[ Contemporary Reviews in Critical Care Medicine ]

CHEST

# Sleep Disturbance and Pain
## A Tale of Two Common Problems

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Chronic pain has been associated with sleep disturbances in a bidirectional manner, with pain disrupting sleep, and sleep deprivation or disturbance increasing pain. This conventional view began to be reassessed with data from longitudinal and microlongitudinal studies investigating the causal relationship. In this review, we examine the current thinking on the temporal associations between sleep and pain, focusing on studies that considered whether sleep disturbances could predispose individuals to pain conditions. The evidence suggests that insomnia predisposes individuals to chronic pain or to the worsening of painful conditions. A limited number of studies are available that explore this outcome in relation to some of the most prevalent sleep disturbances, such as short sleep duration, sleep apnea, narcolepsy, and sleep bruxism conditions. Despite consistent data showing that sleep and pain are related, there are still few longitudinal studies investigating sleep disturbances as a possible pathogenic condition of chronic pain. Because of the effect of pain and sleep problems on quality of life, investigating how sleep and pain are associated is key to improving health outcomes through better treatments and prevention strategies.

CHEST 2018; ■(■):■-■

**KEY WORDS:** chronic pain; sleep; sleep apnea; sleep disturbance; temporal association Q4

Getting a sufficient amount of quality sleep is essential to health and well-being. Sleep is a dynamic state characterized by behavioral, physiological, and electrophysiological parameters. Behaviorally, it could be defined as an increase in sensory threshold to external stimuli, immobility, species-specific sleep posture, and reversibility. On the basis of electrophysiological activity of the brain and peripheral muscles, sleep is defined by two phases that alternate cyclically in the course of night: rapid eye movement (REM) and non-REM (NREM) sleep.[1-3] Other physiological parameters such as temperature, hormonal secretion, and respiratory and cardiovascular regulation, show distinct responses throughout REM and NREM sleep.[2] Despite the increasing knowledge about sleep physiology, the crucial question of why we sleep remains open. What is known is that sleep serves to facilitate the optimal functioning of several physiological systems. Despite the clear importance of sleep, many studies have demonstrated that the prevalence of sleep disorders across a number of different settings is increasing[4,5] and that there is a current widespread trend toward reduced sleep time.[6-8]

**ABBREVIATIONS:** NREM = non–rapid eye movement; REM = rapid eye movement

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Q3 Q16 **FUNDING/SUPPORT:** Supported by the Associação Fundo de Incentivo à Pesquisa.



**DOI:** https://doi.org/10.1016/j.chest.2018.07.019





REV 5.5.0 DTD ■ CHEST1839_proof ■ 6 September 2018 ■ 3:20 pm ■ EO: CHEST-18-0951

Clinical and experimental studies investigating sleep disorders have widely reported changes in pain processing systems. Pain is a physiological response to protect the organism from actual or potential tissue damage.[9] The acute experience of pain is advantageous and essential to survival and ceases when the stimulus is not present; however, the persistence of pain past normal healing time and in the absence of painful stimuli is a pathological condition with no adaptive function. Chronic pain is usually defined as pain that lasts or recurs for more than 3 to 6 months.[10] Contrary to protective acute pain, chronic pain is a dysfunction of the pain system and contributes to both physical and emotional impairment that can severely worsen quality of life. Estimates in different countries of the prevalence of chronic pain range from 10% to 39%.[11-14] Social and economic repercussions from this alarming prevalence of chronic pain make it a world health problem because it affects hundreds of millions of people around the world.

Chronic pain has been associated with sleep disturbances. It has been widely accepted that the relationship between sleep and pain is bidirectional, with pain disrupting sleep and sleep deprivation or disturbance increasing pain. This relationship has already been explored in several experimental, clinical, and review studies[15-17]; however, inconsistent data related to the changes in sleep pattern in chronic pain conditions highlighted the uncertainty of this bidirectional association.[18] In fact, most of the data on this relationship were obtained through studies with observational designs, limiting conclusions about the causality or the directionality of this association. There has been increased focus on the temporal associations of sleep and pain, strengthening the evidence that sleep disturbances are more significant predictors of pain than in the opposite direction.[19,20] In this context, the aims of the present review were to (1) summarize the state of the current knowledge about the temporal associations between sleep and pain, (2) contextualize studies that investigate pain symptoms in patients with a sleep disorder, and (3) highlight the future agenda in sleep and pain.

## Temporal Associations of Sleep and Pain

The conventional view that sleep and pain share a bidirectional relationship began to be reassessed with data from longitudinal studies (with timescales over months or years) and microlongitudinal studies (with timescales over hours and days) investigating causal relations. One of the first studies to analyze day-to-day associations between sleep and pain, considering both directions of the sleep-pain relationship, was by Affleck et al.[21] In a 30-day self-reported analysis of patients with fibromyalgia, the authors showed a sequential relationship between sleep and pain: a night of poor sleep was followed by a painful day, and a more painful day preceded a night of poorer sleep. Of interest, this association was found in relation to the self-reported attention to pain and not to pain intensity. The authors demonstrated that reports of greater pain during the day predicted a worse night's sleep, and that increased attention to pain also predicted poorer sleep. Those individuals who reported sleeping poorly reported more pain and more attention to pain the following day. Data indicated that poor sleep might mediate next-day increased pain resulting from changes in cognitive processes. Similar results were reported in patients with rheumatoid arthritis who were assessed day-to-day for 1 week[22]; however, the authors did not evaluate the effects of daily pain on sleep, making any conclusions on bidirectionality impossible. More studies using data from day-to-day analyses show conflicting results. A national survey conducted in the United States found that pain ratings increase as a function of previous sleep time in a U-shaped curve, with higher pain ratings during the day linked to less sleep the previous night. A weak predictive relationship between pain on sleep was also reported.[23] In a daily process study, using actigraphy to objectively estimate sleep variables and questionnaires to understand the relationship between different variables across days, Tang et al[24] reported that sleep quality is a predictor of increased pain the next day, but presleep pain is not a particularly reliable predictor of subsequent sleep. The sample was of individuals with chronic pain and insomnia. Moreover, pain ratings upon waking, in the first half and second half of the day were predicted by perceived worse sleep quality of previous night. Contrary to these data supporting the often-assumed reciprocal relationship of sleep and pain, O'Brien et al[25] found a bidirectional relationship between sleep and pain measured over 2 weeks using self-report instruments in women with chronic pain (back pain, facial pain, and fibromyalgia). Temporal associations were also reported in longitudinal studies. Nicasio and Wallston[26] evaluated the predictive effects of either prior pain or sleep problems on subsequent pain or sleep problems. Sleep problems reported at baseline were not associated with increased pain in a 2-year follow-up in patients with rheumatoid arthritis. On the basis of the analysis by Nicasio and





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Wallston,[26] Bigatti et al[27] investigated the causal relationships among pain, sleep, physical function, and depression in fibromyalgia. Baseline sleep quality and pain were significant predictors of pain in a 1-year follow-up. No baseline measurements predicted sleep quality changes. In a later study, reports of sleep problems in young adults (average age, 19 years) at baseline were predictors of pain onset and persistence/remittance of chronic pain 3 years later.[28] Recently, Benedito-González et al[29] reported that, in subjects with chronic tension-type headache, higher sensitivity to pressure pain at baseline predicted lower sleep quality at 1-year follow-up. The presence of pain predicting sleep problems was also shown by Skarpsno et al.[30] Subjects with chronic musculoskeletal pain and fatigue had a higher risk of suffering from insomnia symptoms compared with pain-free subjects. Only whether pain predicted sleep was analyzed in both of these studies.

Review articles covering prospective data from 1992 to 2016 published in the past 15 years have concluded that the presence of sleep disturbances is a strong predictor of future pain conditions.[15,19,20] Despite the differences in sample characteristics, experimental design and the instruments used to assess sleep and pain, microlongitudinal and longitudinal analyses suggest a more consistent relationship in which sleep disturbances are linked to next-day increased pain. Briefly, impairments in sleep may be a more reliable and stronger predictor of pain than pain is of sleep impairments,[19] which contradicts the often-assumed reciprocal relationship between pain and sleep and calls for a reconsideration of our ideas about this subject.

## Sleep Disturbance as a Risk Factor for Pain

Sleep disturbances are highly prevalent worldwide. Results from several countries show that the presence of sleep complaints in the general population ranges from 30% to 76%, with the most prevalent being insufficient sleep, insomnia, daytime sleepiness, snoring, and sleep apnea.[31-34] The negative daytime consequences of sleep disturbances (eg, fatigue, cognitive impairment) and the long-term effects on health make sleep problems a public health concern.

The emerging view on the temporal association between sleep and pain adds another important aspect in relation to sleep and health: sleep disturbances could predispose people to pain conditions. The majority of studies investigating the association between sleep and pain have been conducted in patients with chronic pain or in experimental sleep-loss conditions. Because sleep complaints are prevalent in this population and can worsen health outcomes, it is easy to understand why there have been many studies focusing on this area; however, there is also a need to investigate the prevalence and incidence of pain conditions from the perspective of patients with sleep disturbances. Treating pain in patients with sleep disturbances is key to improving health outcomes because of the effect of pain and sleep problems on quality of life.

### Sleep Deprivation

Insufficient sleep, sleep restriction, or sleep deprivation is a condition in which the individual fails to get enough sleep to maintain normal levels of alertness and wakefulness.[35] Sleep deprivation is highly prevalent in modern society, with population data demonstrating a trend of decreasing sleep time,[6-8] whereas there is growing evidence suggesting a link between short sleep duration and impairments in several physiological responses.[36-39]

The association between sleep deprivation and pain response began to be more deeply explored in the 1970s in experimental studies conducted by Moldofsky.[40,41] Reports that sleep-deprived healthy subjects showed increased daytime musculoskeletal pain and fatigue comparable to the symptoms seen in patients with chronic pain highlighted the influence of sleep loss on pain.[40,41] Now, there is extensive literature on sleep deprivation and pain in healthy subjects and on sleep deprivation producing hyperalgesic responses in patients with pain.[16,42,43] Despite the increased number of studies reporting data on the relationship between sleep deprivation and pain, there are still few longitudinal studies investigating sleep deprivation as a possible pathogenic condition of chronic pain.

Reduced sleep time as a risk factor for developing painful conditions has been evaluated in microlongitudinal and prospective studies. Edwards et al[23] evaluated sleep and pain associations for 8 consecutive days and found that reduced sleep time ($< 6$ h) predicted an increase in the frequency of pain report in the general population. Daily pain also predicted next night sleep, although this association was statistically weaker. In patients with knee osteoarthritis, subjective and objective total sleep time predicted clinical pain response at 6-month follow-up.[44] Subjects who reported having at least 6 h of sleep per night were more likely to have improved pain conditions. Similar results were found with actigraphy data, with sleep time





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being the strongest predictor of pain severity. A study by Buchanan et al[45] using actigraphy to objectively predict sleep duration, however, found that sleep efficiency (the ratio of the estimated total sleep time to estimated time in bed) did not predict next-day pain in women with irritable bowel syndrome, although it did predict symptoms of anxiety and fatigue.

Evidence related to sleep deprivation as a risk factor for the development of pain conditions is still weak. Because of the trend of reduced sleep time, further microlongitudinal and longitudinal studies are needed to explore this temporal association.

### Insomnia

According to the International Classification of Sleep Disorders[35] insomnia can be classified as a primary sleep disorder or a symptom secondary to a cooccurring medical condition. It is defined as a frequent and persistent difficulty initiating sleep, waking up during the night with difficulty returning to sleep, or waking up too early, despite having adequate time and circumstances for sleep. Insomnia results in general sleep dissatisfaction and daytime impairment. Common consequences reported by insomnia subjects include fatigue, difficulties in concentrating, reduced attention and memory functioning, reduced motivation, irritability, and daytime sleepiness.[46,47] Furthermore, several studies indicated that insomnia symptoms increase the risk for psychiatric disorders and cardiovascular and inflammatory diseases.[48-51] In this review, we explore studies that investigate insomnia as a risk factor for the development of chronic painful conditions.

A population-based longitudinal study conducted by Gupta et al[52] demonstrated that complaints of insomnia predicted 93% of the risk of new cases of chronic widespread pain in pain-free subjects. Likewise, Jones et al[53] investigated health variables that could be associated with the development of musculoskeletal pain. The authors found that subjects reporting few sleep problems at baseline were > 3 times as likely to not report pain in the following 4 years as those who did. Good sleep, indicated by the absence of insomnia symptoms, was a predictor of musculoskeletal pain-free status.[53] In healthy working adults, insomnia symptoms were found to be a risk factor in the development of back pain. Insomnia complaints increased by 1.4-fold the chance of developing back pain, with no reverse association.[54] Recently, more population-based longitudinal studies also reported that insomnia symptoms might trigger the development of pain conditions.[55-57] This association was further strengthened by data using different experimental designs. Boardman et al[58] showed that the absence of insomnia complaints at baseline in headache suffers was a predictive factor of recovery from headache at the 1-year follow up. In a day-to-day analysis, data from patients with chronic pain and insomnia demonstrated that less pain on the following day was predicted by perceived better sleep quality the previous night.[24] Of interest, sleep efficiency quantified by actigraphy was positively correlated with pain reports, indicating that different sleep parameters might have distinct associations with pain. The treatment of insomnia symptoms in subjects with osteoarthritis and insomnia resulted in improvements in pain severity, osteoarthritis symptoms, and fatigue.[59]

Despite the large amount of evidence showing the unidirectionality of insomnia as a risk factor for the development of chronic pain conditions, some longitudinal data did show a bidirectional association. Patients admitted to the hospital with burn injuries had higher pain severity during long-term follow-up when insomnia symptoms were reported at baseline. In the same way, higher pain reports at baseline increased the rates of new reports of insomnia symptoms.[17] In patients with chronic musculoskeletal pain, complaints of both sleep problems (insomnia symptoms) and pain severity at baseline predicted pain and sleep disturbances at 12-month follow-up.[60] Jansson-Fröjmark and Boersma[61] found that reported pain increased the risk for future insomnia symptoms; however, insomnia was associated with persistence of pain but not incidence of pain in a 1-year follow-up.

Evidence in relation to the association between insomnia and pain seems to suggest that insomnia predisposes individuals to chronic pain or to the worsening of painful conditions. It is important to highlight that not all longitudinal data evaluated both sleep and pain at every study time point. Despite this, diagnosis and assessment of insomnia symptoms should be included in clinical practice and research when investigating chronic pain outcomes.

### OSA

OSA is characterized by five or more events per hour of a partial (hypopnea) or complete obstruction (apnea) of the upper airways and awakenings related to respiratory effort during sleep, with intermittent hypoxemia and associated arousals.[35] The symptomatology includes the





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reporting of nonrestorative sleep, poor sleep quality, snoring, gagging or choking sensation during sleep, awakenings caused by cessation of breathing, and daytime repercussions such as excessive daytime sleepiness and fatigue. The main associated risk factors are older age, being a man, increased BMI and neck circumference, and craniofacial alterations. A study in the city of São Paulo, Brazil, revealed an OSA prevalence of 32.9%, with a higher frequency in men (40.6%) than in women (26.1%).[4] This high prevalence was also reported by other studies using subjective and objective measures.[62,63]

Pain and OSA are commonly associated, mainly in relation to morning headache pain, with a prevalence ranging from 10% to 60%[64,65]; however, morning headaches are a nonspecific symptom of several sleep disorders, and there is no strong evidence associating OSA to the development of headaches.[66] Others chronic pain conditions have been associated with OSA in studies investigating the prevalence of sleep disturbance in patients with chronic pain[67,68] and vice versa.[69]

Previous review articles explored the relationship between pain conditions and sleep-disordered breathing.[66-68] Almoznino et al[66] described the associations of chronic craniofacial pain as a symptom of OSA. Psoriasis, an immune-mediated chronic inflammatory disease that manifests as dermatologic lesions and psoriatic arthritis, is often painful. Authors of a systematic review found that patients with psoriasis presented a higher prevalence of OSA (36%-81.8%), demonstrating a bidirectional relationship, because the heightened pro-inflammatory condition of OSA could exacerbate the psoriasis.[68] OSA shares symptoms, such as morning fatigue and unrefreshing sleep, with fibromyalgia, rheumatic diseases, and some other chronic conditions. In a sample of patients with mild to severe OSA, Aytekin et al[69] reported 55.4% prevalence of chronic widespread pain; with women with OSA having higher pain levels, higher disability levels, and a lower quality of life. Köseoğlu et al[70] showed that in patients with fibromyalgia, OSA was diagnosed in 50% of subjects, and that oxygen saturation during sleep was negatively correlated with subjective symptoms of fibromyalgia. In fact, chronic pain seems to be associated with changes in respiratory parameters. Nocturnal desaturation was associated with self-reported pain during sleep and pain upon waking in patients with OSA.[71] Compared with healthy control patients, women with myofascial pain showed more arousals associated with all types of respiratory events and higher respiratory effort related arousals.[72] Myofascial temporomandibular joint disorder is a condition with an elevated frequency of co-occurrence with OSA (28.4%).[73] The presence of symptomatic OSA was investigated in > 4,000 subjects with chronic spinal pain[73] and, contrary to previous reported data,[68,69,72] authors found a small prevalence of 13%, which was associated with the common risk factors for OSA, including higher BMI, being men, and older age. Contrary to this finding, Li et al[74] reported no association between OSA and musculoskeletal pain. Reports of joint pain were associated with self-reported sleep quality.

Patients who presented both chronic pain and OSA seem to have worse clinical symptoms. Subjects with chronic musculoskeletal pain and OSA had shorter sleep duration, higher REM sleep latency, and lower sleep efficiency compared with patients with pain but not OSA, demonstrating worse sleep quality and quantity.[75] Recently, Silva et al[77] showed that subjects with knee osteoarthritis and OSA had a worse prognosis for pain and physical function compared with patients without OSA. Experimental data also demonstrated the effect of OSA on pain response. In women, it was shown that pain sensitivity differs between patients with and without OSA, with those with OSA presenting more tender points and higher pain sensitivity.[78] Khalid et al[79] demonstrated that improvements in OSA symptoms after CPAP treatment were associated with pain sensitivity reduction in pain-free subjects. CPAP treatment and better pain outcomes were also reported in patients with chronic pain.[80]

Only one longitudinal study investigating sleep and pain in patients with OSA was identified. Chung et al[81] evaluated the incidence of new cases of interstitial cystitis, a chronic condition that causes mild to severe bladder and pelvic pain, in OSA and non-OSA subjects. The authors found a higher incidence of the disease in patients with OSA in a 3-year period. Despite data related to headache as a clinical symptom of OSA,[65] there is no strong evidence of OSA as a predictive factor for chronic pain development.

Collectively, these data present evidence of an association between OSA and pain; however, given the limited number of studies and variations in the sample characteristics, small sample size, study designs, and instruments used to evaluate both sleep and pain, it is not possible to define the directionality of this association. Studies investigating the temporal associations of OSA and pain are scarce. Because of the





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negative health consequences of OSA and chronic pain, it is imperative that clinicians and researchers investigate further the relationship between the two conditions.

### Narcolepsy

Narcolepsy is a disorder primarily characterized by excessive daytime sleepiness and abnormal manifestations of REM sleep, with or without cataplexy episodes.[35] Excessive daytime sleepiness is the main symptom and occurs regardless of patients waking up from a night's sleep feeling refreshed. Sleepiness impairs the ability of the patient to be properly involved in educational, social, and occupational situations. Other REM sleep phenomena, such as sleep paralysis and hypnagogic hallucinations, and the occurrence of other sleep disturbances, including sleep talking, periodic limb movements, sleep-disordered breathing, and REM sleep behavior disorder have also been associated with narcolepsy.[82,83] Narcolepsy comorbidities include psychiatric symptoms, cardiometabolic diseases, and chronic pain conditions.[85-87]

Few longitudinal studies have investigated the temporal associations between narcolepsy and pain. Jennum et al[85] evaluated the presence of comorbidities before and after patients receiving a narcolepsy diagnosis using a clinical database. Musculoskeletal conditions, such as low back pain, arthrosis, and arthritis, were conditions associated with emergence after diagnosis was made, indicating that narcolepsy increased the incidence of musculoskeletal pain. Chronic low back pain has increased odds to occur both at diagnosis and at the end of a 9-year observation period.[87] Dahmen et al[88] reported a prevalence of almost 40% of migraine sufferers in a narcoleptic sample, and temporal analysis indicated that the onset of migraine symptoms occurred after the narcolepsy symptoms. In accordance with these results, observational data demonstrated an elevated prevalence of pain conditions in patients with narcolepsy. Dauvilliers et al[89] showed that in a sample of narcolepsy with cataplexy subjects, > 30% reported experiencing pain at least monthly. Migraine and tension-type headaches were more prevalent in patients with narcolepsy than in healthy control patients.[90] Moreover, complaints of headaches were associated with more frequently experiencing excessive daytime sleepiness in narcoleptic subjects. Despite these results, the evidence is still inconclusive as to whether pain conditions are more associated as a cause or consequence of narcolepsy.

### Sleep Bruxism

Sleep bruxism is defined as a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible during sleep.[35] Population prevalence ranges from 5% to 12%, varying according to the diagnostic method.[91-93] Pain is a clinical symptom of bruxism and a criterion used for diagnosis. Jaw muscle pain, tenderness in the masseter and temporalis muscle regions, morning headaches, and fatigue are commonly reported consequences. A populational survey conducted by Khoury et al[93] found that 33% of subjects with sleep bruxism reported pain complaints; this frequency was significantly higher than that in subjects with no sleep bruxism. In a recent review of chronic craniofacial pain, Almoznino et al[66] found that headache is a frequent symptom in sleep bruxism, and the prevalence of orofacial pain ranges from 66% to 84% of patients. These data add evidence to pain being associated with sleep bruxism but not in all subjects. Despite the clinical signs of pain, sleep bruxism as a contributing factor in the etiology of pain disorders is still controversial.[94-96]

## Mechanisms Involved in Sleep and Pain Interaction

The question of which mechanisms underlie the interactions between sleep and pain have not yet been fully answered. The need to understand the temporal association of sleep disturbances and chronic pain involve uncovering the directionality of the relationship and how one factor predicts another. In a previous review, Finan et al[19] explored the main central pathways related to the modulation of sleep and pain. The authors highlighted changes in the monoaminergic and opioidergic pathways in chronic pain conditions that could explain impairments in sleep and wake states. These systems are also involved in the central dysregulation presented in some sleep disorders that co-occur with pain conditions. Brain image data of patients with insomnia demonstrated hyperactivity in corticolimbic areas involved in wake generation and maintenance, central regions regulated by monoaminergic pathways.[97] These areas are also involved in pathophysiology of some chronic pain conditions[98,99] that seem to be worsened in patients with insomnia. This mechanism could explain the longitudinal data demonstrating that insomnia predicts the development of pain conditions.[55-57] Recently, Afolalu et al[20] conducted an exploratory metaanalysis investigating temporal associations between sleep and





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**TABLE 1** ] Sleep and Pain Interactions in Longitudinal and Microlongitudinal Studies in Patients With Sleep Complaints and Sleep Disturbance

| Reference | Design | Sample | Analysis | Measurements | Main Result |
|---|---|---|---|---|---|
| Agmon and Armon[54] | 18 mo (baseline vs end point) | General population (both sexes, n = 3,421) | Sleep ←→ pain | Self-reported sleep, pain | Insomnia complaints → pain |
| Boardman et al[58] | 1 y (baseline vs end point) | General population (both sexes, n = 1,589) | Sleep → pain | Self-reported sleep, pain | Insomnia complaints → pain |
| Chung et al[81] | 3 y (baseline vs end point) | OSA (both sexes, n = 2,940) | Sleep → pain | Clinical diagnosis | Sleep → pain |
| Cohen et al[87] | 9 y (baseline vs end point) | Narcolepsy (both sexes, n = 68) | Sleep ←→ pain | Clinical diagnosis of pain conditions | Sleep ←→ pain |
| Edwards et al[23] | 8 d (day-to-day) | General population (both sexes, n = 971) | Sleep ←→ pain | Self-reported sleep, pain | Sleep duration ←→ pain |
| Generaal et al[55] | 6 y (baseline vs end point) | General population (both sexes, n = 1,860) | Sleep → pain | Self-reported sleep, pain | Insomnia complaints and sleep duration → pain |
| Gupta et al[52] | 15 mo (baseline vs end point) | General population (both sexes, n = 3,171) | Sleep → pain | Self-reported sleep, pain | Insomnia complaints → pain |
| Jansson-Fröjmark and Boersma[61] | 1 y (baseline vs end point) | General population (both sexes, n = 1,746) | Sleep ←→ pain | Self-reported sleep, pain | Insomnia complaints ←→ pain |
| Jennun et al[85] | 6 y (before vs baseline vs end point) | Narcolepsy (both sexes, n = 757) | Sleep ←→ pain | Clinical diagnosis of pain conditions | Sleep ←→ pain |
| Jones et al[53] | 4 y (baseline vs end point) | General population (both sexes, n = 2,260) | Sleep → pain | Self-reported sleep, pain | Insomnia complaints → pain |
| Koffel et al[60] | 1 y (baseline vs end point) | Insomnia + chronic pain (n = 250) | Sleep ←→ pain | Self-reported sleep, pain | Insomnia complaints ←→ pain |
| Lin et al[56] | 7 y (baseline vs end point) | Insomnia (both sexes, n = 1,579) | Sleep → pain | Clinical diagnosis of insomnia and chronic pain | Insomnia → pain |
| Salwen et al[44] | 6 mo (baseline vs end point) | Insomnia + osteoarthritis (both sexes, n = 74) | Sleep → pain | Actigraphy, sleep diary, self-reported pain | Sleep duration → pain |
| Smith et al[17] | 2 y (baseline vs end point) | Insomnia + burn injuries (both sexes, n = 299) | Sleep ←→ pain | Self-reported sleep, pain | Insomnia complaints ←→ pain |
| Tang et al[24] | 7 d (day-to-day) | Insomnia + chronic pain (both sexes, n = 119) | Sleep ←→ pain | Self-reported sleep quality, sleep efficiency, pain Sleep efficiency (actigraphy) | Sleep quality → pain |
| Uhlig et al[57] | 11 y (baseline vs end point) | General population (both sexes, n = 13,429) | Sleep → pain | Self-reported sleep, pain | Insomnia complaints → pain |
| Vitiello et al[59] | 18 mo (baseline vs 9, 18 mo) | Insomnia + osteoarthritis (both sexes, n = 367) | Sleep → pain | Self-reported sleep, pain | Sleep → pain |

→ = unidirectional: one predicts another; ←→ = bidirectional: both are related.



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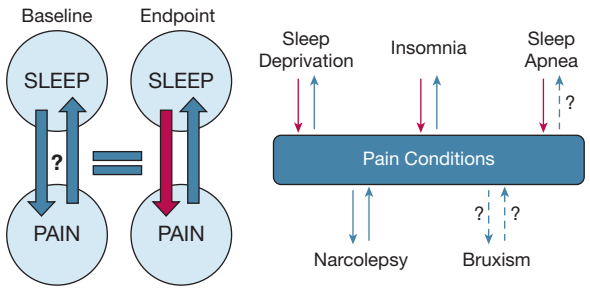


Figure 1 – *Temporal associations between sleep and pain in micro-longitudinal and longitudinal studies. Red arrows indicate more evidence. Blue arrows indicate less evidence. Blue dotted arrow indicates absence of studies.*

pain demonstrating that sleep problems are prospectively associated with pain outcomes. The authors analyzed possible mechanisms related to the development of pain in patients with sleep disturbances. They found that the inflammatory profile induced by sleep disturbance could mediate pain responses. Despite the exploratory analysis, activation of immune system is a common condition in both sleep and pain responses.

The advances in the comprehension of the mechanisms of sleep and pain interaction should be strengthened by preclinical models. Experimental designs exploring the development of painful states in animal models of sleep disturbances are crucial to elucidate this relationship. Moreover, pharmacological experiments can improve not only the knowledge about specific treatments but also clarify the mechanisms involved in the pathophysiology of sleep disturbances and chronic pain.

## Future Agenda

- Investigate the presence of chronic pain conditions as comorbidities of sleep disturbances.
- Investigate pain symptoms in patients with sleep disturbances in experimental and clinical settings using gold-standard methodological tools.
- Conduct longitudinal studies to explore temporal associations between sleep disturbances and chronic pain, exploring the analysis of sleep disturbances as a risk factor for the development of chronic pain conditions.
- Understand the mechanisms associated with pain development in patients with sleep problems.

## Conclusions

The elevated prevalence of sleep disturbances in general society highlights the need to investigate negative health outcomes caused by sleep problems. Extensive literature has demonstrated that pain conditions are commonly associated with sleep disturbances. Our review demonstrated that, compared with observational studies, few longitudinal studies have analyzed the temporal associations between sleep and pain. Data regarding sleep disturbances as a risk factor to predict painful conditions mainly deal with insomnia complaints. The evidence seems to suggest that insomnia symptoms predispose individuals to chronic pain or to the worsening of painful conditions. A limited number of studies have explored chronic pain in relation to short sleep duration, sleep apnea, narcolepsy, and sleep bruxism. Despite this, microlongitudinal and longitudinal analyses suggest a consist unidirectionality in which sleep disturbances are linked to next-day pain; however, more longitudinal data are needed to strengthen the evidence for sleep disturbances being a possible pathogenic condition of chronic pain. Because of the negative effect of pain and sleep problems on quality of life, investigating how the two conditions are associated is key to better treatments and prevention strategies and improved health outcomes.

## Acknowledgments

**Author contributions:** All authors participated in drafting the manuscript or revising it critically for important intellectual content and approved the final version to be published.

**Financial/nonfinancial disclosures:** The authors have reported to *CHEST* the following: M. L. A. and S. T. are recipients of fellowships from CNPq.

**Role of sponsors:** The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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