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ORIGINAL RESEARCH

Poor Sleep Quality and Mood Disorders: Risk Factors of Increasing Chronic Pain in Patients with Insomnia

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Objective: The aim of this study was to examine the prevalence of chronic pain and its risk factors in patients with insomnia.

Methods: We consecutively enrolled patients with chronic insomnia from Sleep Medicine Center in West China Hospital between May 2019 and February 2021. All patients were divided into two groups according to comorbid chronic pain or not. We used subjective questionnaires to assess sleep, daytime sleepiness, mood symptoms, and the characteristics and intensity of pain. Objective sleep quality was measured by polysomnography. The logistic regression analyses were used to identify the risk factors of chronic pain.

Results: Among 358 patients with chronic insomnia, 48.9% had chronic pain. These patients had significantly higher scores in Hamilton Rating Scale for Anxiety (HAMA), Hamilton Rating Scale for Depression (HAMD), Visual Analog Scale (VAS) and Short-Form McGill Pain Questionnaire (SF-MPQ) (all $PS < 0.001$) compared to those without chronic pain. After controlling for the confounding factors, higher HAMA scores adjusted odds ratio = 1.083, 95% CI 1.033–1.135, $P = 0.001$), higher HAMD scores (adjusted odds ratio = 1.109, 95% CI 1.058–1.163, $P < 0.001$) and shorter N3 sleep duration (adjusted odds ratio = 0.969, 95% CI 0.940–0.999, $P = 0.041$) were significantly associated with an increased risk of chronic pain. Multiple linear regression analyses showed that higher scores in Pittsburgh Sleep Quality Index (PSQI) ($\beta = 0.108$, 95% CI 0.026–0.191, $P = 0.010$), HAMA ($\beta = 0.085$, 95% CI 0.043–0.127, $P < 0.001$) and HAMD ($\beta = 0.141$, 95% CI 0.093–0.188, $P < 0.001$) were positively related to pain intensity.

Conclusion: Nearly half of patients with insomnia are comorbid with chronic pain. Poor subjective and objective sleep quality, as well as the anxious and depressive symptoms, are risk factors of chronic pain.

Plain Language Summary:

This study aimed to understand how common chronic pain is among people with insomnia and what factors might increase the risk of chronic pain in these patients. Insomnia is a sleep disorder where people have trouble falling or staying asleep, and it often occurs alongside other health issues like chronic pain, anxiety, and depression. The researchers studied 358 patients with chronic insomnia from the Sleep Medicine Center at West China Hospital between May 2019 and February 2021. They divided the patients into two groups: those with chronic pain and those without. They used questionnaires to assess sleep quality, mood (anxiety and depression), and pain levels. They also used a special test called polysomnography (PSG) to measure objective sleep quality, which tracks brain activity during sleep. This study found that nearly half (48.9%) of the patients with insomnia also had chronic pain. Patients with chronic pain had higher levels of anxiety and depression, as well as more severe pain. Poor sleep quality, especially shorter deep sleep (known as N3 sleep), was linked to a higher risk of chronic pain. Besides, anxiety and depression were also strongly associated with increased pain intensity. The study suggests that poor sleep quality, especially reduced deep sleep, along with anxiety and depression, may increase the risk of chronic pain in people with insomnia. This means that treating sleep problems and mood disorders could be important for managing chronic pain in these patients. This research show the key point that chronic pain is a major health issue that

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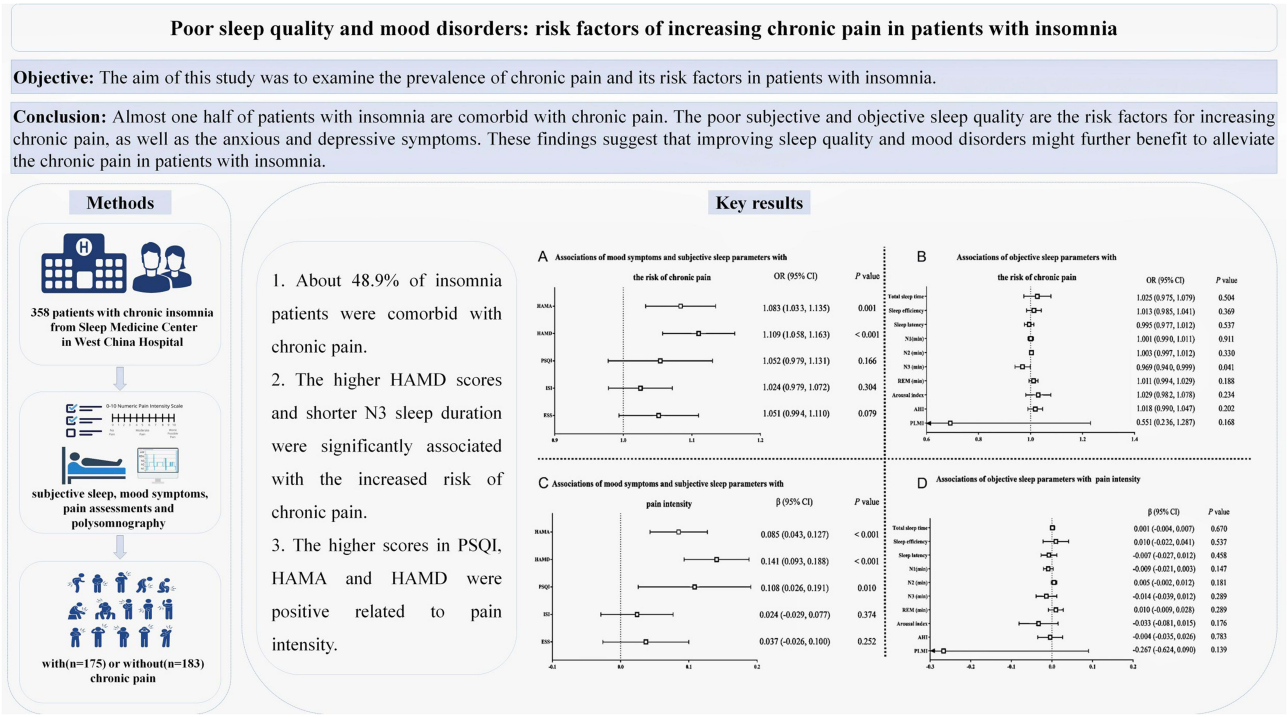
Graphical Abstract



can significantly affect a person's quality of life. By understanding the link between insomnia, mood disorders, and chronic pain, doctors can develop better treatment plans that address both sleep and mental health, potentially improving outcomes for patients.

Keywords: insomnia, chronic pain, mood disorders, sleep quality

Introduction

Insomnia is the most common sleep disorder, affecting around one-third of adults globally.[1] Epidemiological studies reported approximately 6–10% of people experienced chronic insomnia.[2] A meta-analysis showed that the pooled prevalence of insomnia was 15% in the general population of China.[3] Sleep disturbances in patients with insomnia can contribute to or exacerbate both physical and psychological health problems, including pain.[4–6] Notably, during the COVID-19 pandemic, about 52% of COVID-19 patients experienced sleep disturbances due to core symptoms, such as cough, fever, inflammation, and shortness of breath.[7] The increased risk of sleep disturbances in COVID-19 patients was likely due to body pain and medication side effects.[8,9]

Research has consistently shown a strong link between insomnia and chronic pain. Previous studies reported that the prevalence of chronic pain was greater than 50% among individuals with insomnia, which was higher than that of in the general adult population (11–31%).[10] Furthermore, a 5-year community-based follow-up study found that individuals with chronic insomnia who initially had no pain were two to three times more likely to develop new-onset chronic pain conditions.[11] A growing body of longitudinal studies further supported that insomnia may exacerbate existing pain and predict the onset of new pain.[12,13] Similarly, experimental animal studies have shown that REM sleep deprivation could decrease nociceptive thresholds and exacerbate acute and chronic pain.[14]

Around 75% of the patients with chronic pain had self-reported insomnia.[15] And the longitudinal evidence had demonstrated a bidirectional relationship between sleep and pain.[16] However, the underlying pathophysiological

mechanisms linking insomnia and pain had not yet been fully elucidated. Recently, several studies pinpointed sleep disturbances were a stronger and more reliable predictor of pain than pain was of sleep disturbances.[17–20] Nowadays, a series of studies have focused on the potential mechanisms of pain caused by sleep disturbances. The main findings indicated that sleep disturbances could contribute to the high pain sensitivity by enhancing endogenous dopamine tone, dysregulating endogenous opioid systems, and increasing pro-inflammatory cytokines secretion.[21,22] Additionally, psychological factors such as negative mood, pain-related emotions and cognitions (eg, pain helplessness and pain attention) may also deteriorate the pain and insomnia symptoms through the activation of the hypothalamic-pituitary-adrenal (HPA) axis.[23] Taken together, these findings suggest that multiple factors, ranging from endogenous pain modulation and inflammatory processes to mood disturbances and cognitive-emotional regulation, may play a role in the complex interplay between sleep and pain.

In clinical practice, most studies investigating the association between sleep and pain have relied on subjective assessment tools,[24–26] while objective measures remain underexplored. A polysomnography (PSG) study found that the shorter total sleep duration was associated with an increased risk of moderate to severe pain.[27] Subsequently, other findings showed a decreased slow wave sleep across various types of chronic pain.[28] Notably, emerging evidence suggested that prolonging sleep time would decrease daytime pain sensitivity,[29] whereas deprivation of slow wave sleep has been shown to markedly increase pain intensity.[30]

Therefore, chronic insomnia and pain are interacted and influenced mutually. Most existing studies have focused on the impact of subjective sleep on the risk of pain, but lack relevant objective sleep assessments. Meanwhile, the potential risk factors of pain were not yet fully elucidated in patients with insomnia. Thus, the current study was conducted to delineate the risk factors associated with pain in a sample of patients with chronic insomnia.

Methods

Participants

In this study, we enrolled 358 consecutive patients with a diagnosis of chronic insomnia from the Sleep Medicine Center of West China Hospital of Sichuan University from May 2019 to February 2021. Chronic insomnia was diagnosed by a professional sleep specialist, primarily following the criteria in the International Classification of Sleep Disorders, third edition (ICSD-3).[31] The inclusion criteria of patients with chronic insomnia were (1) aged 18–80 years, and (2) did not intake sedative-hypnotic drug, over-the-counter non-steroidal anti-inflammatory drugs, opioid medications, anxiolytics, and selective serotonin reuptake inhibitors for two consecutive weeks prior to the baseline assessment. Participants were excluded if they (1) had hyperthyroidism, major depressive disorders, bipolar disorder, schizophrenia, or dementia, (2) had a disease that can be the underlying reason of chronic pain, such as rheumatoid arthritis, osteoarthritis and cancer, etc. and (3) could not complete questionnaires and clinical examinations. The study was approved by the ethics committee of West China Hospital (Review-No.655) and all patients provided written informed consent.

Measures

Demography and Clinical Information

Demographic characteristics including age, sex, body mass index (BMI), education level, and lifestyle habits (eg, tea and alcohol drinking, and smoking) were collected. Disease duration and comorbid diseases (eg, hypertension, diabetes mellitus, and heart diseases) were interviewed by a senior physician. The history of smoking, tea and alcohol drinking were recorded if the frequency was at least three times per week, respectively.

Subjective Sleep Measures

The Insomnia Severity Index (ISI) (Chinese version) was used to evaluate the symptoms of insomnia in the past month. The total score of ISI ranges from 0 to 28, and the higher score indicates more insomnia symptom burden.[32] A score greater than 14 in ISI indicates clinical insomnia in this study. The Pittsburgh Sleep Quality Index (PSQI) (Chinese version) was used to assess subjective sleep quality.[33] The total score ranges from 0 to 21, and PSQI > 5 indicates poor sleep quality. Subjective excessive daytime sleepiness (EDS) was measured by the Chinese version of Epworth Sleepiness Scale (ESS). The total score of ESS ranges from 0 to 24, and ESS >10 is identified as EDS.[34] In addition,

the tools of ISI, PSQI, and ESS were used exclusively for patient clinical assessment in this study, and all used Chinese-version of the scales were used with the appropriate copyright license.

Polysomnography (PSG)

In our study, the participants entered the lab in the evening, typically between 7:00 PM and 9:00 PM, to allow for electrode placement and preparation before their habitual bedtime. And lab visits were scheduled to align with each participant's habitual sleep schedule to minimize disruptions to their natural sleep patterns. All participants were performed a standardized in-laboratory overnight PSG monitoring. The skin was prepped with an abrasive gel to lower impedance, and electrodes were attached using conductive paste or adhesive. Electroencephalography (EEG) sensors were placed on the scalp according to the International 10–20 System (F3, F4, C3, C4, O1, O2, M1, M2) to monitor brain activity and determine sleep stages. Electrooculography (EOG) sensors were placed near the outer canthus of each eye (one above and one below the horizontal plane) to capture horizontal and vertical eye movements to detect eye movements. Electromyography (EMG) sensors contained two electrodes, chin EMG electrodes were placed on the mentalis and submentalis muscles and leg EMG electrodes were placed on the anterior tibialis muscles of both legs to detect movements. Electrocardiography (ECG) sensors were used by a single modified electrocardiograph Lead II on the torso with electrode placement. A nasal pressure transducer was placed under the nostrils to measure airflow. An oronasal thermal airflow sensor was placed near the nostrils and mouth to detect temperature changes during breathing. The thoracic and abdominal respiratory efforts belts were placed around the chest and abdomen to measure respiratory effort. Pulse oximetry sensor was placed on the fingertip to monitor oxygen saturation. Snoring microphone was placed on the neck to record snoring intensity and frequency. Body position sensor was typically attached to the chest belts to detect changes in body position. Professional technicians manually scored sleep stages and associated events according to the American Academy of Sleep Medicine (AASM) rule (version 2.4).[35] Apnea-hypopnea index (AHI) was calculated as the number of apnea and hypopnea events per hour during sleep. Periodic limb movements index (PLMI) was calculated as the number of periodic limb movements per hour during overnight sleep time.

Mood Symptoms and Pain Evaluation

The 17-item version of the Hamilton Rating Scale for Depression (HAMD) was used to assess the depressive symptom.[36] The 14-item version of the Hamilton Rating Scale for Anxiety (HAMA) was used to evaluate the anxiety symptom.[37] The chronic pain was defined as persistent or recurred pain for over than 3 months according to the criteria of the International Statistical Classification of Disease and Related Health Problems 11th Revision (ICD-11).[38] The Short-Form McGill Pain Questionnaire (SF-MPQ) was used to evaluate pain characteristics,[39] including the Pain Rating Index (PRI), Visual Analog Scale (VAS), and Present Intensity Index (PPI). The PRI was used to measure the pain intensity of 15 descriptors (ie, 11 on sensory and 4 on affective) within the past 24 hours. The VAS indicated the overall pain intensity within the past 24 hours. And the PPI evaluated the present pain intensity ranging from 0 (no pain) to 5 (unbearable pain). The total score of SF-MPQ included the three parts of PRI, VAS and PPI, and the higher score indicated greater pain intensity. The tools of HAMD, HAMA and SF-MPQ were used solely for patient clinical assessment in this study, and all the used Chinese-version scales have obtained the copyright license.

Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were reported as means ± standard deviation (SD) or the median with the interquartile range (IQR) square brackets, as appropriate. Categorical data were represented as frequencies or percentages. The independent sample *t* test or Mann–Whitney *U*-test was performed to calculate the group differences for continuous data. Categorical data were compared by the Chi-square test or Fisher's exact test. After adjusting for age, sex, BMI, education level, tea drinking, smoking, alcohol consumption, comorbidities, and duration of insomnia, a binary backward logistic regression model was used to determine the predictors of pain in chronic insomnia. In addition, the associations between the pain intensity (VAS) as the dependent variable and mood symptoms, subjective and objective sleep parameters as the independent variables were tested using multiple linear regression models. A P value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 358 patients with insomnia (69.6% females, mean age = 48.4 ± 10.9 years) were recruited in the study, in which 175 (48.9%) patients were comorbid with chronic pain. The most common part of chronic pain was limb (38.6%), and almost half the patients (47.2%) had more than two locations with pain. Comparisons of demographic and clinical characteristics between insomnia patients with and without chronic pain are presented in Table 1. The patients with chronic pain had higher BMI comparing to patients without chronic pain, but there were no significant differences in age, sex, education level, tea drinking, alcohol consumption, smoking, and comorbidities (hypertension, diabetes mellitus, and heart diseases) between the two groups. In addition, our results showed that patients with pain had significantly higher scores of HAMA ($P = 0.001$) and HAMD ($P < 0.001$) than that of patients without pain. Undoubtedly, there were higher scores of VAS, PRI, PPI, and SF-MPQ total score in patients with chronic pain (All $PS < 0.001$).

Subjective and Objective Sleep Variables

The comparisons of subjective and objective sleep variables between insomnia patients with and without chronic pain are shown in Table 2. We did not find significant differences in the subjective sleep measures including insomnia severity (ISI), sleep quality (PSQI), daytime sleepiness (ESS) and insomnia duration. In terms of objective sleep parameters, insomnia patients with chronic pain had a significantly shorter N3 duration ($P = 0.018$) and lower N3 percentage (P = 0.033). However, there were no significant differences in other sleep parameters, such as sleep latency, total sleep time,

Table 1 Demographic and Clinical Characteristics of Insomnia with and without Chronic Pain

	All Insomnia Patients (n = 358)	Insomnia without Chronic Pain (n = 183)	Insomnia with Chronic Pain (n = 175)	*P*
Age, years	48.4 ± 10.9	47.6 ± 10.8	49.2 ± 11.1	0.161
Female, n (%)	249 (69.6)	127 (69.4)	122 (69.7)	0.948
BMI, kg/m^2	22.7 ± 3.2	22.3 ± 3.2	23.1 ± 3.2	**0.022***
Education level				0.556
Primary school or below, n (%)	47 (13.1)	22 (12.0)	25 (14.3)	
Junior and high school, n (%)	162 (45.3)	80 (43.7)	82 (46.9)	
College or above, n (%)	149 (41.6)	81 (44.3)	68 (38.9)	
Tea drinking (≥ 3 times/week), n (%)	56 (15.6)	31 (16.9)	25 (14.3)	0.490
Alcohol consumption (≥ 3 times/week), n (%)	6 (1.7)	3 (1.60)	3 (1.7)	0.956
Smoking (≥ 3 times/week), n (%)	32 (8.9)	13 (7.1)	19 (10.9)	0.213
Comorbidities				
Hypertension, n (%)	43 (12.0)	23 (12.6)	20 (11.4)	0.740
Diabetes mellitus, n (%)	8 (2.2)	4 (2.2)	4 (2.3)	0.949
Heart diseases, n (%)	8 (2.2)	3 (1.6)	5 (2.9)	0.436
Mood symptoms				
HAMA score	14.8 ± 7.6	13.0 ± 6.2	16.8 ± 8.5	**0.001****
HAMD score	11.9 ± 5.7	10.7 ± 5.3	13.2 ± 5.9	**<0.001****
Pain measures				
VAS	1.9 ± 2.5	0.0 ± 0.2	3.8 ± 2.3	**<0.001****
PRI	2.52 ± 4.0	0.11 ± 0.6	5.03 ± 4.5	**<0.001****
PPI	0.96 ± 1.30	0.01 ± 1.0	1.95 ± 1.2	**<0.001****
SF-MPQ total score	5.3 ± 7.1	0.1 ± 0.8	10.8 ± 6.7	**<0.001****
Pain disease duration	3.9 ± 5.2	0.10 ± 0.37	4.57 ± 5.39	**<0.001****

Notes: Continuous data are given as mean ± SD or median [interquartile range] as appropriate. *$P < 0.05$; ***$P \leq 0.001$. The bold value means a statistically significant difference.

Abbreviations: BMI, body mass index; HAMA, Hamilton Rating Scale for Anxiety; HAMD, Hamilton Rating Scale for Depression; PPI, Present Pain Intensity; PRI, Pain Rating Index; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, visual analog scale.

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Table 2 Subjective and Objective Sleep Parameters of Insomnia with and without Chronic Pain

	All Insomnia Patients (n = 358)	Insomnia without Chronic Pain (n = 183)	Insomnia with Chronic Pain (n = 175)	*P*
Subjective sleep parameters				
PSQI	14.4 ± 3.6	14.2 ± 3.5	14.5 ± 3.7	0.336
PSQI > 5, n (%)	350 (97.8)	179 (97.8)	171 (97.7)	0.949
ISI	17.6 ± 5.3	17.5 ± 5.5	17.8 ± 5.2	0.713
8 ≤ ISI ≤ 14, n (%)	110 (30.7)	62 (33.9)	48 (27.4)	0.186
ISI > 14, n (%)	248 (69.3)	121 (66.1)	127 (72.6)	0.186
ESS	4 (1, 8)	4 (1, 8)	4 (2, 8)	0.161
ESS > 10, n (%)	51 (14.2)	25 (13.7)	26 (14.9)	0.746
Insomnia duration, years	7.7 ± 8.2	7.8 ± 7.9	7.7 ± 8.4	0.878
Objective sleep parameters				
Sleep latency, min	14.0 (7.0, 33.0)	14.0 (8.0, 28.8)	14.5 (5.5, 41.6)	0.635
TST, min	411.1 (371.5, 457.5)	404.5 (360.0, 443.6)	411.8 (375.1, 467.6)	0.773
Sleep efficiency, %	81.4 (71.8, 90.5)	80.3 (70.9, 87.6)	82.3 (73.6, 91.2)	0.928
Stage N1, min	79.5 (57.3, 108.0)	87.0 (67.5, 109.0)	78.8 (50.0, 105.6)	0.589
Stage N1, %	20.8 (15.3, 31.7)	21.8 (11.7, 31.7)	20.3 (13.9, 31.6)	0.772
Stage N2, min	224.6 (179.6, 262.8)	222.1 (153.5, 250.6)	234.1 (179.7, 272.7)	0.663
Stage N2, %	56.9 (48.2, 64.6)	55.7 (46.3, 62.8)	57.2 (51.1, 64.8)	0.209
Stage N3, min	1.0 (0, 11.5)	1.5 (0, 10.3)	0.0 (0, 9.0)	**0.018***
Stage N3, %	0.2 (0.0, 3.2)	0.5 (0.0, 3.5)	0.0 (0.0, 2.3)	**0.033***
Stage REM, min	72.2 ± 31.8	70.3 ± 24.6	73.7 ± 36.4	0.621
Stage REM, %	17.9 ± 6.0	17.8 ± 5.3	18.0 ± 6.5	0.876
Arousal index, /h	18.4 ± 11.2	17.5 ± 9.2	19.0 ± 12.5	0.537
AHI, /h	12.8 (4.8, 32.1)	14.8 (5.5, 32.1)	10.9 (4.4, 32.6)	0.648
PLMI, /h	0.3 (0, 1.3)	0.3 (0, 2.0)	0.3 (0, 1.1)	0.114

Notes: Continuous data are given as mean ± SD or median [interquartile range] as appropriate. *$P < 0.05$. The bold value means a statistically significant difference.

Abbreviations: AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; N1, Stage 1 of non-rapid eye movement sleep; N2, Stage 2 of non-rapid eye movement sleep; N3, Stage 3 of non-rapid eye movement sleep; PLMI, Periodic limb movement index; PSQI, Pittsburgh Sleep Quality Index; REM, Stage of rapid eye movement sleep; TST, Total sleep time.

sleep efficiency, sleep duration and percentage of stage 1, 2 and REM sleep, arousal index, AHI and PLMI between the groups.

Associations of Mood and Sleep with the Risk of Chronic Pain

The associations of mood symptoms, subjective and objective sleep parameters with the risk of chronic pain in patients with insomnia are shown in Supplementary Table 1. After adjusting for age, sex, education level, BMI, tea drinking, alcohol consumption, smoking, comorbidities and duration of insomnia, the logistic regression models showed mood disorders including anxiety symptoms (adjusted odds ratio (AOR) = 1.083, 95% CI 1.033–1.135, $P = 0.001$) and depressive symptoms (adjusted odds ratio (AOR) = 1.109, 95% CI 1.058–1.163, $P < 0.001$), and decreased N3 duration (AOR = 0.969, 95% CI 0.940–0.999, $P = 0.041$) were significantly associated with an increased risk of chronic pain in insomnia (Figure 1A and B).

Associations of Mood and Sleep with Pain Intensity

The multiple linear regression demonstrated that poor subjective sleep quality, as measured by PSQI ($\beta = 0.108$, 95% CI 0.026–0.191, $P = 0.010$), anxiety symptoms ($\beta = 0.085$, 95% CI 0.043–0.127, $P < 0.001$) and depressive symptoms ($\beta = 0.141$, 95% CI 0.093–0.188, $P < 0.001$) were positively associated with pain intensity in patients with chronic insomnia after controlling for possible confounding factors (Figure 1C and Supplementary Table 2). However, our analysis did not

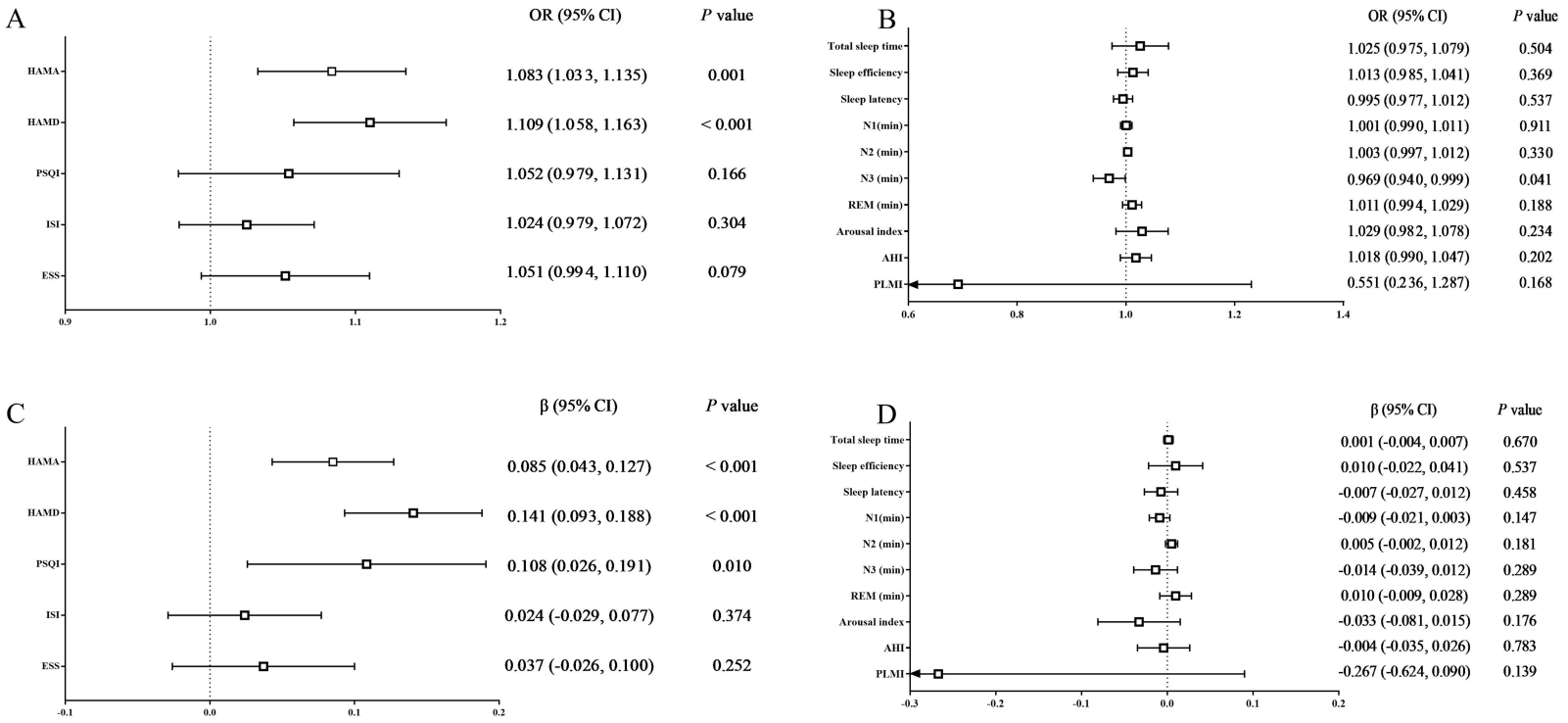

Figure 1 Associations of mood symptoms, subjective and objective sleep parameters with the risk of chronic pain and pain intensity. (**A**) Associations of mood symptoms and subjective sleep parameters with the risk of chronic pain. (**B**) Associations of objective sleep parameters with the risk of chronic pain. (**C**) Associations of mood symptoms and subjective sleep parameters with pain intensity. (**D**) Associations of objective sleep parameters with pain intensity.

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find significant association between objective sleep parameters and pain intensity (All $PS > 0.05$) (Figure 1D and Supplementary Table 2).

Discussion

Our study comprehensively examined the relationship between sleep and pain in patients with insomnia using both subjective and objective sleep assessments. We found that nearly half (48.9%) of patients with chronic insomnia experienced from chronic pain. Furthermore, the risk of chronic pain and its intensity were significantly associated with symptoms of anxiety and depression. Regression analysis on subjective and objective sleep parameters showed that reduced N3 sleep duration was a significant risk factor for chronic pain and the higher PSQI score was positively correlated with pain intensity in patients with insomnia.

The current study showed that prevalence of chronic pain in patients with insomnia was higher than that in the general population (48.9% vs 15–20%).[38] This finding aligns with previous studies reporting that 40–50% of patients with insomnia had comorbid with chronic pain.[10,40] These results suggested that patients with chronic insomnia may have a higher risk of chronic pain compared to those without insomnia. Notably, we found that shorter N3 sleep duration increased the risk of chronic pain in patients with insomnia. Previous research has demonstrated that reductions in total sleep duration were positively associated with increased pain[27] and that N3 sleep deprivation may reduce pain thresholds and increase pain sensitivity.[27,41] Several underlying mechanisms have been proposed to explain this relationship. First, reduced N3 sleep may alter pain perception via disruptions in neuroendocrine function, inflammation, and autonomic nervous system activity.[27] Second, abnormalities in central pain processing and sleep-related neural pathways may contribute to the heightened arousal and increased pain thresholds,[42] which causing habituation to painful stimulation involving antinociceptive systems. Third, shorter deep sleep duration could increase fatigue and sleepiness, leading to secondary effects on mental and sensory processing.[43] Lastly, and perhaps most importantly, N3 sleep has been shown to alleviate nociceptive hyperalgesia caused by sleep deprivation, demonstrating even exhibited stronger analgesic effects than the first-line analgesics (eg, ibuprofen and acetaminophen).[44] In addition, other studies showed that decreased REM sleep or REM deprivation could contribute to more severe pain and increase hyperalgesia in healthy populations.[14,45–47] Numerous animal studies have confirmed that REM sleep deprivation in rats may regulate the descending brainstem modulation of nociception by reducing cholinergic activity, depleting extracellular brainstem levels of serotonin (5-HIAA) and its metabolite, enhancing glutamate and other excitatory amino acids concentrations in the brain.[48–51] Unfortunately, we did not find any significant associations between REM sleep and pain in insomnia patients. Instead, we observed that reduced N3 sleep was the key sleep parameter linked to chronic pain, consistent with previous findings in individuals with primary insomnia.[46]

Previous studies have also established that poor subjective sleep quality contributed to the intensity of patients with chronic pain,[52] and longitudinal studies have also found that higher PSQI score predicts more severe pain.[53] Similarly, our study found that poorer subjective sleep quality (assessed by PSQI) was associated with increased pain intensity (VAS), but we did not find a significant association between objective sleep quality and spontaneous pain intensity. A series of prior experimental sleep deprivation studies in healthy volunteers found that separate deprivation of TST, REM sleep, and N3 sleep (stage 3 and 4 were simplified as N3) may all lead to decrease pain threshold or increased pain intensity.[14,45] A recent study from a cohort of female participants with temporomandibular joint pain demonstrated that greater relative delta power during sleep was associated with lower nocturnal and next-day pain, suggesting that slow wave sleep mediates the mechanisms of chronic pain.[54] The discrepancies between these findings and our results suggested that the different pathophysiological mechanisms existed between insomnia induced by experimental sleep deprivation and in real-life practice, where chronic sleep disturbances develop over time rather than being acutely induced in a controlled setting.

Our study found that patients with chronic insomnia and pain presented more severe anxiety and depressive symptoms than those without pain. This suggests a complex interplay between insomnia, mood disorders, and chronic pain. An epidemiological study reported that insomnia predicted the onset of depression (2.83-fold increase), anxiety (3.23-fold increase), and psychosis (1.28-fold increase) within a follow-up period of more than 12 months.[55] Subsequently, other studies have demonstrated that the anxiety status prior to pain can predict greater pain severity,

and the depressive symptoms can also intensify pain.[56–58] There is growing evidence that mood disorders may mediate the relationship between insomnia and pain.[23] A longitudinal study in the Netherlands reported insomnia and short sleep duration (≤6 hours) were independent predictors of the onset of chronic pain over a 6-year follow-up, and depressive symptoms could partially mediate this relationship.[59] It is likely that the mood disorders, chronic pain and insomnia may share the common neurobiological processes. For instance, N3 sleep has an inhibitory influence on the HPA axis and cortisol secretion. As a result, reduced N3 sleep may cause HPA hyperactivation, leading to increased production of adrenocorticotropic hormone, and high levels of corticosterone and proinflammatory cytokine.[60] Further, longitudinal studies are needed to confirm our findings and to explore the effect of treatments for insomnia and mood disorders on chronic pain.

There are several limitations in this study. This is a cross-sectional study mainly aim to explore the risk factors associated with chronic pain in patients with chronic insomnia. However, we could not establish a causal relationship between insomnia and chronic pain. In addition, this study lacked a healthy control group, which may limit the generalizability of our findings to the broader population.

In conclusion, about half of patients with chronic insomnia have chronic pain, with mood disorders and deep sleep deficiency contributing to an increased risk of the chronic pain. Poor subjective sleep quality, along with anxious and depressive symptoms may increase the propensity of pain intensity. Future therapeutic strategies for chronic pain should take into consideration the combined influence of sleep disturbances and mood disorders to improve treatment outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

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Author Contributions

Liu Liu: Writing-original draft, Methodology, Formal analysis, Data curation, Resources, Investigation. Xianchao Zhao: Writing-original draft, Methodology, Formal analysis, Data curation. Xinyan Zhang: Writing-original draft. Jiafeng Ren: Writing-original draft, Formal analysis, Data curation. Si Zeng: Writing-review & editing, Project administration, Investigation. Yuee Dai: Writing-review & editing, Methodology, Formal analysis. Wensheng Zhang: Writing-review & editing, Conceptualization. Junying Zhou: Writing-review & editing, Writing-original draft, Resources, Funding acquisition, Conceptualization.

All authors made significant contributions to the work reported, including the conception, study design, execution, acquisition of data, analysis, and interpretation. All authors took part in drafting, revising, and critically reviewing the article, gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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