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CLINICAL REVIEW

# Sleep disturbances and sleep disorders as risk factors for chronic postsurgical pain: A systematic review and meta-analysis

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SUMMARY

This systematic review and meta-analysis aimed at evaluating the role of sleep disturbances and sleep disorders in influencing presence and intensity of chronic postsurgical pain (CPSP). We included cohort studies which enrolled adults, assessed sleep disturbances or disorders before surgery, measured pain intensity, presence of pain, or opioid use at least three months after surgery. Eighteen studies were included in a narrative synthesis and 12 in a meta-analysis. Sleep disturbances and disorders were significantly related to CPSP, with a small effect size, r = 0.13 (95% CI 0.06–0.20). The certainty of evidence was rated low due to risk of bias and heterogeneity. In subgroup analyses the above association was significant in studies that used pain intensity as the outcome, but not in those that used presence of pain; in studies on patients who underwent total knee arthroplasty or other surgeries, but not in those on patients who had breast cancer surgery or total hip arthroplasty; in the single study that assessed insomnia and in studies that assessed sleep disturbances as predictors. A meta-regression showed that the follow-up length was positively associated with the overall estimate. Our findings suggest that presurgical sleep disturbances and disorders should be evaluated to detect patients at risk for CPSP.

Registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=272654



## Introduction

Chronic postsurgical pain (CPSP) is defined as pain that develops or increases in intensity after a surgical intervention, persists for at least three months, and affects the individual's quality of life [1]. CPSP is a long-term adverse event after surgical procedures that has a high incidence and that remains often undermanaged. Indeed, evidence suggests that 3%–56% of patients experience chronic pain after common surgical interventions such as joint replacement surgery, cholecystectomy, or hernia repair, and that these percentages increase up to 80% after surgical interventions such as amputation and thoracotomy [2,3].

The most critical consequences of this condition are functional limitations, poorer quality of life, psychological distress, prolonged use of opioids, and high utilization and cost of health care [4]. Since chronic pain is difficult and costly to treat, and the available pharmacological treatments for the prevention of CPSP have shown underwhelming results, the identification of modifiable risk factors is necessary to develop better prevention and risk reduction strategies [3,5,6]. Various presurgical and perioperative predictors of

*Abbreviations:* CI, confidence interval; CPSP, chronic postsurgical pain; ICD-11, international classification of diseases 11; ICSD-3, international classification of sleep disorders; NRS, numeric rating scale; OA, osteoarthritis; PSQI, pittsburgh sleep quality index; THA, total hip arthroplasty; TKA, total knee arthroplasty; VAS, visual analogue scale.

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CPSP have been identified, such as genetic predisposition [7,8], female sex, younger age, preoperative pain, previous chronic pain [5], psychosocial factors [9–12], duration of surgery [2,13], surgical technique [14] and severity and duration of acute postsurgical pain [15–17]. Identifying patients at risk and providing preventive pharmacological and non-pharmacological treatments tailored to the patient's risk factors has been suggested as a potential way to improve the ability of health systems to reduce the incidence of CPSP [5].

Despite the well-known nexus between sleep and pain [18], only recently research among modifiable risk factors has highlighted the emerging role of sleep disturbances and sleep disorders in the development of CPSP. For the purposes of this systematic review, the term “sleep disturbance” refers to poor sleep quality [19,20]. Sleep quality is a multifaceted term that encompasses quantitative aspects of sleep, including sleep duration and sleep latency, as well as more qualitative dimensions, such as “depth” or “restfulness” [21,22]. Differently, sleep disorders (e.g., insomnia, sleep-related breathing disorders, and central disorders of hypersomnolence) are conditions including subjective complaints variably coupled with objective evidence, according to the International Classification of Sleep Disorders 3 (ICSD-3) or the International Classification of Diseases 11 (ICD-11) [23,24].

Sleep and pain have a bidirectional relationship [25,26], with pain leading to sleep disturbances [27,28], and sleep disturbances contributing to increased pain [29–31]. However, in various chronic pain conditions, sleep disturbances have been found to be better predictors of increased pain than vice versa [30,32,33].

Regarding postsurgical pain, current evidence suggests that preoperative [34] and perioperative sleep disturbances and disorders are a risk factor for acute postsurgical pain [35–37]. However, it is less clear whether they are also risk factors for CPSP.

Our research aimed to evaluate if preoperative and perioperative sleep disturbances and disorders are risk factors for CPSP. We hypothesized that there would be a statistically significant effect of both sleep disturbances and disorders on pain intensity, presence of pain, and opioid use after at least three months from surgery. We also aimed to explore without pre-existing hypotheses whether different operationalizations of sleep disturbances and disorders (e.g., self-reported sleep disturbances, sleep duration, medical diagnosis of sleep disorders) and different surgical procedures had a different impact on CPSP.

## Methods

### *Search method and study selection*

The reporting of this study follows the Preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) guidelines [38]. The systematic review was registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=272654.

The electronic search was performed using the following electronic databases: PubMed, Embase, Scopus, and Web of Science. Details of the electronic search strategy are reported in the supplementary materials (Supplementary materials, Table S1). To reduce the presence of publication bias, the grey literature was also searched using Google Scholar, OpenGrey, and GreyNet. These searches were performed on August 1, 2021. Only records written in English, French, German, Italian, and Portuguese were considered. No publication date restrictions were applied.

Studies were included if: 1) they were retrospective or prospective cohort studies; 2) sleep disturbances and sleep disorders were assessed using polysomnography, clinical diagnosis, or validated questionnaires during the preoperative and perioperative period; 3) the intensity of pain, the presence of pain, and/or the use of opioids were evaluated at follow-up after at least three months from the surgical intervention; and 4) adult patients undergoing any type of surgery were included. Studies were excluded if they included participants with age <18.

The records retrieved during the electronic search were uploaded to the online software Rayyan [39]. A reviewer supervised the deletion of duplicate records. Then, two reviewers independently screened the titles and abstracts of the remaining records according to the inclusion and exclusion criteria. The interrater agreement for the screening of the articles, measured using Cohen's k, was moderate ($k = 0.79$). Conflicts were resolved by consensus.

Then, the records of the articles were uploaded to the CADIMA online software. Two reviewers accessed the full text of records and decided on their inclusion or exclusion in the review. When reviewers had concerns about the inclusion or exclusion of abstracts from conference proceedings due to a lack of information, the authors of those abstracts were contacted by email and asked for additional information. Disagreements between reviewers were resolved by consensus. The studies that met the inclusion criteria and did not meet any of the exclusion criteria were included in the systematic review. Studies presented in multiple records (e.g., multiple scientific articles, or both articles and conference proceedings) were considered as individual studies.

### *Data extraction*

Two reviewers independently extracted data using a prespecified structured form using the CADIMA web tool. The following data were extracted: the country where the study was conducted, the study design (i.e., retrospective or prospective), the sex distribution of the sample, the mean and standard deviation of the age of the participants, the number of participants enrolled in the study, the number of participants at the last follow-up, the diagnosis of the condition that led to surgical intervention, the name of the surgical procedure, the sleep-related variable assessed (e.g., obstructive sleep apnea syndrome, sleep quality, diagnosis of insomnia), the measurement instrument used to assess the sleep-related variable, the timing of the assessment of the sleep-related variable (i.e., preoperative or perioperative), the outcome variable (i.e., pain intensity, presence of pain or opioid use), the measurement instrument used to assess the outcome, the last follow-up available, the results at the last follow-up available. If the study was reported as an abstract in conference proceedings, the authors of the abstract were contacted and asked for the study data set or, if available, the coefficient describing the association between the sleep variable and postsurgical pain in the original analysis or, if unavailable, the results of a Pearson product–moment correlation between the sleep variable and postsurgical pain. Inconsistencies were resolved by consensus.

### *Risk of bias*

The risk of bias assessment of the included studies was performed independently by two reviewers using the Quality In Prognosis Studies (QUIPS) tool [40]. This instrument was chosen because it was specifically developed to assess the risk of bias in studies focusing on health-related predictors. The QUIPS covers six domains: 1) study participation, 2) study attrition, 3) prognostic factor measurement, 4) outcome measurement, 5) study

confounding, and 6) statistical analysis and reporting. Each domain is composed of subitems, that are combined to formulate an overall rating for each domain. As suggested by Grooten et al. [41], before the use of QUIPS, the reviewers discussed the interpretation of each of the sub-items, the operational rules to be used to rate them, and the weight to be given to each of them to formulate the overall rating of the domain. This process was supervised by a third reviewer. The reviewers then provided a comment reflecting the results of this discussion for each subitem. The QUIPS and comments are reported in the supplementary materials (Supplementary materials, Table S2). The risk of bias was rated as low, moderate, or high for each domain. In the case of discrepancies between the two reviewers, the conflicts were resolved by consensus under the supervision of the third reviewer.

The results of the risk of bias assessment were used to describe the quality of the included studies in the narrative synthesis. These results were also converted into a numerical format to create a quality indicator for the studies that would be included as a fixed effect in the meta-regression (see the section Quantitative synthesis). For each domain, a grade of 2, 1 or 0 was assigned when there was, respectively, a low, moderate or high risk of bias. The quality indicator of the studies was calculated as the sum of the grades of the six domains.

*Narrative synthesis*

First, a narrative synthesis of the results of all included studies was performed to assess the consistency of the association between preoperative and perioperative sleep disturbances, sleep disorders, and CPSP, also considering the methodological quality of the studies. The narrative synthesis also provides a preliminary evaluation of studies that were not subsequently included in the quantitative synthesis.

*Quantitative synthesis*

According to our protocol, multiple meta-analyses were planned to analyse sleep-related variables measured in the preoperative period separately from those measured in the perioperative period and outcomes related to CPSP separately from outcomes related to opioid use. For this synthesis, only studies that provided the coefficients representing the association between sleep-related variables and CPSP or opioid use and studies whose authors provided these coefficients were considered. Since no study analysed the impact of perioperative sleep-related variables on CPSP or opioid use, and only one study analysed the impact of preoperative sleep-related variables on opioid use, a single random-effect meta-analysis assessing the impact of preoperative sleep disturbance on CPSP was performed.

To perform the meta-analysis, all coefficients and effect sizes extracted from the original studies, calculated using the available original data sets of the included studies, or provided by the authors of the studies, were first converted to Pearson's r using standard formulae and then converted to Fisher's z to be pooled [42,43]. The result of each meta-analysis was finally back-transformed to Pearson's r for a more immediate interpretation. Estimates from bivariate analyses (e.g., Pearson's r, coefficients of bivariate linear regressions) were included in the analysis when both bivariate and multivariable analyses were present. According to the protocol, data from different time points, subscales (e.g., the subscales of the Pittsburgh sleep quality index), outcome measurement instruments (e.g., Visual analogue scale, Numerical rating scale) or subgroups (e.g., primary knee arthroplasty and revision knee arthroplasty) within a single study, if comparable, were aggregated using standard formulae [42].

The presence of publication bias was investigated by a visual analysis of a funnel plot. In addition, the trim-and-fill method was used as a sensitivity analysis. This procedure provides an estimate of the number of missing studies due to publication bias and the effect that these studies might have on the overall effect.

The presence of heterogeneity was evaluated based on Cochran's Q, and the amount of heterogeneity was assessed using the $I^2$ index. The index can be interpreted as the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Values of 25%, 50%, and 75% were used as cut-off points for low, medium, and high inconsistency. As per protocol, separate subgroup analyses grouping studies based on type of outcome, type of predictor, and type of surgery were performed. Based on available data, the following three subgroups were created: 1) studies that considered continuous outcomes (e.g., Numeric rating scale scores) vs. studies that considered dichotomous outcomes (e.g., Numeric rating scale scores >3); 2) studies that evaluated the predictive value of variables related to sleep disturbance vs. studies that evaluated the predictive value of the presence of insomnia; 3) studies that included samples of patients undergoing total knee arthroplasty (TKA) vs. total hip arthroplasty (THA) vs. breast surgery vs. other surgical procedures.

A meta-regression was then performed to determine other potential sources of heterogeneity. The variables included in the meta-regression model were: 1) sex composition of the sample, 2) the mean age of the sample, 3) methodological quality, and 4) the follow-up timing of the coefficient included in the meta-analysis. The $\alpha$ level was set at 0.05. The analyses were performed using the R (version 4.0.3) package *metafor* [44].

*Assessment of the certainty of the evidence*

An overall assessment of the certainty of the evidence on the association between preoperative sleep disturbances, sleep disorders and CPSP was performed according to the GRADE guidelines for the evaluation of evidence on prognostic factors [45]. The GRADE system classifies the certainty of evidence into one of four levels, namely: high, moderate, low, and very low. The certainty of evidence begins as high and is rated down for each concern in one of the following domains: risk of bias, inconsistency, imprecision, indirectness, and publication bias. To perform this procedure, both the results of the narrative and quantitative synthesis were considered.

## Results

The first database, following the removal of duplicates, was composed of 6262 records. After the abstract and full text screening, 21 articles or abstracts of conference proceedings, corresponding to 18 studies (n = 8408), were included in the systematic review. Table S3 (Supplementary materials) reports the studies that appeared to meet the inclusion criteria but were later excluded, with reasons for their exclusion. Fig. 1 shows the flow diagram summarizing the study selection process.

Table 1 reports the description of the included studies. Among them, four were published in the form of abstracts of conference proceedings and 14 were published in the form of journal articles. Sixteen studies were prospective, while two were retrospective. The samples consisted predominantly of women (mean female percentage: 68%), and middle-aged participants (mean age: 60.7). The median sample size was 159. The most common surgical procedure was total knee arthroplasty (TKA; seven studies), followed by breast surgery (three studies), total hip arthroplasty (THA; two studies), thoracotomy (two studies), hip surgery (one study),

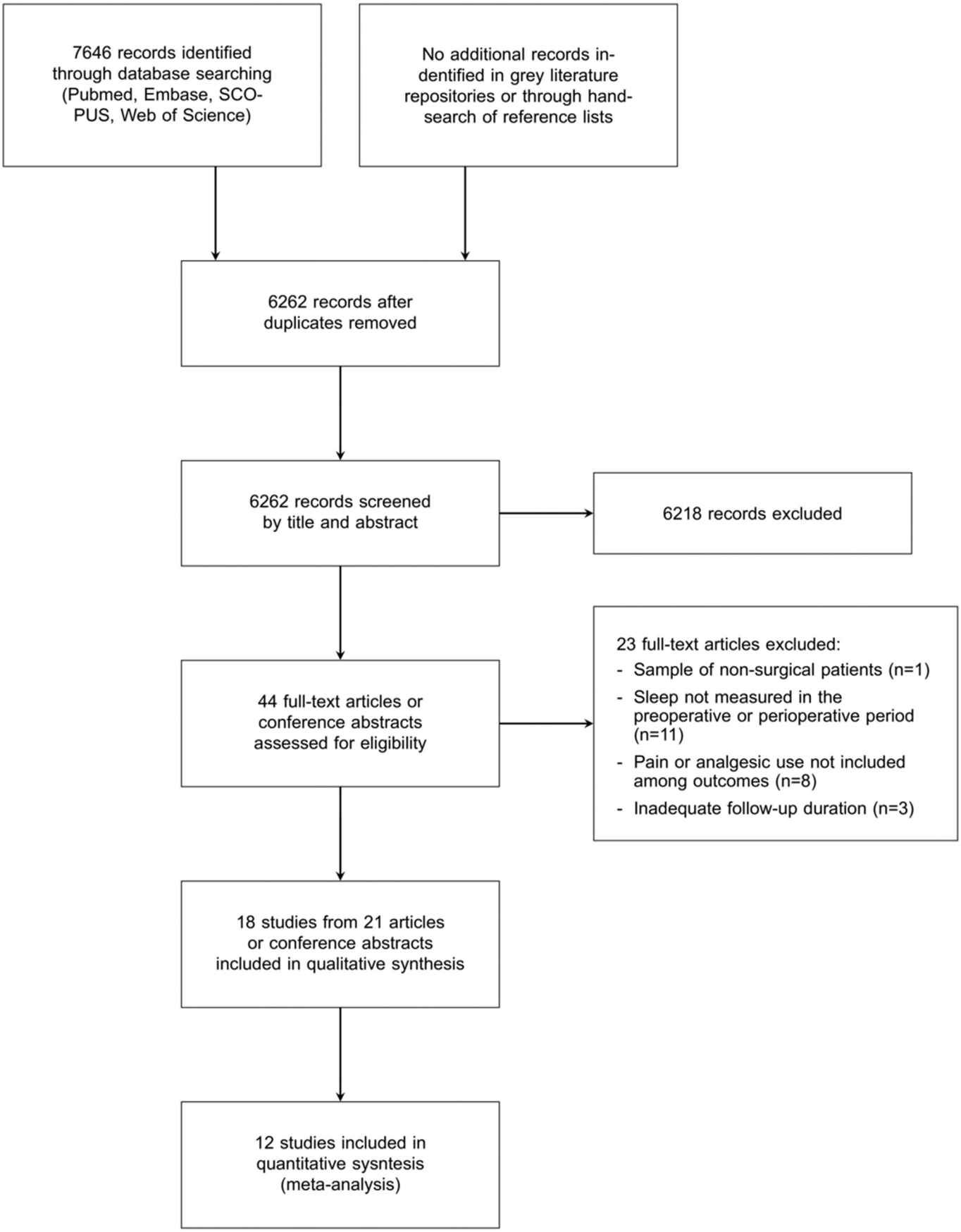


**Fig. 1.** Flow diagram of the systematic review.

**Table 1**
Characteristics of included studies.

| First Author | Country | Design | F%* | Age M(ds) | N | N at last follow-up | Diagnosis | Surgery | Sleep-related variable | Measurement instrument | Outcome | Outcome measurement instrument | Follow-up duration | Confounders | Synthesis of results |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baeyens et al., 2019 [60] | Belgium | Prospective | 56 | 59 (14) | 167 | 97 | n/a | Any type | Sleep quality | PROMIS-29 | Presence of pain | NRS≥3 | 6 | Preoperative pain, age, sex, ASA score, catastrophizing, anxiety, depression, fatigue, participation in social roles, functional expectation, pain expectation | Preoperative sleep quality predicted presence of pain in the period from three to six months after surgery in a model including all the confounders. In a second analysis employing a stepwise selection method, sleep quality was kept in the final model. |
| Bayman et al., 2017 [63] | USA | Prospective | n/a | n/a | 107 | 99 | n/a | Thoracotomy | Sleep disturbance | n/a | Presence of pain | NRS>5 | 3 | Anxiety, depression, physical role function, fatigue, post-traumatic stress disorder, catastrophizing, psychological acceptance, pain threshold to cold, pain magnitude to supra-threshold cold | Sleep disturbance was not associated with persistent pain after thoracic surgery in a multivariable model which included all the confounders. |
| Bjurström et al., 2021 [47] | Sweden | Prospective | 59.6 | 70.4 (8.3) | 52 | 52 | Hip OA | THA | Sleep disturbance | PSQI | Pain intensity | BPI | 6 | Age, BMI, catastrophizing, baseline pain intensity | Preoperative sleep quality before surgery predicted pain intensity scores in both a bivariate model and in a multivariable model including the confounders. Depression was not associated with sleep quality and was not included in the regression models. |
| Bogoch et al., 2010 [49] | Canada | Prospective | 67 | 61.8 (12.8) | 96 | 86 | OA | THA | Sleep quality | VAS | Pain intensity | VAS | 12 | | Preoperative sleep quality was correlated with pain intensity at the follow-up in a bivariate analysis. |
| Chen et al., 2016 [54] | USA | Prospective | 61.8 | 65.4 (9.2) | 34 | 23 | OA | TKA | Sleep quality | PSQI | Pain intensity | VAS | 6 | | Sleep quality was not correlated with pain intensity in a bivariate analysis (data provided by the authors). |
| Cho et al., 2015 [57] | Korea | Prospective | 57 | 57 (8) | 58 | 47 | Rotator cuff tear | Rotator cuff repair | Sleep quality | PSQI | Pain intensity | VAS | 12 | Anxiety, depression | Preoperative insomnia did not predict pain intensity in a multiple regression including anxiety and depression. |
| Getachew et al., 2021 [64] | Norway | Prospective | 66 | 68 (9) | 202 | 187 | Knee OA | TKA | Sleep quality | PSQI | Presence of pain | BPI≥4 | 12 | Sex, age, preoperative pain, fatigue, depression | Sleep quality was not associated with moderate or severe pain in a multiple logistic regression model. |
| Greco et al., 2017 [50] | USA | Prospective | 58 | 64 (8.8) | 153 | 153 | OA | TKA | Sleep disturbance | PROMIS | Pain intensity | BPI-PS | 6 | Baseline pain intensity, perceived stress, somatization, neuroticism, and the magnification subscale of the pain catastrophizing scale | Sleep disturbance was included in a multiple robust linear model along with baseline pain intensity, stress, somatization, neuroticism and the magnification subscale of the Pain Catastrophizing Scale. Depression was not associated with pain intensity and was not included in the final model. In the final model, the effect |

(*continued on next page*)

**Table 1** (*continued*)

| First Author | Country | Design | F%* | Age M(ds) | N | N at last follow-up | Diagnosis | Surgery | Sleep-related variable | Measurement instrument | Outcome | Outcome measurement instrument | Follow-up duration | Confounders | Synthesis of results |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | of sleep disturbance was not significant. |
| Grén et al., 2018 [59] | Finland | Retrospective | 100 | 57.4 (9.4) | 689 | 689 | Breast Cancer | Breast Surgery | Presence of insomnia | Non-validated item | Presence of pain | NRS≥4 | 12 | Age, BMI, axillary operation type, preoperative pain, previous chronic pain, smoking, depression, menopausal symptoms | In the bivariate analysis, insomnia was associated to pain. In the multivariable model, the association between insomnia and pain decreased, but remained significant. |
| Hastie et al., 2013 [62] | USA | Prospective | n/a | n/a | 37 | 37 | n/a | Thoracotomy | Sleep disturbance | n/a | Presence of pain | n/a | 6 | | Sleep disturbance was associated with persistent pain, the analysis type and how confounders were controlled for are not reported. |
| Kornilov et al., 2018 [52] | Russia | Prospective | 95 | 63 (8) | 100 | 79 | OA | TKA | Sleep disturbance | PSQI | Average pain intensity | BPI | 12 | | Sleep disturbance was not associated with severe pain after breast cancer surgery in a bivariate analysis (data provided by the authors). |
| Luo et al., 2019 [53] | China | Prospective | TKA: 75.8 THA: 44.8 | TKA: 64.28 (9.68) THA: 54.85 (13.20) | TKA: 471 THA: 523 | TKA: 471 THA: 523 | TKA: OA THA: OA | TKA THA | Sleep quality | PSQI | Pain intensity | VAS | 3 | | Preoperative sleep quality was not correlated with postoperative pain in bivariate analyses in both samples. |
| Miaskowki et al., 2012 [61] | USA | Prospective | 100 | 54.5 (11.1) | 410 | 398 | Breast Cancer | Breast cancer surgery | Sleep disturbance | GSDS | Presence of pain | BSQ | 6 | | In a bivariate analysis, patients with higher preoperative sleep disturbance were more likely to have a mild, moderate or severe pain trajectory rather than having no pain at any of the six assessment sessions. |
| Rhon et al., 2018 [66] | USA | Retrospective | 45.9 | 32.5 (8.2) | 1642 | 1642 | FAI | Hip Surgery | Diagnosis of insomnia | Medical records | Having three or more opioids' prescriptions from surgery to the 24th month, still receiving prescriptions at one year or greater | Archival data | 24 | A first analysis included socioeconomic status and active duty status as confounders. A second multivariable model included the following variables: sex, preoperative use of prescription opioids, high health-seeking behaviours, substance abuse, non-opioid pain medication prescription, mental health disorder diagnosis | Having a diagnosis of insomnia before surgery predicted having three or more opioid prescriptions in the period from surgery to the 24th mo in both analyses but did not predict taking opioids one year after surgery in both analyses. |
| Rhon et al, 2019 [65] | USA | Retrospective | 44.5 | 32.2 (8.1) | 1870 | 1870 | FAI | Hip Surgery | Diagnosis of insomnia | Medical records | Having three or more opioids' prescriptions from surgery to the 24th month, still receiving prescriptions at one year or greater, being in the upper median of the total days' supply of opioids | Archival data | 24 | Postoperative hip infection, service branch, socioeconomic status, preoperative post-traumatic stress disorder, metabolic disorder, mental health disorder, cardiac disorder, substance abuse, chronic pain | Having a pre-operative diagnosis of insomnia predicted having three or more opioid prescriptions from surgery to the 24th month, but did not predict being in the upper median of the total days' supply of opioids and still taking opioids at one year after surgery |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schreiber et al., 2016a [55], 2016b [56], 2021 [46] | n/a | Prospective | 100 | 55.5 | 259 | 201 | Breast cancer | Breast cancer surgery | Sleep disturbance | PROMIS-SF | Pain intensity, pain frequence and severity | BPI, Breast Cancer Pain Questionnaire | 12 | Age, BMI, education status, alcohol use, total exercise, bilateral surgery, surgical procedure, previous breast surgery, radiation therapy, chemotherapy, opioid use, severity of other chronic pain, Brief Symptom Inventory scores, coping strategies, affective state, catastrophizing, anxiety, depression, quantitative sensory testing results, preoperative pain intensity and pain functional impact | Preoperative sleep disturbance was an independent predictor of pain severity and pain impact after mastectomy in a bivariate analysis and remained significant in a LASSO regression which included all the confounding variables. |
| Shim et al., 2018 [48] | UK | Prospective | 52.6 | Median: 68.6 (IQR 11.3) | 972 | 721 | OA | TKA | Sleep disturbance | Sleep problems scale | Pain intensity | Chronic Pain Grade | 12 | | Preoperative sleep disturbance was significantly correlated with pain intensity at the follow-up in a bivariate analysis (data provided by the authors). |
| Soni et al., 2020 [51] | UK | Prospective | 52 | Median:70 | 96 | 96 | OA | TKA | Sleep disturbance | PSQI | Pain intensity | NSR | 12 | | Sleep disturbance was significantly correlated with pain intensity at the follow-up (data provided by the authors). |
| Walker et al., 2015 [58] | USA | Prospective | 60 | 66.21 (8.28) | 159 | 159 | n/a | TKA | Sleep duration | n/a | Pain intensity | BPI | 12 | Age, depression, preoperative pain | After controlling for the confounders, preoperative sleep duration was a predictor of pain intensity at three months and 12 months, but not at six months. |

Notes. The records whose first author and year are Rhon et al., 2018 and Rhon et al., 2019 were considered as presenting a single study since their samples and aims largely overlap. Nonetheless, the data from these records are presented separately they include different analyses. The records whose first author and year are Schreiber 2016a, Schreiber 2016b and Schreiber 2021 are presented in the same line since they employed the same sample and the first two records are abstracts of conference proceedings presenting ad interim results.
*Percentage of female participants.
Abbreviations: n/a: not available; THA: Total hip arthroplasty; VAS: Visual analogue scale; OA: Osteoarthritis; PSQI: Pittsburgh sleep quality index; BPI: Brief pain inventory; BPI-PS: Brief pain inventory - pain severity scale; NRS: Numeric rating scale; TKA: Total knee arthroplasty; BSQ: Breast symptoms questionnaire; FAI: Femoroacetabular impingement syndrome; PROMIS-29: Performance of the patient-reported outcomes measurement information system 29; PROMIS-SF: Patient-reported outcomes measurement information system-short form; PROMIS-29: Patient-reported outcome measurement information system- 29; GSDS: General sleep disturbance scale; PROMIS: Patient reported outcomes measurement information system; QUIPS: Quality in prognostic studies tool.

rotator cuff repair (one study), any type of surgery (one study), and one remaining study reported results for both TKA and THA. The duration of follow-up ranged from three months to 12 months, with a mode and a median of 12 months.

The most common diagnosis was osteoarthritis (OA; nine studies), followed by breast cancer (three studies), femoroacetabular impingement syndrome (one study) and rotator cuff tear (one study). The diagnosis was unclear for four studies, reported as abstracts of conference proceedings.

The included studies assessed only self-reported sleep disturbances, sleep duration and medical diagnosis of insomnia as predictors of CPSP or opioid use. Sleep disturbances were evaluated using validated questionnaires (i.e., Pittsburgh sleep quality index, Visual analogue scale, PROMIS Profile-29 – Sleep problems subscale, PROMIS short form – Sleep disturbance subscale, and General sleep disturbance scale) or, in one study, using a single ad hoc question.

The outcomes of the included studies were pain intensity (11 studies), presence of pain (six studies), and chronic opioid use (one study). Pain intensity was assessed using the pain severity subscale of the Brief pain inventory (four studies), Visual analogue scales (four studies), numerical rating scale (one study), and the Chronic pain grade (one study). In one study pain intensity was assessed using both Brief pain inventory and Breast cancer pain questionnaire. The instrument used to measure pain intensity was not reported in one abstract. The presence of pain was assessed as having a pain intensity $\geq$3 (one study), $\geq$4 (one study) or >5 (one study) measured using a Numeric rating scale, or $\geq$4 as measured by the pain severity subscale of the Brief pain inventory (one study). In one study that used Breast symptoms questionnaire for assessing the presence of CPSP was not specified if any cut-off was used, and another study did not specify how the presence of pain was evaluated. Chronic opioid use was defined as the presence of more than three prescriptions of opioids after the initial perioperative prescription or still receiving new opioids' prescriptions after one year from surgery (one study).

### *Methodological quality*

The quality of the studies included in this review was variable. Fig. 2 represents the results of the risk of bias assessment for each study. Three studies were rated as having a low risk of bias in all QUIPS domains, and one study was rated as having a high risk of bias in all QUIPS domains. A low risk of bias was detected in more than half of the studies in the following QUIPS domains: study attrition (61.1%), prognostic factor measurement (66.7%), outcome measurement (94.4%) and study confounding (55.6%). On the other hand, only 33.3% of the studies were rated as having a low risk of bias in the study participation domain and 50.0% in the statistical analysis and reporting domain.

### *Narrative synthesis*

Table 1 reports the syntheses of the results of the studies and the confounders that were controlled for when assessing the association between sleep disturbances and sleep disorders in multivariable models, if any. A spreadsheet including the data reported in Table 1 is provided in the Supplementary Materials and can be used to filter the studies and their results based on their characteristics.

### *CPSP pain intensity*

The association between sleep disturbances and CPSP intensity in bivariate analysis resulted significant in six prospective studies, three with high methodological quality [46–48], two of moderate methodological quality [49,50] and one of low methodological quality [51]. In contrast, this association was found to be not significant in two studies of high methodological quality [52,53] and one study with low methodological quality [54].

When this association was assessed in multivariable analyses, the results varied. Two prospective studies conducted bivariate and multivariable analyses and found a statistically significant association between sleep disturbance and pain intensity at six months, controlling for age, BMI, and baseline pain severity [47], and at 12 months, in a multivariable prediction model which included demographic, clinical, pain-related, and psychological variables, including depression [46,55,56]. Both studies have high methodological quality. A prospective study with moderate methodological quality found statistically significant associations between sleep disturbance and pain severity at 6 months, controlling for perceived stress, somatization, neuroticism, and the magnification subscale of the pain catastrophizing scale [50]. One low-quality study did not find a significant association between sleep quality and pain intensity, controlling several confounders including anxiety and depression [57].

A prospective study found a statistically significant association between self-reported sleep duration and pain intensity at 3 and 12 months, but not at 6 months, after controlling for age, depression, and preoperative pain; in this study, the methodological quality was low [58]. This was the only study to evaluate self-reported sleep duration, although it was not specified how this factor was assessed.

### *Presence of CPSP*

Next, the results of studies that evaluated the role of sleep disturbances and disorders on the presence of CPSP are presented. Three prospective and one retrospective studies (one of high methodological quality, two of moderate methodological quality, and one of low methodological quality) found statistically significant associations between the preoperative presence of insomnia [59], sleep quality [60], sleep disturbance [61,62] and the presence of pain at follow-up in bivariate analyses. These effects were present also after controlling for preoperative pain-related, demographic, clinical, and psychological confounders, including depression [59,60]. In contrast, one study of high methodological quality and one study with low methodological quality found no associations in multivariable models between sleep disturbance and the presence of pain at three months in patients undergoing thoracotomy [63], controlling for anxiety, depression, physical role function, fatigue, post-traumatic stress disorder, catastrophizing, psychological acceptance, pain threshold to cold, pain magnitude to supra-threshold cold, and at 12 months in patients undergoing TKA [64], controlling for sex, age, preoperative pain intensity, fatigue, and depression.

### *Opioid use*

Regarding opioid use, a single retrospective study of high quality found that the diagnosis of medical insomnia before surgery predicted having three or more opioid prescriptions from surgery to the 24th mo after surgery after controlling for multiple confounders in patients undergoing hip surgery (i.e., postsurgical hip infection, service branch, socioeconomic status, preoperative post-traumatic stress disorder, metabolic disorder, mental health disorder, cardiac disorder, substance abuse, and chronic pain) [65,66].


**Fig. 2.** Methodological quality of the included studies according to the QUIPS tool.

*Meta-analysis*

It was possible to extract or retrieve the coefficients representing the association between preoperative sleep variables and CPSP from 12 studies. One of these coefficients was calculated based on the original dataset obtained from the study authors [54], four coefficients were provided by the study authors upon request [48,51,52,59]. One article reported separate results for a cohort of patients undergoing TKA and a cohort of patients undergoing THA, therefore the coefficients of the two cohorts were included in the analyses separately [53]. All these coefficients were included in a meta-analysis.

This meta-analysis detected a significant weak effect of sleep disturbances and disorders on CPSP, with an estimate of r = 0.13 (95% CI 0.06–0.20; p < .01) (Fig. 3). Heterogeneity among the studies was moderate ($I^2$ 66.81%; Q (12) = 38.78, p < .01). Visual inspection of the funnel plot revealed a slight asymmetry in the left part of the plot, possibly due to publication bias (Fig. 4). However, the trim-and-fill procedure showed that the inclusion of two potential missing studies would have only slightly reduced the overall estimate, which would have retained its significance (r = 0.10, 95% CI 0.04–0.17, p < .01).

*Subgroup analysis and meta-regression*

Table 2 shows the coefficients resulting from the subgroup analyses. Forest plots resulting from this analysis are reported in the Supplementary materials (Figs. S-1–S-3). The coefficients of the subgroups created based on the use of a dichotomous outcome (i.e., the presence of CPSP) or a continuous outcome (i.e., pain intensity at follow-up) were of similar size, but the coefficient relative to studies assessing dichotomous outcomes was not significant. The subgroup analysis based on the type of sleep-related variables was influenced by the imbalance in the number of studies for each subgroup, as 12 coefficients referred to sleep disturbance and only one coefficient to the presence of insomnia. The coefficient relative to the presence of insomnia was higher than the coefficient relative to sleep disturbance. The subgroup analysis performed based on the type of surgery was influenced by the fact that the subgroups were small. The coefficient of the subgroup of studies assessing patients that had TKA was significant and similar to the overall coefficient. The coefficients of the studies investigating samples of patients that had breast surgery or THA were not significant and had a very wide confidence interval. Finally, the subgroup that included studies of patients that had other surgery types (e.g., rotator cuff repair, mixed surgeries) had a small but significant coefficient.

The results of the meta-regression are reported in Table 3. Follow-up duration was the only fixed effect that showed a positive association with the overall effect. The inclusion of all fixed effects in the model reduced $I^2$ to 0% (test for residual heterogeneity Q (8) = 8.53, p = .38).

*Assessment of the certainty of the evidence*

Although study quality was not significantly associated with the overall estimate in the meta-regression, we judged that there was a potential impact of the risk of bias on the results of the meta-analysis since most of the included studies had at least one moderate risk in the domain of the QUIPS. The results suffered from inconsistency due to the presence of heterogeneity. Since all studies assessed the impact of a sleep variable on CPSP, the

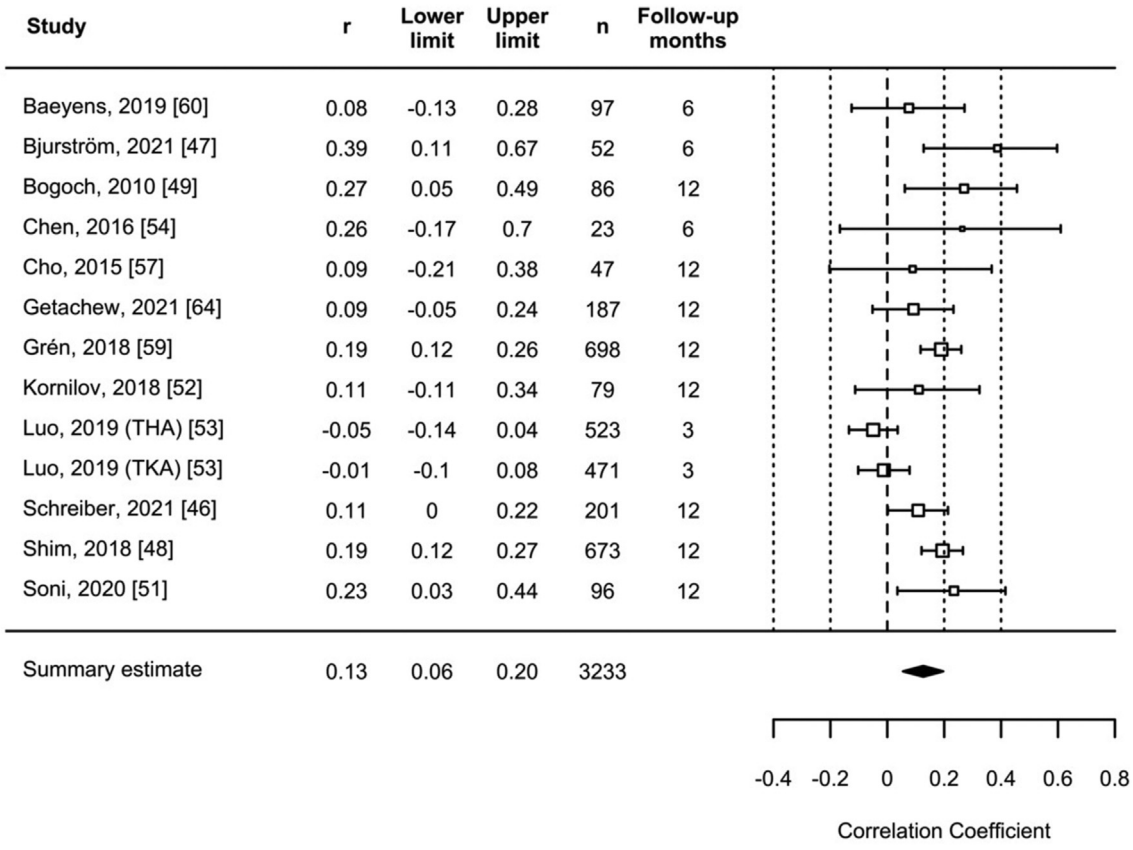


**Fig. 3.** Forest plot for the meta-analysis on the association between preoperative sleep disturbances and chronic postsurgical pain.

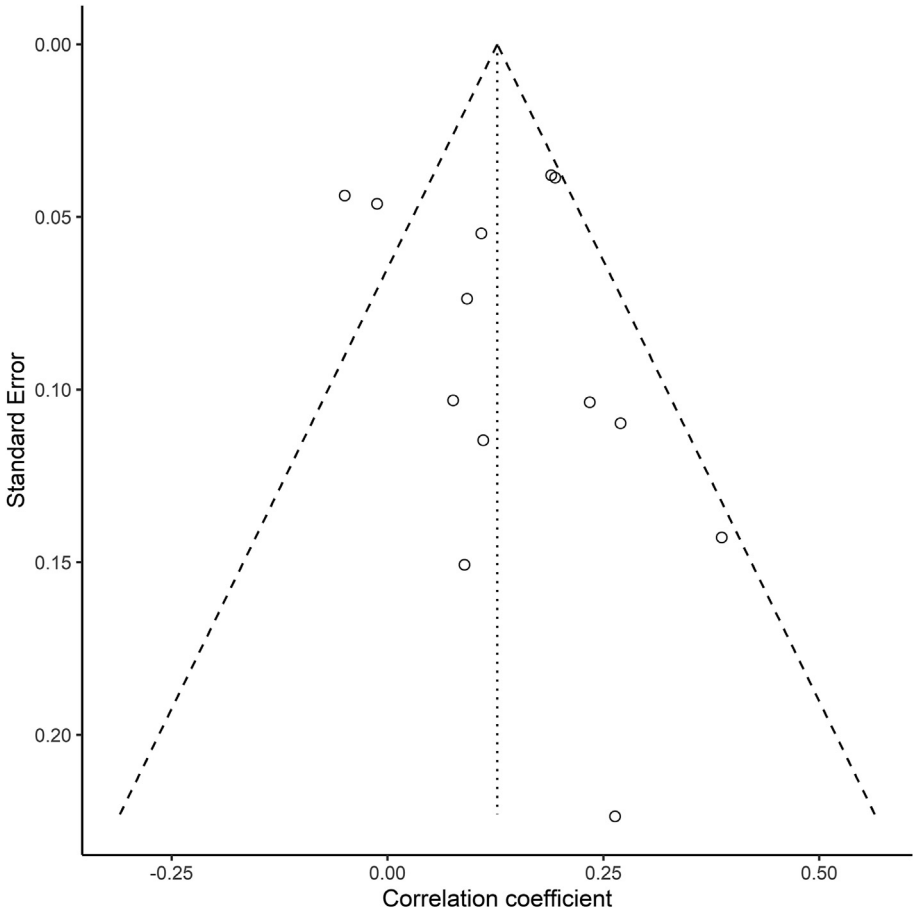


**Fig. 4.** Funnel plot for the meta-analysis on the association between preoperative sleep disturbances and chronic postsurgical pain.

**Table 2**
Results of the subgroup analyses.

| Subgroup | Number of estimates | Overall estimate (95% confidence interval) |
|---|---|---|
| **Outcome type** | | |
| Continuous | 10 | 0.13 (0.03−0.23)* |
| Dichotomous | 3 | 0.15 (−0.01 − 0.31) |
| **Sleep-related variable** | | |
| Sleep disturbance | 12 | 0.12 (0.04−0.20)* |
| Insomnia | 1 | 0.19 (0.12−0.26)* |
| **Surgery type** | | |
| THA | 3 | 0.19 (−0.41 − 0.78) |
| TKA | 6 | 0.12 (0.01−0.23)* |
| Breast surgery | 2 | 0.15 (−0.37 − 0.68) |
| Other | 2 | 0.08 (0.00−0.16)* |

Notes. *p < .05.

results of the meta-analysis were considered as not being affected by indirectness. The imprecision was not significant since the confidence intervals of the coefficient of the meta-analysis were not extended to thresholds of no effect or of medium effect. Although a slight left asymmetry in the funnel plot suggested that the presence of missing studies might have influenced the overall effect, the trim-and-fill procedure showed that the impact of these missing studies on the overall estimate would be minor. Therefore, we decided not to rate down the certainty of evidence based on potential publication bias. Taking all these criteria into account, we judged the certainty of the evidence to be low.

## Discussion

This study aimed to review the growing area of sleep disturbances and sleep disorders as risk factors for the development of CPSP. To our knowledge, the current study is the first systematic review and meta-analysis on this topic.

One interesting finding from our work is that all the studies evaluated sleep from a self-reported perspective. Only one study used a medical diagnosis of insomnia without specifying how the diagnosis was made (e.g., according to ICD vs ICSD) and none used polysomnography or actigraphy. Both self-reported and objective aspects are important and should be assessed because they

**Table 3**
Results of the meta-regression.

| Variable | Overall estimate (95% confidence interval) |
|---|---|
| Intercept | −0.23 (−0.89 − 0.43) |
| Female % | 0.00 (−0.01 − 0.01) |
| Age | 0.01 (−0.01 − 0.01) |
| Methodological quality | −0.02 (−0.06 − 0.11) |
| Follow-up duration | 0.02 (0.01−0.03)* |

Note. *p < .05.

measure different dimensions of sleep. Despite the conflicting evidence [67,68], the majority of studies suggest that objective and subjective measures of sleep are not necessarily associated [69−71]. Thus, more research combining objective measurements with self-reported measures (e.g., actigraphy, polysomnography) is needed to provide an accurate assessment of sleep architecture and to clarify the neurobiological mechanisms through which sleep influences postsurgical pain.

Results of meta-analysis showed that preoperative sleep disturbances and sleep disorders are significant predictors of CPSP. However, as with the other genetic, demographic, clinical, surgery-related, and psychological risk factors studied thus far [10,11,72,73] the overall effect size was small. This suggests that sleep disturbances and disorders add up to a multiplicity of predictors, each of which accounts for a small part of the variance in pain intensity and the presence of pain at follow-up.

Due to the presence of risk of bias in most of the studies included in the review and the heterogeneity between the different estimates, the confidence in the estimate was low. Risk of bias was present in the participation, analysis, and reporting domains of the QUIPS. The presence of bias in the analysis and reporting domains can be explained by the fact that many abstracts from recent conference proceedings were included, suggesting that this study field is beginning to attract interest from researchers. The presence of bias in the participation domain, on the other hand, suggests that future studies should include large and representative samples to enhance the confidence in the association between sleep disturbances, sleep disorders and chronic postsurgical pain. Regarding heterogeneity, the meta-regression showed that studies with longer follow-up found higher associations between sleep disturbances, sleep disorders and chronic postsurgical pain. Future research should evaluate the possibility that sleep disturbances and disorders have an impact on CPSP pain that increases over time.

Importantly, our results are consistent with those of systematic reviews and meta-analyses conducted on chronic pain conditions. For example, evidence suggests that sleep disturbances are a risk factor for back pain [74], persistent spinal pain [75], and that poor sleep quality negatively affects pain-related health outcomes [31]. Regarding postsurgical pain, evidence reported that improved perioperative sleep could reduce acute postsurgical pain after TKA and THA [76]. In both a recent systematic review with meta-analysis [34,77] and a qualitative systematic review [78], preoperative sleep difficulties were found to be a prognostic factor for poor acute postsurgical pain control [34,78].

Evidence suggests that sleep disturbances and disorders affect pain via mediators such as impaired immunity, elevated inflammatory responses, and elevated levels of cytokines (i.e., interleukin-6, C-reactive protein, and cortisol) that have a pain facilitatory effect and can alter pain modulation processing [79−81]. High levels of these markers have been reported in several chronic diseases and contribute to the onset and maintenance of chronic pain conditions [82,83]. The endogenous opioid system is involved in the regulation of pain experience [84] and could be another potential mechanism by which sleep could have a direct impact on pain [85]. In fact, preliminary evidence shows that sleep deprivation can alter endogenous opioid function. These findings suggest that sleep disruption appears to have a deactivating effect on systems with analgesic properties, and an activating effect on systems with hyperalgesic properties [86].

Interestingly, mood is another possible mediator of the association between sleep and pain. Indeed, sleep quality predicts next-day mood [87,88], and negative mood increases self-reported pain, decreases pain tolerance [89], and alters pain responses [90]. Depression, for example, was found to account for a significant portion of the variance in the relationship between sleep and pain in adults with heterogeneous chronic pain conditions [91]. Other evidence suggests that sleep disturbances impact pain interference through negative affect (i.e., the extent to which a person experiences subjective distress, unpleasant engagement, and emotional pain [92]) in adults and older patients [93], as well as in children with sickle cell disease [94] and chronic pain [95].

In this review, ten studies assessed preoperative depression. Unfortunately, because the multivariable models that included it were composed of heterogeneous sets of confounders and because it was measured with different instruments, it was not possible to account for the potential confounding effect of this factor in the meta-analysis or the meta-regression. Nonetheless, the results of the studies included in this review appear to indicate that accounting for the confounding effect of depression is not sufficient to explain the association between sleep disturbances, sleep disorders, and CPSP or analgesic use. In fact, in the multivariable models that included depression, the association between sleep disturbances, sleep disorders, and CPSP or opioid use at follow-up was significant in five studies [46,58−60,65,66] and non-significant in three studies [57,63,64]. Whereas in two studies this factor was excluded from the multivariable models since it was not associated with pain intensity [47,50]. Although it is not possible to disentangle the effect of depression from the effects of the other variables included in these models, it can be argued that the mere inclusion of this factor does not account for the association between preoperative sleep and CPSP.

Several considerations must be made. A possible explanation for our results might be that patients with preoperative sleep disturbances or sleep disorders had a general worse health status, which could have influenced the occurrence of CPSP. However, according to our narrative synthesis, even controlling for confounding factors such as preoperative pain level and other health-related variables, the effect of sleep remains significant. Furthermore, most of the studies included relied on the overall scores of self-reported measures of sleep disturbances. Although sleep is a complex phenomenon, this approach might not accurately capture specific components of the sleep experience. We recommend evaluating sleep latency, total sleep time, and sleep continuity in addition to overall perceived sleep quality.

It should be noted that there is a lack of studies that investigated the influence of preoperative sleep disturbances and disorders on the chronic use of opioids in the postsurgical period. Preliminary evidence in burn injury survivors indicates that poor sleep quality might be associated with increases on the next day in opioids' doses [96]. This could also be an interesting area of research in CPSP. Indeed, reducing the prescriptions of opioids for postsurgical pain is compelling given their dramatic increase [97] and detrimental health consequences [98]. In addition, we emphasize that only one study distinguished between primary and secondary sleep disorders [65]. None of the other studies clarified whether sleep disturbances existed prior to the condition that led to surgery. Although this is beyond the scope of our study, it may be important in future research to take this distinction into account.

The studies included in this review used either the intensity of postsurgical pain or the probability of having pain above a certain threshold as outcomes. Although these outcomes can be used as proxies for the presence of CPSP, the medical diagnosis of this condition requires the presence of additional criteria, such as pain that affects the patient's quality of life, pain that is localised to the surgical area or projected into the innervation territories of the nerves located there, and no other explanatory cause [1]. This shortcoming is common to most reviews investigating predictors of postsurgical pain [10,11], and is due to the methodological choice of most original articles to measure only pain intensity, or the presence of pain intensity above a threshold, as an outcome. Because the original studies did not evaluate all the CPSP criteria, it is difficult to drawn precise conclusions about whether predictors actually influence CPSP. We suggest that future studies addressing predictors of CPSP should consider using the medical diagnosis of CPSP as an outcome.

This study broadens our knowledge about the relationship between sleep and pain. Routine screening for sleep disturbances and disorders in patients undergoing surgery should be prioritized. In addition to self-report questionnaires that assess sleep quality, screening could be done using wearable devices (e.g., actigraphy) that provide reliable home monitoring of several sleep parameters [99]. A multidisciplinary evaluation with both pain and sleep experts could be beneficial in order to minimize CPSP. Early intervention at a preoperative level aimed at improving sleep quality and reducing sleep disorders might be a potential preventive strategy. Moreover, despite the low certainty of the evidence, our study may point in a promising direction for future research. For example, prospective studies on early treatment of preoperative sleep disturbances in patients undergoing surgeries should be conducted to investigate whether they can prevent the development of CPSP. This may provide evidence of the causal association between preoperative sleep and CPSP.

## Limitations

Due to the lack of a clear and consistent definition of sleep disturbance and sleep disorders across studies, researchers have used different questionnaires and cutoff scores to evaluate sleep, which may have captured different aspects of sleep. In fact, sleep is a multidimensional experience encompassing objective and subjective factors [100]. Indeed, it has been suggested that different aspects of sleep, such as sleep quality and sleep duration, have a specific effect on pain outcomes [31]. Therefore, it might be worthwhile to investigate the role of specific aspects of sleep in the presence of CPSP. In future research, a clear distinction should be made between sleep disturbances and sleep disorders because they may have differential effects on pain. Furthermore, there is a lack of evidence regarding the role of perioperative sleep on CPSP. Finally, the primary outcome of this study was pain intensity. Other important aspects of pain have a significant impact on a patient's quality of life, such as pain interference. In future research, this aspect should be considered.

## Conclusion

This systematic review and meta-analysis showed that preoperative sleep disturbance (i.e., mostly reflecting the poor-sleep quality/insomnia domain) negatively contributes to the development and intensity of CPSP. Early detection of sleep disturbances and sleep disorders in patients undergoing surgical intervention considered in this study could lead to more tailored interventions, better pain management, and reduced use of pain medications. Greater awareness of the importance of sleep could aid in the development of personalized preoperative care pathways. Patients undergoing surgery may benefit from a multidisciplinary preoperative evaluation, as well as early preoperative sleep modification, to help reduce the occurrence of postsurgical pain. However, generalization to surgical interventions different from those examined is not warranted.

**Practice point**

- Preoperative sleep disturbances and sleep disorders are predictors of chronic postsurgical pain intensity.
- Patients should be screened prior to surgery to identify those who are at risk for sleep disturbances and sleep disorders.
- Incorporating sleep assessment into a multidisciplinary preoperative evaluation and improving preoperative sleep could help reduce the presence and intensity of chronic postsurgical pain.

**Research agenda**

- Prospective studies of interventions aimed at reducing sleep disturbances and disorders preoperatively in patients undergoing surgery should be conducted to investigate whether early treatment of sleep disturbances and disorders can prevent the presence of chronic postsurgical pain.
- In addition to sleep disturbances, future studies should investigate the role of specific sleep disorders (e.g., insomnia, obstructive sleep apnea syndrome) in the development of chronic postsurgical pain.
- We recommend following established diagnostic criteria when diagnosing insomnia and other sleep disorders and indicating which set of criteria was used.
- More studies are needed to evaluate preoperative and perioperative sleep disturbances and disorders as risk factors for chronic use of opioids in the postsurgical period.
- There is a lack of evidence regarding the role of perioperative sleep disturbances and disorders on chronic postsurgical pain; future research should fill this gap.
- In future research, objective measures of sleep disturbances and disorders should be used alongside self-reported measures
- It could be important to evaluate in future research how mood disturbances (e.g., depression) and sleep interact and contribute to chronic postsurgical pain.

## Previous presentation

None.

## Disclaimer

None.

**Institution at which the work was performed**

Università Cattolica del Sacro Cuore, Milan, Italy.

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None.

**Authors' contributions**

All authors contributed to the manuscript as follows:
GV conceived the study, designed the study, performed the electronic search, acquired data, performed the screening of the records and the data extraction, performed the analyses, interpreted the data, drafted the manuscript.
EMG designed the study, performed the electronic search, acquired data, performed the screening of the records, performed the analyses, interpreted the data, drafted the manuscript.
CM performed the screening of the records and the data extraction, interpreted the data, drafted the manuscript.
GC interpreted the data, revised content critically.
FP interpreted the data, revised content critically.
CF interpreted the data, revised content critically.
GP interpreted the data, revised content critically.
All authors have revised the content critically, have read and approved the final manuscript.

**Conflicts of interest**

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101630.

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