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The bi-directional relationship between sleep problems and chronic musculoskeletal pain – A systematic review with meta-analysis

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The bi-directional relationship between sleep problems and chronic musculoskeletal pain – A systematic review with meta-analysis

Chronic musculoskeletal pain and sleep problems/disorders exhibit a recognized bi-directional relationship, yet systematic investigations of this claim, particularly in a prospective context, are lacking. This systematic review with meta-analysis aimed to synthesize the literature on the prospective associations between sleep problems/disorders and chronic musculoskeletal pain. A comprehensive search across six databases identified prospective longitudinal cohort studies in adults examining the relationship between sleep problems/disorders and chronic musculoskeletal pain. Random-effects meta-analyses, using the Hartung-Knapp adjustment for 95% confidence intervals (CIs), were conducted and all results presented as Odds ratios (ORs). Certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach. Including 16 papers from 11 study populations (116,746 participants), meta-analyses indicated that sleep problems at baseline may heighten the risk for chronic musculoskeletal pain in both short- (OR 1.64, 95% CI 1.01 to 2.65) and long-term (OR 1.39, 95% CI 1.21 to 1.59). The evidence for different sleep problem categories was very uncertain. Chronic musculoskeletal pain at baseline may increase the risk for short-term sleep problems (OR 1.56, 95% CI 1.02 to 2.38), but long-term evidence was very uncertain. The impact of only local or only widespread pain on short-term sleep problems was very uncertain, while widespread pain may elevate the risk for long-term sleep problems (OR 2.0, 95% CI 1.81 to 2.21). In conclusion, this systematic review with meta-analysis suggests that sleep problems are associated with an increased risk for chronic musculoskeletal pain, but the bidirectional nature of this relationship requires further investigation.

Introduction

Painful chronic musculoskeletal conditions represent a major global health issue, afflicting more than one billion individuals worldwide[73]. Aside of the persistent pain, individuals grappling with chronic musculoskeletal pain (CMP) experience a multitude of other consequences, including a lower quality of life, elevated levels of depression, and increased disability levels when compared to those without pain[3]. The socio-economic ramifications of CMP are substantial, presenting a significant financial burden on healthcare systems and societies worldwide[27,70]. Despite significant progress in the field of healthcare, the incidence of CMP is rapidly growing[38]

Sleep problems (e.g. poor sleep[40]), and sleep disorders (e.g. insomnia[41] or obstructive sleep apnoea[8,26]) are other highly prevalent serious health issues. Impaired sleep has been linked to lower quality of life, poorer general health, higher levels of depression[40] and decreased physical function[15,19]. This is a striking parallel to CMP and, potentially not surprisingly, the prevalences of sleep problems and sleep disorders in people with CMP are very high with around 75%[65] and 44%[39] respectively.

Large numbers of studies have investigated the general link between sleep problems and CMP. The prevailing consensus in the field is that there is a bidirectional relationship between the two, with research indicating that CMP can exacerbate pre-existing sleep problems and vice versa, while both also serve as mutual risk factors for the development of the respective other condition[21,24,55]. Research on risk factors, defined here as a variable that precede the outcome and is associated with it[17], can be difficult to probe with predictive and causal interpretations often being mixed when it comes to relevant conclusions[17]. An enhanced understanding on the relationship between a risk factor and an outcome can be instrumental for identifying individuals at an elevated risk of developing a condition[17,67], potentially offering them increased general support. Though, it would be misguided to develop interventions targeting the risk factor based only on predictive evidence because causality cannot be implied[17]. In contrast, when a risk factor is deemed to exert a substantial causal

influence on the development of a condition, it can become a potential target for direct preventive interventions in specific populations and the findings can significantly influence policies[67].

Remarkably, despite the increased interest in the sleep-pain link in recent years, there is a paucity of comprehensive reviews regarding the prospective bi-directional relationship between sleep problems and chronic musculoskeletal pain, more specifically on their association with the development of sleep or pain new problems. The majority of existing reviews in this context primarily investigated general[24], post-surgical[69], paediatric pain populations[4] and specific CMP populations (e.g. Low back pain)[68]. Others focussed on the role of changes in sleep rather than the presence of a sleep problem [1] or on prognosis rather than the development of new sleep or pain problems [58]. The reviews were often narrative (or used narrative syntheses)[24,68] and only one systematic review with meta-analysis dedicated to the investigation of CMP has been published[55]. This sole systematic review offered support for the reciprocity between sleep problems and pain, but it had various limitations. For example, in their analyses, several studies examining the identical study populations were included, resulting in double counting of thousands of participants e.g.[48,63] or [44,66] and the utilization of unadjusted values did not allow for any potential causal interpretations due to the likely unaccounted confounding[55]. Therefore, the evidence in this field remains limited. Even more, previous reviews have not explored differences between different sleep problems/disorders, although this is an important gap in the literature as people with sleep problems/disorders are not a homogenous group. The same holds for the exploration of different pain problems, with no attention towards the differences between local vs. widespread pain so far. Therefore, this systematic review with meta-analysis aimed not only to overcome the limitations of the prior reviews but also to provide a more comprehensive overview of the current evidence on the following research questions:

1. Are sleep problems/disorders at baseline associated with an increased risk for the development of chronic musculoskeletal pain?

2. How are different categories of sleep disorders/problems at baseline associated with an increased risk for the development of chronic musculoskeletal pain?

3. Is chronic musculoskeletal pain at baseline associated with an increased risk for the development of sleep problems/disorders?

4. How are different chronic musculoskeletal pain problems (categorized as local vs. widespread) associated with an increased risk for the development of sleep problems/disorders?

Methods

For this review, the PRISMA guidelines[50] and the PERSiST guidance were followed[5]. The review protocol was prospectively registered on PROSPERO (CRD42023427992).

Search strategy and screening

Six databases (PubMed (including MEDLINE), Embase, Cochrane Library, Scopus, Web of Science and PsycINFO (via ProQuest)) were searched from inception till 20.07.2023 using relevant search terms for each of the concepts. The full search strings and results for each database can be found in supplementary file 1. The search strategy was developed with the support of two experienced librarians. The records found in each database were transferred to EndNote (desktop version) for duplicate removal. The removal of duplicates was done following a structured step-wise approach[22]. The resulting list of records was then transferred to Rayyan[49] where two independent researchers (NR, IA) screened titles, abstracts and full-texts. In case of disagreements, a third reviewer made the final decision (LDB). Forward and backwards citation tracking was used and the citations were also independently screened by the two researchers (Date: 23.08.2023). Furthermore, two trial registration databases were searched for any missing registered studies (https://www.who.int/clinical-trials-registry-platform and ClinicalTrials.gov) (Date: 12.09.2024). In a final step, two experts in the field were contacted and asked for any potentially missing studies. If there were doubts about study eligibility from the information provided in the study manuscript, authors of the respective studies were contacted two times within two weeks to inquire.

Eligibility criteria

Prospective longitudinal cohort studies with reports that were fully published and peer-reviewed were included in this review. Cross-sectional studies were excluded. To be included studies had to either investigate the association of sleep problems or sleep disorders at baseline with CMP at follow-up (Research aims 1 and 2) or the association of CMP at baseline with sleep problems or sleep disorders at follow-up (Research aims 3 and 4). This means that for aims 1 and 2, only studies investigating participants without CMP at baseline have been included and for aims 3 and 4 only studies investigating participants without sleep problems at baseline have been included. Studies that had CMP as outcome (Research aims 1 and 2) were only included if they specifically outlined that they had ensured that included participants were free of any (chronic) musculoskeletal pain at baseline even if the outcome was chronic widespread pain. Studies that provided data on mixed populations were included if it was possible to extract the data for the pain-free population at baseline.

CMP was defined using the International Association for the Study of Pain definition of chronic primary musculoskeletal pain and chronic secondary musculoskeletal pain with any conditions falling under these terms being included[25]. CMP had to be defined as having persisted for three months or longer. Additionally, studies that investigated people with chronic widespread pain, complex regional pain syndrome and post-surgical or post-traumatic chronic pain (E.g. after spinal surgery, arthroplasty, whiplash injury or musculoskeletal injury) were included, if fitting all other criteria, because these are commonly seen in musculoskeletal practice.

Any sleep problems, for example poor quality of sleep or perceived sleep disturbance, or sleep disorders (diagnosed using established diagnostic criteria), such as insomnia disorder, sleep apnoea or narcolepsy, were included in this review.

For all research aims, the exposure and outcome had to be presented as binary variable (present or absent) or data must have been presented in a way that allowed for the creation of two categories (present or absent). Studies only presented as abstracts, study protocols, conference papers, unpublished data, pre-prints and posters were excluded.

Outcomes

The outcome for research aims 1 and 2 was CMP. Any measurements (e.g. questionnaires, clinical interviews etc.) of CMP were allowed as long as they were fitting the criteria outlined above (i.e. pain duration >3 months and presented in a way that allowed to interpret the result as present/absent). For the research aims 3 and 4, the outcome was any sleep problem/disorder. Any subjective or objective measurements were allowed to measure the outcome as long as the result was presented as present/absent (or it could be recoded as such).

Data extraction

Two independent reviewers (TVW, JVH) performed the data extraction of the general study summaries using a standardized extraction form. The statistical data were extracted separately by two other independent researchers (IA, NR). Individual extraction tables were used for each research question. In all cases, a third reviewer was available for discussion and a final decision if there were any discrepancies between the extractions. All available statistical data including adjusted and unadjusted risk ratios (RRs), odds ratios (ORs) and raw data for 2x2 tables were extracted where available within the primary studies. Data were separated based on follow-up durations with short-term having been defined as 3 months to 3 years and long-term as longer than 3 years. If studies provided outcome data on more than one time point within one follow-up duration, the time point closest to the lower boundary of each grouping was used (i.e. closest to 3 months for short-term, closest to 3 years for long-term). If more than one group for exposure or outcome were presented in one paper, best fitting groups were created, and data combined using the inverse variance weight method[10]. More detail on the methods for combining groups are outlined in supplementary file 2. Measures of association that were provided as RRs were transformed into ORs using established formulas if adjusted values were available or 2x2 tables if only raw data were available[28]. The baseline risk of the control group was calculated for each study to perform the conversion from RRs to ORs. A sensitivity analysis was performed removing studies that originally provided RRs from studies that provided ORs if more than five studies were included in an analysis.

Authors of primary studies for which more information in context of the data extraction was required (e.g. missing data or unclear presentation) were contacted two times via e-mail (find an overview of the contacts and received responses in supplementary file 3).

For research aim 2, categories of sleep disorders were pre-specified, though no studies investigating specific sleep disorders were included. Details on the categories can be found in the pre-registered study protocol. For sleep problems, we were not able to pre-specify categories. Therefore, studies were grouped together and presented if two or more studies investigated reasonably comparable sleep problems based on their definitions.

Risk of bias assessment

The risk of bias (RoB) assessment was done by two independent researchers (NR, JP) using the ROBINS-E tool[53]. Any disagreements were resolved by discussion, but a third researcher would have been available to make the final decision (IA). RoB was assessed for each exposure individually, which means that different exposures within one study were assessed independently.

In the study protocol, a minimal set of confounders was pre-specified: age, sex, BMI and depression and anxiety at baseline. In case, only raw data were provided in a primary study or raw data had to be used for the analyses for a different reason (e.g. combination of groups was necessary via 2x2 table or transformation gave unreasonable results) then this study was rated as not having adjusted for the minimal set of confounders.

Data synthesis

Meta-analyses were performed if two or more studies were available for a research aim within one follow-up period. Inverse variance random-effects meta-analyses using the Paule-Mandel estimator to estimate between-study variance were performed with Hartung-Knapp adjustment (with ad-hoc adjustment) for the estimation of 95% CIs[34,57]. If available, maximally adjusted ORs from primary studies were used for the main analysis. If these were not given in primary studies, we transformed maximally adjusted RRs to ORs using the *effectsize* package in R. All ORs were log-transformed before the pooling to achieve approximate normality and back-transformed afterwards to ease interpretation.

The results are presented as estimated average ORs and 95% CIs as measures of precision. Bootstrapped 95% Prediction Intervals (PIs) were estimated as measures of heterogeneity[45] and for all meta-analyses the Q-statistics testing for heterogeneity as well as proportion of between-study variability using I^2 with 95% CI are presented[31]. Absolute risk differences for each outcome were estimated based on the given ORs and 95% CIs. The baseline risk was estimated based on the control group median baseline risk in the largest meta-analyses for each direction of effect. The absolute risk difference is described for each analysis that was statistically significant. Sensitivity analyses with slightly higher and lower baseline risks were performed and can be found in the supplementary files for each separate analysis.

Established algorithms for the detection of outliers and influential studies were used in analyses with more than five studies (Supplementary file 2).

All analyses were performed using the *meta*[6] and *metafor* packages in R[72]. The full R code can be found here https://osf.io/q6ba9/?view_only=1e4e4e5ad3074bfea43b2fbbdf7915bd.

Pre-planned sensitivity analyses were performed for analyses with five or more included studies (See details on sensitivity and sub-group analyses in supplementary file 4).

Certainty of evidence

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was used to assess the certainty of evidence for each meta-analysis[29]. A detailed outline of the used approach can be found in supplementary file 5. Publication bias was assessed using funnel plots and the Peter`s test if 10 or more studies were available in a meta-analysis[64].

Changes to pre-registered protocol

No significant changes to the pre-registered protocol were made.

Results

Study selection

19,120 records were retrieved from the database searches. 8,192 duplicates were removed and the titles and abstracts of the remaining 11,320 records were screened. The full-texts of 104 remaining records were retrieved and screened which resulted in a final set of 16 included papers. Detailed reasons for exclusion at full-text stage can be found in supplementary file 6. Of these 16 papers, nine reported on the same study (HUNT study)[42,43,48,59–63,66] but on different time points resulting in 11 different study populations overall included in the meta-analyses (Figure 1). Below more details on the HUNT study and how it was handled within this review are shown (see section on study and participant characteristics).

Figure 1

Study and participant characteristics

Nine of the 16 included papers reported on results of the HUNT study[42,43,48,59–63,66], a large prospective observational study within the Nord-Trøndelag County in Norway. Details on how the overlapping populations from the HUNT papers were handled in this review are outlined in supplementary file 7.

116,746 participants were included in the 11 different study populations. The different study populations came from Norway (n=6), Sweden (n=4) and Brazil (n=1). Nine of the 11 study populations were recruited from the general population, one included only teachers[12] and one university students[37]. Relevant details on all included studies can be found in supplementary file 8. Data from three study populations[12,13,37] were available for short-term analyses. For the long-term follow-up, data from nine study populations[2,32,33,37,43,47,48,59,66] were available.

Exposures and outcomes

Of the 11 different study populations, eight reported on sleep problems as exposure and CMP as outcome[2,13,33,37,43,47,59,66], one on CMP as exposure and sleep problems/disorders as outcome[48] and two reported on associations in both directions[12,32]. All included studies provided

data on sleep problems while no study used established diagnostic criteria to identify people with specific sleep disorders. Sleep problems were defined in various ways with 12 studies using self-developed questions. Only two included studies used existing validated questionnaires [2,12]. One study used an adapted version of a questionnaire [32] and one study used a previously published sleep-wakefulness form [37]. Many studies based their questioning on established diagnostic criteria for sleep disorders but did not use the criteria in full [e.g.][32,59]. As with the definition of sleep problems, questioned timeframes varied between studies with most studies asking for problems during the last one or three months.

A variety of different sleep problems were reported, in the 10 studies used in the main analyses in which sleep problems were the exposure. Only for two sleep problems, insomnia symptoms[37,59] (defined as problems falling asleep, staying asleep or with early awakening) and non-restorative sleep[2,37,47], two or more studies provided data for the same follow-up duration (Research question 2 – Long-term). Regarding the outcome in these 10 studies, in nine the outcome was local pain (including also people with possible widespread pain) and in one widespread pain only[2]. In 12 studies, no specific CMP problem was investigated but rather people with CMP in general. In one study each, investigation focussed on either chronic low back pain alone[12], chronic low back pain and neck pain [33], chronic low back pain and/or chronic lower limb pain [32] or chronic low back pain, neck and shoulder pain [13]. Of the three studies in which data on CMP as exposure was provided, two studies provided data on local pain (including also people with possible widespread pain)[12,32] and one study on both local and widespread pain combined and separately[48]. The outcomes in these three studies were insomnia symptoms in two studies[32,48] and poor sleep quality[12].

All included studies assessed sleep problems and pain via self-report.

Risk of Bias

Risk of bias was assessed on outcome level. 30 different outcomes were assessed of which 20 had some concerns and 10 were of high risk of bias. The most common issues were the lack of pre-

registration of protocols and analysis plans. The second most common issue was lack of adjustment for covariates or that adjustment did not include all pre-specified covariates. The overview of risk of bias per analysis is shown in the supplementary files for each outcome.

Research question 1: Are sleep problems/disorders at baseline associated with an increased risk for the development of chronic musculoskeletal pain?

Short-term

Based on the pooled results obtained in three studies[12,13,37], sleep problems at baseline may increase the risk of CMP at follow-up but the evidence is very uncertain (OR 1.64, 95% CI 1.01 to 2.65, 95% PI 0.57 to 4.26, GRADE: very low certainty) (Figure 2). Assuming a baseline risk of 20% (see Data synthesis section in the Methods), 91 more people per 1,000 (95% CI 2 to 198) with baseline sleep problems will develop CMP in the short-term compared to people without sleep problems at baseline.

FIGURE 2

Sensitivity analyses: The sensitivity analysis using a different adjustment model (with less variables that were in the pre-defined minimal adjustment set for this study) in one study[12] found that the 95% CI was crossing 1. The other analysis (minimally/unadjusted values) found no relevant differences to the main analysis. The results and forest plots of all sensitivity analyses can be found in supplementary file 9a (Tables 1 and 2; figures 2 and 3).

Long-term

Very low certainty evidence from eight studies[2,32,33,37,43,47,59,66] suggests that sleep problems at baseline may result in an increase in CMP at long-term follow-up (OR 1.39, 95%CI 1.21 to 1.59; 95% PI: 1.01 to 1.91, GRADE: very low certainty) (Figure 3). Assuming a baseline risk of 20%, 58 more people per 1,000 (95% CI 32 to 84) with baseline sleep problems will develop CMP in the long-term compared to people without sleep problems at baseline.

FIGURE 3

Sensitivity analyses: The sensitivity analysis using minimally/unadjusted values for all studies found a larger effect size (OR 1.51, 95% CI 1.22 to 1.87). All other sensitivity analyses found no relevant differences to the main analysis. The results and forest plots of all sensitivity analyses can be found in supplementary file 9b (Table 1; figures 2-9).

Influential studies: No study was identified as influential study. The results of the leave one out analysis can be found in supplementary file 9b (Figure 10).

Research question 2: How are different categories of sleep disorders/problems at baseline associated with an increased risk for the development of chronic musculoskeletal pain?

Short-term

For no sleep problem/disorder category more than one study was available to answer this research questions.

Long-term

Insomnia symptoms

The evidence from two studies[37,59] is very uncertain about the effect of insomnia symptoms at baseline on CMP at long-term follow-up (OR 1.35, 95% CI 0.02 to 103.32; 95% PI: 0.00 to 10931.61; GRADE: very low certainty) (Figure 4).

FIGURE 4

Sensitivity analyses: No sensitivity analyses found a relevant difference to the main analysis. The results and forest plots of all sensitivity analyses can be found in supplementary file 10 (Table 1, Figures 2 and 3).

Non-restorative sleep

The evidence from three studies[2,37,47] is very uncertain about the effect of non-restorative sleep at baseline on CMP at long-term follow-up (OR 1.25, 95% CI 0.65 to 2.41; 95% PI: 0.31 to 4.65, GRADE: very low certainty) (Figure 5).

FIGURE 5

306 *Sensitivity analyses*: No sensitivity analyses found a relevant difference to the main analysis. The
307 results and forest plots of all sensitivity analyses can be found in supplementary file 10 (Table 2,
308 Figures 5 and 6).
309 **Research question 3: Is chronic musculoskeletal pain at baseline associated with an increased risk**
310 **for the development of sleep problems/disorders?**
311 Short-term
312 CMP at baseline may increase the risk for sleep problems at short-term follow-up but the evidence
313 from one study[12] is very uncertain (OR 1.56, 95% CI 1.02 to 2.38; GRADE: very low certainty).
314 Assuming a baseline risk of 10% (see Data synthesis section in the Methods), 48 more people per
315 1,000 (95% CI 2 to 109) with baseline CMP will develop sleep problems compared to people without
316 CMP at baseline.

317 *Sensitivity analyses:* The sensitivity analysis using a different adjusted model (with less variables than
318 were in the pre-defined minimal adjustment set for this study) in one study[12] found that the 95%
319 CI was crossing 1. The other analysis (minimally/unadjusted values) found no relevant differences to
320 the main analysis. The results and forest plots of all sensitivity analyses can be found in
321 supplementary file 11a (Table 1, Figures 2 and 3).
322 Long-term
323 The evidence from two studies[32,48] is very uncertain about the effect of CMP at baseline on sleep
324 problems in the long-term follow-up (OR 1.56, 95% CI 0.21 to 11.34, 95% PI: 0.02 to 135.44, GRADE:
325 very low certainty) (Figure 6).
326 FIGURE 6
327 *Sensitivity analyses*: No sensitivity analyses found a relevant difference to the main analysis. The
328 results and forest plots of all sensitivity analyses can be found in supplementary file 11b (Table 2,
329 Figures 2 and 3).
330 **Research question 4: How are different chronic musculoskeletal pain problems (categorized as local**
331 **vs. widespread) associated with an increased risk for the development of problems/disorders?**

Local pain – Short-term

Local CMP at baseline may increase the risk for sleep problems at short-term follow-up but the evidence from one study[12] is very uncertain (OR 1.56, 95% CI 1.02 to 2.38; GRADE: very low certainty). Assuming a baseline risk of 10%, 48 more people per 1,000 (95% CI 2 to 109) with baseline local CMP will develop sleep problems compared to people without CMP at baseline.

Sensitivity analyses: The sensitivity analysis using a different adjusted model (with less variables that were in the pre-defined minimal adjustment set for this study) found that the 95% CI was crossing 1. The other analysis (minimally/unadjusted values) found no relevant differences to the main analysis. The results and forest plots of all sensitivity analyses can be found in supplementary file 12a (Table 1, Figures 2 and 3).

Local pain - Long-term

The evidence from two studies[32,48] is very uncertain about the effect of local CMP on sleep problems in the long-term (OR 1.48, 95% CI 0.44 to 4.99; 95% PI: 0.08 to 25.54; GRADE: very low certainty) (Figure 7).

FIGURE 7

Sensitivity analyses: No sensitivity analyses found a relevant difference to the main analysis. The results and forest plots of all sensitivity analyses can be found in supplementary file 12b (Table 2, Figure 2).

Widespread pain – Short-term

No studies provided data on the effect of widespread pain on sleep problems in the short-term.

Widespread pain – Long-term

The evidence from one study[48] suggests that widespread pain at baseline results in an increased risk for sleep problems at long-term follow-up (OR 2.0, 95% CI 1.81 to 2.21, GRADE: low certainty). Assuming a baseline risk of 10% (see Data synthesis section in the Methods), 127 more people per 1,000 (95% CI 111 to 143) with baseline widespread pain will develop sleep problems compared to people without CMP at baseline.

Sensitivity analysis: The sensitivity analysis with unadjusted/minimally adjusted values found a larger effect size (OR 2.64, 95% CI 2.41 to 2.89). The results and forest plots of all sensitivity analyses can be found in supplementary file 12b (Table 3, Figure 4).

GRADE

The detailed GRADE assessment for each meta-analysis can be found in supplementary file 13.

Discussion

This systematic review with meta-analysis investigating the bilateral prospective associations between sleep problems/disorders and CMP included 16 reports from 11 different study populations.

Very low certainty evidence was found for sleep problems at baseline being a risk factor for CMP at the short-term and the long-term follow-up. For the short-term, only three studies were included and the was PI very wide, indicating that future studies could change this finding. This uncertainty was also supported by the finding of a sensitivity analysis that using a different adjustment model from one included study changed the results to not statistically significant (crossing 1). In contrast, the long-term results remained highly stable in all sensitivity analyses and the PI also did not cross 1 giving confidence in the results. Though, downgrading of the meta-analysis to very low certainty was necessary due to the observational nature of the included studies and because the 95% CI for the risk difference crossed an effect size threshold. Insomnia symptoms and non-restorative sleep at baseline as exposures for the long-term follow-up were the only sleep problems investigated in two or more studies. For both, the available data was insufficient to reach any conclusions. No studies investigated specific sleep disorders at baseline as exposure.

For the association between CMP at baseline as exposure and sleep problems/disorders as outcome, very low certainty evidence found a negative effect for the short-term. Though, this result came from only one study and was not stable in sensitivity analyses. For the long-term, two studies found very

low certainty evidence for no effect. One needs to consider in this context that the 95% CI was very wide as was the PI, making it likely that future studies might change this result. This review further investigated if dominant local pain as exposure was linked to sleep problems. For the short-term, very low certainty from one study found an effect of local pain at baseline as exposure though sensitivity analyses using a different adjustment model from the included study reached non-significant results. For the long-term, very low certainty found no effect but also here one needs to consider the wide 95% CI and PI. For WPS at baseline as exposure, low certainty from one study showed it to be a risk factor for the development of sleep problems. This result was only downgraded for the observational nature of the included study.

The results of this systematic review are mostly in line with other publications in this field [24,56,68]. However, there were some relevant differences to a recent systematic review with meta-analysis by Santos et al. (2023)[56] who investigated the prospective bilateral association between sleep problems and CMP. As in this review, they also found an association between sleep problems at baseline and future CMP but also an association for the other direction. The latter is different to this review where only an association in the short-term was found. Also, the effect sizes found in Santos et al. (2023)[56] were significantly larger. These differences can be explained by a number of reasons: 1) stricter inclusion criteria used in this review, especially for CMP; 2) the separation of follow-up durations in this review into short- and long-term versus a single analysis for all follow-up durations in Santos et al. (2023)[56]; 3) the unit of analysis error in Santos et al. (2023)[56] due to the inclusion of different HUNT studies that investigated the same study population in the same analyses 4) the use of unadjusted data for the analyses in Santos et al. (2023)[56] versus the use of adjusted data in this review.

Research implications

There are a number of research implications in context of this review. First, due to ethical reasons (i.e. it is unethical to experimentally induce long-term sleep problems or CMP in people) it is not possible to investigate the prospective associations between sleep problems and CMP in a randomized

controlled trial. This means that to be able to explore causality between sleep problems/disorders and CMP, one can only rely on prospective longitudinal cohort studies whereby strong assumptions around relevant confounders need to be made in context of their interaction with the exposure and outcome variables but also other relevant factors[67]. While in the included primary studies, variables for adjustments were mostly described, the reasoning behind their choice was generally missing or only described in short. Future studies should use methods like directed acyclic graphic (DAGs) to make the underlying assumptions on variable interactions transparent and to clearly outline the reasoning for covariate adjustments[67]. Ideally, DAGs and set of confounders should be specified in a protocol or analysis plan pre-registration. Additionally, studies using experimental sleep fragmentation and deficiency paradigms can strengthen the argument for a causal link between sleep problems and CMP by identifying potential mechanisms of action. Recent reviews in this context have shown that there are a number of different potential pathways that could explain a causal influence though the research is currently limited [14,30] and further well designed studies are needed to strengthen the current knowledge base.

Second, future studies should pre-register their protocols and analysis plans before starting recruitment. None of the primary studies included in this review did this which means that there was a possibility for post-hoc adaptions of analyses and study protocols, a significant problem in clinical research. Third, all included primary studies in this review used complete-case analyses, mostly without providing detailed information on the missing participants, reasons for missingness and without performing sensitivity analyses. This makes it difficult to judge the influence of the missing data on the overall analysis. Future studies should consider established methods to deal with missing data (e.g. multiple imputation) and ideally pre-register a plan on how handling of missing data will be done[35]. Fourth, the sleep problems used and their definitions in the included primary studies, were highly heterogeneous. There are commonly utilized and validated ways of assessing different aspects of sleep such as poor sleep quality (Pittsburgh sleep quality index [PSQI][11]) or also insomnia (Diagnostic and Statistical Manual of Mental Disorders 5 [DSM-5] criteria[52] and insomnia severity

index [ISI][7]) in research. For comparability purposes, researchers should prefer the use of these over self-developed questions, less commonly used questionnaires or adaptions of questionnaires and diagnostic criteria. This will improve the ability to pool studies in future reviews and allow for more in-depths analyses (e.g. compare different sleep disorders). Fifth, none of the included studies specifically investigated people diagnosed with sleep disorders (e.g. insomnia disorder) using a full set of established criteria. Considering that people with diagnosed sleep disorders tend to have more significant symptoms compared to people with merely a sleep problem, it remains unclear whether there is a difference in risk for future CMP between the two groups. The hypothesis that increased sleep problems might be linked to an increased risk for CMP is supported by the findings of a number of studies included in this review that used some sort of grading within the group of people with sleep problems (e.g. based on frequency or number of symptoms)[2,43,59]. In these studies, people with more sleep problems had a higher risk to develop future CMP than people with less sleep problems but this was not specifically investigated as part of this review. Considering that people with sleep problems are not a homogenous group it is therefore pertinent to investigate specific groups of sleep problems/disorders in detail. Even further, sub-groups of these disorders that have been found to be of higher risk for other conditions (e.g. hypertension, diabetes, depression), e.g. people with insomnia and objective short sleep duration[18,23,71], could be a specific focus. Sixth, all studies but one were performed in Scandinavian countries (i.e. Norway and Sweden) and 9 of 16 included studies within the same study set-up (The HUNT study), which may limit the generalizability of the findings. More large-scale studies in countries outside of Scandinavia and Europe need to be performed to be able to increase confidence in the transferability of the results. Seventh, for research aims 3 and 4, included studies did not present data on the percentage of people that had received musculoskeletal surgery within the group of CMP cases. Considering that sleep outcomes in patients with post-surgical CMP might differ from people with CMP of other causes, more research into these specific subgroups is required.

Clinical implications

The findings of this review have clinical implications. Sleep problems were found to be a risk factor for CMP. While this means that an association was found, it is difficult to judge, based on the current evidence, if this link is causal (see discussion above). Though, a number of mechanisms have been proposed in the literature on how sleep problems could possibly increase the risk for CMP including increased systemic low-grade inflammation, higher levels of depression and anxiety and increased nociceptive facilitation[20,30,46]. While having evidence on possible mediating mechanisms can support the notion for a causal link, more research is needed to investigate causality of this link. In the meantime, one should consider screening for sleep problems/disorders in clinical practice and the general population, not only to potentially reduce cases of incident CMP (if there is a causal link) but also to help to prevent a host of other conditions linked with sleep problems/disorders (e.g. depression, hypertension, cardiovascular diseases[36]). There have been recent calls for this as compelling data shows that sleep problems/disorders are highly prevalent worldwide[36]. The availability of easy-to-use assessment tools and questionnaires (Stop-Bang questionnaire[16], ISI[7], PSQI[11]) means that investigating sleep issues can be done in a time-efficient manner.

The uncertain results on the association between CMP and future sleep problems should not discourage clinicians from screening for CMP. As with sleep problems, CMP is a public health concern[73] and screening is indicated for a variety of reasons in different settings. Importantly, when a person with CMP has been identified, pain management options and support need to be available which go beyond medication which can in itself at times have negative impact on sleep[9,54].

Strengths and limitations

This study has different strengths. A detailed protocol, including analysis plan, sensitivity analyses and minimal set of confounders was pre-registered and followed as planned. The search strategy was extensive and has been developed with support of experienced librarians. Strict inclusion criteria for CMP were used to be able to make specific conclusions. Adjusted results of most primary studies (only one study did not provide results without adjustments) were used in the analyses and sensitivity analyses were performed to check the robustness of the findings. The R code for the full analysis was

shared on the open science framework platform to increase transparency and to allow other researchers to re-use it.

This review has also some limitations. First, the baseline risks for the absolute difference were based on the control groups of the largest meta-analyses and not pre-specified. It was felt that this is most appropriate as comparable data (considering population and follow-up durations) is limited in the literature. Sensitivity analyses with higher and lower values are presented in the supplementary file for full transparency. Second, adjusted results from primary studies were used for the analyses but no multivariate meta-analyses were performed due to the variable availability of data on important confounders in primary studies. Third, it was not possible to perform sub-group or meta-regression analyses due to the small numbers of included studies. This prevented further testing of potential sources of heterogeneity. Fourth, the decision on the minimal set of confounders was made based on discussions between the authors but without the use of any more formal and transparent tools (e.g. DAGs)[67].

Conclusions

The findings of this systematic review with meta-analysis, encompassing 16 papers from 11 different study populations, indicate with very low certainty evidence that sleep problems/disorders at baseline are a risk factors for CMP in both short-term and long-term. Further analyses on different sleep problems were inconclusive due to the limited number of available studies. Very low-certainty evidence indicates an association between CMP at baseline and sleep problems/disorders in the short- but not the long-term. Low certainty evidence showed that widespread pain at baseline might be a risk factor for sleep problems/disorders in the long-term. The evidence for local pain was inconclusive. However, these analyses were based on a small number of studies and should be considered with caution.

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Figure legends:

Figure 1: PRISMA flow diagram[51] showing the structure of the search and screening process

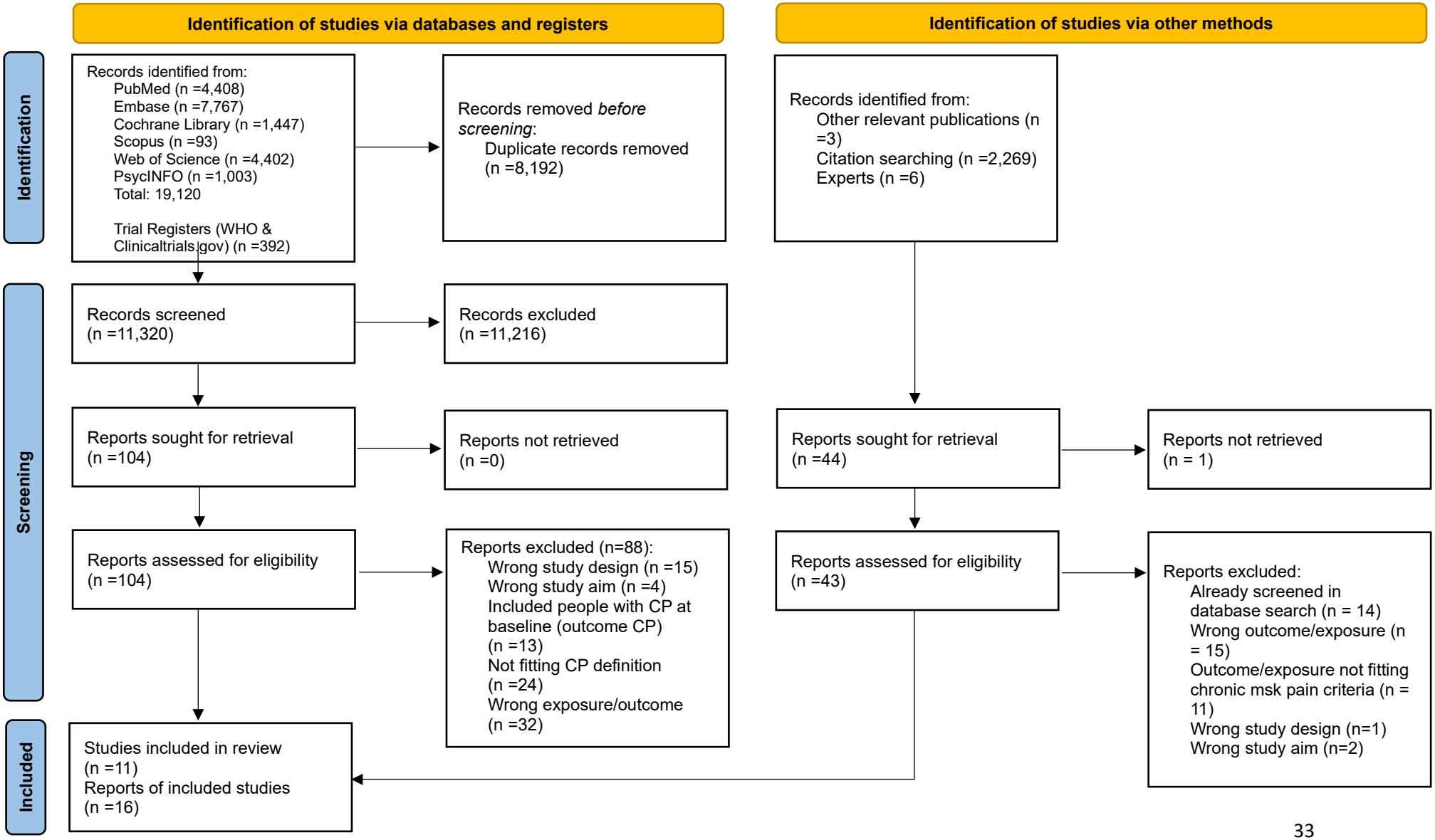

Figure 2: Forest plot showing the results of the meta-analysis for sleep problems/disorders at baseline on chronic musculoskeletal pain at short-term follow-up (Abbreviations: CI = Confidence interval, HK = Hartung-Knapp, OR = Odds ratio).

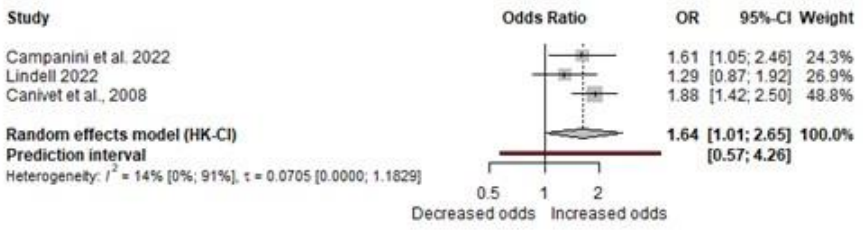

Figure 3: Forest plot showing the results of the meta-analysis for sleep problems/disorders at baseline on chronic musculoskeletal pain at long-term follow-up (Abbreviations: CI = Confidence interval, HK = Hartung-Knapp, OR = Odds ratio).

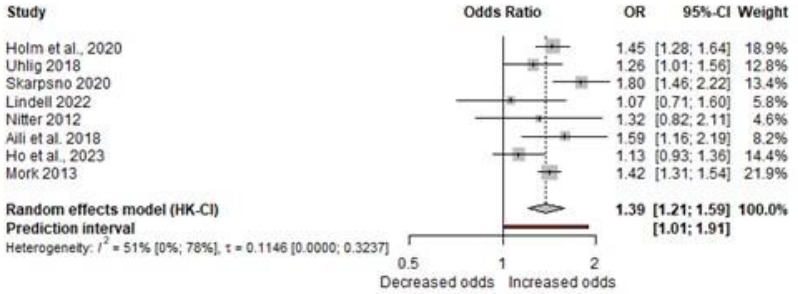

Figure 4: Forest plot showing the results of the meta-analysis for insomnia symptoms at baseline on chronic musculoskeletal pain at short-term follow-up (Abbreviations: CI = Confidence interval, HK = Hartung-Knapp, OR = Odds ratio).

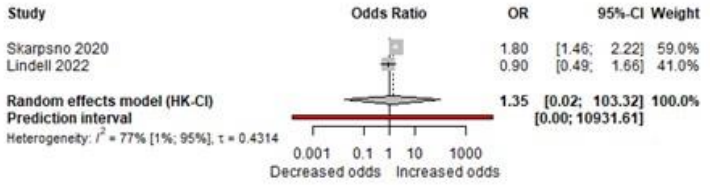

Figure 5: Forest plot showing the results of the meta-analysis for non-restorative sleep at baseline on chronic musculoskeletal pain at short-term follow-up (Abbreviations: CI = Confidence interval, HK = Hartung-Knapp, OR = Odds ratio).

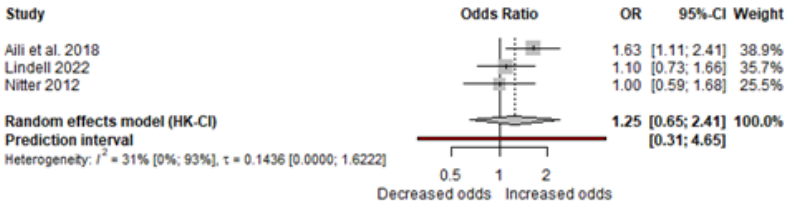

Figure 6: Forest plot showing the results of the meta-analysis for chronic musculoskeletal pain at baseline on sleep problems/disorders at long-term follow-up (Abbreviations: CI = Confidence interval, HK = Hartung-Knapp, OR = Odds ratio).

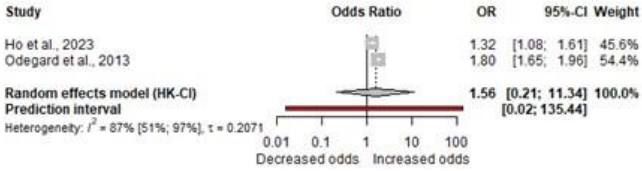

Figure 7: Forest plot showing the results of the meta-analysis for local chronic musculoskeletal pain at baseline on sleep problems/disorders at long-term follow-up (Abbreviations: CI = Confidence interval, HK = Hartung-Knapp, OR = Odd