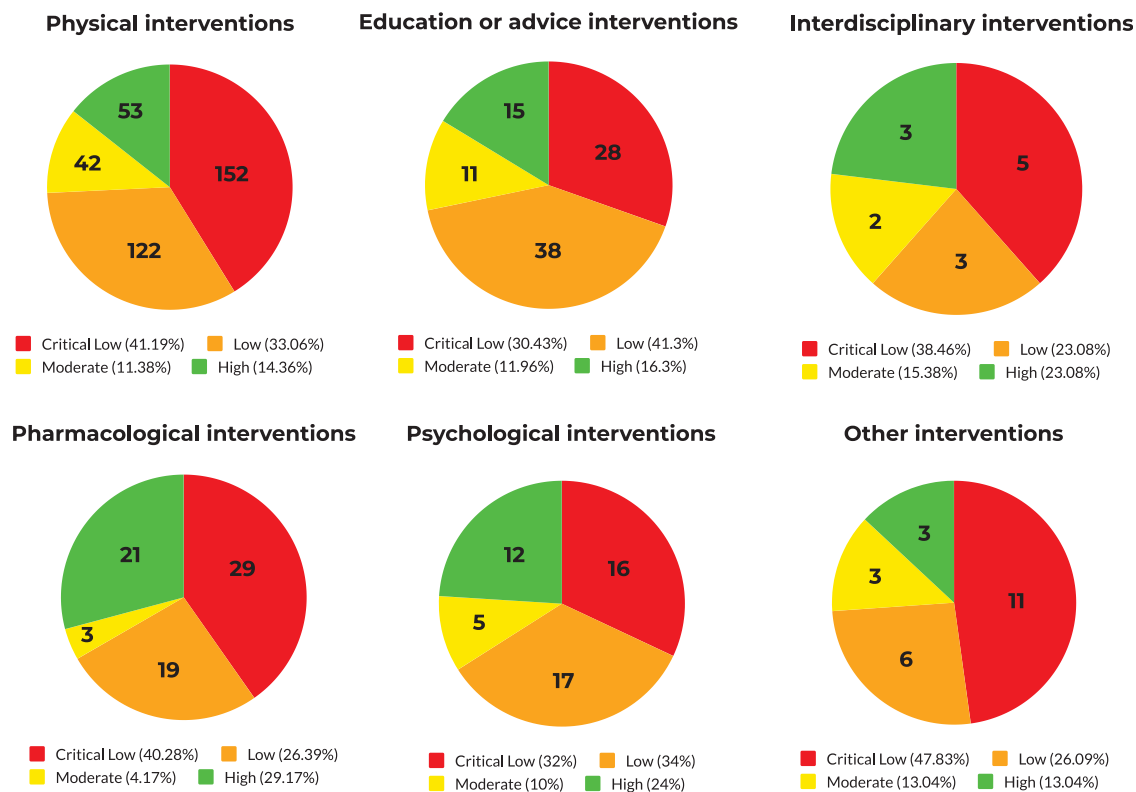


Figure 3. Distribution of evidence quality across intervention categories. Distribution (% , percentage) of the evidence quality across intervention categories. Numbers in circles refers to the number of papers within each category within each intervention. Red colour indicated critically low quality, orange colour indicates low quality, yellow colour indicates moderate quality, and green colour indicates high quality.

to understand the risks associated with the interventions being implemented. Adverse events describe unexpected medical problems that occur during treatment, but these were only reported in 26% of the included reviews.³⁰ Knowledge on adverse events is a key consideration that needs to be discussed with patients before recommending a certain management strategy. This issue was also raised by Howick et al.¹⁰ who surveyed health interventions examined by Cochrane and found that benefits were more often reported or tested compared with harm. As highlighted by Shaheed et al.,³⁰ nonpharmacological interventions often lack reporting on adverse events which makes it difficult to assess the “true” effectiveness of these interventions. Finally, Karran et al.¹⁵ highlighted the association with social disparities in lower back pain outcomes and interventions suited to target these may improve outcomes related to reducing health inequities. Therefore, it is crucial for future studies within all types of interventions to appropriately collect and report information regarding sociological factors and adverse events. In addition, it is important for future studies to evaluate interventions through economic lenses using health economic evaluation frameworks such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).¹¹ The absence of reporting other relevant outcomes in reviews neglects the possibility of interventions being successful within domains other than pain and physical functioning.

4.3. Comparison with other evidence and gap maps

Recently, 2 similar EGMs within paediatric chronic pain^{4,5} demonstrated that most systematic reviews examined the effect of psychological interventions and only 15% of the included

systematic reviews tested physical interventions.⁴ In this EGM, 81% of all interventions were physical and only 11% were psychological interventions. One might speculate that this difference may arise from the difference in professions managing the conditions, with psychologists often being involved in the management of children with long-standing pain, whereas physiotherapists, surgeons, and rheumatologists are more commonly involved in treating chronic musculoskeletal pain in adults. In Birnie et al. (2020), one third of the included reviews were rated high quality (34%), whereas the current study only found 16.9% of the studies included to be of high quality, indicating an overall lower quality of systematic reviews within research in adults living with chronic MSK pain. One of the explanations for the overall low quality of the evidence may be the inclusion of literature from the past 20 years. Reviews published in the early 2000s were conducted when it was not yet recommended to prospectively register systematic reviews. In addition, no sources were available to assist the reporting such as the PRISMA reporting guidelines for both protocols and final reports. These factors may partially explain the varying quality of systematic reviews within this area.

4.4. Comparison with priority setting partnerships

Involvement of stakeholders within research on their own conditions has increasingly gained favour through the last decade. Stakeholder involvement can be performed in many ways, with various degrees of involvement and in different steps of the research cycle. Recently, research priorities were captured from over 1000 people living with chronic MSK pain, their relatives, and healthcare practitioners.¹⁸ The results highlighted

the need for increased attention towards improvement of chronic MSK pain management education expressed both by the people suffering from pain and the relevant healthcare practitioners. Interestingly, 20% of the studies in the EGM used an educational intervention. Hence, this warrants further investigation into the components needing more research to match the need for improved knowledge on the condition. Similar priorities have been seen in paediatric chronic pain research and general chronic pain care.^{3,32} The least used intervention in our study was the interdisciplinary intervention. From previous priority setting partnership studies, it is known that an increased focus on improving interdisciplinary care is warranted across both the broad domain of chronic MSK pain, common hand and wrist conditions, fractures of the lower limb, and knee arthroplasty.^{7,14,19} Previously, a comparison between the priorities set by the important stakeholders and the existing evidence has been conducted.⁴ Hopefully, researchers within this field can benefit from comparing the existing literature mapped in this EGM and priority setting partnerships to increase the relevancy of their research and, ultimately, improve the future care for people living with chronic MSK pain.

4.5. Limitations

A potential limitation in this EGM is the search strategy. For pragmatic reasons, we were unable to tailor our search strategy to each specific site and the accompanying diagnoses across all musculoskeletal disorders, which may mean that we missed specific conditions. Similarly, we restricted our inclusion criteria to include only systematic reviews covering 3 or more RCTs and discarded citation tracking. This may have excluded systematic reviews based on a small number of trials and potentially also other relevant systematic reviews although it is unlikely that this would have changed our overall conclusions. Furthermore, some of the interventions may have been categorised in multiple categories (eg, injectional therapies), which might have influenced the distribution of the EGM. Future EGMs might benefit from a more detailed categorisation of interventions and control groups, as a more detailed description would provide researchers with more guidance on where to focus their research. Settings can be categorised differently across countries, thereby influencing the categorisation of settings in this study. However, most of the studies included in the EGM did not describe the settings adequately. These discrepancies warrant increased focus on aligning the description of settings across countries and ensuring that future studies describe the settings in detail.

4.6. Implications

Comparing the findings from this study with existing priority setting partnership studies highlighted the limitations of traditional systematic reviews as many research questions require alternative methods to be assessed. Furthermore, considering the contrasts between our priority setting partnership study¹⁸ and this EGM, we suggest that future research prioritizes mission-oriented strategies that link activities and objectives between all stakeholders and take advantage of the interplay between these organizations to ensure relevant populations, interventions, and outcomes are included.¹³ Potentially, a more patient-centred approach to how we conduct our research can move our field to the better and facilitate high-value care. Future reviews may need to think outside the traditions of systematic reviews with meta-analyses and turn towards methods embracing complexity and more open-scoped research questions, such as mixed-methods

studies or realist reviews aiming to explain what works for whom, under what circumstances, and how.^{16,25,26} Finally, future studies need to adhere more to existing reporting guidelines in terms of describing intervention used. Greater clarity in the description of the intervention will help both researchers and clinicians in interpreting the effectiveness of the respective intervention and increase the likelihood of successful implementation into clinical practice.

5. Conclusion

This contemporary EGM of management strategies for people living with chronic MSK pain emphasises the current low proportion of high-quality systematic reviews. The EGM provides guidance to future research with knowledge on the evidence and gaps within the field of chronic MSK pain. From this study, it was evident that most of the included reviews focused on physical interventions and pain intensity as the outcomes for the management of chronic MSK pain. The results from this study highlight that more high-quality research is warranted and that specific attention to pharmacological, psychological, and interdisciplinary interventions is needed. Finally, future research should consider using other outcomes such as symptoms, adverse events, participant rating of improvement, participant disposition, and work, sleep, and economic-related outcomes.

Conflict of interest statement

M. S. Hoegh has received support from nonindustrial, professional, private, and scientific bodies (reimbursement of travel costs and speaker fees) for lectures on pain, and he receives book royalties from Gyldendal, Munksgaard Denmark, FADL, and Muusmann publications. Otherwise, none of the authors declare conflicts of interest.

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Contributions: K. D. Lyng and M. S. Rathleff drafted the first version of the protocol. All authors, except C. Djurtoft and M. K. Bruun, contributed to the conception and design, including decisions of the primary and secondary outcomes, and provided critical scientific input to the protocol. K. D. Lyng, R. E. Lauritsen, and an experienced research librarian developed the search strategy for this study. K. D. Lyng, C. Djurtoft, M. K. Bruun, M. N. Christensen, and R. E. Lauritsen conducted the screening and data extraction process. K. D. Lyng, C. Djurtoft, M. K. Bruun, and M. S. Rathleff performed the data analysis. All authors provided substantial input and feedback to the manuscript and approved the final version of the manuscript. All authors have read and approved this manuscript.

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