Sleep Medicine Reviews 71 (2023) 101835

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

The impact of sleep disturbance on pain perception: A systematic review examining the moderating effect of sex and age

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ARTICLE INFO

Handling Editor: M Vitello

Keywords:
Sleep deprivation
Nociceptive threshold
Pain perception
Sex
Age

ABSTRACT

Females have increased pain sensitivity and are more vulnerable to chronic pain conditions. Sleep disturbances are comorbid with chronic pain and exacerbate pain symptoms. Different types of sleep disturbance affect pain perception distinctly, but it is not clear if these effects are equal in men and women. This systematic review investigated potential differences in how sleep disturbance affects pain in males and females. We searched EBSCO, MEDLINE, Psych INFO, Science Direct, and Web of Science from January 2001 to November 2022 and found 38 studies with 978 participants. Separate random-effects models were used to estimate the pooled effect sizes based on standardized mean differences (SMDs) of experimental sleep disturbance paradigms on various pain outcomes. Sex moderated the effect of sleep disturbance on pain facilitation (SMD = 0.13; 95%CI: 0.004 to 0.022; p=.009) and pain inhibition (SMD = 0.033; 95%CI: 0.011 to 0.054; p=.005), with increased facilitation and decreased inhibition in females, but the opposite effect in males. Further, age moderated the effects of total sleep deprivation (SMD = −0.194; 95%CI -0.328 to -0.060; p=.008) on pain sensitivity and fragmented sleep (SMD = −0.110; 95%CI: 0.148 to -0.072; p<.001) on pain threshold. While the moderating effect of sex and age on the sleep-pain relationship was small, these factors need to be considered in future sleep-pain research.

1. Introduction

Chronic pain (CP) is a significant burden on patients and society, with a high prevalence and disabling nature [1,2]. Studies indicate that females have a higher susceptibility to chronic pain than males, as seen in conditions like migraines, musculoskeletal pain, inflammatory joint disorders, fibromyalgia, and irritable bowel syndrome [3].

Chronic pain is often accompanied by sleep disturbance, with up to 88% of chronic pain patients reporting comorbid sleep problems [4,5]. These sleep problems are characterized by reduced sleep duration, fragmented sleep, increased awakenings, and decreased sleep efficiency [6,7].

In addition to sleep alterations being observed in individuals with CP, research has shown that sleep disturbance can also affect pain perception in healthy populations, with a stronger causal impact on pain than pain has on sleep [8]. A longitudinal study conducted over 17 years found that sleep difficulties can predict the onset of pain in initially pain-free women [9]. There is also a disparity in sleep problems between the sexes, with a greater prevalence of difficulties in initiating and maintaining sleep among females [6,7]. This is supported by a risk ratio of 1.58 for insomnia [95% confidence interval: 1.35, 1.85] when compared to males [12].

Studies investigating the impact of sleep disturbance on pain have examined various sleep interventions in healthy individuals, including total sleep deprivation [8] sleep restriction [9], sleep disruption without altering sleep duration [10], and combinations of different sleep protocols. A recent meta-analysis evaluated the influence of different sleep loss paradigms on pain perception in healthy individuals. The analysis concluded that total sleep deprivation had the most significant impact on pain threshold, while fragmented sleep had the least effect, and sleep restriction had no effect [11]. This review clearly demonstrates that different forms of sleep loss can have distinct effects on pain perception [11] in a combined group of males and females.

Apart from manipulating sleep in various ways, experimental studies have measured pain perception differently. They have used different painful stimuli, such as thermal, mechanical, and pressure pain [10, 12–15], and different pain assessment methods, including static versus

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https://doi.org/10.1016/j.smrv.2023.101835
Received 31 October 2022; Received in revised form 27 July 2023; Accepted 6 August 2023
Available online 7 August 2023

dynamic pain measurements [10,11]. Static pain measurement objectively assesses an individual's response to painful stimuli [16], evaluating pain sensitivity and threshold. The pain threshold refers to the lowest level of intensity at which an individual perceives a stimulus as painful. On the other hand, pain sensitivity is the overall ability of an individual to perceive pain and is often assessed using numerical rating scales (NRS) or visual analog scales (VAS). People with high pain sensitivity are more likely to rate their pain as more severe at lower levels of stimulus intensity, whereas people with low pain sensitivity may rate their pain as less severe at the same level of intensity. Dynamic pain measurements assess the central nervous system's ability to modulate pain through processes such as facilitation [20], represented by temporal summation (increased pain perception with repeated stimuli), or inhibition, represented by conditioned pain modulation (decreased pain perception in the presence of a second pain stimulus) [18]. By using these techniques, dynamic pain measurements can provide a more comprehensive understanding of pain perception than static pain measurements alone [12]. Collectively, the use of different sleep paradigms and pain assessment methods in experimental studies yields highly variable results regarding how sleep disturbance impacts pain perception in healthy individuals without pain.

Recent evidence has shown that the impact of sleep disturbance on pain perception may differ between sexes, although research on this topic has yielded mixed results [13,14]. Several studies have suggested that sleep disturbance improves pain inhibition in females [15,16]. In contrast, other studies have revealed that sleep disturbance reduces pain inhibition in females while increasing it in males [13]. Moreover, when analysing both sexes together, some studies have shown no significant alterations in pain perception after sleep disturbance [18–21].

In addition to the potential sex disparity in the effect of sleep on pain perception, age-related changes may also exist as both sleep [14] and pain [15,16] change with aging. Pain sensitivity is lower in older adults than younger individuals in response to acute painful stimuli. However, older adults have lower pain tolerance when it comes to deeper and more prolonged forms of pain, such as pressure pain and cold pressor tests [15]. Small to moderate differences in responses to heat stimuli have also been observed between middle-aged and older adults [17] and age has also been found to be significantly associated with conditioned pain modulation (CPM), but not with temporal summation. CPM was significantly lower in older than younger individuals [16]. Thus, it appears that the effects of aging on pain perception may depend on the type of pain stimuli. However, how age-related changes to painful stimuli differ under various forms of sleep disturbance is still unclear.

Since diverse sleep disturbance methods and pain protocols have been utilized in sleep-pain research and factors such as sex and age might contribute to shaping the pain response, it is imperative to examine the impact of these factors on pain perception in response to various forms of sleep disturbance. To the authors' knowledge, no study has systematically reviewed how men and women respond to pain under various forms of sleep disturbance.

The current systematic review aims to specifically explore the moderating effect of sex on changes in pain perception in response to different types of sleep disturbance, including total sleep deprivation, restricted sleep, selective sleep deprivation, and fragmented sleep. The secondary objectives include: 1) evaluating the moderating effect of age on changes in pain sensation in response to sleep disturbance, and 2) conducting a meta-analysis to determine the overall effect of sleep disturbance on pain perception, as measured through quantitative sensory testing (QST) techniques, such as experimentally induced nociceptive pain threshold, temporal summation (TS), and conditioned pain modulation (CPM).

2. Methods

2.1. Study design and registration

The current review followed the Cochrane Handbook for Systematic Reviews of Intervention [18] and was registered with the International Prospective Register of Systematic Reviews (CRD42022318540). The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [22].

2.1.1. Differences between protocol and review

The protocol for this systematic review deviated from the original plan. Initially, the review aimed to explore the effect of sleep disturbance on pain perception in healthy humans. However, because a recent systematic review already investigated the effects of different forms of experimental sleep deprivation on pain [11], we decided to conduct a meta-regression analysis to examine how sex and age moderated the sleep-pain interaction, which had not been explored before. We

Glossary of Terms

Conditioned pain modulation (CPM) is a phenomenon in which the perception of pain in one area of the body is reduced when another painful stimulus is introduced to a different area. This is thought to be mediated by the descending pain pathway, which is a system of nerves that runs from the brain to the spinal cord and helps to regulate pain perception.

Chronic pain (CP) is pain that persists for over three months and is often not fully relieved by medical treatment.

Dynamic pain measurements refer to the assessment of pain over time rather than at a single point in time. The methods used to measure dynamic pain include conditioned pain modulation and temporal summation.

Hyperalgesia or hypersensitivity refers to experiencing high amounts of pain from a relatively benign painful stimulus.

Quantitative sensory testing (QST) objectively measures an individual's responses to sensory stimuli, including heat, cold, and pressure. QST can involve static and dynamic pain measurements.

Static pain measurements assess pain at a specific moment by applying painful thermal, mechanical, electrical, or chemical stimuli. Pain is quantified as the pain sensitivity (e.g. using a rating scale for a given stimulus intensity), or the pain threshold (minimum intensity at which a stimulus is perceived as painful).

Sleep disturbance is a term that has been used as an umbrella term to encompass any form of sleep manipulation within the context of this article.

Temporal summation (TS) is a phenomenon in which the perception of pain increases with repetitive painful stimuli. TS is a correlate of pain facilitation, increasing pain perception.

acknowledge that this deviation from the original protocol may impact the study's results, and interpreting these factors requires caution. We followed the guidance of the Cochrane Handbook [18] for Systematic Reviews of Interventions regarding the protocol deviation.

2.2. Data source and search strategy

Regarding the screening phase, we followed the PRISMA guidelines and conducted a comprehensive search of five electronic databases, including EBSCO, MEDLINE, Psych INFO, Science Direct, and Web of Science. We used a combination of keywords and subject terms related to sleep disturbance and pain perception, capturing experimental sleep manipulations and experimentally-induced pain as the outcome. The full list of search terms is included in the supplementary file. For static pain measurements, the search terms included "Sleep deprivation," "Sleep disturbance," "Sleep restriction," "Sleep loss," and "Sleep fragmentation" combined with "Pain perception," "Pain tolerance," "Pain threshold," "Pain intensity," "Hyperalgesia," "Hypoalgesia," "Hyposensitivity." For dynamic pain measurements, the search terms included the same sleep terms combined with "Temporal summation," "Wind-up pain," "Conditioned pain modulation," "Diffuse noxious inhibitory controls,". The last search was conducted on November 1st, 2022.

Two independent reviewers (J.T & S.R) screened titles and abstracts for potentially eligible articles. All potentially eligible studies were imported into EndNote, and the full-text articles were reviewed for inclusion criteria. Two independent reviewers then screened the titles and abstracts of the identified articles to select potentially relevant studies, and finally, the reference lists of the included manuscripts were manually screened to retrieve any additional eligible studies. Any disagreements between the reviewers were resolved through discussion and consensus.

2.3. Inclusion and exclusion criteria

Inclusion criteria:

- Population: Healthy pain-free adults
- Comparison: Studies manipulating sleep, including total sleep deprivation, restriction, selective sleep deprivation, and fragmented sleep, as well as night shift workers who meet the criteria for one of the sleep manipulation categories.
- Outcome: Experimentally induced pain using thermal, mechanical, or pressure stimuli using static and/or dynamic pain paradigms.
  - o Static pain measurements: Experimentally induced pain stimuli were assessed through either pain threshold or pain sensitivity testing.
  - o Dynamic pain measurements: CPM was assessed by measuring the differences in test stimuli before and after conditioning stimuli using various endpoints, such as the detection threshold, pain threshold, and tolerance threshold. TS was assessed by measuring the various endpoints over time.
- Study type: Experimental studies including randomized control trials (RCT) and quasi-experimental studies were included.
- Publication date: only papers published after 2000 were included.
- Language: Studies published in English.

Exclusion Criteria:

- Population: Studies on clinical populations (patients with sleep disorders) or paediatric population.
- Studies on psychological therapy
- Drug trials. However, if any drug trials include two arms with a control group, the control group must meet the inclusion criteria to be included.
- Articles published in languages other than English.
- Articles published in non-peer-reviewed journals. The complete list of criteria is provided in the supplementary file.

2.4. Data extraction and risk of bias

We extracted the following data from all included studies: study design: first author and published year, sleep manipulations: type and duration, participant characteristics: age, gender, and female to male ratio, and pain outcomes. This information was used to conduct a systematic review and meta-analysis of the effects of different types of sleep disturbance on pain perception in men and women.

The types of sleep disturbance that were categorized in the review were:

Fragmented sleep [19]: disrupting sleep continuity with multiple and prolonged nightly awakenings.

Sleep restriction [19]: shortening sleep time without interrupting sleep continuity.

Selective sleep deprivation [20]: depriving one or more sleep stages with or without reducing sleep amount.

Total sleep deprivation [21]: depriving sleep for the entire night in which no sleep would be allowed.

The current review only included studies where participants were exposed to sleep disturbance for up to one week. This allows for a specific focus on the immediate effects of sleep disturbance on pain perception rather than the long-term effects.

We also extracted data from studies on conditioned pain modulation and temporal summation. For studies on conditioned pain modulation, the following data was extracted: type and intensities of conditioning and test stimuli, order of pain induction (simultaneously or sequentially), and body parts investigated in the study (Table 1). For studies on temporal summation, the following data was extracted: type of stimuli, number of stimuli, inter-stimuli intervals, endpoints for test stimuli, body parts investigated in the study (Table 2).

Additionally, the study extracted data separately for different body parts if multiple body parts were investigated under the same sleep condition and pain measurement. If studies split data based on sex, the data from males and females were extracted separately. The data extracted was used to conduct a systematic review and meta-analysis of the effects of different types of sleep disturbance on pain perception in men and women.

In cases where studies did not report data in either text or tables, the study used Web Plot Digitizer to extract data from figures.

To assess the quality of randomized controlled trials, we used the Cochrane Collaboration tool. However, for crossover studies, we used the cross-over version of the Cochrane Risk of Bias tool for non-randomized studies (RoB 2) [23]. It is specifically designed to evaluate the quality of studies that use a controlled design but do not use randomization to allocate participants to intervention groups, such as quasi-randomized trials, non-randomized controlled trials, and interrupted time series studies. The tool assesses the risk of bias in five domains: 1) bias arising from the intervention, 2) bias arising from the selection of participants, 3) bias arising from the measurement of outcomes, 4) bias arising from departures from the intended interventions, and 5) bias arising from missing data. More details on the risk of bias for crossover trials are provided in Table S3.

2.5. Data analysis

In this study, we conducted a meta-analysis to examine the effects of different types of sleep disturbance on various pain outcomes. We used separate random-effects models to estimate the pooled effect sizes based on standardized mean differences (SMD), a commonly used method in meta-analyses. SMD is a way to compare the mean of two groups by considering the variability of the groups. Using this approach, we analysed the effects of different experimental sleep disturbance paradigms on different pain outcomes and calculated an overall effect size by

Table 1
Conditioned pain modulation studies.

Study	SD duration	Study design	Participants characteristics			CS			TS			Simultaneously (SIM) or Sequentially (SEC)	Results	Risk of Bias
			Gender	F/M ratio	Age	Type	Duration	Body type	Type	Body type	Endpoint measure			
Stroemel-et al, 2019 [43]	SR<1h 1 n	Cross-Over	Mixed	14/6	47.4	Hot water 46 °C	–	R hand	Pressure	L hand	50%above PPT	SIM	NS	Mod
Karmann et al., 2018 [45]	SR<1h 1 n	Cross-Over	Mixed	20/20	38.8	Hot water 46 °C	6 min	R hand	Pressure	L hand	PPT	SIM	NS	Mod
Matre et al., 2016 [33]	SR>4h 2n	Cross-Over	Mixed	14/8	23.2	Cold water 7°C	120sec	Hand (contra)	Heat	Volar forearm	Pain6	SIM	NS	Mod
Staffe et al., 2019 [31]	TSD 1n	Cross-Over	Mixed	8/16	22.6	75% of the PTT	–	Non-dominant leg	Pressure	Dominant leg	PDT	SIM	Impaired	Low
Schuh-Hofer et al., 2018 [26]	TSD 1n	Cross-Over	Mixed	10/10	F (24) M (23.4)	Cold water 0-2°C	180sec	Dominant hand	Pressure	Thenar of the dominant hand	PPT	SIM	Impaired only in females; males showed a stronger CPM effect	Mod
Eichhorn et al., 2018 [13]	TSD 1n	Cross-Over	Mixed	18/18	F (23.8) M (23.3)	Cold water 0-2°C	180sec	Dominant hand up to the forearm	Pressure	Thenar of the non-dominant hand	PTT	SEC	Impaired only in females, not males	Mod
Matre et al., 2017 [38]	TSD 2-4n NSW	Cross-Over	Females	40/0	31.6	Cold water 7°C	120sec	Hand (contra)	Heat	Volar forearm	Pain6	SIM	A stronger CPM effect	Mod
Kristiansen et al., 2017 [34]	TSD 1n	Cross-Over	Mixed	6/9	23.1	Cold water 1-4°C	120sec	Dominant hand	Pressure	Temporal &masseter muscle	PPT	SIM	NS	Mod
Rosseland et al., 2018 [50]	FS 1n	Cross-Over	Mixed	19/16	21.8	Cold water 2°C	120sec	Dominant hand up to wrist	Pressure	The palm of the dominant hand	PPT	SEC	NS	Low
Smith et al., 2007 [19]	SR FS 3n	RCT with 3 groups	Mixed	8/9	F (25.1) M (24.7)	Cold water 4 °C	–	L hand up to wrist	Pressure	R brachioradialis or trapezius	PPT	SIM	FS only impaired, but not SR	Low
Stroemel et al., 2022 [57]	TSD 1n	Cross-over	Mixed	15/15	33.70	Hot water 46°C	–	R hand up to the wrist	Pressure	Middle of the fingertip L hand	PPT	SIM	NS	Mod

Table 1. CPM, conditioned pain modulation; CS, conditioning stimuli, FS, fragmented sleep; L, left; NSW, night shift workers; NS, non-significant; PDT, pressure detection threshold; PPT, pressure pain threshold; PTT, pressure tolerance threshold; pain 6, pain rating 6 out of 10 on a numerical rating scale; R, right; SEC, sequentially; SR, sleep restriction; SIM, simultaneously; TS, testing stimuli; TSD, total sleep deprivation.

Table 2
Temporal summation of pain studies.

Study	SD duration	Study design	Participants characteristics			TS					Results	Risk of Bias
			Gender	F/M ratio	Age	Type	Numb stimuli	Endpoint measure	ISI	Phasic/ tonic	body part		
Stroemel et al., 2019 [43]	SR<1h 1 n	Cross-Over	Mixed	14/ 6	47.4	Pressure algometer	1	50% above threshold	–	Tonic without interval 60sec	Middle fingertip of L hand	Intensified during the first night (shorter TST)	Mod
Karmann et al., 2018 [45]	SR<1h 1 n	Cross-Over	Mixed	20/ 20	38.8	Pressure algometer	1	50% above threshold	–	Tonic without interval 60sec	Middle fingertip of L hand	–	Mod
Matre et al., 2016 [33]	SR>4h 2n	Cross-Over	Mixed	14/ 8	23.2	Heat Peltier thermode Somedic	1	PPT6	–	Tonic without interval 120sec	Volar forearm	Intensified	Mod
Staffe et al., 2019 [31]	TSD 1n	Cross-Over	Mixed	8/ 16	22.6	Mechanical pressure	10	PTT	1sec	Phasic	Dominant leg	Intensified	Mod
Eichhorn et al., 2018 [13]	TSD 1n	Cross-Over	Mixed	18/ 18	F (23.8) M (23.3)	Mechanical pressure	10	256 mN	1sec	Phasic	Thenar of the non-dominant hand	NS (but data is not provided)	Mod
Smith et al., 2019 [51]	FS 2n	Cross-Over	Mixed	46/ 33	27.18	Mechanical pressure	10	512 mN	1 s	Phasic	Volar forearm	Intensified in females, not males	Low
Ødegård et al., 2015 [25]	SR 1n	Cross-Over	Mixed	16/ 17	22.9	Heat Peltier thermode Somedic	1	NRS6	–	Tonic without interval 30sec	L forearm & L temple	NS. Only significant at 10 s	Mod
Schuh-Hofer et al., 2013 [8]	TSD 1n	Cross-Over	Mixed	6/8	23.5	Pressure	10	256 mN	1sec	Phasic	Dorsum of L&R hand	NS	Mod
Smith et al., 2005 [49]	SR<1h 1n	Cross-Over	Females	16/ 0	24	Heat contact probe	10	51 °C	2.5sec	Phasic	Dorsal of the Forearm	NS	Uncontrolled
Neverdahl et al., 2021 [40]	SR>4h 1n	Cross-Over	Mixed	23/ 8	36.2	Pressure	1	PPT5	–	Tonic	Trapezius muscle both R&L	NS	Low
Simpson et al., 2018 [41]	SR (4) 5ns	Cross-over	Mixed	8/9	25.1	Cold water 2-3°C	1	Sec30	–	Tonic	Hand up to the forearm	NS in the first week,	Low
Matre et al., 2017 [38]	TSD 2-4n NSW	Cross-Over	Females	40/ 0	31.6	Cold water 7°C		120sec	—	Tonic	Hand up to the wrist	NS	Mod
Stroemel et al., 2022 [57]	TSD 1n	Cross-over	Mixed	15/ 15	33.70	Pressure algometer	5	50% above PPT	8 s	Phasic	Middle of the fingertip L hand	NS	Mod

Table 2. ISI, inter-stimulus interval; FS, fragmented sleep; L, left; NSW, night shift workers; NS, non-significant; PDT, pressure detection threshold; PPT, pressure pain threshold; PTT, pressure tolerance threshold; pain 6, pain rating 6 out of 10 on a numerical rating scale; R, right; SR, sleep restriction; SIM, simultaneously; TS, testing stimuli; TSD, total sleep deprivation; TST, total sleep time.

combining the results from multiple studies [24].

Our meta-analysis was conducted using IBM SPSS Statistics 28.0.1 and focused on continuous outcomes, using raw data to calculate the effect size using Hedges' g with a random-effects model to account for the variability among studies. To make the data comparable, we transformed all raw data (mean and standard deviation) into a unified metric, effect size (Hedge's g), a common method used to synthesize data from various studies regardless of their study design. The estimated model used in our study was restricted maximum likelihood (REML) with standard error adjustment using Knapp-Hartung. We followed a similar method as previous studies in conducting this meta-analysis [11,25].

The study employed various statistical techniques to analyze and present the findings. A forest plot was used to visualize each effect size, based on the upper and lower confidence intervals and p-values of each study. The Chi-square (Q statistic) was used to estimate between-study variability, and the I-squared percentage was used to quantify the heterogeneity of the included studies. I-squared values range from 0 to 100%, with higher values indicating more heterogeneity among studies. The study also used Egger's regression-based test and funnel plots to detect potential publication bias and outliers.

Meta-regression analysis was conducted to investigate the potential moderators of sex and age on pain perception in response to sleep disturbance. Bubble plots with a 95% confidence interval were used to visualize the potential moderator of the calculated effect size. The study

used residual heterogeneity (R2 (%)) to determine between-study variability. Additionally, a sub-group analysis was conducted to explore the hyperalgesic effect of sleep disturbance on different pain modalities. The meta-regression was conducted based on the predicted value of effect size and its estimated standard error at a significant level of 0.05. The model coefficient test was used for the meta-regression analysis based on the predicted effect size value (REML model).

Results are presented divided into static pain measurements (such as pain threshold and pain sensitivity), and dynamic pain measurements (such as CPM and TS) to provide a clear distinction between the different methods used to measure pain.

3. Results

3.1. Static pain measurements

The current review included 36 studies in the meta-analysis, with a total sample size of 928 participants. Fig. 1 provides more details on the publication inclusion process.

3.1.1. Sex and age moderating effect of total sleep deprivation on pain perception

Fourteen studies [8,13,26–37] that explored total sleep deprivation were included in the meta-analysis. All studies used a crossover design, except for two which used parallel design [29,37]. The sample size ranged from 10 to 48 participants, with a total of 356 participants. The participants' average age range was between 20.8 and 31.6 years old, except for one study which did not report the age range [37]. Most studies induced pain using a heat, electrical shock, cold, pressure, or mechanical stimuli. Pain sites varied between studies, with some targeting the thenar eminence, temporal and masseter muscles, and trapezius muscle, while others used the volar forearm and dorsum of the hands. Total sleep deprivation ranged from 1 night to 4 nights. Various sleep assessments were used, including sleep diary, actigraphy, polysomnography, and self-reported scales such as Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS). All studies reported the gender distribution of participants, and most reported the gender ratio to be nearly equal, except for one study which had all female participants [38]. The risk of bias was generally low or moderate, except for one study which had a high risk of bias. Tables S1 and S4 provide detailed information on these studies.

Total sleep deprivation decreased pain threshold (regardless of pain modality) by at least one unit with a large effect size (SMD = -1.768; CI95: -0.989, -2.547; p<.001; I-squared = 92.8%; Fig. S2). Furthermore, total sleep deprivation increased pain sensitivity, as measured by pain ratings, with a large effect size (SMD = 1.81; CI95: 1.098, 2.529; p<.001; I-squared = 92.0%; Fig. S3) compared to normal nocturnal sleep. There was no effect of sex on the hyperalgesic effect of total sleep deprivation (p = .106). Table S2 provides detailed information on gender distributions of included studies. However, age significantly

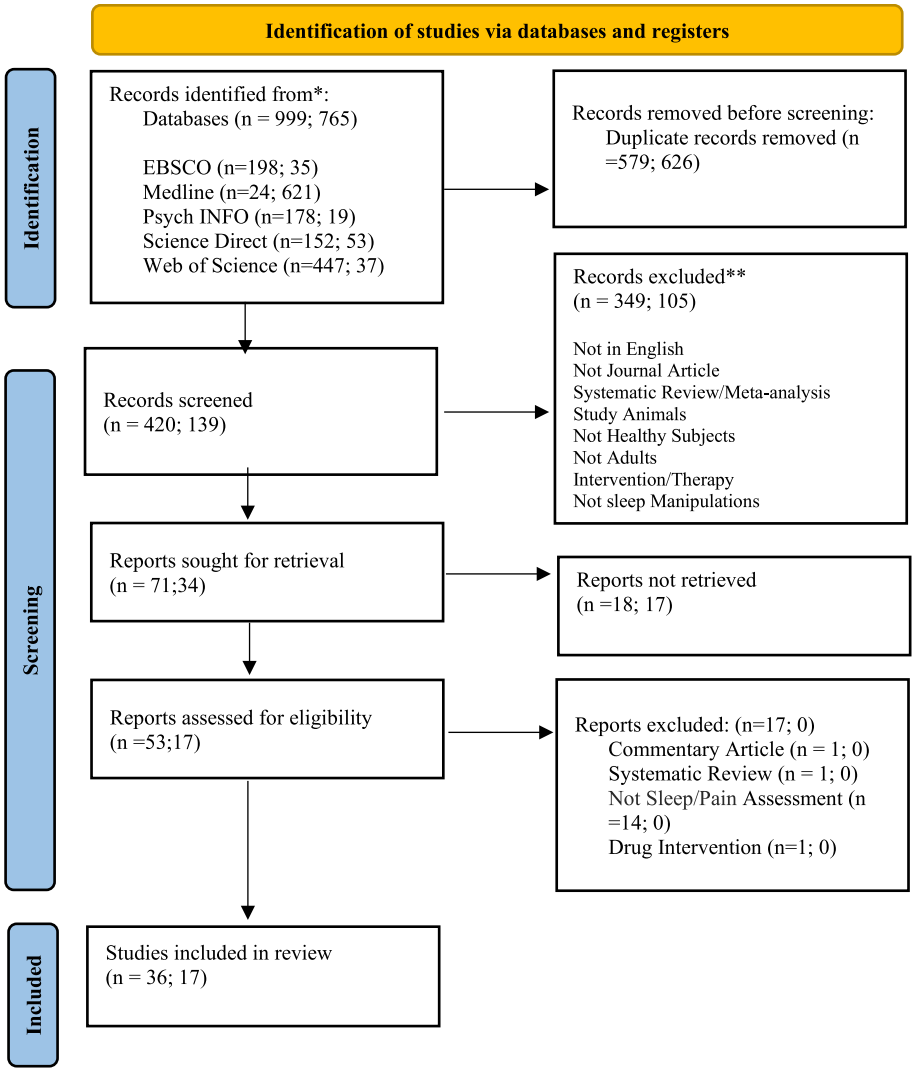


Fig. 1. PRISMA flow diagram
Fig. 1.The PRISMA flow diagram provides the search strategy of the current review. It depicts the two distinct search strategies employed in the current study: the search for static and dynamic pain studies. The number of studies identified and screened for each search strategy is presented in a bracket, with the first representing static and the second representing dynamic pain studies.

moderated the effect of total sleep deprivation on pain sensitivity (coefficient = 9.790; SMD = −0.194; 95%CI -0.328 to −0.060; p = .008; I-squared = 96.4%; R2 = 39.8; Fig. S1) with a small effect size. Notably, these results should be interpreted with caution given that the age range of the studies was quite limited, only including participants between the ages of 22.5 and 35.

Pain type subgroup. Total sleep deprivation decreased heat (SMD = -2.455; 95%CI: -4.549 to −0.361; p = .03; I-squared = 94.4%; Fig. S4) and mechanical (SMD = -2.228; 95%CI: -3.949 to −0.506; p = .026; I-squared = 82.6%; Fig. S4) pain thresholds; whereas it increased cold pain sensitivity (SMD = 1.691; 95%CI 0.949 to 2.434; p< .001; I-squared = 88.3%; Fig. S5). Results for the pressure pain threshold were not significant (p = .098; Fig. S4). It is difficult to determine the overall effect of total sleep deprivation on heat and pressure pain sensitivity due to the limited number of studies that have been conducted on the topic (Fig. S4). Without enough studies, it is not possible to calculate an accurate effect size.

Publication bias. Visual interpretation of the funnel plot and results from Egger's regression test (coefficient = 1.909; p<.001) showed an overall publication bias, specifically in the heat pain modality (coefficient 1.759; p = .044), but not for pressure, cold, and mechanical pain threshold (p>.05). This finding suggests that the high level of heterogeneity might contribute to the heat pain results (Fig. S6). According to the high heterogeneity observed, we conducted a trim-and-fill analysis with four imputed studies. The effect size was reduced, but still indicated a large effect size (SMD = -1.214; 95%CI -2.097 to −0.331; p = .010; Table S7).

3.1.2. Sex and age moderating effect of sleep restriction on pain perception

Sixteen studies [9,19–21,25,33,39–49] investigated the effect of restricted sleep on pain thresholds with an overall combined sample size of 360. Four studies conducted between-group comparisons of different sleep conditions; in this sub-section, only the restricted consolidated sleep group and its comparison with the healthy/control group was included (n = 329). Tables S1 and S5 provide more information on these studies. Restricted sleep reduced the pain threshold resulting in a large effect size (SMD = -.913; CI95: -1.562, −0.264; p = .009; I- squared = 89.2%; Fig. S7). However, restricted sleep did not increase pain sensitivity (p = .06; Fig. S8). The meta-regression found that neither sex (p = .625) nor age (p = .262) influenced the hyperalgesic effect of sleep restriction. Table S2 provides detailed information on gender distributions of included studies.

Pain type subgroup. Restricted sleep decreased heat (SMD = -1.608; 95%CI: -3.128 to −0.089; p = .041; I-squared = 93.3%; Fig. S7), and pressure (SMD = −0.199; 95%CI: 0.369 to −0.029; p = .030; I-squared = 0%; Fig. S7) pain threshold but not cold pain threshold (p = .124; Fig. S7).

Publication bias. The study also found an overall publication bias as visual interpretation of the funnel plot and results from Egger's regression test (coefficient = -7.190; p = .002; Fig. S9) showed an overall publication bias. However, there was no publication bias under heat, pressure, and cold pain threshold (p>.05). The study suggests that the high level of heterogeneity might account for the results (Fig. S9).

3.1.3. Sex and age moderating effect of fragmented sleep on pain perception

Seven studies [10,19,50–54] with a total sample size of 243 investigated the effect of sleep fragmentation on pain thresholds. Tables S1 and S6 provide more information on these studies. The studies implemented slightly different protocols for sleep fragmentation, with one study awakening participants every 80 min and the other studies adhering to a protocol where one of eight 1-h sleep bouts is randomly chosen to be awake, and seven remaining 1-h blocks are subdivided into tertiles, with one 20-min block chosen to be awake. One study also implemented 36 h of total sleep deprivation followed by forced awakening, so the results may not solely be attributable to sleep continuity disruption. One protocol did not provide sufficient information (only F-value was reported) concerning pressure pain threshold, so it was excluded from the meta-analysis [19].

Fragmented sleep decreased pain threshold compared to uninterrupted sleep, but the effect size was small (SMD = -.283; CI95: 0.458, −0.107; p = .005; I-squared = 0%; Fig. S11). Meta-regression analysis showed no sex effect of fragmented sleep on pain threshold (p = .645). Table S2 provides detailed information on gender distributions of these studies. However, age moderated the effect of fragmented sleep on pain threshold (coefficient 46.650; SMD = −0.110; 95%CI: 0.148 to −0.072; p< .001; I-squared = 0%; R2 = 100%, Fig. S10). The effect of fragmented sleep on pain threshold decreased with age.

Pain type subgroup. Fragmented decreased heat pain threshold (SMD = -.253; CI95: 0.496, −0.010; p = .029; I-squared = 0%; Fig. S11), but not cold pain threshold (p = .123; Fig. S11).

Publication bias. Visual interpretation of the funnel plot and results from Egger's regression test (coefficient = 1.535; p = .202) showed no publication bias. Studies were homogenous (chi-square = 0.081; p = .776, I-squared = 0; %; Fig. S12).

3.1.4. Sex and age moderating effect of selective sleep deprivation on pain perception

Four studies [20,21,49,55] investigated the effect of selective sleep deprivation on pain threshold. The overall sample size of these studies was 51 participants. Table S5 provides more information on these studies. There was no effect of selective sleep deprivation on pain threshold when compared to habitual sleep, as indicated by the p-value of .054 (Fig. S13). The results of a meta-regression analysis showed that neither age (coefficient = 2.413; p = .195) nor sex (coefficient = 0.171; p = .700) moderate the effect of selective sleep deprivation on pain threshold.

Pain type subgroup. Selective sleep deprivation did not reduce heat (p = .079; Fig. S13) or mechanical pain threshold (p = .33; Fig. S13). We could not calculate the effect of selective sleep deprivation on pressure pain threshold since there was only one study that investigated the topic [55]. Likewise, we could not calculate the effect size of selective sleep deprivation on pain sensitivity as there was only one study [2].

Publication bias. Visual interpretation of a forest plot and the results of an Egger's regression test showed no publication bias but high heterogeneity (chi-square = 66.505; p<.001, I-squared = 95.5%). Thus, the studies included in the analysis have a high degree of variability, which contribute to the high heterogeneity in the results.

3.1.5. Sex and age: moderators of sleep disturbance effects on different sensory modalities

When all sleep disturbance types were combined, meta-regression analysis showed that sex moderated the effect of sleep disturbance on both heat pain threshold (coefficient = 4.771; SMD = 0.27; 95%CI: 0.001 to 0.053; p = .043; I-squared = 92.2%; R2 = 22.2%; Fig. S14) and heat pain sensitivity (coefficient = 21.300; SMD = −0.029; 95%CI: 0.045 to −0.013; p = .006; I-squared = 68.8%; R2 = 86.2%; Fig. S15). With an increase in the proportion of females in the studies, the effect size was approaching zero in response to the heat pain threshold following sleep disturbance. In contrast, with an increase in the proportion of males, the effect size sloped towards negative with a robust effect size (SMD = -4.931). Likewise, with an increase in the female proportion, the pain sensitivity to heat stimuli after sleep disturbance decreased, while with an increased number of males, pain hypersensitivity increased. Age did not moderate the effect of sleep disturbance on heat pain (p = .845).

In contrast, the meta-regression indicated that neither sex nor age moderated the effect of sleep disturbance on cold pain (p = .431 and p = .189, respectively). Similarly, neither sex nor age moderated the effect of sleep disturbance on pressure pain (p = .58; p = .260, respectively).

3.2. Dynamic pain measurements (CPM and TSP)

Seventeen studies in total, including 11 focused on CPM (conditioned pain modulation) and 13 on TS (Temporal summation of pain) were included in this analysis. The total sample size of all the studies included in the analysis was 456 participants, with 271 females and 185 males.

3.2.1. Sex and age moderating effect of sleep disturbance on CPM

The eleven studies [13,19,26,31,33,34,38,43,45,56,57] on conditioned pain modulation (CPM) included one randomized control trial (RCT) and 10 randomized cross-over studies. The overall sample size of these studies was 299 participants (172 females and 127 males) with an age range of 18-59 and a mean age of 28.29 ± 7.07. The majority of the studies included young adults, with one study conducted on older adults and one study exclusively in females. The most frequently explored sleep manipulation was total sleep deprivation (6 studies), followed by restricted sleep (4 studies) and fragmented sleep (2 studies). The cold-water bath was the most commonly used conditioning stimulus (7 studies) followed by the hot-water bath (3 studies). The temperature of the cold-water bath varied between 1 and 7 °C, while all three studies using the hot-water bath used the temperature of 46 °C. The most common test stimulus was pressure (9 studies) and 2 studies administered heat pain. Only two studies applied conditioned and test stimuli sequentially, while the other 9 studies conducted them simultaneously. The majority of the studies applied the conditioning and testing stimuli on the hand (8 on contralateral sides, 2 on homotopic sides) and only one study applied them on the leg (heterotopic sides). The studies are summarized in Table 1.

The results showed that sleep disturbance did not change CPM (p = .90), regardless of the type of sleep manipulation used when both sexes are combined.

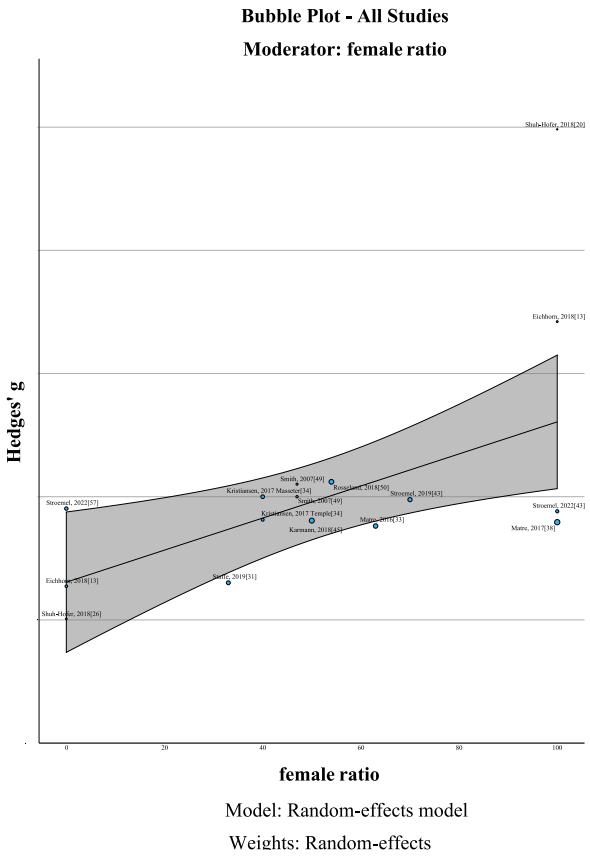
Subgroup analysis showed that fragmented sleep impaired CPM (SMD = .233; 95%CI: 0.023 to 0.443; p = .045; I-squared (%) = 0; Fig. S16), with the small effect size. However, other sleep manipulations, total sleep deprivation (p = .83; Fig. S16) and sleep restriction (p = .08; Fig. S15), did not have a statistically significant effect on CPM. The high heterogeneity in the total sleep deprivation (I-squared (%) = 97.6) studies may have contributed to the insignificant result. Given total sleep deprivation and fragmented sleep tended to impair pain inhibition, while sleep restriction appeared to enhance CPM, pooling these different types of sleep disturbance together was not feasible.

Meta-regression analysis revealed that sex significantly moderated the sleep disturbance-CPM association, with a small effect size (SMD = .033; 95%CI: 0.011 to 0.054; p = .005; I-squared = 89.6%; Fig. 2). Sleep disturbance impaired CPM in females but strengthened it in males. Additionally, sex contributed to the heterogeneity of the effect size, reducing the heterogeneity from high to moderate (I-squared = 89.6%; R2 = 57.0%; p<.001). Furthermore, the effect size was negative in studies that investigated only males but changed from negative to positive when the ratio of females increased.

Upon visual inspection of Fig. 2 and analysis of the data extracted from the forest plot (Fig. S16), one study was an outlier. Subsequently, a sensitivity analysis was conducted which involved the exclusion of the study from the effect size calculation [38]. Excluding this study increased the moderating effect of sex on CPM in response to sleep disturbance (SMD = 0.046; 95%CI: 0.025 to 0.067; p<.001; I-squared = 77.1%), with small effect size and moderate heterogeneity. Notably, this study was conducted on night shift workers and only females were included. This study showed that sleep-deprived females had stronger CPM and perceived less pain than those in habitual sleep conditions (SMD = -0.41). This contradicts the overall findings of the current review.

Age did not moderate the effect of sleep disturbance on CPM (coefficient = 0.69; p = .797).

Publication bias. A visual interpretation of a forest plot and the results of an Egger's regression test found no overall publication bias



Model: Random-effects model

Weights: Random-effects

Fig. 2. Sex moderating effect of sleep loss on CPM

Fig. 2 The figure depicts the moderating effect of sex on the relationship between sleep loss and conditioned pain modulation (CPM). The y-axis represents the effect size (standardized mean difference or SMD), while the x-axis shows the proportion of females in each study. As the proportion of females increases, the CPM slope tends to be positive, indicating an impaired pain-inhibitory response following sleep loss.

(coefficient = -1.775; p = .083) but highlighted there may be publication bias present in the studies that conducted total sleep deprivation (coefficient = -2.977; p = .025), or it could be accounted for by high heterogeneity in those studies.

3.2.2. Sex and age moderating effect of sleep disturbance on TS

Thirteen studies [8,13,25,31,33,38,40,41,45,49,51,57] were included in the analysis of sleep disturbance and its effect on temporal summation (TS) with a total sample size of 402 participants, including 244 females and 158 males. They were all randomized cross-over design studies. The age range of participants was 18-57 with a mean of 29.7 ± 7.51. Twelve studies included young adults, and one recruited older adults. Two studies exclusively studied females, while others had a mix of participants with a higher preponderance of females (60%). The most common type of sleep manipulation studied was restricted sleep (7 studies), followed by total sleep deprivation (5 studies), and the least studied was fragmented sleep (1 study). The most common test stimuli were pressure pain (8 studies), followed by heat pain (3 studies) and cold-water tank (2 studies). Seven out of 13 TS studies used tonic pain as test stimuli without intervals, while six used phasic pain with several inter-stimuli intervals. The body part most commonly used was the hand (12 studies), only one study used the dominant leg. This information is summarized in Table 2.

Regardless of the type of sleep manipulation, the results revealed no effect of sleep disturbance on TS (p = .228). Although statistically non-significant, sleep disturbance tended to increase temporal summation of pain. The results showed a high degree of heterogeneity among the

studies included in the analysis (I-squared = 80.6%) and the potential source of high heterogeneity could be due to the Smith et al. study reporting TS for females and males separately [51].

Subgroup analysis demonstrated that none of the sleep interventions significantly enhanced the temporal summation of pain: total sleep deprivation (SMD = .085; 95%CI: 0.447 to 0.647; p = .662; I-squared = 13.8%; Fig. S17), sleep restriction (SMD = 0.269; 95%CI: 0.174 to 0.712; p = .199; I-squared = 53%; Fig. S17), and fragmented sleep (SMD = 0.245; 95%CI: -15.815 to 16.304; p = .878; I-squared = 98%; Fig. S17).

Sex moderated the association between sleep disturbance and temporal summation of pain (coefficient = 9.368; p = .009), with a small effect size (SMD = 0.13; 95%CI: 0.004 to 0.022; p = .009; I-squared = 67.7%; Fig. 3). Sleep disturbance increased TS in females but reduced it in males, indicating elevated threshold in response to painful stimuli under disturbed sleep conditions. Additionally, sex contributed to the heterogeneity of the effect size, considering sex as a moderator reduced the heterogeneity to a medium level (I-squared = 67.7%; R2 = 48.4%; p<.001). Age did not moderate the effect of sleep disturbance on TS.

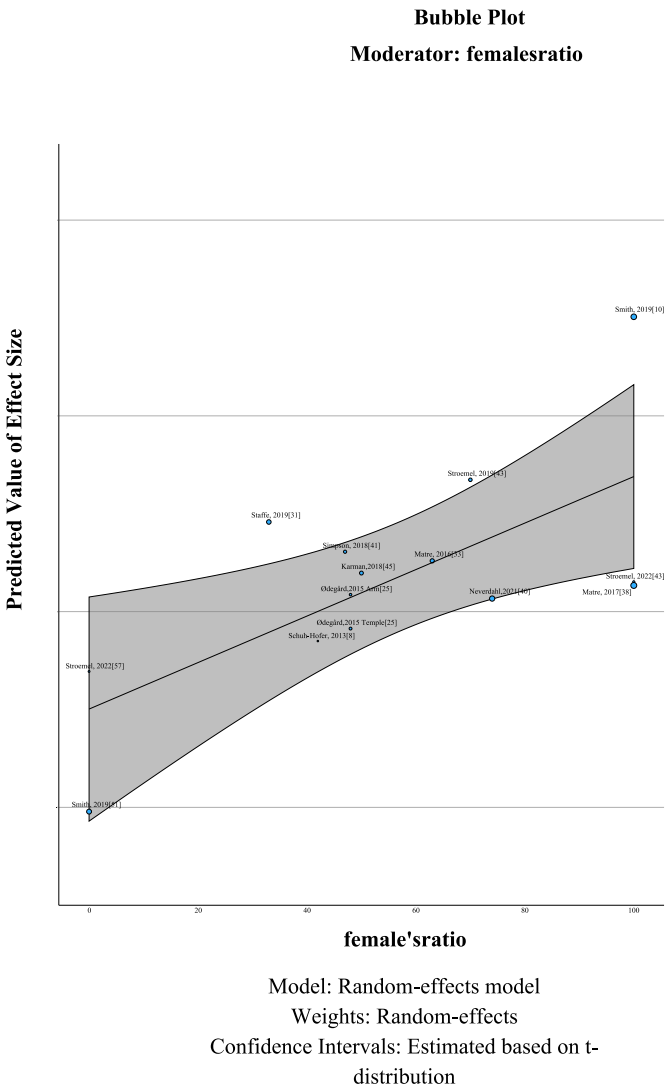


Fig. 3. The effect of sleep loss on TS
Fig. 3 The figure illustrates the moderating effect of sex on the relationship between sleep loss and temporal summation (TS). The y-axis represents the effect size in terms of standardized mean difference (SMD), whereas the x-axis shows the proportion of females in each study. As the proportion of females in a study increases, the TS slope tends to become more positive, indicating pain facilitation following sleep loss.

The meta-regression analysis on different types of sleep disturbance revealed that sex had a moderating effect solely on the impact of fragmented sleep on temporal summation and not on other forms of sleep disturbance. Fragmented sleep decreased temporal summation in males (SMD = -1.02; p<.001), whereas it increased it in females (SMD = 1.51; p<.001). The results showed no moderating effect of age on TS (p = .691) in response to sleep disturbance.

Publication bias. We used visual analysis of a forest plot and Galbraith plot, as well as the results of an Egger's regression test, to check for publication bias. The results of the test (coefficient = 2.786, p = .332) indicate that there is no publication bias in the studies included in the analysis.

4. Discussion

The current review aimed to assess the impact of sex on the relationship between sleep disturbance and pain. The results showed that sex had no meaningful effect on static pain, apart from heat pain. However, sex was found to significantly moderate the relationship between sleep disturbance and dynamic pain (TS and CPM). Conversely, age did not have a significant effect on the relationship between sleep disturbance and dynamic pain but moderated the effect of total sleep deprivation and fragmented sleep effects on static pain. These findings emphasize the importance of considering both sex and age in research exploring the link between sleep disturbance and pain.

4.1. Sex moderating effect on pain perception in response to sleep disturbance

The current review demonstrated that sleep-deprived females display augmented pain sensitivity, heightened temporal summation of pain, and reduced pain inhibition. These findings are consistent with a recent experiment involving 24 healthy individuals (50% females) [60]. Participants experienced a 19-day period of sleep disturbance characterized by fragmented sleep conditions and reduced sleep duration (4 h). CPM was measured by inducing heat pain (test stimuli) and hot water at 47° Celsius (conditioning stimuli). The results showed no significant effect of sleep disturbances on CPM in the combined group of males and females. However, a significant sex difference was observed, with females exhibiting impaired pain inhibition and males demonstrating improved pain inhibition in response to sleep disturbances [58].

These findings are also consistent with prior research that has documented sex disparities in pain sensitivity. A prior systematic review [3] retrieved data from a review of 122 studies conducted between 1998 and 2008 and similarly confirmed sex differences in pain sensitivity. Females generally have lower pain thresholds, decreased pain tolerance, and higher pain ratings in response to noxious stimuli than males, although the extent of this difference may vary across different pain modalities and measurement tools [3]. Furthermore, sex-based differences have been observed in all pain modalities, including heat, ischemic, cold, and pressure pain thresholds, though the effect sizes ranged from small to large, with cold pain being the smallest [53].

Further support for the differential effects of sleep disturbance on pain in men and women comes from a study on patients with knee osteoarthritis, which found that sensitivity to pain, as measured by quantitative sensory testing, was negatively correlated with insomnia severity in males, but positively associated in females [59]. This suggests that severe insomnia in females is associated with increased sensitivity to pain, while it is associated with less sensitivity in males. These findings suggest that the relationship between sleep disturbance and pain perception may differ between males and females.

Differences in pain perception between males and females might partially arise from variations in sex hormones and differences in pain modulatory circuits [3,60–63]. It has been suggested that sex hormones may play a role in how males and females respond to pain [3,60,61].

Gonadal hormones, including estrogen and testosterone, have both been implicated in pain processing [34,61,64]. Estrogen [60,61] is known to affect several neurotransmitters, including dopamine, beta-endorphin, acetylcholine, and serotonin, all of which are involved in modulating pain perception. Research has demonstrated that estrogen can increase serotonin levels [60], and a reduction in estrogen levels may correspondingly decrease serotonin levels. This decrease in serotonin levels resulting from fluctuations in estrogen levels may reduce self-inhibitory effects at the serotonin receptor level, which has been postulated as a potential contributor to increased headaches [60]. In contrast, research indicates that males tend to exhibit lower sensitivity to pain, in part due to the analgesic effects of testosterone. This hormone has been shown to possess pain reducing properties [65,66]. Research has indicated that testosterone levels are lower in males with rheumatoid arthritis when compared to healthy males [61]. Moreover, testosterone administration has been shown to enhance pain tolerance and increase heat and mechanical pain thresholds [66].

One study investigated the impact of severe sleep restriction (4 h in bed) compared to habitual sleep (9 h in bed) over a 5-night period on plasma testosterone levels in healthy young males. The study showed no significant change in testosterone concentrations and no main effect of sleep duration ($p = .13$) on testosterone levels [67]. These findings support the notion that acute sleep disturbance may not affect pain perception in males, which is consistent with the current review. The heightened sensitivity to pain exhibited by females may be also attributed to a less effective endogenous pain inhibitory response, as measured by conditioned pain modulation (CPM) [68]. A previous systematic review [68] has reported that in studies utilizing subjective pain measurements, such as visual analogue scale (VAS), numerical pain rating (NPR), or pain threshold, the average CPM ratio between females and males was 0.58, indicating that the pain inhibitory capacity was approximately 1.7 times less effective in females compared to males. The reduced pain inhibitory capacity in females has been consistently observed across various pain modalities, including electrical, pressure, thermal, mechanical, and chemical pain stimulation [68]. A literature review that examined the influence of sex on CPM reached no definitive conclusion due to a similar number of studies reporting a significant sex effect and no significant difference. However, in light of the current review findings, among the studies that did detect a sex difference, there is evidence to suggest that males exhibit a more pronounced CPM effect than females (approximately 40% of the literature demonstrating greater CPM in males [69] under the normal sleep condition).

It was previously known that females are at a heightened risk of developing chronic pain given that dysfunctional or less efficient pain inhibitory responses increase the likelihood of developing chronic pain conditions [70], and females possess less efficient pain inhibitory capacity compared to males [63,68]. In the current review we now additionally show that acute sleep disturbance impairs pain inhibitory response in females. Collectively, the combination of compromised pain inhibitory capacity and sleep deficiency may render females more susceptible to the onset of chronic pain conditions [59]. These findings suggest that females may be at a higher risk of developing chronic pain when exposed to sleep deficiency.

The current review on the effects of sleep disturbance on pain perception is only applicable to acute sleep deprivation and may not accurately reflect the impact of prolonged sleep deficiency or accumulated sleep debt. The study conducted on night shift workers revealed an increase in pain inhibition, with a 66.9% rise after night shift work compared to habitual sleep [38]. This finding contrasts with the overall findings of the present review. The study on night shift workers employed a paired cross-over design with two sleep conditions: habitual sleep, where participants had at least two nights of regular sleep, and sleep restriction, which involved at least two consecutive night shifts at work. To eliminate the influence of sleep deficiency due to shift work before the habitual sleep experiment, night-shift workers were required to have at least three nights of habitual sleep; however, they still exhibited a more robust pain inhibitory response. One possible explanation for this phenomenon is the development of an adaptive habituation process that counteracts the acute hyperalgesic effect of shift work related sleep loss [19,38]. Previous research has proposed that over three weeks of sleep deficiency attenuated the pain hypersensitivity due to habituation [41]. An additional potential explanation for the observed phenomenon is the alteration in pain modulatory circuits, which has been observed in patients with primary insomnia who have been exposed to prolonged sleep disturbances. This is supported by the findings of Haack et al. [71], who examined the relationship between primary insomnia and pain perception using temporal summation of pain and discovered that individuals with primary insomnia exhibited reduced pain summation. This effect may be attributable to the maximal activation of pain-inhibitory processes [25,71,72]. However, more research is needed to fully understand the distinct effects of acute and chronic sleep deficiency on pain perception.

4.2. Age moderating effect on pain perception in response to sleep disturbance

This systematic review is the first to explore the effect of age on pain perception in response to sleep disturbance. The results of the review indicate that overall age does not have an effect on pain perception across multiple modalities, including heat, cold, and pressure pain. This is consistent with the findings of a study by Edward et al., which compared experimentally-induced pain in young and older adults and found no significant differences between the two groups in terms of heat, pressure, and ischemic pain [15,68,73]. Although the results were not statistically significant, Edward et al. did find that older participants had a 1.7-degree higher pain threshold, indicating that older adults may have less pain sensitivity [68].

However, the current systematic review found that there is an inverse correlation between age and pain sensitivity under total sleep deprivation, regardless of the pain modality. This suggests that as individuals age, they respond less to painful stimuli under sleep deprivation conditions. Previous studies reported that older adults are generally less sensitive to thermal stimuli than their middle-aged counterparts and that this decrement in sensitivity increases with age [17,74]. A possible explanation for this is that older adults have less efficient primary afferents, which may lead to a dampened sensory component of pain [17]. It has also been suggested that older adults rely more on unmyelinated sensory transmission, which may contribute to decreased pain sensitivity [16]. The current review also found that age moderated the effect of pain threshold in response to fragmented sleep. However, it is worth noting that the age range in the current review was narrow, most of the included studies only recruited young adults between the ages of 20-35. Therefore, if sleep-pain studies were to investigate a broader range of ages, including middle age and older groups of participants, variations in pain sensitivity may be more apparent.

The current systematic review found that there is no age-moderating effect on central sensitization, as measured by temporal summation (TS) and conditioned pain modulation (CPM), in response to sleep disturbance. This aligns with a study that compared the effect of TS in younger and older participants, ranging from 45 to 76 years old, and found no effect of age [75]. This lack of effect may be partly due to the limited age range in the included studies, as most of the sample was between 22 and 25 years. Additionally, it is not surprising that the current review did not find an age-moderating effect on CPM, as research has shown that it starts to decline in middle age [74], with less CPM in participants over 35 years.

4.3. Differential effect of sleep disturbance types on pain perception

The current review also summarized the differential hyperalgesic effect of different forms of sleep disturbance on pain perception in healthy population. The study found that total sleep deprivation had the

largest effect, sleep restriction had a smaller but noticeable effect, and fragmentation had the slightest (but measurable) effect. However, selective sleep deprivation did not induce any change in pain perception. The current review aligns with the recent meta-analysis [11] which found that total sleep deprivation and fragmented sleep exerted a large and small effect size, respectively. However, the previous review reported that sleep restriction did not affect pain perception, while the current meta-analysis found that it did. The inconsistency is likely due to the previous meta-analysis not including studies that showed significant hyperalgesic effects due to sleep reduction. The previous meta-analysis included the effects of both acute and chronic sleep-restricted exposure, with data from the last week of a three-week sleep-deficiency study [41]. In contrast, the current meta-analysis only reviewed the hyperalgesic effect of acute sleep deficiency and only extracted data from the first week of the same trial [41], in line with other studies that were included in the analysis. This difference in data extraction could explain the difference in results between the two meta-analyses.

One potential explanation for the differential effect of sleep disturbance types, including total sleep deprivation, restricted sleep, and fragmented sleep, on pain perception might be due to changes in sleep architecture [55]. Total sleep deprivation has the greatest impact on sleep architecture, followed by sleep restriction, while fragmentation causes the least changes [19]. Total sleep deprivation affects all sleep stages, while the sleep restriction used by studies in this meta-analysis reduces light sleep, non-rapid eye movement (NREM) stages 1 (23 ± 14 min versus 43 ± 13 habitual sleep) and 2 (78 ± 37 min versus 170 ± 53 habitual sleep), and rapid eye movement (REM) sleep (58 ± 24 min versus 91 ± 36 habitual sleep), while also reducing sleep time to half (247 ± 76 min versus 410 ± 89 habitual sleep) [19].

Fragmented sleep used by Letzen. et al. in this meta-analysis led to an increase in the time spent in NREM 1 (25.1 ± 11.3 versus 17.5 ± 9.3 min) and a decrease in the time spent in NREM stages 3 and 4 (121.3 ± 30.3 versus 191.6 ± 77.8 min), and REM sleep (42.8 ± 29.3 versus 88.6 ± 28.4 min) but the extent of sleep reduction (269.3 ± 53.9 versus 415.9 ± 81.9 min) is less than total sleep deprivation or sleep restriction [19,52]. Moreover, sleep fragmentation also disrupts sleep continuity, leading to frequent awakenings during the night [19]. Therefore, future studies are required to investigate sleep stage alterations and their effect on pain perception. Another study found that fragmented sleep increased NREM stage 1 duration in females but not males [51]. Moreover, fragmented sleep decreased NREM (stage 3 and 4) and REM sleep in both males and females, but the extent of its decrement in NREM stage 3 (males 55.18 ± 58.32 versus females 68.87 ± 39.89) and REM (males 25.41 females 28.68 versus females 37.03 females 29.06 females) was greater in males [51]. Although the findings from the current study and previous reviews support the differential effect of sleep disturbance paradigms on pain perception, how alterations in sleep architecture affect pain perception and whether these changes differ between males and females require further investigation [51,52].

Collectively, the findings of this systematic review have several potential clinical implications:

1. Women with sleep disturbance appear to be at a greater risk of central sensitization, a hallmark of chronic pain susceptibility, than men. Therefore, it may be important to improve sleep in women with sleep disturbance in order to prevent chronic pain in women. On the other hand, acute sleep restriction may help to reduce pain in men.
2. Younger adults are more sensitive to pain than older adults following sleep disturbance, so optimizing sleep in young people could potentially be a target to prevent the development of chronic pain.
3. Minor sleep disruption, such as fragmented sleep, has a negligible effect (small effect size) on pain perception, at least when acute. However, extreme sleep changes, such as total sleep deprivation or significant sleep reduction, may increase the risk of pain hypersensitivity (large effect size) and the development of chronic pain conditions. Therefore, longer sleep periods may help compensate for disrupted sleep and reduce the risk of hyperalgesia.

4.4. Limitations

The current systematic review has several limitations. 1. Only a small number of studies separated the pain measurements by sex, and the moderated analysis was quantified based on the female proportion in each study, so it may affect the results of sleep-related hyperalgesia between the sexes. 2. The age range of the study was limited, only including participants between the ages of 25 and 35. This means that the findings may not be generalizable to older populations. 3. Some potential confounders could not have been included, such as the time of day of assessment [76], as this information was not available in all included studies. 4. The current review only included studies that investigated the effect of acute sleep deficiency on pain perception, so the results cannot be generalised to prolonged sleep deficiency. 5. The small number of studies that specifically investigated the effects of forced awakenings, as opposed to total sleep deprivation or restricted sleep, may affect the statistical power of the overall findings as studies with a larger sample size would provide more robust and reliable results. 6. An imbalance in the types of pain thresholds that are assessed in studies investigating the effects of sleep disturbance on pain perception could potentially affect the results. Many studies have focused on assessing heat pain thresholds rather than mechanical or cold pain thresholds. 7. The high heterogeneity and potential risk of bias were seen in the current meta-analysis but are inherent in many systematic reviews. The sub-group analyses of sleep types, pain modalities, and sexes were performed to address the high heterogeneity, but it is not enough to eliminate the heterogeneity. 8. Only studies published in English were included in the review, so a number of studies published in other languages were not considered. 9. The analyses were conducted retrospectively rather than prospectively, so the results need to be interpreted with caution. 10. The publication date restriction was applied, and only studies published after 2000 were included. While this approach was taken to ensure that over two decades of research were covered, it may have resulted in the exclusion of relevant studies published before 2000. Although we used The RoB. 2 tool to evaluate the methodological quality of cross-over study trials, for non-randomized controlled trials, it is also suggested to use the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool. Last but not least, the current study was conducted on healthy, pain-free adults, so the results should be extended to the clinical populations, including chronic pain patients, with caution. In sum, more research is needed to confirm these findings to fully understand the role of sex in the relationship between sleep and pain.

5. Conclusion

The current systematic review highlights that pain perception is altered differentially by sleep disturbance in men and women. The findings suggest that the hyperalgesic effect of sleep disturbance is greater in females than in males, and that sex-based differences should be considered when investigating the effects of sleep disturbance on pain sensitivity. The review also suggests that sleep disturbance impairs endogenous pain modulation in females but strengthens the pain inhibitory response in males. Additionally, the review found that even small differences in age can affect sleep-pain relationship, and that sleep-pain studies should consider the age-moderating effect on pain perception. With respect to clinical implications, our findings suggest that an early diagnosis of sleep disturbance among females may prevent its cumulative effect on pain, improving chronic pain conditions or preventing pain chronicity. Moreover, restricting sleep may reduce pain perception in males with acute pain, such as those in post-operative recovery.

6. Practice points

1. Effects specific to women: The current review demonstrated that women may be more susceptible to the negative effects of sleep disturbance on pain perception than men. Women with sleep disturbance are at a greater risk of developing central sensitization, which is a hallmark of chronic pain susceptibility. Therefore, it may be important to target sleep disturbances in women as a way of preventing chronic pain. It is also important to note that targeting sleep disturbances in women can be a therapeutic approach to treating chronic pain.
2. Effects specific to men: The current review suggests that acute sleep restriction may have a pain-reducing effect in men. However, acute sleep restriction should be used under the guidance of a healthcare professional, as it may have negative effects on overall health. Additionally, it is not a long-term solution for chronic pain management, as chronic sleep restriction can have detrimental effects on physical and mental health.
3. Overall, across both sexes: Acute sleep restriction, such as a single night of sleep fragmentation, typically has a minimal effect on pain perception. However, extreme sleep changes, such as prolonged total sleep deprivation, can increase the risk of pain hypersensitivity and the development of chronic pain conditions, at least in females. To reduce the risk of hyperalgesia, it can be beneficial to try to compensate for disrupted sleep by getting longer sleep periods.

7. Research agenda

1. The current review showed that sleep-loss-related hyperalgesia differed between males and females. These findings need to be confirmed by further research, which should include larger sample size and more controlled experiments. Splitting the results by sex in sleep-pain studies would help to provide a more detailed understanding of the effects of sleep loss on pain perception in men and women and how they differ. Future research needs to consider other factors, such as age, race, and overall health status, that might also affect pain perception.
2. The current review has shown that acute sleep disruption can negatively affect pain perception, and that it may affect men and women differently. However, the long-term effects of sleep restriction (which is common in society) on pain perception are still not fully understood. More research is needed to understand the underlying mechanisms and the long-term effects of sleep restriction on pain perception in both men and women.
3. Many studies on the effects of sleep disruption on pain perception have focused on young adults, with the age range typically between 22 and 35 years old. While these studies have provided valuable insights, it is important to note that the effects of sleep disruption on pain perception may be different in older adults. Therefore, more research is needed to investigate the moderating effect of age on the relationship between sleep disruption and pain perception in older adults, specifically those above 35 years old. Studies that include older adults would help to provide a more complete understanding of how age affects pain perception in response to sleep loss, which would be beneficial for developing effective pain management strategies for older adults.

8. Summary of the findings

The impact of sleep disturbance on pain varies based on the type of sleep manipulation, pain modality, sex, and age. The review revealed that sleep disturbance affects conditioned pain modulation (CPM) differently for males and females, impairing it in females and strengthening it in males. Sleep disturbance also affects the temporal summation of pain (TS) differently for males and females, facilitating pain responses in females and reducing the summation effect in males. In contrast, age moderates the effect of total sleep deprivation on pain sensitivity, with increased age resulting in decreased sensitivity, but does not moderate the effect of sleep disturbance on either CPM or TS.

Funding

SR was funded by the University of Melbourne (Melbourne Research Scholarship) doctoral studentship. NEB was supported by the Australian Research Council DE180100893 and Melbourne School of Psychological Sciences Research Fellowship.

Declaration of competing interest

Authors have no conflicts to state.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2023.101835.

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Abbreviations

CP: chronic pain
CPM: conditioned pain modulation
NREM-sleep: non-rapid-eye-movement sleep
RCT: randomized controlled trial
REM-sleep: rapid-eye- movement sleep
ROB-2: risk of bias for cross-over studies
SMD: standardized mean difference
TS: temporal summation