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Original Article

The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis

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ABSTRACT

Background: There is strong evidence indicating an interaction between sleep and pain. However, the size of this effect, as well as the clinical relevance, is unclear. Therefore, this meta-analysis was conducted to quantify the effect of sleep deprivation on pain perception.
Methods: A systematic literature search was conducted using the electronic databases PubMed, Cochrane, Psyndex, Psycinfo, and Scopus. By conducting a random-effect model, the pooled standardized mean differences (SMDs) of sleep deprivation on pain perception was calculated. Studies that investigated any kind of sleep deprivation in conjunction with a pain measurement were included. In cases of several pain measurements within a study, the average effect size of all measures was calculated.
Results: Five eligible studies ($N = 190$) for the between-group analysis and ten studies ($N = 266$) for the within-group analysis were identified. Sleep deprivation showed a medium effect in the between-group analysis (SMD = 0.62; CI95: 0.12, 1.12; $z = 2.43$; $p = 0.015$) and a large effect in the within-group analysis (SMD = 1.49; CI95: 0.82, 2.17; $z = 4.35$; $p < 0.0001$). The test for heterogeneity was not significant in the between-group analysis ($Q = 5.29$; df = 4; $p = 0.2584$), but it was significant in the within-group analysis ($Q = 53.49$; df = 9; $p < 0.0001$).
Conclusion: This meta-analysis confirms a medium effect (SMD = 0.62) of sleep deprivation on pain perception. As this meta-analysis is based on experimental studies in healthy subjects, the clinical relevance should be clarified.

1. Introduction

Chronic pain and sleep disorders are common in the general population. The prevalence of chronic pain ranges from 10% to 40% [1], which is comparable with the prevalence of sleep disorders (10–36% [2–9]).

Increasingly more studies indicate a reciprocal relationship between sleep and pain [2–6,10]. This hypothesis is based on epidemiological, pharmaceutical, clinical, and experimental studies. For example, 50–88% of patients with chronic pain also suffer from sleep disorders [11–13]. Alternatively, > 40% of patients with insomnia also report chronic pain [6]. Several pharmaceutical studies, including studies on eszopiclone [14], triazolam [15], or pregabalin [16], showed a simultaneous improvement of both sleep and pain. In addition, clinical trials highlight a bidirectional relationship between sleep and pain. Patients with a range of sleep disorders, such as obstructive sleep apnea syndrome (OSAS) [17] and restless legs syndrome (RLS) [18], seem to be hyperalgesic. The pain sensitivity improves with effective treatment of the respective sleep disorder. This improvement has been demonstrated in both pharmacological interventions, such as levodopa (L-DOPA) therapy for RLS [18], as well as non-pharmacological interventions, such as continuous positive airway pressure (CPAP) treatment for OSAS [17]. The latter study is of particular interest, as the improvement disappears immediately upon the discontinuation of CPAP therapy [17].

The first experimental study that showed an effect of sleep deprivation on pain perception was published in 1975 [19]. Since then, several studies have confirmed these results [7,20,21]. A review from 2006 showed a clear effect of sleep deprivation on pain perception in animals, whereas human data were inconclusive [22]. The same study group extended the systematic review in 2014 and found evidence of the hyperalgesic effect of sleep deprivation, both in animals

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and humans [23]. By focusing solely on controlled trials, a review indicated conclusive evidence of an increase of bodily complaints, or a decrease of pain thresholds, following sleep deprivation [24].

Varying explanations exist for the reciprocity between sleep and pain. For example, sleep and pain could share similar neurotransmitter systems, such as the dopaminergic system [25] and the serotonin system [26], or influence the endogenous opioid system [27]. In addition, substance P, which is involved in pain processes, interferes with sleep by reducing sleep efficiency or increasing awakenings [28]. However, the pathway of this interaction is not sufficiently clarified by the present research.

In summary, there is a large body of evidence for the interaction between sleep and pain. However, the size of this effect is unclear and the clinical relevance uncertain. Therefore, this meta-analysis was conducted to quantify the effect of sleep deprivation on pain perception.

2. Methods

2.1. Search strategy

Five electronic scientific databases, namely PubMed, Cochrane, Psyndex, Psycinfo, and Scopus, were used. The search was conducted on December 5, 2014, with no limitations on the publication date. All terms that were appropriate in former reviews were used [22–24,29].

Sleep AND pain AND ("sleep restriction" *OR* "sleep deprivation" *OR* "sleep loss" *OR* "sleep interruption" *OR* "hyperalgesia" *OR* "total sleep deprivation" *OR* "partial sleep deprivation" *OR* "sleep fragmentation")

One author (M.S.) and one research assistant (F.H.) independently screened the titles and abstracts for eligibility (Fig. 1) with a high inter-rater reliability (Cohen's Kappa $\kappa = 0.96$) [30] by at least one of the reviewers read the full text for all studies that were not excluded after screening the titles and abstracts. One author (M.S.) performed the final study selection, controlled by a second author (C.P.). The reference lists of former reviews about sleep deprivation and pain perception were screened [22–24,29] for additional eligible studies.

2.2. Inclusion and exclusion criteria

Experimental studies included a study sample of healthy adult humans (older than 18 years). Sleep deprivation had to be used as an independent variable and pain perception as a primary outcome. Only articles published in a peer-reviewed journal written in English language were included in the meta-analysis. Studies had to contain all necessary data for calculating standardized mean differences. The corresponding authors were contacted for necessary data, if incomplete.

2.3. Data extraction and risk of bias

Characteristics of intervention and sample, duration of sleep deprivation, type of pain measurement, and data needed for effect-size calculation were extracted.

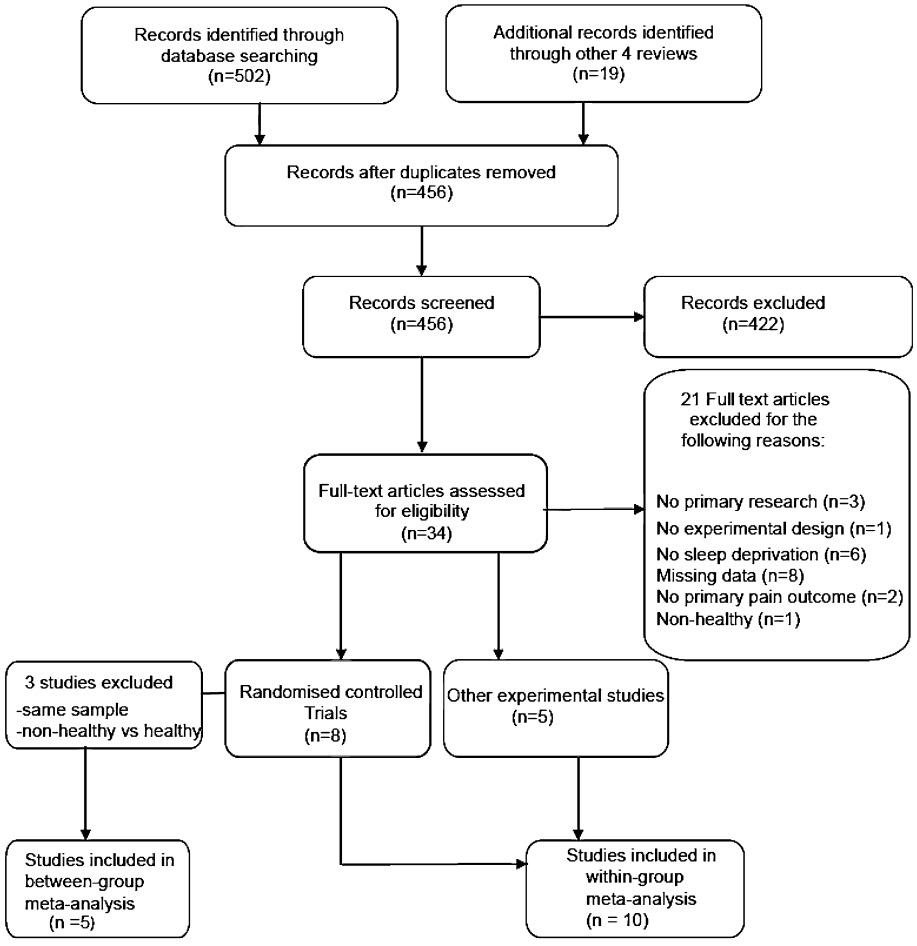

Fig. 1. Flow diagram for search procedure

The risk of bias in this study was assessed only for between-group analysis. The Cochrane Collaboration's tool was used for assessing the risk of bias in randomized trials [31]. We rated the study quality of included studies for between-group analyses with six of the seven criteria of the assessment tool (random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). The criterion of blinding participants was excluded due to unfeasibility blinding condition in sleep deprivation. The risk of bias was rated as low when five or six criteria were met, as medium when three or four criteria were fulfilled, and as high when two or fewer criteria were met. The risk of bias was not assessed in studies with crossover or uncontrolled design.

To calculate effect size, means and standard deviations of all pain outcomes (eg, heat pain threshold, visual analog scale, mechanical pain threshold) at baseline and after sleep deprivation were extracted. If eligible, outcomes measured at the same time of the day were extracted. If one study reported several pain measurements, the mean effect size of all measures was calculated.

2.4. Data analysis

A meta-analysis of between-group effect sizes and within-group effect sizes was conducted.

Standardized mean differences for between-group effect sizes (SMD_B) were calculated. We used a formula described by Morris and colleagues [32,33] and a simple bias adjustment for small sample sizes recommended by Becker [34]:

$$SMD_B = c_T\left(M_{CHANGE\text{-}T}/SD_{PRE\text{-}T}\right) - c_C\left(M_{CHANGE\text{-}C}/SD_{PRE\text{-}C}\right).$$

$M_{CHANGE\text{-}T}$ is the mean of the change scores in the treatment group, $M_{CHANGE\text{-}C}$ is the mean of the change scores in the control group, $SD_{PRE\text{-}T}$ is the standard deviation before sleep deprivation for the treatment group, *and* $SD_{PRE\text{-}C}$ is the standard deviation before sleep deprivation for the control group. Because of the small sample sizes in our meta-analysis, a simple bias adjustment (c_T and c_C) was used [34], approximated by

$$c_j = 1 - \left(3/\left(4\left(n_{pre(j)} + n_{post(j)} - 2\right) - 1\right)\right).$$

If the mean and standard deviation were not available, but the *t*- or *F*-values were reported, these were converted to effect sizes with the following formulas [35]:

$$SMD_B = c_T \frac{2t}{\sqrt{df}}$$

$$SMD_B = c_T \frac{2\sqrt{F(1,x)}}{\sqrt{df}}$$

Accordingly, the following formula was used for within-group effect-size calculations (SMD_W):

$$SMD_W = c_T\left(M_{CHANGE\text{-}T}/SD_{PRE\text{-}T}\right).$$

Effect sizes of 0.2 were interpreted as small, 0.5 as medium, and 0.8 as large [36]. Positive effect sizes indicate increasing pain.

A *H–V* random-effect method was used to estimate effect sizes and model parameters because the included studies vary in several conditions that may moderate effect sizes [37]. We conducted a *Q*-test and reported τ^2 to estimate the between-study variability. I^2-statistic was used for relative heterogeneity. An I^2 of 0% indicates no heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity [38].

Using Microsoft Office Excel®, single effect sizes were calculated. To perform the meta-analysis and generate corresponding graphics and plots [39], the *metafor* package for R was used. To check publication bias, forest plots displaying single and pooled effect sizes with 95% confidence intervals and funnel plots were created.

3. Results

3.1. Study selection

Fig. 1 shows the study selection process. A total of 456 records were found in the searching procedure after removing duplicates. By screening the titles and abstracts, 34 potential eligible studies were identified. After full-text analyses, 21 studies were excluded for the following reasons: no primary research [40–42], no experimental design [43], no sleep deprivation [44–49], no primary pain outcome [50,51], only non-healthy participants [52], and no opportunity to calculate effect size [2,7,9,19,53–56]. From the remaining 13 studies, eight were randomized controlled trials (RCTs) and five were uncontrolled. The study by Haack et al. [57] was excluded because it was a subsample of another study [58]. The study by Irwin et al. [59] was excluded because it compared a healthy to a non-healthy group, and its within-group analyses did not include all of the necessary data for calculating effect size. Schey et al. [60] also compared a healthy to a non-healthy group, but only the healthy subgroup was included. Although Schey et al. [60] used a crossover design for the healthy group, data for calculating the between-group effect were not reported, so the study for between-group effect analyses was excluded, but the healthy subgroup in the within-group effect analyses was included.

3.2. Between-group meta-analysis

Five studies in the between-group meta-analysis with a total of 190 subjects was included [20,21,58,61,62]. The participants were completely sleep deprived in three studies [20,21,62] and sleep restricted (4–6 h sleep per day) in two studies [58,61]. All five studies used one or more visual analog scales (VAS) to measure pain, and two studies additionally analyzed pain threshold using quantitative sensory testing (QST) [20,62]. The risk of bias was low for all five of these studies. Table 1 shows detailed information of included studies.

The pooled between-group meta-analysis resulted in a significant medium effect size of sleep-deprived conditions in comparison to non-sleep deprived conditions (SMD = 0.62; CI_{95}: 0.12, 1.12; $z = 2.43$; $p = 0.0152$, Fig. 2).

The test for heterogeneity in effect sizes was not significant ($Q = 5.29$; df = 4; $p = 0.2584$), and no remarkable variance was found in the between-group effect-size distribution ($\tau^2 = 0.2816$; $I^2 = 24.45\%$). The funnel plot to check potential publication bias is symmetrical (Fig. 3).

3.3. Within-group meta-analysis

One study from the between-group effect-size meta-analysis could not be included in the within-group meta-analysis [61] due to insufficient information to calculate the within-group effect size (only the *F*-value was reported). In addition to the four remaining studies for between-group effect sizes [20,21,58,62], six other studies were included in the meta-analysis for within-group effect sizes [60,63–67], ten studies and 266 subjects in total. Detailed information is also provided in Table 1. Four studies assessed participants with total sleep deprivation [20,21,62,66], whereas the participants in two studies were subjected to only slow-wave-sleep deprivation [63,64]. In the remaining four studies, the participants were only allowed to sleep for 2–4 h per night [58,60,65,67].

Table 1
Detailed information of included studies.

Author (year)	Study design	N (IG/CG)	Descriptives: *M* age (*SD*/range), % male, *n*	Sleep deprivation	Pain outcomes	Risk of bias[a]
Ablin et al. (2013) [61][a]	RCT with four groups[c]	*n* = 87	Full sample: 27.2 years (SD = 5.6); 52% male	Sleep restriction (6 h of sleep per night for ten days)	VAS from the short-form McGill Pain Questionnaire	Low
Arima et al. (2001) [63][b]	Uncontrolled	*n* = 10	22.7 years (SD = 0.9); 100% male	Slow-wave-sleep deprivation (three nights)	VAS (headache, pain in jaw muscles, soreness in jaw muscles, stiff in jaw muscles, pain in neck/should region), Pain pressure threshold[d]	
Azevedo et al. (2011) [20][a,b]	RCT with three groups[e]	*n* = 19 (9/10)	Full sample: range 19–28 years; 100% male	Total sleep deprivation for two consecutive nights	Laser-evoked pain, VAS pain	Low
Haack and Mullington (2005) [58][a,b]	RCT	*n* = 40 (22/18)	SDG: 26.0 years (SD = 4.9); 63% male CG: 26.6 years (SD = 5.1); 67% male	Sleep restriction (4 h of sleep per night for 12 days)	VAS generalized body pain	Low
Haack et al. (2009) [21][a,b]	RCT	*n* = 24 (16/9)	SDG: 37.9 years (SD = 6.5); 73% male CG: 30.4 years (SD = 5.6); 67% male	Total sleep deprivation (88 h)	VAS spontaneous pain	Low
Kundermann et al. (2004) [62][a,b]	RCT	*n* = 20 (10/10)	SDG: 34.9 years (SD = 2.3); 60% male CG: 36.6 years (SD = 2.0); 50% male	Total sleep deprivation for two nights	Cold pain threshold, heat pain threshold, pain questionnaire	Low
Lentz et al. (1999) [64][b]	Uncontrolled	*n* = 12	44 years (SD = 6.2); 0% male;	Slow-wave-sleep deprivation (three nights)	Tender point pain threshold	
Schestatsky et al. (2013) [65][b]	Uncontrolled	*n* = 19	24.3 years (range 22–30 years); 100% male	Work-induced sleep restriction for one night (*M* = 120 min (SD = 28) sleep)	Heat pain threshold, electrical painful threshold	
Schey et al. (2007) [60][b]	RCT with cross-over[f]	*n* = 10	36.9 years (SD = 17.08); 50% male	Sleep restriction (≤3 h of sleep for one night)	Lag time to symptom report, intensity rating, acid perfusion sensitivity score	
Schuh-Hofer et al. (2013) [66][b]	Cross-over	*n* = 14	23.5 years (SD = 4.1); 57% male	Total sleep deprivation for one night	Cold pain threshold, heat pain threshold, pressure pain threshold, mechanical pain threshold, mechanical pain sensitivity	
Tiede et al. (2010) [67][b]	Uncontrolled	*n* = 10	25.3 years (SD = 2.2); 80% male	Sleep restriction (4 h of sleep for one night)	Laser-evoked pain, VAS pain	

Note: SDG: intervention group; CG: control group; RCT: randomized controlled trial; VAS: visual analog scale.
[a] Extracted for between-group analysis.
[b] Extracted for within-group analysis.
[c] Two groups with sleep restriction and two groups without sleep restriction.
[d] No data available.
[e] Only total sleep deprivation included.
[f] Only healthy participants included.

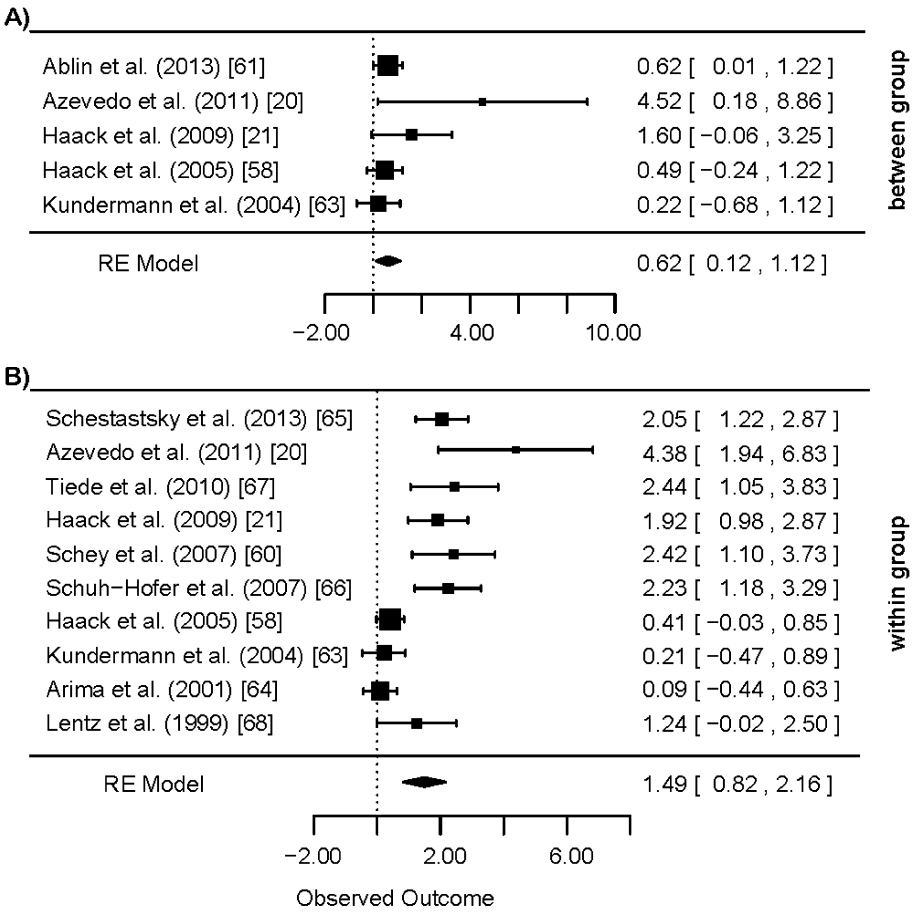

Fig. 2. Single and pooled effect sizes and 95% confidence interval for between-group (A) and within-group (B) meta-analysis. The squares represent the single effect sizes of each study, and the size of the squares are proportional to the precision of the estimates. The vertical line indicates the confidence interval of the effect size. Random-effect (RE) model shows the pooled effect size with 95% confidence interval.

QST was used in seven of the included studies [20,62–67] and VAS in six studies [20,21,58,62,63,67], and one study used stimulus response functions to acid to measure pain [60].

The pooled within-group effect size was large and significant (SMD = 1.49; CI_{95}: 0.82, 2.17; $z = 4.35$; $p < 0.0001$, Fig. 2). A significant heterogeneity of effect sizes ($Q = 53.49$; df = 9; $p < 0.0001$) and a high variance level were found in the within-group effect-size distribution ($\tau^2 = 0.9361$; $I^2 = 83.17\%$). The funnel plot of potential publication was asymmetrical (Fig. 3); a single sample with large standard errors produced the largest effect size [20,21,58,63]. Without this sample, we still found a large significant pooled effect size (SMD = 1.33; CI_{95}: 1.69, 1.98; $z = 4.03$; $p < 0.0001$).

4. Discussion

This meta-analysis confirms the effect of sleep deprivation on pain perception. A medium effect (SMD = 0.62) was found for the between-group analysis and a large effect (SMD = 1.49) was found for the within-group analysis. Sleep deprivation increases self-reported pain and affects evoked pain responses obtained through somatosensory testing protocols (eg, heat pain thresholds, pressure pain thresholds, or laser-evoked pain).

Patients with chronic pain exhibit several changes in sleep, such as frequent sleep-stage shifts, increased nocturnal awakenings, and decreased slow-wave or rapid-eye-movement sleep [68]. A recent review on 29 controlled polysomnographic studies found fragmentation of sleep to be the most common alteration of sleep in patients with chronic pain [69]. In addition, increased amounts of superficial sleep and decreased levels of slow-wave sleep were found, whereas sleep architecture was commonly preserved. A consistent pattern of objective sleep disturbances was not found in nonmalignant chronic pain populations [69].

It is evident that the results from sleep deprivation and pain perception studies in an experimental design cannot be extended directly to sleep disorders or chronic pain. However, there are several relevant studies on this topic. Pain threshold was lower in pain patients with endometriosis [70] as well as with juvenile idiopathic arthritis [71]. In addition, the pain threshold correlates with functional scores in patients with osteoarthritis [72], although the results are still inconsistent. For example, sleep deprivation led to an increase of clinical pain complaints but an unaltered experimental pain threshold in patients with somatoform disorders [53]. This could be because self-reported pain is more closely associated with anxiety than with pain threshold [73]. Sleep and pain are critical homeostatic systems that interact in a bidirectional manner [69]. For example, <6 h of sleep per night is associated with greater pain the following day [74], and sleep quality is a consistent predictor of pain the next day [75,76]. Short-term sleep improvement predicts long-term pain improvement in patients with comorbid osteoarthritis and insomnia [77]. Insufficient sleep, in both quantity and quality, is predictive of pain three years in the future [78]. In a sample of 24 women, Wright et al. [79] found that lower sleep efficiency is a significant predictor of greater pain severity after breast surgery. The hyperalgesic effect of sleep deprivation seems reversible by

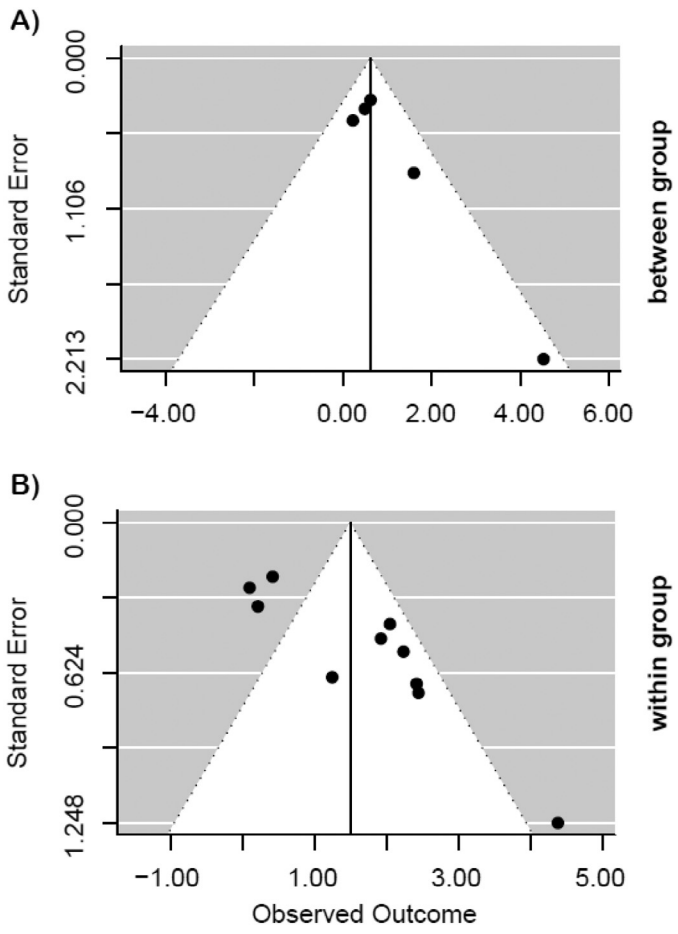

Fig. 3. Funnel plots of publication bias for between-group and within-group meta-analyses.

napping [80] as well as by effective treatment of sleep disorders [17]. Roehrs et al. [81] showed that extended sleep reduces pain sensitivity, and poor sleep quality is a risk factor for the development of chronic widespread pain [82].

In addition, several pharmaceutical studies demonstrated simultaneous changes in sleep and pain. Eszopiclone improves sleep and pain in patients with insomnia and comorbid rheumatoid arthritis [14], as well as in patients with chronic back pain [83]. Similarly, anticonvulsives, such as pregabalin, reduce pain and improve pain-related sleep interference [84]. However, as drugs often have multiple effects, a simultaneous interference could be mediated through an underlying but independent link. This also applies to similar comorbidities of sleep disorders and chronic pain, such as obesity [85], type 2 diabetes [86,87], or depression [88,89].

Several explanations exist for the interaction of sleep and pain. Paiva et al. [90] investigated the sleeping behavior of adolescents and found a correlation between quality of life, health complaints, and sleep. The interaction between sleep and pain could also be mediated by negative emotions [91]. Sleep loss can affect mood states in healthy adolescents [92], and sleep deprivation decreases positive and increases negative mood [58,66,93]. These findings suggest that addressing negative mood directly, or by addressing sleep disturbances in patients with chronic pain, may have a beneficial impact on patients' pain [91]. In addition, neurotransmitters, such as dopamine, play a role in sleep and pain [25]. In addition, sleep deprivation decreases morphine analgesia, possibly by decreasing descending pain inhibitory activity and by increasing descending pain facilitatory activity [94]. Conversely, sleep improves on intrathecal morphine infusion in patients with severe pain [95]. A recent meta-analysis showed that sleep disturbance is associated with an increase in markers of systemic inflammation [96]. Systemic inflammation resulted in a lower pain threshold [97]. In addition, the tumor necrosis factor (TNF) system [98] as well as the hypothalamic–pituitary–adrenal axis [99] are influenced by sleep and pain. Melatonin, which is an essential regulator of the circadian rhythm, also interacts with pain [100,101].

The calculated effect size of sleep deprivation on pain perception is comparable with effect sizes achieved through chronic pain treatment. A recent meta-analysis showed medium effects for several pharmacological therapies, such as non-opioids (SMD = 0.41), "weak" opioids (SMD = 0.44), and "strong" opioids (SMD = 0.46) for the treatment of chronic pain [102]. Not only pain but also analgesics can alter sleep architecture by suppressing slow-wave or rapid-eye-movement sleep [68]. The effects of non-pharmaceutical interventions vary distinctly according to the control conditions (waiting list vs. active control group). On average, physiotherapy (SMD = 0.52) seems more beneficial than psychotherapy (SMD = 0.39) in cases of chronic pain [102]. There is evidence that patients with chronic pain and insomnia would benefit from sleep treatment in both disorders [14,83].

The following limitations should be considered when interpreting this data: (1) From our point of view, the major limitation of this study is its small sample size. Only five studies, with a total of 190 subjects, fulfilled the inclusion criteria and could be included in the meta-analysis. (2) Different types of sleep deprivation (total sleep deprivation, sleep restriction and partial sleep deprivation, such as slow-wave-sleep deprivation) and pain outcomes (visual analog scale, quantitative sensory testing such as heat and cold pain threshold, mechanical pain threshold, and laser-evoked pain threshold) were compared within the sample. Different sensory modalities correspond to different types of nociceptors in experimental pain threshold procedures. For example, cold pain seems to correspond with c-fibers, while heat pain corresponds with aδ-fibers [103]. Visual analog scales may be influenced by previous experiences, mood [104], and anxiety [73]. According to the Cochrane Handbook for Systematic Reviews, mixing of outcomes is applicable when calculating mean differences in meta-analysis [105]. If multiple parameters within one study sample are measured, then averaging all outcome parameters is recommended [106,107]. (3) A relevant number of studies [2,7,9,19,53–56] had to be excluded due to insufficient data. Retrieving data from figures would have been possible in some of these studies, but the selection would have been barely comprehensible. (4) The focus on RCTs (in the main analysis) and exclusion of studies that have not been published in peer-reviewed journals in the English language may affect generalizability. (5) The funnel plot for the within-group meta-analysis indicated publication bias (Fig. 3). (6) Due to the experimental design, the clinical relevance of the results is uncertain.

In summary, this meta-analysis confirms the effect of sleep deprivation on pain perception. Considering the prevalence of sleep disorders and chronic pain, future research should clarify the clinical relevance of these results. Continuing efforts in experimental and clinical research are needed to develop a translational understanding of how insomnia and pain are related.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.07.022.

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