Sleep quality as a mediator of the relation between depression and chronic pain: A systematic review and meta-analysis

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Abstract

Introduction: Chronic pain and depression represent two global health problems with considerable economic consequences. While the existing literature reported on the relation between depression and pain conditions, meta-analytic evidence backing the mediating role of sleep disturbance as one of the main symptoms of depression is scarce. To examine the extent to which sleep disturbance mediates the depression- chronic pain association, we conducted a systematic review and meta-analysis of the associations of chronic pain, depression, and sleep quality.

Methods: We systematically searched for literature in Medline and other relevant databases and identified cohort and case-control studies on depression, sleep disturbance, and chronic pain. Fourty-nine studies were eligible, with a total population of 120,489 individuals. We obtained direct and indirect path coefficients via two-stage meta-analytic structural equation modelling (TSSEM), examined heterogeneity via subgroup analyses, and evaluated primary studies quality.

Results: We found a significant, partial mediation effect of sleep disturbance on the relation between depression and chronic pain. The pooled path coefficient (coef.) of the indirect effect was 0.03 (95% confidence interval (CI): 0.01-0.05) and accounted for 12.5% of the total effect of depression on chronic pain. This indirect effect also existed for cohort studies (coef. = 0.02, 95%CI: 0.002-0.04), European studies (coef. = 0.03, 95% CI: 0.004-0.05), and studies that adjusted for confounders (coef. = 0.04, 95% CI: 0.01-0.09).

Conclusion: Sleep disturbance partially mediates the association between depression and pain. Although plausible mechanisms could explain this mediation effect, other explanations, including reverse causation, must be further explored.

Keywords: Depression; meta-analysis; pain; sleep; structural equation modelling

1. Background

Depression and pain contribute largely to the global burden of disease.[1] A study in European countries indicated that almost 30% of patients with major depressive disorders reported a pain episode.[2] The direction of the relation between depression and pain, however, is not straightforward. Previous reviews have shown some evidence of the bidirectional relationship between pain and depressive disorders,[3] with pain being either a predictor or a consequence of depression.[4] Furthermore, it has been shown that pain often induces depression.[5] Longitudinal studies have assessed the effect of depression on pain and indicated that remission of depression was associated with a significant decline in pain.[6,7] However, this effect could have been mediated by other factors, such as sleep quality. Indeed, previous studies have shown an association between sleep quality and pain,[8,9] and the risk of pain development was 50% higher among people who reported sleep disturbance.[10] Sleep disturbance is one of the most consistent symptoms associated with depressive disorder.[11] This association is probably bidirectional, and both variables may play the role of cause or consequence. Nonetheless, these findings suggest that depression, pain, and sleep disturbance are interrelated. As pain, sleep, and depression co-exist and their detrimental impact on individuals and society is large, and as the evidence on the indirect effects varies across primary studies,[12–14] elucidating the relations between these factors through a meta-analytic clarification of pooled effect sizes could contribute to the improvement of the life of individuals suffering from pain.[15]

Consequently, the present study aims to synthesize the indirect effect of depression on pain via sleep disturbance. Specifically, we conducted a meta-analysis of longitudinal studies (i.e., non-cross-sectional studies). Using the PECO framework (Population, Exposure, Comparison and Outcome), we formulated our research question as follows: To what extent does sleep disturbance, self-reported or measured by a validated

questionnaire, mediate the relation between exposure to depression and the outcome "chronic pain", defined as pain in any site of the body that persists or recurs for longer than 3 months in a population of any age?

2. Methods

We registered this meta-analysis at Prospero (CRD42022338201) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[16]

2.1. Search strategy

To identify relevant primary studies, we searched the following databases: MEDLINE, PsycInfo, Scopus, Conference Proceedings Citation Index (Web of Science), Open Access Theses and Dissertations (OATD), and WHO Global Index Medicus (GIM) with its five databases: African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asia Region (IMSEAR), and Latin America and the Caribbean Literature on Health Sciences (LILACS). The general search strategy in Medline was: ((depress*[Title/Abstract]) OR (depression[Title/Abstract]) OR ("depressive disorder"[Title/Abstract]) OR ("mood disorder"[Title/Abstract]) OR ("depressive neuroses"[Title/Abstract]) OR (melancholia[Title/Abstract])) AND ((pain[Title/Abstract]) OR (fibromyalgia[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR (osteoarthritis[Title/Abstract]) OR (migraine[Title/Abstract]) OR (headache[Title/Abstract]) OR (neuralgia[Title/Abstract]) OR (complex regional pain syndrome [Title/Abstract]) OR (Chronic widespread pain [Title/Abstract]) OR (neuropathic pain [Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract])) AND (("sleep disorders"[Title/Abstract]) OR ("dyssomnias"[Title/Abstract]) OR ("insomnia"[Title/Abstract]) OR ("sleep apnea"[Title/Abstract]) OR

("narcolepsy"[Title/Abstract])) Filter: Observational studies. Similar strategies were used for the other databases. Table S1 in the supplementary material shows the detailed search strategy. Each database was searched up until 21 May 2022. The search was not confined to specific countries or languages, and reference lists from relevant articles were explored manually.

In case of queries regarding the data, the authors of published studies were contacted for clarification or additional data request. The search was independently completed by two authors (RK and NM), one of the authors subsequently reviewed the strategy (BT), and the results were compared. Duplicates were removed.

2.2. Eligibility criteria

The search was filtered for longitudinal studies only, and articles were screened based on their title, abstract, and full text. We included cohort and case-control studies that measured at least one of the associations between depression, chronic pain, and sleep disturbance, on the condition that sleep disturbance and depression preceded pain. The included studies had to provide association measures [e.g., odds ratios (ORs) or incidence rate ratios (RRs), Cohen's *d* or Hedges' *g*, or correlation coefficients such as Pearson's *r*], their corresponding 95% confidence intervals (95% CIs) or standard errors, or sufficient data for their calculation. Letters, commentaries, editorials, opinion pieces, *in vitro* studies, or studies on nonhuman subjects were excluded. Due to the impossibility to ensure that exposure and mediation factors preceded the pain outcome, cross-sectional studies were excluded. Studies on acute or undefined pain were excluded.

Subsequently, we performed a restricted analysis in which we excluded studies that assessed the relation between depression and sleep disturbance but did not assess pain.

2.3. Data extraction and collection

Two authors screened the titles and abstracts obtained through electronic and manual search, selected studies for full-text review, reviewed those selected studies, and extracted the data from eligible studies independently. Discrepancies on the eligibility of the articles were resolved by consensus. Extracted data included the first author's last name, year of publication, study location, sample size (*N*), study design (i.e. cohort versus case-control study), type of relation (i.e. depression-sleep disturbance, sleep-pain, or depression-chronic pain), correlation coefficient *r*, outcome measurement tool, exposure measurement tools, and adjustment, restriction, or matching factors. When adjusted association measures were not available, we used crude association measures. When a single study provided estimates for different depression/sleep/pain variables, we used each estimate separately. We transformed all association measures to Pearson's correlation coefficient *r*.

2.4. Risk of bias (quality) assessment

The quality of eligible papers was independently evaluated by two authors (RK and NM), using an adapted version of the critical appraisal tool developed by Lee et al.[17] and standard guidelines.[18,19] As a result, a checklist of eight items, coded as 0=No or 1=Yes), was obtained (Table S2 in the supplementary material). The items were as follows: 1) clear description of the objectives, 2) appropriate study design, 3) representative sample, 4) psychometric characteristics of the mediator and outcome variables reported, 5) whether changes in the mediating variable preceded changes in the outcome variable, 6) whether changes in the predictor variable preceded changes in the mediator variable and outcome variable, 7) findings clearly described, and, 8) control for at least two main potential confounders (age and sex). Disagreements between reviewers were resolved by consensus, with the participation of a third reviewer when necessary (BT). We categorized studies into low quality (scores =< 6) and high-quality studies (scores > 6) for the subsequent subgroup analyses.

2.5. Data analysis

To synthesize the correlation matrices across studies and perform structural equation modelling, we used a two-stage structural equation modelling (TSSEM) approach.[20] In stage one, we pooled the correlation matrices using a multivariate random-effects model with maximum-likelihood estimation, accounting for the dependence between multiple correlations within studies.[21,22] In stage two, we specified and estimated a structural equation model, using the pooled correlation matrix and the total sample size as input. This model quantified the indirect effect of sleep disturbance, along with all possible direct effects. Figure 1 displays the proposed mediation model. The corresponding path coefficients are labelled as "a" (depression and sleep disturbance), "b" (sleep disturbance and chronic pain), and "c" (the direct effect of depression on chronic pain). The direct, indirect (path a*b) and total (c + a*b) effects were obtained from the output of TSSEM in stage 2. In case of partial mediation and the same sign of direct and indirect effects, the variance accounted for by the indirect effect (*VAF*) represents the ratio of the indirect effect of the depression on pain via sleep disturbance and the total effect of depression on chronic pain:[23]

$$VAF = \frac{\text{Indirect effect}}{\text{Total effect}}$$

To quantify heterogeneity in correlations, we estimated the I^2 statistic and performed the heterogeneity test based on the Q statistic.[24] Finally, we evaluate the potential sources of any significant heterogeneity, conducting subgroup analyses on the basis of extracted covariates.[25] To test the robustness of our findings, we further restricted the analysis to the studies that presented data on chronic pain and excluded studies that presented data on sleep disturbance and depression only.[26–32]

We performed TSSEM using the R package "metaSEM" version 1.2.3,[33] and assumed that missing correlation coefficients within studies were missing at random (MAR).

TSSEM handles these missing coefficients via the full-information maximum-likelihood procedure under MAR.[34]

We used STATA version 14.0 (StataCorp, 2015) to check for publication bias using the funnel plot and Egger's regression test. The R codes used for this meta-analysis is available at osf.io/9ekwg.

2.6 Certainty of evidence

The assessment of the certainty of evidence was conducted under the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines (Supplementary Table S3).[35]

3. Results

Figure 2 summarizes the results of different stages of the systematic search strategy. Initially, a total of 4,467 records were selected as eligible to be screened by title and abstract; after duplication removal, 171 were retrieved as potential relevant full-text and screened to determine eligibility. Among them, 107 did not meet the inclusion criteria and were excluded. Finally, 49 different study units, published in 45 articles, met the inclusion criteria and were included in the meta-analysis[26–32, 36–73]. Nine studies were excluded from the restricted analysis as they reported the association between depression and sleep only without including chronic pain. Two of the 49 studies were subject to discrepancy between authors concerning their inclusion, but this non-unanimous evaluation was solved after careful revision by the senior author and the studies were finally included in the meta-analysis.

3.1. Description of the primary studies

Study characteristics are summarized in Table 1. Participants were predominantly female (75.8%); six studies included only women, while one employed only men. The age of participants within studies ranged from 16 to 103 years. Five studies used a case-control design, and 44 had a cohort design. Sample sizes ranged from 16 to 35,248 participants, and the overall sample size in our meta-analysis was 120,489.

Participants with depression were mainly diagnosed using the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), and the Centre for Epidemiologic Studies Depression (CES-D) scale. Furthermore, chronic pain and sleep disturbance were assessed using various self-report measures. The quality assessment scores ranged between 4 and 8 (Table S2 in the supplementary material).

3.2. Publication bias

Study characteristics for articles reporting the associations are summarized in Table 1. Egger's test yielded non-significant test statistics for the correlations between depression-pain ($p=0.14$), sleep disturbance-pain ($p=0.42$), and depression-sleep disturbance-pain ($p=0.63$), and the funnel plots showed some dispersion but no evidence of asymmetry (Figure 3).

To further evaluate the possibility that our results could be due to publication bias, we recalculated the pooled estimates of correlations under the following extreme assumptions: (a) published studies represent only half of the studies identifying any of the correlations between depression, sleep disturbance, and pain; (b) all unpublished studies found a zero correlation; and (c) the unpublished studies have a sample size equal to the average sample size of the published studies. Under these extreme assumptions, the pooled correlation between depression and sleep disturbance (0.26; 95% CI [0.09, 0.42]), sleep disturbance and pain (0.18; 95% CI [0.07. 0.29]), and depression and pain (0.25;

95% CI [0.10, 0.35]) were still significant. These analyses do not provide evidence for publication bias in the three correlations.

3.3. Meta-analytic structural equation modelling

Table 2 provides the pooled correlation matrix that resulted from stage 1 of TSSEM. The pooled correlations between depression and sleep disturbance, sleep disturbance and pain, and depression and pain were 0.24 (95% CI: 0.09, 0.38), 0.19 (95% CI: 0.10. 0.25), and 0.27 (95% CI:0.11, 0.39) respectively, and indicated small positive associations among the variables. The I^2 statistic (94 to 97%) and the results of the Q tests indicated large heterogeneity for the overall sample (Table 2). Heterogeneity was similarly high for the different subgroups of studies as well as for the restricted analysis in which we excluded studies that assessed the relation between depression and sleep disturbance, but did not assess pain. (Table 3).

The meta-analytic estimates of the direct, indirect, and total effects, along with their confidence intervals, and VAF values are presented in Table 3. For both the main analysis and the restricted analysis we observed a partial mediation effect of sleep disturbance on the association between depression and pain. Overall, 12.5% of the total effect of depression on pain was explained by the indirect effect of sleep disturbance.

In the subgroup analyses, we observed a significant indirect effect among cohort studies and studies carried out in the general population in both main and restricted analyses. A significant indirect effect among adjusted studies, high quality studies, and European studies was observed in the main analysis only. For studies conducted in Europe, about 27% of the total effect was due to the mediation effect via sleep disturbance. For non-European studies, no mediation was evident. Concerning the study designs, the percentage of the total effect explained by the indirect effect was 9% among cohort studies and 11.5% among the case-control studies. For studies with incomplete

adjustment for confounders, no mediation was evident; in contrast, about 33.3% of the total effect could be explained by the indirect effect for studies adjusting for at least age and sex. For high-quality studies, the VAF was 25%, and the mediation effect for low-quality studies was non-significant.

Only 4 studies determined depression via clinical observation. The results of the analysis restricted to studies using screening tools of depression instead of a complete diagnosis were almost identical to the main results: Direct Effect = 0.22 (95% CI: 0.04-0.40), Indirect Effect = 0.02 (95% CI: 0.003-0.06), Total Effect =0.24 (95% CI: 0.09-0.39), VAF = 10.0%.

3.4. Certainty of evidence

The certainty of evidence for meta-analytic outcomes was rated as Moderate, which means that the team is moderately confident in the effect estimate. The true effect is likely to be close to our estimate, but there is a possibility that it is substantially different.

4. Discussion

The present study explored the mediating role of sleep disturbance in the association between depression and pain. It confirmed that depression is correlated with worse sleep disturbance and pain and revealed that sleep disturbance may emerge as a mediating factor in the relationship between depression and pain. In addition to the general analysis in which all studies were included, the mediation effect of sleep disturbance in the association between depression and pain was observed among cohort studies, European studies, adjusted studies and high quality studies, but this effect was non-significant in non-European, unadjusted, and low-quality studies.

The non-European subgroup is comprised of many different countries all over the world. Therefore, the impact of ethnic and/or cultural differences in depression and pain perceptions,[74] could contribute to the lack of a significant indirect effect of sleep disturbance in the association between depression and pain in this subgroup. When we restricted our analysis to the studies carried out in the United States, no substantial change in the results was observed. There could be a stronger association between depression and pain in ethnic groups such as African Americans than among Caucasians,[75] as the former group is more frequently subject to a variety of adverse psychosocial outcomes due to its increased levels of distress.[76] In this case, the direct effect of depression on pain in the non-European subgroup, including the American population is so strong that the indirect effect via sleep disturbance is small. In other words, the direct relationship rather than the indirect mechanism dominates.

The relation between depression and pain found in our study is consistent with previous studies which have reported emotional distress as a risk factor of chronic pain.[77,78] Moreover, our findings support the overall relation between sleep disturbance and pain, yet with small effect sizes and variation across study subgroups. Previous studies have reported that sleep quality predicts pain, which might be due to the fact that low sleep quality can exaggerate pain sensation,[79] and weaken the ability to disengage from painful stimuli.[80]

As mentioned earlier, our meta-analysis supports the hypothesis that sleep disturbance mediates the association between depression and pain. However, prior research has documented different directions of the relations among the three constructs.[81–83] The interrelation between these variables explains the inconsistencies in the literature regarding these pathways. Studies have previously focused on depression as a mediator between pain and sleep.[84,85] Also, pain can contribute to sleep and mood disturbance independently, suggesting that pain may affect sleep fragmentation and nightly

awakenings, leading to reduced sleep quality,[86] and depression over time.[87] Although our study was restricted to longitudinal designs, the aforementioned reciprocal interactions could prove the possibility of reverse causation between the observed associations in this study.

A plausible pathobiological mechanism that could explain these associations is that pain, sleep, and depression share common neurobiological pathways, and alterations in these pathways could explain the observed association. Serotonin, for example, has long been recognized as a critical regulatory neurotransmitter in the sleeping and wakening cycle.[88] Serotonin is also believed to play an essential role in the pathobiology of depression,[89] and has been involved in pain modulation.[90] Therefore, some studies have suggested serotonergic signalling dysfunction as the underlying mechanism connecting pain, sleep dysfunction, and depression.[91]

Furthermore, sleep disturbance may also serve as a moderator, with good sleep quality attenuating the effect of depression on pain, and poor sleep quality amplifying the effect of depression on pain. Sleep disturbance has been broadly associated with depression through common biochemical pathways and genetic factors.[92] The interaction between depression and sleep disturbance could worsen pain perception.[93]

To the best of our knowledge, this is the first meta-analysis assessing the indirect effect of a range of common sleep disorders in the association between depressive disorders and pain syndromes in the clinical and subclinical samples at any age. This study is particularly robust as we included longitudinal studies only. This knowledge represents a novelty in pain research and allows the design of better assessments and interventions. Nevertheless, our results should be interpreted in light of several limitations. First, although the findings from the restricted analyses largely agreed with the main analyses, publication bias may still influence the model parameters and effects. Second, most studies in this meta-analysis used self-report measures to assess depression, pain, and

sleep. These measures may not reflect the symptoms as accurately as objective measures.[94] However, all three factors are subjective in essence and it is their perception by the subject that takes a toll on the subjects' health. Third, between-study heterogeneity in the pooled effects was high in this meta-analysis and did not subside after stratification. This heterogeneity can be partially explained by differences in population characteristics and possibly unmeasured variables.[95] In our meta-analysis, we interpreted the results based on random-effects estimates as recommended.[23] Meta-analysis experts emphasise the fact that no degree of heterogeneity is unacceptable if the data are correct,[96] and that heterogeneity, because data are collected using different methods in different populations, should be viewed as the 'expectation, rather than the exception'.[97] Fourth, given the design of some of the primary studies, strict causal inference cannot be drawn. Future studies should prospectively explore the mediating mechanisms by implementing designs that ascertain the precedence of the independent variable (depression) on the mediator (sleep disturbance) and the mediator on the dependent variable (pain). Furthermore, future work needs to refine the constructs used in this meta-analysis to shed more light on potential causal pathways.

Understanding the nature and dynamics of the relations between depression, sleep disturbance, and pain can help develop an effective model for pain management. The certainty of evidence of the mediation effect of sleep disorders rated as "moderate" in our GRADE assessment, should guide clinicians in the development and administration of interventions that focus not only on depression but also on sleep quality and disorders, in order to explore better therapeutic outcomes for pain management.

Authors′ Contributions: BT: conceived the research idea, designed the study, and supervised the data analysis and interpretation; RK: conducted the literature review and drafted the manuscript; RK and RRC: extracted the data; RS and RK: carried out data analysis and interpretation; RK and NM carried out the quality scoring of the studies. NM and RS: critically reviewed and revised the manuscript. All authors reviewed the manuscript and approved it for publication.

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6. Tables

Table 1. Characteristics of the included studies.

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Cohort studies										
Pilowsky et al. [26] **1985**	Hospital patients (mean age 43.5 yrs)	100	Australia	0.12	-	-	Crude	Depression/ SDS	Sleep disturbance/ Researcher made questionnaire	-
Ford et al. [27] **1989**	General population (18-65+ yrs)	7954	USA	0.55	-	-	Sex, age, socioeconomic status, race, marital status	Major depression/ DSM-III	Hypersomnia/ DSM-III	-
Von Korff et al. [36] **1993**	General population (18-44 yrs)	1016	USA	-	-	-0.18	Age, sex, education	Depression/ SCL90	-	Back pain/ Self report
Leino et al.[37] **1993**	Industry employees (40-68 yrs)	607	Finland	-	-	0.13	Age, baseline depression, stress scores	Depressive symptoms/ DSS	-	Musculoskeletal pain/Self report
Magni et al. [38] **1994**	General population (25-74 yrs)	2324	USA	-	0.06	0.006	Crude	Depression/ CES-D	Restless sleep/ Self report	Chronic musculoskeletal pain/ Health records
Pietri-Taleb et al. [39] **1994**	Industry employees (25-49 yrs)	1015	France	-	-	0.01	Age, marital status, smoking, physical exercise	Depression/ MHQ	-	Neck trouble/ Self report
Affleck et al. [40] **1996**	Hospital patients (mean age 43.8 yrs)	50	USA	-	-0.28	-	Between-persons variation and autocorrelation	-	Mean sleep quality ratings/ Researcher made questionnaire	Fibromyalgia/ Clinical diagnosis
Breslau et al. [28] **1996**	General population (21-30 yrs)	1007	USA	0.61	-	-	Sex, nicotine dependence, insomnia, hypersomnia	Major depression/ Diagnostic interview	Insomnia/ Diagnostic interview	-
Breslau et al. [28] **1996**	General population (21-30 yrs)	1007	USA	0.57	-	-	Sex, nicotine dependence, insomnia, hypersomnia	Major depression/ Diagnostic interview	Hypersomnia/ Diagnostic interview	-

Breslau et al. [28] 1996	General population (21-30 yrs)	1007	USA	0.71	-	-	Sex, nicotine dependence, insomnia, hypersomnia	Major depression/ Diagnostic interview	Insomnia and Hypersomnia/ Diagnostic interview	-
Agargun et al. [42] 1999	Hospital patients (mean age 30.3 yrs)	16	Turkey	-	-0.58	-	Crude	-	Sleep quality/ PSQI	Fibromyalgia/ Algometers
Zautra et al. [45] 2001	Postmenopausal women (42-76 yrs)	188	USA	-	-	0.93	Age	Depressive symptoms/ MHI	-	RA/ Self report
Zautra et al. [45] 2001	Postmenopausal women (42-76 yrs)	188	USA	-	-	0.91	Age	Depressive symptoms/ MHI	-	OA/Self report
Brander et al. [46] 2003	Hospital patients (36-85 yrs)	116	USA	-	-	0.43	Crude	Depression/ BDI	-	Knee pain/ MPQ
Carroll et al. [47] 2004	At risk general population (20-69 yrs)	1131	Canada	-	-	0.02	Education, age	Depression/ CES-D	-	Neck and low back pain/ CPGQ
Hasler et al. [30] 2005	General population (19-40 yrs)	499	Switzerland	0.10	-	-	Sex, age, baseline psychopathology, trouble falling asleep, impaired sleep quality, awakenings during sleep period, waking up too early, trouble getting up in the morning	Major depression/ SPIKE	EDS/SPIKE	-
Larson et al. [49] 2004	General population (18-65< yrs)	4349	USA	-	-	0.34	Sex, age, education, income	Depressive disorder/ CES-D	-	Back pain/ Self reported
Boardman et al. [50] 2006	General population (18-90 yrs)	1589	UK	-	0.19	0.24	Age, sex, headache disability level	Depression/ HADS	Sleep problem/ Jenkins questionnaire	Headache/ Self report
Gupta et al. [51] 2007	General population (25-65 yrs)	3185	UK	-	0.26	0.22	Age, sex	Depression/ HADS	Sleep problems/ SQS	CWP/ACR criteria
Kaila-Kangas et al. [52] 2006	Factory employees (24-41 yrs)	902	Finland	-	0.24	-	Age, sex, occupational class	-	Sleep disturbances/ Researcher made questionnaire	Back pain/Self report
Jansson-Fröjmark et al. [31] 2008	General population (20-60 yrs)	1273	Sweden	0.32	-	-	Crude	Depression/HADS	Insomnia/DSM	-

Morphy et al. [53] **2007**	General population (18-98 yrs)	2662	UK	0.05	0.20	-	Age, sex, social class, anxiety, depression, pain areas	Depression/HADS	Insomnia/ Researcher made questionnaire	Widespread pain/ Self report
Bigatti et al. [55] **2008**	Hospital patients (mean age 54 yrs)	492	USA	0.36	0.27	0.36	Crude	Depression/CES-D	Sleep quality/ PSQI	Fibromyalgia/MPQ
Edwards et al. [56] **2008**	General population (mean age 47 yrs)	1031	USA	-	-0.03	-	Age, sex, BMI, number of chronic conditions, use of prescription medications, chronic sleep difficulties, the presence of an emotional disorder, persistent pain condition	-	Sleep duration/ Self reported	Daily pain/Self report
Smith et al. [57] **2008**	Hospital patients (mean age 40.9 yrs)	333	USA	-	0.80	-	Crude	-	Insomnia/BSI	Arthritis Pain/SF-36
Young et al. [58] **2007**	Hospital patients (mean age 46.9 yrs)	84	USA	-	-	0.07	Crude	Depressive symptoms/ CES-D	-	Back pain/PBPI
Edwards et al. [59] **2009**	Hospital patients (mean age 34 yrs)	53	USA	-	0.07	-	Crude	-	Sleep efficiency/ PSG	Overall pain/ DNIC
Kim et al. [32] **2009**	Elderly population (20-41 yrs)	83	Korea	0.23	-	-	Age, sex, education, housing, past occupation, current employment, living area, life events, social deficit, physical activity, anxiety, daily drinking	Depression/ GMS	Insomnia/ Researcher made questionnaire	-
Quartana et al. [60] **2010**	Hospital patients (mean age 33.7 yrs)	53	USA	-	0.08	-	Crude	-	Insomnia/ISI	TMD/BPI
Mork et al. [63] **2012**	General population (20-70 yrs)	12350	Norway	-	0.25	-	Age	-	Sleep problems/ Self report	Fibromyalgia/ Clinical diagnosis
Nitter et al. [64] **2012**	General population (20-50 yrs)	2498	Norway	-	0.20	-	Age	-	Sleep disturbance/ Self report	Chronic regional pain/ Researcher made questionnaire
Sanders et al. [68] **2016**	General population (18-44 yrs)	2453	USA	-	0.10	-	Age, sex, study site, race/ethnicity	-	Sleep quality/ PSQI	Painful TMD/ QST

Walton et al.[71] **2016**	Hospital patients (18-68 yrs)	276	Canada	-	0.21	0.05	Crude	Depression/ HADS	Sleep disturbance/ Self report	Regional pain/ PCS
Daly et al. [72] **2017**	Pregnant women (mean age 31.4 yrs)	186	UK	-	-	0.04	Anxiety, deprivation score, and presence of preoperative pain	Depression/ EPND	-	Persistent pain/ VAS
Generaal et al. [73] **2017**	General population (18-65 yrs)	1860	Netherlands	-	0.12	-	Sex, age, years of education, BMI, smoking, alcohol intake, physical activity, number of chronic diseases	-	Insomnia/IRS	Multisite musculoskeletal pain/ CPG
Pinheiro et al. [76] **2017**	General population of twins (43-71 yrs)	1098	Spain	-	-	0.10	Age and sex	Depression/ ST-Dep	-	LBP/ Self report
Aili et al. [77] **2018**	General population (20-74 yrs)	1249	Sweden	-	0.24	-	Age and sex	-	Initiating sleep disturbance/ USI	CWP/ ACR criteria
Aili et al. [77] **2018**	General population (20-74 yrs)	1249	Sweden	-	0.26	-	Age and sex	-	Maintaining sleep disturbance/ USI	CWP/ ACR criteria
Datema et al. [78] **2018**	Hospital patients (49-73 yrs)	227	The Netherlands	-	-	0.01	Crude	Depression/ CES-D	-	Palmar pain/ BCTQ
Uhlig et al. [79] **2018**	General population (20-70 yrs)	13429	Norway	-	0.17	-	Age, education, smoking, physical activity	-	Insomnia/ DSM-IV	CWMSC/ ACR criteria
Wiklund et al. [83] **2020**	General population (16-85 yrs)	959	Sweden	-	0.19	-0.006	Age, sex, education, depressive symptoms, anxiety symptoms, level of pain catastrophizing, pain intensity	Depression /GWBS	Insomnia/ISI	Local pain/PCS
Wolfe et al. [85] **2022**	Hospital patients (21-103 yrs)	35248	USA	-	-	0.09	Age, sex	Depression/ Self report	-	Local pain/PCS
Skarpsno et al. [87] **2021**	General population (mean age 54.7 yrs)	6033	Norway	-	0.07	-	Age, sex, education, BMI, relative change in body weight, leisure time, physical activity, smoking status	-	Sleep quality/ Self report	CWP/ SNQ
Yabe et al. [88] **2021**	General population and natural disaster survivors (18-65 yrs)	2059	Japan	-	0.14	-	Sex, age, body mass index, living area, smoking, drinking, comorbid conditions, working status, walking time, economic condition, psychological distress, social isolation	-	Sleep disturbance/ Self report	Low Back Pain/ Self report

Case-control studies										
Sayar et al. [29] **2002**	Cases: hospital patient; Controls: general healthy population (mean age 36.7)	40/40	Turkey	0.6	-	-	Age, sex, pain duration, disability, pain intensity, anxiety	Depression/ BDI	Sleep quality/ PSQI	-
Tekeoglu et al. [65] **2013**	General population (18-65 yrs)	40/43	Turkey	-	0.49	-	Age, sex, educational status, BMI	-	Sleep quality/ PSQI	Shoulder pain/ SDQ
López-López et al. [75] **2017**	Hospital patients vs. general population (19-65 yrs)	82/82	Spain	-	-	0.06	Age and sex	Depression/ BDI	-	SLBP/ TQTFSD
Palomo-López et al. [80] **2019**	Hospital women patients vs. general population healthy women (19-94 yrs)	100/100	Spain	-	-	0.56	Crude	Depression/ BDI	-	Fibromyalgia/ Clinical diagnosis
Toprak et al. [82] **2019**	Cases: hospital patient; Controls: general healthy population (18-65 yrs)	76/72	Turkey	0.22	-0.14	-0.05	Crude	Depression/ BDI	Sleep quality/ PSQI	Shoulder pain/ VAS

Note. r, correlation coefficient; Dep, depression; Sl, sleep disturbance; Pa, pain; BMI, body mass index; MDD, major depressive disorder; GWBS. general well-being schedule; HADS, hospital anxiety and depression scale; PHQ, patient health questionnaire; BDI, beck depression inventory; SDS, Zung self-rating depression scale; CES-D, center for epidemiologic studies depression scale; MHI, mental health inventory; MHQ, middle-sex hospital questionnaire; DSS, Depressive symptoms score; HAMD, Hamilton depression scale; ST-DEP, state-trait depression questionnaire; SCL-90, symptom checklist-90; EPND, Edinburgh postnatal depression score; ISI, insomnia severity index; DSM, diagnostic and statistical manual of mental disorders; BSI, brief symptom inventory; PSQI, Pittsburgh sleep quality index; SQS, Sleep Quality Scale; IRS, insomnia rating scale; SDSC, sleep disturbance scale for children; PSG, Polysomnography; USI, Uppsala sleep inventory; GMS, geriatric mental state diagnostic schedule; SPIKE, structured psychopathological interview and rating of the social consequences for epidemiology; EDS, excessive daytime sleepiness; ACR, American college of rheumatology; CWP, chronic widespread pain; RA, rheumatoid arthritis; OA, osteoarthritis; SDQ, shoulder disability questionnaire; DNIC, diffuse noxious inhibitory controls; TBI, traumatic brain injury; EI, extracranial/bodily injury; CPG, chronic pain grade; TMD, temporomandibular joint disorders; LBP, low back pain; SLBP, subacute low back pain; MPQ, McGill pain questionnaire; QST, quantitative sensory testing; TMD, temporomandibular disorder; SNQ, Standardized Nordic questionnaire; SF-36, health survey short form – 36; VAS, visual analogue scale; CWMSC, chronic widespread musculoskeletal complaints; PCS, pain catastrophizing scale; MIDAS, Migraine disability assessment; CPGQ, chronic pain grade questionnaire; BCTQ, Boston carpal tunnel questionnaire; NRS, numeric rating scale; TQTFSD, the Quebec task force on spinal disorders; SAQ, Seattle angina questionnaire; PBPI, pain behavior and perception inventory.

Table 2. Pooled correlation coefficients ($\bar{r}$).

	k	Sample size (N)	$\bar{r}$	95% confidence interval		I^2	p-value Q test
				Lower limit	Upper limit		
Depression-Pain	24	54787	0.24	0.09	0.38	97%	< 0.001
Sleep disturbance-Pain	22	61652	0.19	0.10	0.25	96%	< 0.001
Depression-Sleep disturbance	12	640	0.27	0.11	0.39	94%	< 0.001

Note. k = Number of primary studies, $\bar{r}$ = Pooled correlation coefficient.

Table 3. Direct, indirect, and total effects in the meta-analytic mediation models.

	Main analyses					Restricted analyses[#]				
	k	Direct effect (95% CI)	Indirect effect (95% CI)	Total effect (95% CI)	VAF (%)	*k*	Direct effect (95% CI)	Indirect effect (95% CI)	Total effect (95% CI)	VAF (%)
All studies	49	0.21 (0.05-0.38)	0.03 (0.01-0.05)	0.24 (0.09-0.38)	12.5	40	0.22 (0.04-0.40)	0.02 (0.003 -0.06)	0.24 (0.09-0.39)	9.1
Subgroup analysis										
Type of pain										
Widespread / fibromyalgia	14	0.40 (0.21-0.60)	0.01 (-0.03-0.03)	0.41 (0.23-0.59)	2.4	-	-	-	-	
Regional pain	35	0.19 (0.04-0.37)	0.03 (-0.02 -0.07)	0.22 (0.06-0.38)	13.6	26	0.18 (0.03-0.32)	0.03 (0.01-0.06)	0.21 (0.05-0.39)	15.7
Study population										
General population	33	0.19 (0.001-0.42)	0.03 (0.01-0.07)	0.22 (0.01-0.44)	13.6	26	0.20 (0.01-0.45)	0.02 (0.008-0.09)	0.22 (0.03-0.48)	10.5
Hospital patients	16	0.31 (0.09-0.56)	-0.04 (-0.16-0.03)	0.27 (0.07-0.46)	-	14	0.30 (0.06-0.52)	-0.03 (-0.10-0.04)	0.27 (0.05-0.48)	-
Region										
European	21	0.08 (-0.05-0.22)	0.03 (0.004-0.05)	0.11 (0.04-0.24)	27.2	-	-	-	-	-
Non-European	28	0.34 (0.08-0.61)	-0.02 (-0.12-0.04)	0.32 (0.10-0.53)	-	21	0.36 (0.10-0.43)	-0.01(-0.06-0.03)	0.35 (0.12-0.57)	0.4
USA	19	0.47 (0.11-0.85)	-0.08 (-0.24-0.02)	0.40 (0.12-0.67)	-	15	0.45 (0.10-0.80)	-0.05 (-0.17-0.01)	0.40 (0.11-0.66)	-
Study design										
Cohort	44	0.21 (0.04-0.38)	0.02 (0.002-0.04)	0.23 (0.08-0.39)	8.7	38	0.22 (0.05-0.41)	0.02 (0.003-0.05)	0.24 (0.08-0.41)	17.6
Case-control	5	0.23 (0.05-0.80)	0.03 (-0.28-0.34)	0.26 (0.15-0.67)	11.5	-	-	-	-	-
Adjustment										
Unadjusted	17	0.44 (0.15-0.73)	-0.004 (-0.05-0.04)	0.44 (0.18-0.69)	-	15	0.45 (0.15-0.75)	-0.002 (-0.02-0.05)	0.45 (0.19-0.70)	2.8
Adjusted	32	0.08 (-0.08-0.24)	0.04 (0.01-0.09)	0.12 (0.02-0.26)	33.3	-	-	-	-	-
Quality assessment score										
Low	12	0.45 (0.09-0.84)	-0.05 (-0.25-0.04)	0.40 (0.08-0.70)	-	9	0.46 (0.10-0.86)	-0.04 (-0.21-0.03)	0.42 (0.11-0.73)	-3.1
High	37	0.12 (0.01-0.26)	0.04 (0.01-0.06)	0.16 (0.03-0.28)	25.0	-	-	-	-	-

Note. *k* = Number of primary studies, 95% CI = 95% confidence interval, VAF = Variance accounted for by the indirect effect. The VAF is only reported for partial mediation models with the same sign of the direct and indirect effects. [#] The primary studies excluded from these analyses did not measure pain and only measured the association between depression and sleep disturbance.

Figures legend:

Figure 1. Hypothesized mediation model.

Figure 2. PRISMA flow chart of literature inclusion.

Figure 3. Funnel plots of the correlations.

Figures

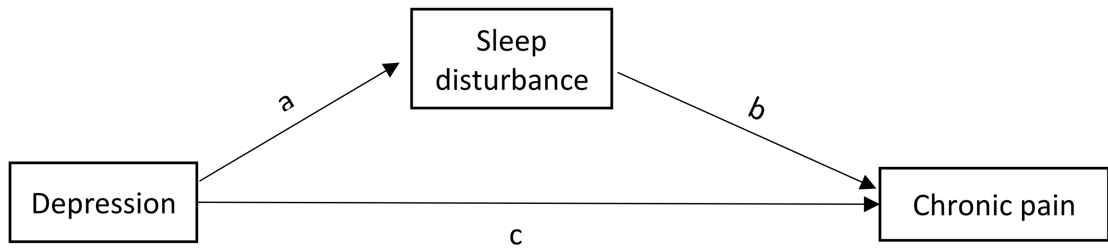


Figure 1. Hypothesized mediation model.

Note. Path "a" = Effect of depression on sleep disturbance; path "b" = Effect of sleep disturbance on pain; path "c" = Direct effect of depression on chronic pain controlling for sleep disturbance.

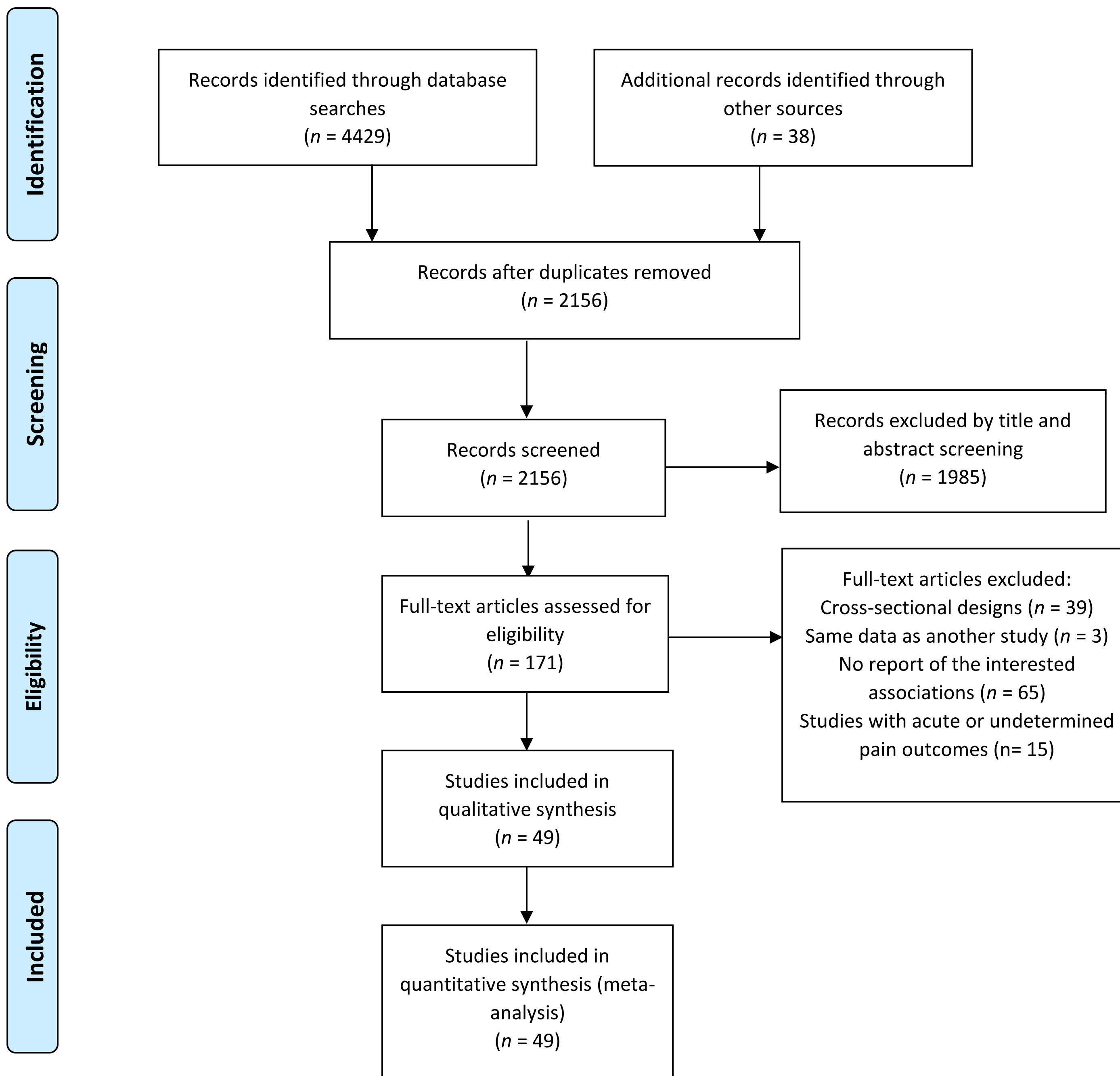
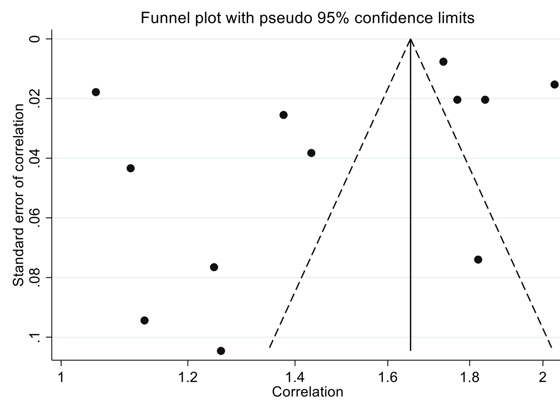


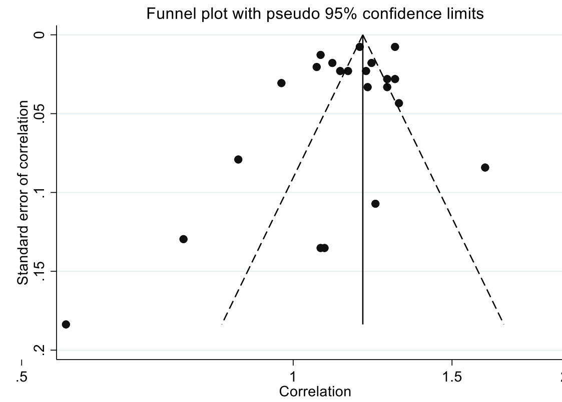
Figure 2. PRISMA flow chart of literature inclusion.

Correlation between depression and sleep disturbance



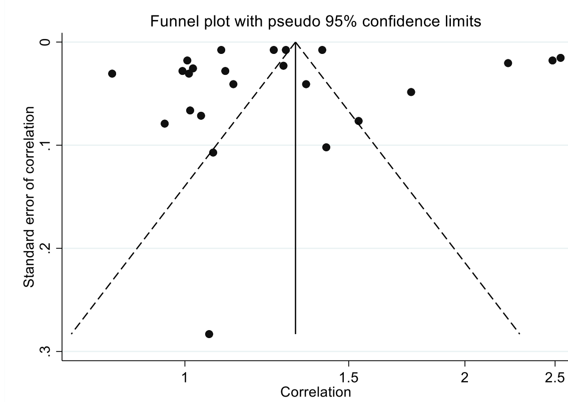
Egger's regression test
p-value=0.15

Correlation between sleep disturbance and chronic pain



Egger's regression test
p-value=0.42

Correlation between depression and chronic pain



Egger's regression test
p-value=0.63

Figure 3. Funnel plots of the correlations.

Sleep Quality as a mediator of the relation between depression and chronic pain: a systematic review and meta-analysis

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Table S1. Search history (Status: updated on 21 May 2022)

Step	Databases	Search Strategy (Pubmed)	Results
1	**Search engines**		
	MEDLINE	**Depression-sleep disturbance-pain:** ((depress*[Title/Abstract]) OR (depression[Title/Abstract]) OR ("depressive disorder"[Title/Abstract]) OR ("mood disorder"[Title/Abstract]) OR ("depressive neuroses"[Title/Abstract]) OR (melancholia[Title/Abstract])) AND ((pain[Title/Abstract]) OR (fibromyalgia[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR (osteoarthritis[Title/Abstract]) OR (migraine[Title/Abstract]) OR (headache[Title/Abstract]) OR (neuralgia[Title/Abstract]) OR (complex regional pain syndrome [Title/Abstract]) OR (Chronic widespread pain [Title/Abstract]) OR (neuropathic pain [Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract])) AND ((“sleep disorders”[Title/Abstract]) OR (“dyssomnias”[Title/Abstract]) OR (“insomnia”[Title/Abstract]) OR (“sleep apnea”[Title/Abstract]) OR (“narcolepsy”[Title/Abstract])) Filter: Observational studies **Sleep disturbance-pain:** ((“sleep disorders”[Title/Abstract]) OR (“dyssomnias”[Title/Abstract]) OR (“insomnia”[Title/Abstract]) OR (“sleep apnea”[Title/Abstract]) OR (“narcolepsy”[Title/Abstract])) AND ((pain[Title/Abstract]) OR (fibromyalgia[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR (osteoarthritis[Title/Abstract]) OR (migraine[Title/Abstract]) OR (headache[Title/Abstract]) OR (neuralgia[Title/Abstract]) OR (complex regional pain syndrome [Title/Abstract]) OR (Chronic widespread pain [Title/Abstract]) OR (neuropathic pain [Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract])) Filter: Observational studies **Depression-pain:** ((depress*[Title/Abstract]) OR (depression[Title/Abstract]) OR ("depressive disorder"[Title/Abstract]) OR ("mood disorder"[Title/Abstract]) OR ("depressive neuroses"[Title/Abstract]) OR (melancholia[Title/Abstract])) AND ((pain[Title/Abstract]) OR (fibromyalgia[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR (osteoarthritis[Title/Abstract]) OR (migraine[Title/Abstract]) OR (headache[Title/Abstract]) OR (neuralgia[Title/Abstract]) OR (complex regional pain syndrome [Title/Abstract]) OR (Chronic widespread pain [Title/Abstract]) OR (neuropathic pain	1227
	PsycInfo		1705
	Scopus		1047
	Global Index Medicus		107

	[Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract])) Filter: Observational studies	
2	**Congress papers**	
	Conference Proceedings Citation Index (Web of Science)	75
3	**Dissertations**	
	Open Access Theses and Dissertations (OATD)	268

Table S2. Assessment of primary study quality

The following questions indicate different aspects of primary study quality and are coded with binary labels (*0=no, 1=yes*).
Q1= Is the hypothesis/aim/objective of the study clearly describe? (i.e., objectives are formulated precisely, clearly, and comprehensively)?
Q2 = Is the study design appropriate to achieve the objectives?
Q3 = Is the study sample representative (i.e., participants are recruited from a representative setting that relates to the study's aims and hypotheses)?
Q4 = Were the psychometric characteristics of the mediator and outcome variables reported? (e.g., psychometric characteristics, such as reliability estimates or validity evidence, computed from the present study or a reference provided)
Q5 = Were statistically appropriate/acceptable methods of data analysis used?
Q6 = Did the study ascertain whether changes in the predictor or mediating variable preceded changes in the outcome variable?
Q7 = Are the main findings of the study clearly described? (Note: Simple outcome data should be reported for all major findings so that the reader can check the major analysis and conclusions.)
Q8 = Did the study control for possible confounding factors (i.e., variables that may impact on results are identified and controlled for in terms of statistical analysis)?

Author/Year	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Sum score**
Bigatti et al. 2008	1	1	0	1	1	1	1	0	6
Toprak et al. 2019	1	1	0	1	1	0	1	0	6
Affleck et al. 1996	1	1	0	0	0	1	1	0	4
Agargun et al. 1999	1	1	0	1	1	0	1	0	5
Aili et al. 2018	1	1	1	0	1	1	1	1	7
Boardman et al. 2006	1	1	1	1	1	1	1	1	8
Breslau et al. 1996	1	1	1	1	1	1	1	1	8
Ediz et al. 2013	1	1	0	1	1	1	1	0	6
Edwards et al. 2008	1	1	0	1	1	1	1	1	7
Edwards et al. 2009	1	1	1	0	1	1	1	1	7
Ford et al. 1989	1	1	1	0	1	1	1	0	6
Generaal et al. 2017	1	1	1	1	1	1	1	1	8
Gupta et al. 2006	1	1	1	1	1	1	1	1	8
Halser et al. 2004	1	1	1	1	1	1	1	0	7
Jansson-Fröjmark et al. 2007	1	1	1	1	1	1	1	0	7
Kaila-Kangas et al. 2006	1	1	1	0	1	1	1	1	7
Kim et al. 2009	1	1	1	1	1	1	1	0	7
Magni et al. 1994	1	1	1	0	1	1	1	1	7
Mork et al. 2012	1	1	1	0	1	1	1	1	7

Morphy et al. 2007	1	1	1	1	1	0	1	0	6
Nitter et al. 2012	1	1	1	1	1	0	1	1	7
Pilowsky et al. 1985	1	1	1	1	1	0	1	0	6
Quartana et al. 2010	1	1	0	1	1	0	1	0	5
Sanders et al. 2016	1	1	1	1	1	1	1	1	8
Sayer et al. 2002	1	1	1	1	1	0	1	0	6
Skarpsono et al. 2021	1	1	1	1	1	1	1	1	8
Smith et al. 2008	1	1	1	1	1	0	1	1	7
Uhlig et al. 2018	1	1	1	1	1	1	1	1	8
Walton et al. 2016	1	1	0	1	1	0	1	0	5
Wiklund et al. 2019	1	1	1	1	1	0	1	1	7
Yabe et al. 2021	1	1	1	1	1	0	1	1	7
Brander et al. 2003	1	1	1	1	1	1	1	1	8
Carroll et al. 2004	1	1	1	1	1	1	1	1	8
Daly et al. 2017	1	1	1	1	1	1	1	0	7
Datema et al. 2018	1	1	1	1	1	0	1	1	7
Kroff et al. 1993	1	1	1	1	1	0	1	1	7
Larson et al. 2004	1	1	1	1	1	0	1	1	7
Leino et al. 1993	1	1	1	1	1	0	1	1	7
Lopez et al. 2017	1	1	0	1	1	1	1	0	6
Palomo-Lopez et al. 2019	1	1	1	1	1	0	1	1	7
Pietri-Taleb et al. 1994	1	1	1	1	1	0	1	1	7
Pinheiro et al. 2017	1	1	1	1	1	1	1	1	8
Wolfe et al. 2020	1	1	1	1	1	0	1	1	7
Young et al. 2008	1	1	0	1	1	1	1	1	7
Zautra et al. 2001	1	1	1	1	1	0	1	0	6

Table S3: GRADE criteria

GRADE Domain	Criteria used in the review
Risk of Bias	Low risk (+1) *In general, the included studies had a low risk of bias when applying tools for evaluation.*
Inconsistency	High risk (-1) *A substantial heterogeneity was present (I^2 value >50%).*
Indirectness	Low risk (+1) *Studies used the depression and sleep disturbances as the exposure and the pain that lasts more than three months as the outcome, and directly answer the result raised in the PECO question.*
Imprecision	Low risk (+1) *Studies have sufficient sample size. Studies met Optimal Information Size (OIS).*
Publication Bias	Low risk (+1) There is no evidence of asymmetry in the funnel plots, or statistical evidence ($p<0.05$) from the Eggers test.