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Review Article

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

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Abstract

Background: Chronic pain and depression represent two global health problems with considerable economic consequences. Although existing literature reports 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. Forty-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, 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).

Conclusions: 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.

Systematic review protocol: PROSPERO CRD42022338201.

Keywords: chronic pain; depression; meta-analysis; pain; sleep; structural equation modelling

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Editor's key points

- There is a bidirectional association between depression and chronic pain. However, the effect of other factors, such as sleep quality, in this association is still unknown.
- Sleep disturbance appears to partially mediate the association between depression and chronic pain.
- Understanding the nature of the relation between pain and depression, sleep disturbance, and other variables has the potential to help in the development of an effective model for pain management.
- These findings could assist clinicians in the development and administration of interventions aimed at the control of chronic pain that focus not only on depression but also on sleep disorders.

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 amongst 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 aimed to synthesise 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?

Methods

We registered this meta-analysis at the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022338201) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16]

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), Western Pacific Region Index Medicus (WPRIM), 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. Supplementary Table S1 shows the detailed search strategy. Each database was searched up until May 21, 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.

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 or incidence rate ratios; Cohen's *d* or Hedges's *g*; or correlation coefficients, such as Pearson's *r*), their corresponding 95% confidence intervals (CIs) or standard errors, or sufficient data for their calculation. Letters, commentaries, editorials, opinion pieces, *in vitro* studies, or studies on non-human subjects were excluded. Because of 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.

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 *vs* 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*.

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 and colleagues[17] and standard guidelines.[18,19] As a result, a checklist of eight items, coded as 0=no or 1=yes, was obtained (Supplementary Table S2). The items were as follows: (i) clear description of the objectives, (ii) appropriate study design, (iii) representative sample, (iv) psychometric characteristics of the mediator and outcome variables reported, (v) whether changes in the mediating variable preceded changes in the outcome variable, (vi) whether changes in the predictor variable preceded changes in the mediator variable and outcome variable, (vii) findings clearly described, and (viii) 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 categorised studies into low-quality (scores $\leq$6) and high-quality (scores >6) studies for the subsequent subgroup analyses.

Data analysis

To synthesise the correlation matrices across studies and perform structural equation modelling, we used a two-stage structural equation modelling (TSSEM) approach.[20] In Stage 1, 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 2, 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 (VAF) by the indirect effect 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]:

$$VAF = \frac{indirect\ effect}{total\ effect}$$

To quantify heterogeneity in correlations, we estimated the I^2 statistic and performed the heterogeneity test based on the Q-statistic.[24] Finally, we evaluated 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] (R Foundation for Statistical Computing, Vienna, Austria) and we 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, College Station, TX, USA, 2015) to check for publication bias using the funnel plot and Egger's regression test. The R codes used for this meta-analysis are available at osf.io/9ekwg.

Certainty of evidence

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

Results

Figure 2 summarises the results of different stages of the systematic search strategy. Initially, a total of 4467 records were selected as eligible to be screened by title and abstract;

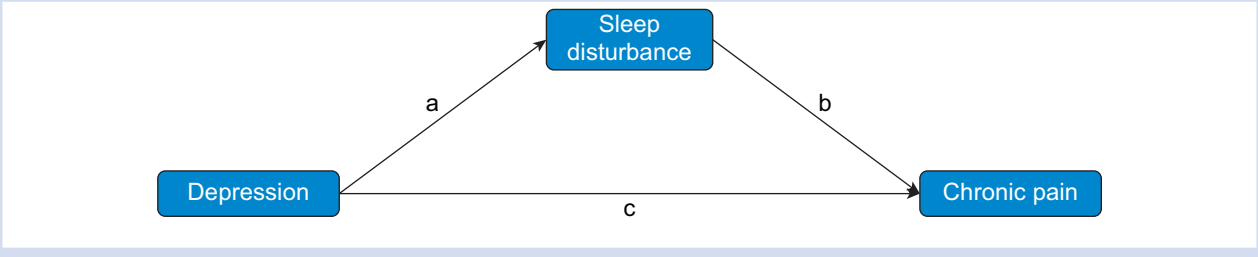

Fig 1. Hypothesised mediation model. Path 'a', effect of depression on sleep disturbance; path 'b', effect of sleep disturbance on pain; path 'c', direct effect of depression on chronic pain controlling for sleep disturbance.

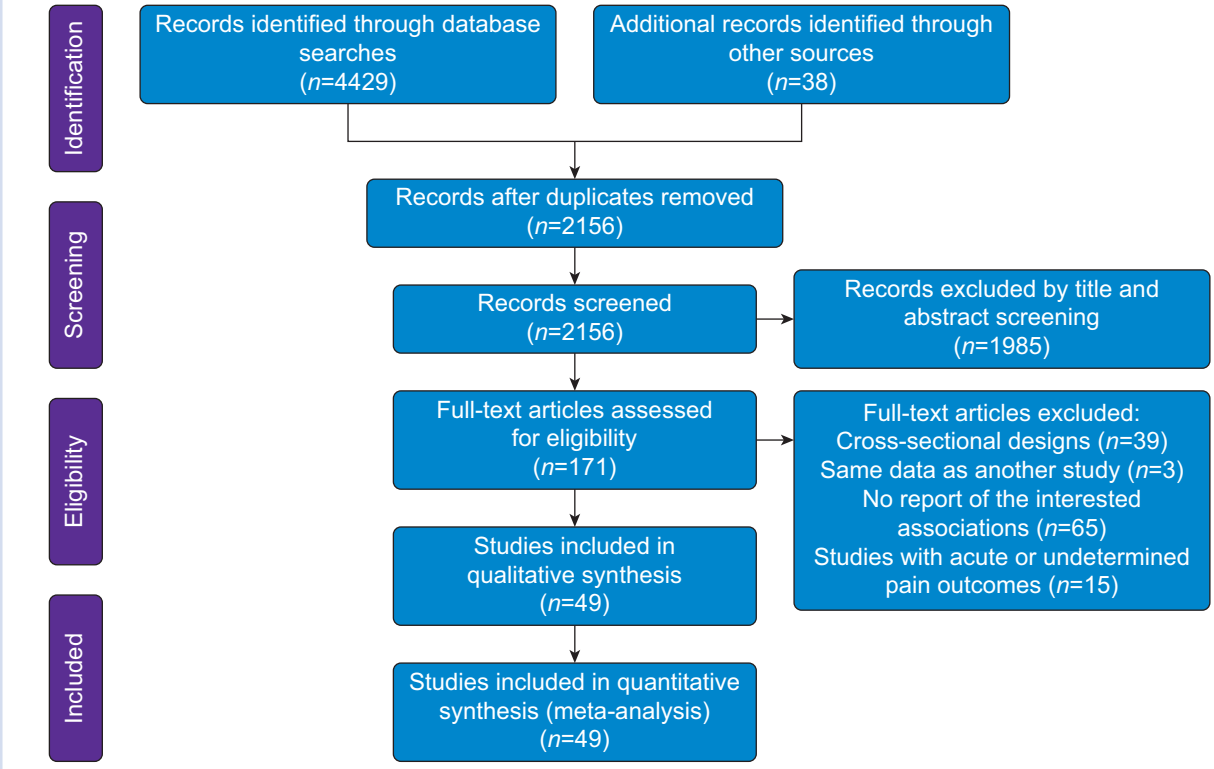

Fig 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of literature inclusion.

after duplication removal, 171 were retrieved as potential relevant full text and screened to determine eligibility. Amongst 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.

Description of the primary studies

The study characteristics are summarised in Table 1. Participants were predominantly female (75.8%); six studies included only women, whereas one included only men. The age of participants within studies ranged from 16 to 103 yr. 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 Center for Epidemiological 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 (Supplementary Table S2).

Publication bias

The study characteristics for articles reporting the associations are summarised 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 (Fig 3).

To further evaluate the possibility that our results could be attributable to publication bias, we recalculated the pooled estimates of correlations under the following extreme assumptions: (i) published studies represent only half of the studies identifying any of the correlations between depression, sleep disturbance, and pain; (ii) all unpublished studies found a zero correlation; and (iii) the unpublished studies have a sample size equal to the average sample size of the published studies. Under these extreme assumptions, the pooled correlations 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) are still significant. These analyses do not provide evidence for publication bias in the three correlations.

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 are 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

Table 1 Characteristics of the included studies. ACR, American College of Rheumatology; BCTQ, Boston Carpal Tunnel Questionnaire; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; CES-D, Center for Epidemiological Studies Depression scale; CPG, chronic pain grade; CPGQ, chronic pain grade questionnaire; CWMSC, chronic widespread musculoskeletal complaint; CWP, chronic widespread pain; Dep, depression; DNIC, diffuse noxious inhibitory controls; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; DSS, depressive symptoms score; EDS, excessive daytime sleepiness; EI, extracranial/bodily injury; EPND, Edinburgh postnatal depression score; GMS, geriatric mental state diagnostic schedule; GWBS, general well-being schedule; HADS, Hospital Anxiety and Depression Scale; HAMD, Hamilton depression scale; IRS, insomnia rating scale; ISI, Insomnia Severity Index; LBP, low back pain; MDD, major depressive disorder; MHI, Mental Health Inventory; MHQ, Middlesex Hospital Questionnaire; MIDAS, Migraine Disability Assessment; MPQ, McGill Pain Questionnaire; NRS, numeric rating scale; OA, osteoarthritis; Pa, pain; PBPI, pain behaviour and perception inventory; PCS, Pain Catastrophizing Scale; PHQ, Patient Health Questionnaire; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; QST, quantitative sensory testing; *r*, correlation coefficient; RA, rheumatoid arthritis; SAQ, Seattle Angina Questionnaire; SCL-90, symptom checklist-90; SDQ, Shoulder Disability Questionnaire; SDS, Zung Self-rating Depression Scale; SDSC, Sleep Disturbance Scale for Children; SF-36, health survey short form-36; Sl, sleep disturbance; SLBP, subacute low back pain; SNQ, Standardized Nordic questionnaire; SPIKE, structured psychopathological interview and rating of the social consequences for epidemiology; SQS, Sleep Quality Scale; ST-DEP, state-trait depression questionnaire; TBI, traumatic brain injury; TMD, temporomandibular joint disorder; TQTFSD, The Quebec Task Force on Spinal Disorders; USI, Uppsala Sleep Inventory.

Author (year)	Sample type	Study size or no. of cases/ no. of 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 and colleagues[26] (1985)	Hospital patients (mean age 43.5 yr)	100	Australia	0.12	—	—	Crude	Depression/SDS	Sleep disturbance/ researcher-made questionnaire	—
Ford and Kamerow[27] (1989)	General population (18–65+ yr)	7954	USA	0.55	—	—	Sex, age, socioeconomic status, race, and marital status	Major depression/ DSM-III	Hypersomnia/ DSM-III	—
Von Korff and colleagues[36] (1993)	General population (18–44 yr)	1016	USA	—	—	−0.18	Age, sex, and education	Depression/ SCL90	—	Back pain/self-report
Leino and Magni[37] (1993)	Industry employees (40–68 yr)	607	Finland	—	—	0.13	Age, baseline depression, and stress scores	Depressive symptoms/ DSS	—	Musculoskeletal pain/self-report
Magni and colleagues[38] (1994)	General population (25–74 yr)	2324	USA	—	0.06	0.006	Crude	Depression/CES-D	Restless sleep/ self-report	Chronic musculoskeletal pain/health records
Pietri-Taleb and colleagues[39] (1994)	Industry employees (25–49 yr)	1015	France	—	—	0.01	Age, marital status, smoking, and physical exercise	Depression/ MHQ	—	Neck trouble/self-report
Affleck and colleagues[40] (1996)	Hospital patients (mean age 43.8 yr)	50	USA	—	−0.28	—	Between-person variation and autocorrelation	—	Mean sleep quality ratings/ researcher-made questionnaire	Fibromyalgia/ clinical diagnosis
Breslau and colleagues[28] (1996)	General population (21–30 yr)	1007	USA	0.61	—	—	Sex, nicotine dependence,	Major depression/	Insomnia/ diagnostic interview	—

Continued

Table 1 Continued

Author (year)	Sample type	Study size or no. of cases/ no. of controls	Country	r, Dep-Sl	r, Sl-Pa	r, Dep-Pa	Adjustment variables	Exposure/ measurement tool	Mediator/ measurement tool	Outcome/ measurement tool
							insomnia, and hypersomnia	diagnostic interview		
Breslau and colleagues[28] (1996)	General population (21–30 yr)	1007	USA	0.57	—	—	Sex, nicotine dependence, insomnia, and hypersomnia	Major depression/ diagnostic interview	Hypersomnia/ diagnostic interview	—
Breslau and colleagues[28] (1996)	General population (21–30 yr)	1007	USA	0.71	—	—	Sex, nicotine dependence, insomnia, and hypersomnia	Major depression/ diagnostic interview	Insomnia and hypersomnia/ diagnostic interview	—
Ağargün and colleagues[41] (1999)	Hospital patients (mean age 30.3 yr)	16	Turkey	—	−0.58	—	Crude	—	Sleep quality/ PSQI	Fibromyalgia/ algometers
Zautra and Smith[42] (2001)	Postmenopausal women (42–76 yr)	188	USA	—	—	0.93	Age	Depressive symptoms/ MHI	—	RA/self-report
Zautra and Smith[42] (2001)	Postmenopausal women (42–76 yr)	188	USA	—	—	0.91	Age	Depressive symptoms/ MHI	—	OA/self-report
Brander and colleagues[43] (2003)	Hospital patients (36–85 yr)	116	USA	—	—	0.43	Crude	Depression/BDI	—	Knee pain/MPQ
Carroll and colleagues[44] (2004)	At-risk general population (20–69 yr)	1131	Canada	—	—	0.02	Education and age	Depression/CES-D	—	Neck and low back pain/CPGQ
Hasler and colleagues[30] (2005)	General population (19–40 yr)	499	Switzerland	0.10	—	—	Sex, age, baseline psychopathology, trouble falling asleep, impaired sleep quality, awakenings during sleep period, waking up too early, and trouble getting up in the morning	Major depression/ SPIKE	EDS/SPIKE	—
Larson and colleagues[45] (2004)	General population (18–65 yr)	4349	USA	—	—	0.34	Sex, age, education, and income	Depressive disorder/CES-D	—	Back pain/self-reported
Boardman and colleagues[46] (2006)	General population (18–90 yr)	1589	UK	—	0.19	0.24	Age, sex, and headache disability level	Depression/ HADS	Sleep problem/ Jenkins questionnaire	Headache/self-report
Gupta and colleagues[47] (2007)	General population (25–65 yr)	3185	UK	—	0.26	0.22	Age and sex	Depression/ HADS	Sleep problems/ SQS	CWP/ACR criteria

Continued

Table 1 Continued

Author (year)	Sample type	Study size or no. of cases/ no. of controls	Country	*r*, Dep-Sl	*r*, Sl-Pa	*r*, Dep-Pa	Adjustment variables	Exposure/ measurement tool	Mediator/ measurement tool	Outcome/ measurement tool
Kaila-Kangas and colleagues[48] (2006)	Factory employees (24–41 yr)	902	Finland	—	0.24	—	Age, sex, and occupational class	—	Sleep disturbances/ researcher-made questionnaire	Back pain/self-report
Jansson-Fröjmark and Lindblom[31] (2008)	General population (20–60 yr)	1273	Sweden	0.32	—	—	Crude	Depression/ HADS	Insomnia/DSM	—
Morphy and colleagues[49] (2007)	General population (18–98 yr)	2662	UK	0.05	0.20	—	Age, sex, social class, anxiety, depression, and pain areas	Depression/ HADS	Insomnia/ researcher-made questionnaire	Widespread pain/ self-report
Bigatti and colleagues[50] (2008)	Hospital patients (mean age 54 yr)	492	USA	0.36	0.27	0.36	Crude	Depression/CES-D	Sleep quality/ PSQI	Fibromyalgia/MPQ
Edwards and colleagues[51] (2008)	General population (mean age 47 yr)	1031	USA	—	−0.03	—	Age, sex, BMI, number of chronic conditions, use of prescription medications, chronic sleep difficulties, presence of an emotional disorder, and persistent pain condition	—	Sleep duration/ self-reported	Daily pain/self-report
Smith and colleagues[52] (2008)	Hospital patients (mean age 40.9 yr)	333	USA	—	0.80	—	Crude	—	Insomnia/BSI	Arthritis pain/SF-36
Young and colleagues[53] (2008)	Hospital patients (mean age 46.9 yr)	84	USA	—	—	0.07	Crude	Depressive symptoms/ CES-D	—	Back pain/PBPI
Edwards and colleagues[54] (2009)	Hospital patients (mean age 34 yr)	53	USA	—	0.07	—	Crude	—	Sleep efficiency/ PSG	Overall pain/DNIC
Kim and colleagues[32] (2009)	Older population (20–41 yr)	83	Korea	0.23	—	—	Age, sex, education, housing, past occupation, current employment,	Depression/GMS	Insomnia/ researcher-made questionnaire	—

Continued

Table 1 Continued

Author (year)	Sample type	Study size or no. of cases/ no. of controls	Country	r, Dep-Sl	r, Sl-Pa	r, Dep-Pa	Adjustment variables	Exposure/ measurement tool	Mediator/ measurement tool	Outcome/ measurement tool
							living area, life events, social deficit, physical activity, anxiety, and daily drinking			
Quartana and colleagues[55] (2010)	Hospital patients (mean age 33.7 yr)	53	USA	—	0.08	—	Crude	—	Insomnia/ISI	TMD/BPI
Mork and Nilsen[56] (2012)	General population (20–70 yr)	12 350	Norway	—	0.25	—	Age	—	Sleep problems/ self-report	Fibromyalgia/ clinical diagnosis
Nitter and colleagues[57] (2012)	General population (20–50 yr)	2498	Norway	—	0.20	—	Age	—	Sleep disturbance/ self-report	Chronic regional pain/researcher-made questionnaire
Sanders and colleagues[59] (2016)	General population (18–44 yr)	2453	USA	—	0.10	—	Age, sex, study site, and race/ethnicity	—	Sleep quality/ PSQI	Painful TMD/QST
Walton and colleagues[60] (2016)	Hospital patients (18–68 yr)	276	Canada	—	0.21	0.05	Crude	Depression/ HADS	Sleep disturbance/ self-report	Regional pain/PCS
Daly and colleagues[61] (2017)	Pregnant women (mean age 31.4 yr)	186	UK	—	—	0.04	Anxiety, deprivation score, and presence of preoperative pain	Depression/ EPND	—	Persistent pain/ VAS
Generaal and colleagues[62] (2017)	General population (18–65 yr)	1860	Netherlands	—	0.12	—	Sex, age, years of education, BMI, smoking, alcohol intake, physical activity, and number of chronic diseases	—	Insomnia/IRS	Multi-site musculoskeletal pain/CPG
Pinheiro and colleagues[64] (2017)	General population of twins (43–71 yr)	1098	Spain	—	—	0.10	Age and sex	Depression/ST-Dep	—	LBP/self-report
Aili and colleagues[65] (2018)	General population (20–74 yr)	1249	Sweden	—	0.24	—	Age and sex	—	Initiating sleep disturbance/ USI	CWP/ACR criteria
Aili and colleagues[65] (2018)	General population (20–74 yr)	1249	Sweden	—	0.26	—	Age and sex	—	Maintaining sleep disturbance/ USI	CWP/ACR criteria
		227	Netherlands	—	—	0.01	Crude	Depression/CES-D	—	Palmar pain/BCTQ

Continued

Table 1 Continued

Author (year)	Sample type	Study size or no. of cases/ no. of controls	Country	*r*, Dep-Sl	*r*, Sl-Pa	*r*, Dep-Pa	Adjustment variables	Exposure/ measurement tool	Mediator/ measurement tool	Outcome/ measurement tool
Datema and colleagues[66] (2018)	Hospital patients (49–73 yr)									
Uhlig and colleagues[67] (2018)	General population (20–70 yr)	13 429	Norway	—	0.17	—	Age, education, smoking, and physical activity	—	Insomnia/DSM-IV	CWMSC/ACR criteria
Wiklund and colleagues[70] (2020)	General population (16–85 yr)	959	Sweden	—	0.19	−0.006	Age, sex, education, depressive symptoms, anxiety symptoms, level of pain catastrophising, and pain intensity	Depression/ GWBS	Insomnia/ISI	Local pain/PCS
Wolfe and colleagues[71] (2020)	Hospital patients (21–103 yr)	35 248	USA	—	—	0.09	Age and sex	Depression/self-report	—	Local pain/PCS
Skarpsno and colleagues[72] (2021)	General population (mean age 54.7 yr)	6033	Norway	—	0.07	—	Age, sex, education, BMI, relative change in body weight, leisure time, physical activity, and smoking status	—	Sleep quality/ self-report	CWP/SNQ
Yabe and colleagues[73] (2022)	General population and natural disaster survivors (18–65 yr)	2059	Japan	—	0.14	—	Sex, age, BMI, living area, smoking, drinking, comorbid conditions, working status, walking time, economic condition, psychological distress, and social isolation	—	Sleep disturbance/ self-report	Low back pain/ self-report
Case–control studies										
Sayar and colleagues[29] (2002)	Cases: hospital patient; controls: general healthy population	40/40	Turkey	0.6	—	—	Age, sex, pain duration, disability, pain intensity, and anxiety	Depression/BDI	Sleep quality/ PSQI	—

Continued

Table 1 Continued

Author (year)	Sample type	Study size or no. of cases/ no. of controls	Country	r, Dep-Sl	r, Sl-Pa	r, Dep-Pa	Adjustment variables	Exposure/ measurement tool	Mediator/ measurement tool	Outcome/ measurement tool
	(mean age 36.7 yr)									
Tekeoglu and colleagues[58] (2013)	General population (18–65 yr)	40/43	Turkey	—	0.49	—	Age, sex, educational status, and BMI	—	Sleep quality/ PSQI	Shoulder pain/ SDQ
López-López and colleagues[63] (2017)	Hospital patients *vs* general population (19–65 yr)	82/82	Spain	—	—	0.06	Age and sex	Depression/BDI	—	SLBP/TQTFSD
Palomo-López and colleagues[68] (2019)	Hospital women patients *vs* general-population healthy women (19–94 yr)	100/100	Spain	—	—	0.56	Crude	Depression/BDI	—	Fibromyalgia/ clinical diagnosis
Toprak and Erden[69] (2019)	Cases: hospital patient; controls: general healthy population (18–65 yr)	76/72	Turkey	0.22	−0.14	−0.05	Crude	Depression/BDI	Sleep quality/ PSQI	Shoulder pain/VAS

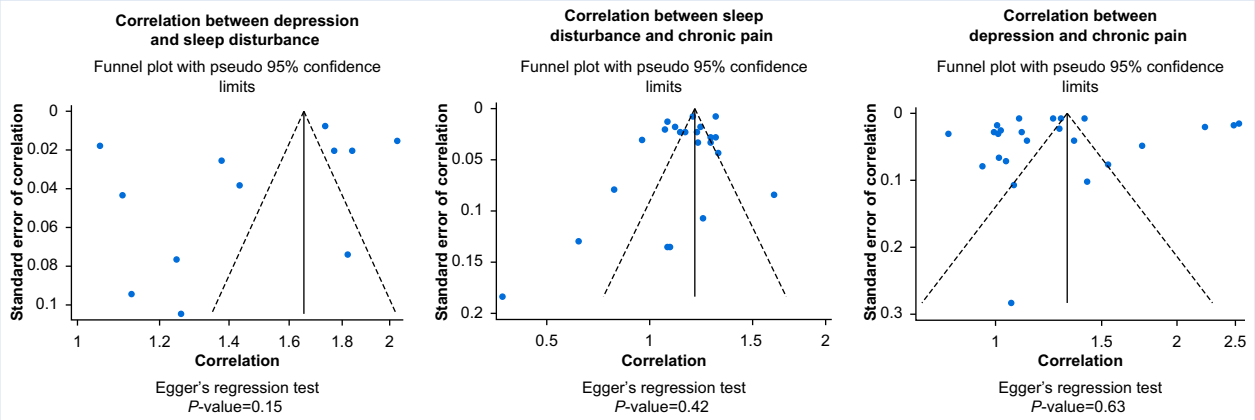

Fig 3. Funnel plots of the correlations between depression, sleep disturbance and chronic pain.

indicate small positive associations amongst the variables. The I^2 statistic (94–97%) and the results of the Q tests indicate large heterogeneity for the overall sample (Table 2). Heterogeneity was similarly high for the different subgroups of studies and 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 CIs, 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 is explained by the indirect effect of sleep disturbance.

In the subgroup analyses, we observed a significant indirect effect amongst cohort studies and studies carried out in the general population in both main and restricted analyses. A significant indirect effect amongst 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 attributable 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% amongst cohort studies and 11.5% amongst 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 four studies determined depression via clinical observation. The results of the analysis restricted to studies using screening tools of depression instead of a complete diagnosis are 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), and VAF 10.0%.

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.

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 amongst 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 comprised many different countries all over the world. Therefore, the impact of ethnic or

Table 2 Pooled correlation coefficients ($\bar{r}$). *k*, number of primary studies; $\bar{r}$, pooled correlation coefficient.

	k	Sample size (*N*)	$\bar{r}$	95% Confidence interval		I^2 (%)	*P*-value Q-test
				Lower limit	Upper limit		
Depression–pain	24	54 787	0.24	0.09	0.38	97	<0.001
Sleep disturbance–pain	22	61 652	0.19	0.10	0.25	96	<0.001
Depression–sleep disturbance	12	640	0.27	0.11	0.39	94	<0.001

Table 3 Direct, indirect, and total effects in the meta-analytic mediation models. CI, confidence interval; k, number of primary studies; 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.

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 to 0.03)	0.41 (0.23–0.59)	2.4	—	—	—	—	
Regional pain	35	0.19 (0.04–0.37)	0.03 (−0.02 to 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 to 0.03)	0.27 (0.07–0.46)	—	14	0.30 (0.06–0.52)	−0.03 (−0.10 to 0.04)	0.27 (0.05–0.48)	—
Region										
European	21	0.08 (−0.05 to 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 to 0.04)	0.32 (0.10–0.53)	—	21	0.36 (0.10–0.43)	−0.01 (−0.06 to 0.03)	0.35 (0.12–0.57)	0.4
USA	19	0.47 (0.11–0.85)	−0.08 (−0.24 to 0.02)	0.40 (0.12–0.67)	—	15	0.45 (0.10–0.80)	−0.05 (−0.17 to 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 to 0.34)	0.26 (0.15–0.67)	11.5	—	—	—	—	—
Adjustment										
Unadjusted	17	0.44 (0.15–0.73)	−0.004 (−0.05 to 0.04)	0.44 (0.18–0.69)	—	15	0.45 (0.15–0.75)	−0.002 (−0.02 to 0.05)	0.45 (0.19–0.70)	2.8
Adjusted	32	0.08 (−0.08 to 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 to 0.04)	0.40 (0.08–0.70)	—	9	0.46 (0.10–0.86)	−0.04 (−0.21 to 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	—	—	—	—	—

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 amongst Caucasians,[75] as the former group is more frequently subject to a variety of adverse psychosocial outcomes because of 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 attributable 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 amongst the three constructs.[81–83] The interrelation between these variables explains the inconsistencies in the literature regarding these pathways. Studies have focused previously 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 recognised 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 percept-ion.[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 to explore better therapeutic outcomes for pain management.

Authors' contributions

Research idea conception: BT
Study design: BT
Literature review: RK
Quality scoring of studies: RK, NM
Data extraction: RK, RR-C
Data analysis/interpretation: BT, RS, RK
Drafting of paper: RK
Critical review/revision of paper: NM, RS
Review/approval of paper for publication: all authors

Declaration of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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