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ORIGINAL RESEARCH

Subjective Sleep Disruption and Mood Disorders are Associated with the Risk of Chronic Pain in Patients with Obstructive Sleep Apnea

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Objective: This study aimed to determine the prevalence of chronic pain and its risk factors in patients with obstructive sleep apnea (OSA).

Methods: A total of 145 patients diagnosed with OSA were consecutively recruited from the Sleep Medicine Center in West China Hospital. All patients were divided into two groups including OSA with and without chronic pain. They were assessed the subjective sleep (Pittsburgh Sleep Quality Index, Insomnia Severity Index), objective sleep (polysomnography), mood symptoms (Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale), and pain characteristics (Short-Form McGill Pain Questionnaire). Demographic, clinical, subjective and objective sleep parameters were compared between OSA patients with and without chronic pain. Binary logistic regression models and linear regression models were used to examine the risk factors of chronic pain in OSA.

Results: Fifty-five (37.9%) patients with OSA were diagnosed with chronic pain. There were more severe subjective sleep disruption and symptoms of anxiety and depression in patients with chronic pain compared to those without chronic pain. After controlling for potential confounders, poor subjective sleep quality and severe insomnia and mood disorders (all $ps < 0.05$), but not objective sleep fragmentation or nocturnal hypoxemia (all $ps > 0.05$) were associated with the increased risk of pain and pain intensity, respectively.

Conclusion: More than one-third of patients with OSA had chronic pain. Subjective sleep disruption and mood disorders are the risk factors of chronic pain in OSA. Our findings suggest that subjective sleep quality should be valued highly in the relationship between OSA and pain.

Keywords: obstructive sleep apnea, subjective sleep disruption, insomnia, anxiety, depression, chronic pain

Introduction

Obstructive sleep apnea (OSA) is a sleep disorder characterized by repetitive episodes of upper airway collapse during sleep, leading to sleep fragmentation and recurrent hypoxemia.[1] It is estimated that approximately 9–38% of the general adult population suffers from OSA.[2] Patients with OSA often complain of poor sleep quality, and a substantial proportion (38%) of OSA overlaps with insomnia.[3] It has been widely recognized that OSA is associated with a constellation of negative consequences, including diminished quality of life, impaired cognitive function, and psychological disturbance (eg, depression, anxiety).[1] In addition, OSA has been found to be an independent risk factor for hypertension, cardiac disease, diabetes, and all-cause mortality.[1]

Chronic pain is one of the common medical conditions in OSA patients, with a prevalence of 51–76%, which is considerably higher than that in the general population (15–29%).[4,5] Emerging evidence suggests a bidirectional

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relationship between OSA and pain,[6] namely, OSA is associated with increased pain,[7] and the use of pain medications (eg, opioids) could increase the severity of OSA.[8,9] Specifically, several cross-sectional studies have demonstrated that OSA is associated with higher odds of many painful conditions, such as headaches,[10] fibromyalgia,[11] and chronic widespread pain.[12] Furthermore, patients with OSA have been shown to experience a decrease in pain threshold and an increase in pain sensitivity and spontaneous pain compared to healthy controls.[13–15] Similarly, prospective cohort studies have found that OSA could predict the risk of developing temporomandibular disorder and bladder pain.[16,17]

Although OSA and pain are closely related, the relevant mechanism is still unclear. Sleep fragmentation and nocturnal hypoxemia have been suggested as potential pathophysiologic mechanisms, but the findings remain inconsistent.[13,18] A series of studies have investigated that experimental fragmentation or deprivation of sleep can increase pain in healthy participants[19] via descending pain modulating pathways and enhancing neuro-inflammatory response.[20,21] However, indicators of sleep fragmentation (eg, apnoea–hypopnoea Index [AHI]) were not related to the severity of pain in a group of OSA patients.[12] Some studies have shown that chronic exposure to intermittent hypoxia is associated with increased pain,[13,18] while other studies did not verify the result.[4,22–24] In addition to these inconsistent results, most previous studies focused on the relationship between objective sleep parameters (especially AHI and nocturnal hypoxemia) and pain in OSA. Furthermore, few studies reported the relationships between mood symptoms and pain in OSA patients. In a small study of 31 female OSA patients, the higher levels of depression symptoms were associated with lower myalgic pain,[13] which seemed to contrast with the findings in the general population that depression symptoms were positively associated with pain.[25] Up to now, relatively little research has examined the effects of subjective sleep disruption and mood disorder on pain, whereas these factors have been linked to pain in the general population and non-OSA patients.[26,27]

Therefore, we conducted a cross-sectional study in patients with OSA to (1) determine the prevalence of chronic pain among patients with OSA; (2) examine the differences in demographic and clinical characteristics, mood symptoms, and subjective and objective sleep parameters between OSA patients with and without chronic pain; and (3) investigate the risk factors of chronic pain and pain intensity in patients with OSA.

Participants and Methods

Subjects

A total of 145 patients who underwent an overnight polysomnography (PSG) with a diagnosis of OSA were consecutively recruited in the study from the sleep clinic in West China Hospital of Sichuan University between May 2019 and February 2021. The diagnosis of OSA was in accordance with the International Classification of Sleep Disorders-Third Edition (ICSD-3) criteria. The inclusion criteria of OSA were (1) patients aged 18–80 years and (2) patients with newly diagnosed OSA who did not receive OSA treatment. Patients were excluded if they (1) had major depressive disorders, bipolar affective disorders, or schizophrenia, as identified by the Structured Clinical Interview for DSM-IV-TR (SCID) Research Version by the psychiatrists[28,29]; (2) had a disease that can be the underlying cause of chronic pain, such as chronic renal, hepatic, and thyroid diseases, 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 in Sichuan University. Informed consent was obtained from all patients included in this study. The study complies with the Declaration of Helsinki.

Demography and Clinical Information

Demographic and clinical characteristics of patients with OSA were collected. All patients underwent detailed clinical assessments, including demographic characteristics (eg, age, sex, education level), lifestyle habits (eg, tea and alcohol drinking history, and smoking history), and comorbid diseases (eg, hypertension, diabetes mellitus, and heart diseases), by a clinically experienced sleep medicine physician. Height and body weight were measured to calculate body mass index (BMI). Drinking tea and alcohol were defined as drinking tea and alcohol at least three times per week, respectively. Smoking history was defined as smoking cigarettes at least three times per week.

Subjective Sleep Measures

The Pittsburgh Sleep Quality Index (PSQI) (Chinese version)[30] was used to assess subjective sleep quality during the previous month. The total score ranges from 0 to 21 and a PSQI score greater than 5 indicates poor sleep quality.[31] The Insomnia Severity Index (ISI) (Chinese version)[32] was used to measure insomnia symptoms. The total score of ISI ranges from 0 to 28, and a higher score indicates more severe insomnia symptoms. An ISI of 8–14 indicates possible insomnia, and of more than 14 indicates clinical insomnia.[33] The Chinese version of the Epworth Sleepiness Scale (ESS)[34] was used to measure self-reported excessive daytime sleepiness (EDS). The total score of ESS ranges from 0 to 24, and the ESS score >10 indicates EDS.[34]

Objective Sleep Measures (Polysomnography, PSG)

All patients underwent one overnight PSG assessment using Alice 6 diagnostic equipment (Respironics Inc., Murrysville, PA, USA). PSG was performed according to the standard procedures.[35] Sleep stages and associated events were manually scored in 30s epochs according to the American Academy of Sleep Medicine (AASM) Manual (version 2.4).[36] The sleep parameters from PSG recording included total sleep time, sleep efficiency, sleep latency, percentage of time spent in each stage of sleep (N1, N2, N3, REM sleep), arousal index, AHI, minimum arterial oxygen saturation (SaO_2) and periodic limb movement index (PLMI). The AHI was calculated as the number of apnea and hypopnea events per hour of sleep. OSA was defined as AHI ≥5 events per hour.

Mood Symptoms and Pain Measures

Hamilton Depression Rating Scale (HAMD, 17 items)[37] and Hamilton Anxiety Rating Scale (HAMA, 14 items)[38] were used to assess the symptoms of depression and anxiety, respectively. Chronic pain was defined as pain that persisted or recurred for more than 3 months according to the International Statistical Classification of Disease and Related Health Problems 11th Revision (ICD-11) criteria. The Short-Form McGill Pain Questionnaire (SF-MPQ)[39] was used to measure pain characteristics. The SF-MPQ includes three parts: the Pain Rating Index (PRI), a Visual Analog Scale (VAS), and the Present Pain Intensity (PPI) index. The PRI was used to measure patients' pain intensity of 15 descriptors (11 sensory, 4 affective) within the past 24 hours. The total score of PRI ranges from 0 to 45. The VAS was used to measure the overall pain intensity within the past 24 hours using a 10 cm line ranging from "No pain" (0 cm) to "Worst pain possible" (10 cm). A present pain intensity (PPI) was used to evaluate the present pain intensity ranging from 0 (no pain) to 5 (unbearable pain). The SF-MPQ total score was obtained by summing the scores of the three parts, and the higher score indicates greater pain intensity.

Sample Size and Statistical Analysis

The sample size was selected to detect the associations of subjective and objective sleep parameters with pain. G*Power software (V.3.1.9.7) was used to calculate the sample size.[40] Based on previous studies reporting associations between sleep variables and pain in patients with OSA,[18,41] 84 patients were required to detect Pearson correlations $r \geq 0.30$, with a statistical power of 0.80 and alpha of 0.05.

Statistical analysis was performed using SPSS version 24 (IBM Corp., Armonk, NY, USA). Continuous data were reported as mean ± standard deviations (SD) or as the median with the interquartile range (IQR) square brackets, as appropriate. Categorical data were reported as frequencies (percentages). Group differences were calculated by Student' *t*-test or the Mann–Whitney *U*-test for continuous data. Differences in categorical data were analyzed using the Chi-squared test or Fisher's exact test. The effect size was calculated by Cohen's d to indicate the standardized difference between two means (ie, OSA patients with chronic pain minus OSA patients without chronic pain) and Cohen's h to indicate the standardized difference between two proportions.

Binary logistic regression models were used to evaluate the associations between the dependent variable (chronic pain: no = 0, yes = 1) and each independent variable, including mood symptoms, and subjective and objective sleep parameters. Linear regression models were used to analyze the associations of the dependent variable (pain intensity: VAS) with each independent variable, including mood symptoms, and subjective and objective sleep parameters, in patients with OSA. Unadjusted and adjusted models were estimated. The following potential covariates were selected and

included in the adjusted models based on previous reports of their associations with chronic pain and pain intensity,[42–44] including age, sex (female = 0, male = 1), BMI, and education level (below college level = 0, college level or above = 1). Results were considered statistically significant at $p < 0.05$.

Results

Demographic and Clinical Characteristics

This study included 145 patients with OSA (mean age: 49.9 ± 11.2 years), of which 93 (64.1%) were males and 52 (35.9%) were females. Fifty-five (37.9%) patients were diagnosed with chronic pain. Comparisons of demographic and clinical characteristics between patients with and without chronic pain are presented in Table 1. Compared to OSA patients without chronic pain, OSA patients with chronic pain showed a tendency for a greater proportion of females (45.5% vs 30%, $p = 0.06$) and a lower education level ($p = 0.009$). However, there were no significant differences in age, BMI, lifestyle habits, including tea, alcohol and smoking consumption, and comorbidities (hypertension, diabetes mellitus, and heart diseases) between patients with or without chronic pain. In addition, OSA patients with chronic pain showed significantly higher scores of HAMD ($p < 0.001$) and HAMA ($p = 0.018$) than those without chronic pain. As expected, there were higher scores of VAS, PRI, PPI, and SF-MPQ total score in patients with chronic pain compared to those without chronic pain (All ps < 0.05).

Subjective and Objective Sleep Variables

The comparisons of subjective and objective sleep variables between OSA patients with and without chronic pain are shown in Table 2. OSA patients with chronic pain had a significantly higher PSQI total score ($p < 0.001$) and a higher rate of patients with poor sleep quality (PSQI > 5, 78.2% vs 56.7%, $p = 0.008$) than those without chronic pain. Similarly, there was a significantly higher ISI score ($p = 0.008$) and a higher rate of clinical insomnia (ISI > 14, 45.5% vs 21.1%,

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

	All OSA Patients (N = 145)	OSA without Chronic Pain (n = 90)	OSA with Chronic Pain (n = 55)	*p*	Effect Size Cohen's d/h
Age, years	49.9 ± 11.2	49.3 ± 11.4	50.8 ± 10.8	0.460	0.13
Female, n (%)	52 (35.9)	27 (30)	25 (45.5)	0.060^	0.32
BMI, kg/m^2	24.7 [22.9, 27]	24.5 [22.9, 26.4]	24.7 [21.7, 27.3]	0.839	−0.06
Education level, college and above, n (%)	78 (53.8)	56 (62.2)	22 (40)	**0.009****	−0.45
Tea (≥3 times/week), n (%)	46 (31.7)	31 (34.4)	15 (27.3)	0.368	−0.16
Alcohol (≥3 times/week), n (%)	12 (8.3)	9 (10)	3 (5.5)	0.514	−0.04
Smoking (≥3 times/week), n (%)	31 (21.4)	17 (18.9)	14 (25.5)	0.349	0.16
Comorbidities, n (%)					
Hypertension	32 (22.1)	21 (23.6)	11 (20.4)	0.654	−0.08
Diabetes mellitus	8 (5.5)	5 (5.7)	3 (5.6)	1	−0.14
Heart diseases	9 (6.2)	5 (5.7)	4 (7.4)	0.956	0.24
Mood symptoms					
HAMD score	8 [3, 12]	5.5 [2, 10]	10 [7, 14]	**<0.001*****	3.01
HAMA score	11.5 [7.8, 18]	10 [7, 16.5]	16.5 [12.3, 21.5]	**0.018***	1.55
Pain measures					
VAS	0 [0, 3]	0 [0, 0]	4 [2, 5]	**<0.001*****	3.00
PRI	0 [0, 3]	0 [0, 0]	3 [2, 7]	**<0.001*****	2.62
PPI	0 [0, 2]	0 [0, 0]	2 [1, 3]	**<0.001*****	0.71
SF-MPQ total score	0 [0, 8]	0 [0, 0]	10 [6, 15]	**<0.001*****	0.68

Notes: Continuous data are given as mean ± SD or median [interquartile range] as appropriate. ^p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001. The bold value means a statistically significant difference.

Abbreviations: HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; OSA, Obstructive Sleep Apnea; PPI, Present Pain Intensity; PRI, Pain Rating Index; SD, Standard Deviation; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, Visual Analogue Scale.

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

	All OSA Patients (N = 145)	OSA without Chronic Pain (n = 90)	OSA with Chronic Pain (n = 55)	*p*	Effect Size Cohen's d/h
Subjective sleep parameters					
PSQI	8 [5, 14]	6 [4, 11]	12 [7, 16]	**<0.001*** **	0.65
PSQI > 5, n (%)	94 (64.8)	51 (56.7)	43 (78.2)	**0.008** **	0.47
ISI	10 [2, 16.5]	7 [2, 14]	19 [13, 22.4]	**0.008** **	0.44
8 ≤ ISI ≤ 14, n (%)	41 (28.3)	25 (27.8)	16 (29.1)	0.865	0.03
ISI > 14, n (%)	44 (30.3)	19 (21.1)	25 (45.5)	**0.002** **	0.52
ESS	6 [2, 11]	7 [2, 12]	5 [2,10]	0.587	−0.10
ESS > 10, n (%)	39 (26.9)	27 (30)	12 (21.8)	0.281	−0.19
Objective sleep parameters					
Total sleep time, min	425.8 [372, 467.3]	416.3 [357.6, 459.5]	439.6 [392.9, 482.3]	0.073^	0.23
Sleep efficiency, %	84.6 [73.6, 91.3]	81 [70.6, 89.7]	86.5 [77, 93.4]	0.106	0.21
Sleep latency, min	10.3 [4.4, 22.6]	10.5 [5.8, 23.9]	10.3 [4, 10.2]	0.522	0.07
Stage N1, %	27.8 [19.3, 35.4]	28 [20.5, 39.6]	23.8 [17.4, 35.1]	0.221	−0.30
Stage N2, %	52.4 [42.2, 60.6]	51.7 [40.1, 60.5]	53.7 [43.5, 60.7]	0.365	0.25
Stage N3, %	0.1 [0, 2.6]	0 [0, 1.7]	0.4 [0, 3.6]	0.266	−0.05
Stage REM, %	17.5 [12.7, 21.5]	16.9[12.7, 20.6]	19.1 [12.7, 22.8]	0.229	0.22
Arousal index, /h	21.4 [14.1, 30.4]	22 [15.9, 30.4]	20.8 [12.4, 30.5]	0.313	−0.19
AHI, /h	28.3 [13.8, 57.1]	32.8 [16.5, 61]	19.7 [10.6, 46.1]	0.080^	−0.26
Minimum SaO_2, %	83 [76.8, 88]	81.5 [76.0, 87]	84 [78.3, 88]	0.422	−0.08
PLMI, /h	0.4 [0.1, 1.5]	0.2 [0, 2.1]	0.5 [0.1, 1.6]	0.501	−0.13

Notes: Continuous data are given as mean ± SD or median [interquartile range] as appropriate. ^p < 0.1; **p < 0.01; ***p < 0.001. The bold value means a statistically significant difference.

Abbreviations: AHI, Apnoea–Hypopnoea Index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; OSA, Obstructive Sleep Apnea; PLMI, Periodic Limb Movement Index; PSQI, Pittsburgh Sleep Quality Index; REM, Rapid Eye Movement; SaO_2, Arterial Oxygen Saturation; SD, Standard Deviation.

$p = 0.002$) in OSA patients with chronic pain. However, there were no significant differences in the ESS score and the proportion of patients with EDS between the two groups. In addition, OSA patients with chronic pain showed a marginal significant longer total sleep time ($p = 0.073$) and a slightly nonsignificant decreased AHI ($p = 0.08$) compared with those without chronic pain. There were no significant differences in sleep latency, sleep efficiency, percentage of sleep stages (N1-3 and REM sleep), arousal index, minimum SaO_2, and PLMI between the groups.

Associations of Mood and Sleep with the Risk of Chronic Pain

Table 3 shows the associations of mood symptoms, subjective and objective sleep parameters with the risk of chronic pain in all patients with OSA. After controlling for age, sex, BMI, and education level, multivariable logistic regression models showed significant positive associations of depressive symptoms (as measured by HAMD; adjusted odds ratio (AOR), 1.11, 95% CI 1.04–1.18, $p = 0.002$), anxiety symptoms (as measured by HAMA; AOR, 1.09, 95% CI 1.01–1.17, $p = 0.033$), subjective poor sleep quality (as measured by PSQI; AOR, 1.12, 95% CI 1.04–1.20, $p = 0.003$), and insomnia symptoms (as measured by ISI; AOR, 1.05, 95% CI 1.01–1.11, $p = 0.031$) with an increased risk of chronic pain. However, no significant associations were found between ESS or objective sleep parameters (eg, AHI, arousal index, minimum SaO_2, etc.) and the risk of chronic pain (All *p*s > 0.05) in patients with OSA.

Associations of Mood and Sleep with Pain Intensity

Table 4 shows the associations of mood symptoms, and subjective and objective sleep parameters with pain intensity in all patients with OSA. In the adjusted model after controlling for age, sex, BMI, and education level, there were positive associations of depressive symptoms (*St.* $\beta = 0.37$, $p < 0.001$), anxiety symptoms (*St.* $\beta = 0.37$, $p = 0.003$), subjective poor sleep quality (*St.* $\beta = 0.29$, $p = 0.001$), and insomnia symptoms (*St.* $\beta = 0.18$, $p = 0.034$) with pain intensity in

Table 3 Associations of Mood Symptoms, Subjective and Objective Sleep Parameters with the Risk of Chronic Pain

	Unadjusted Models				Adjusted Models[§]			
	OR	**Lower 95% CI**	**Upper 95% CI**	***p***	**AOR**	**Lower 95% CI**	**Upper 95% CI**	***p***
Mood symptoms								
HAMD	1.12	1.05	1.19	**<0.001*** **	1.11	1.04	1.18	**0.002** **
HAMA	1.08	1.01	1.16	**0.032***	1.09	1.01	1.17	**0.033***
Subjective sleep parameters								
PSQI	1.13	1.06	1.21	**<0.001*** **	1.12	1.04	1.20	**0.003** **
ISI	1.06	1.01	1.10	**0.013***	1.05	1.01	1.11	**0.031***
ESS	0.98	0.92	1.04	0.553	0.99	0.93	1.06	0.773
Objective sleep parameters								
Total sleep time, min	1.00	1.00	1.01	0.248	1.00	1.00	1.01	0.175
Sleep efficiency, %	1.01	0.99	1.04	0.29	1.02	0.99	1.05	0.204
Sleep latency, min	1.00	0.99	1.02	0.702	1.00	0.98	1.01	0.700
Stage N1, %	0.98	0.95	1.01	0.129	0.98	0.95	1.01	0.183
Stage N2, %	1.02	0.99	1.05	0.212	1.02	0.99	1.05	0.284
Stage N3, %	0.99	0.90	1.08	0.811	1.00	0.91	1.10	0.937
Stage REM, %	1.03	0.97	1.10	0.273	1.03	0.97	1.10	0.353
Arousal index, /h	0.99	0.96	1.01	0.345	0.99	0.97	1.02	0.657
AHI, /h	0.99	0.97	1.01	0.18	1.00	0.98	1.01	0.566
Minimum SaO_2, %	0.99	0.96	1.03	0.673	0.97	0.93	1.01	0.193
PLMI, /h	0.89	0.57	1.38	0.596	0.88	0.54	1.41	0.583

Notes: [§]Models controlled for age, sex, BMI, and education level. *p < 0.05; **p< 0.01; ***p< 0.001. The bold value means a statistically significant association.
Abbreviations: AHI, Apnoea–Hypopnoea Index; AOR, Adjusted Odds Ratio; CI, Confidence Interval; ESS, Epworth Sleepiness Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; ISI, Insomnia Severity Index; OSA, Obstructive Sleep Apnea; PLMI, Periodic Limb Movement Index; PSQI, Pittsburgh Sleep Quality Index; REM, Rapid Eye Movement; SaO_2, Arterial Oxygen Saturation.

patients with OSA. Notably, there were similar results that no significant associations were found between ESS or objective sleep parameters and pain intensity (All ps > 0.05).

Discussion

In the current study, we reported that the prevalence of chronic pain in patients with OSA was 37.9%. In addition, this is the first study investigated that mood disorders (anxiety and depression) and subjective sleep disruption were the risk factors of chronic pain in OSA patients, but not the objective sleep fragmentation or nocturnal hypoxemia.

The finding of the prevalence (37.9%) of chronic pain in OSA patients is lower than those previously reported (50.9–76.2%)[4,5,45] in OSA cohorts but still higher than that in the general population (15–29%).[46,47] In line with a higher prevalence of chronic pain conditions in females than males in the general population,[48] our study showed a trend of a higher proportion of females in OSA patients with chronic pain (45.5% vs 30%, $p = 0.06$). Several possible factors have been suggested as the contributors to the gender difference in pain, such as gonadal hormones and cognitive and affective states. However, the detailed mechanism underlying the gender difference in pain is unclear, and additional studies are needed to provide further insight. In addition, we also found that OSA patients had a lower education level in the chronic pain group, which is rather similar to the results of previous studies in the general population.[44]

In line with a recent meta-analysis reporting a high proportion of insomnia symptoms in patients with OSA,[3] our study found more than one-third of OSA patients have comorbid clinical insomnia. Furthermore, we found that OSA patients with chronic pain had more insomnia symptoms and worse sleep quality than those without chronic pain, and these poor subjective sleep disruptions were significantly associated with an increased risk of chronic pain and pain intensity in patients with OSA. A previous study reported that up to 100% of the patients with comorbid OSA and

Table 4 Associations of Mood Symptoms, Subjective and Objective Sleep Parameters with Pain Intensity[†]

	Unadjusted Models					Adjusted Models[§]				
	Non-Standardized Coefficients		Standardized Coefficients			Non-Standardized Coefficients		Standardized Coefficients		
	B	Standard Error	Beta	t	*p*	B	Standard Error	Beta	t	*p*
Mood symptoms										
HAMD	0.14	0.03	0.36	4.60	**<0.001*****	0.15	0.03	0.37	4.36	**<0.001*****
HAMA	0.08	0.03	0.38	3.00	**0.004****	0.08	0.03	0.37	3.11	**0.003****
Subjective sleep parameters										
PSQI	0.14	0.04	0.29	3.64	**<0.001*****	0.14	0.04	0.29	3.39	**0.001****
ISI	0.05	0.03	0.17	2.02	**0.045***	0.06	0.03	0.18	2.14	**0.034***
ESS	−0.03	0.04	−0.07	−0.78	0.435	−0.02	0.04	−0.04	−0.39	0.696
Objective sleep parameters										
Total sleep time, min	0.00	0.00	0.13	1.33	0.186	0.01	0.00	0.14	1.49	0.140
Sleep efficiency, %	0.02	0.02	0.11	1.10	0.275	0.02	0.02	0.12	1.27	0.207
Sleep latency, min	0.00	0.01	0.00	0.01	0.993	−0.01	0.01	−0.07	−0.71	0.482
Stage N1, %	−0.02	0.02	−0.14	−1.51	0.134	−0.02	0.02	−0.13	−1.31	0.194
Stage N2, %	0.02	0.02	0.09	0.92	0.361	0.02	0.02	0.11	1.1	0.272
Stage N3, %	0.03	0.06	0.04	0.46	0.647	0.06	0.06	0.1	0.98	0.331
Stage REM, %	0.05	0.04	0.12	1.30	0.197	0.05	0.04	0.12	1.18	0.240
Arousal index, /h	−0.02	0.02	−0.14	−1.47	0.143	−0.02	0.02	−0.12	−1.18	0.240
AHI, /h	−0.02	0.01	−0.18	−1.85	0.068^	−0.01	0.01	−0.13	−1.23	0.220
Minimum SaO_2, %	0.01	0.02	0.04	0.46	0.650	−0.01	0.03	−0.02	−0.2	0.844
PLMI, /h	−0.17	0.30	−0.07	−0.58	0.566	−0.15	0.28	−0.06	−0.54	0.589

Notes: [†]Pain intensity was measured by a visual analog scale (VAS). [§]Models controlled for age, sex, BMI, and education level. ^$p < 0.1$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. The bold value means a statistically significant association.

Abbreviations: AHI, Apnoea–Hypopnoea Index; ESS, Epworth Sleepiness Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; ISI, Insomnia Severity Index; OSA, Obstructive Sleep Apnea; PLMI, Periodic Limb Movement Index; PSQI, Pittsburgh Sleep Quality Index; REM, Rapid Eye Movement; SaO_2, Arterial Oxygen Saturation.

insomnia had chronic pain, and patients with these comorbidities showed higher pain intensity than those with either disease alone.[4] Patients with primary insomnia have been shown to have lower mechanical and thermal pain thresholds, reduced pain facilitation, and attenuated pain inhibition than healthy controls,[49] which could explain the increased risk of chronic pain and pain intensity, especially for patients with comorbid OSA and insomnia. In addition, poor subjective sleep quality (defined as PSQI > 5) has been found to be associated with pain in a study conducted in a community-dwelling sample of men.[41] In a longitudinal study of 2453 individuals, the baseline poor subjective sleep quality was observed to be associated with an increased risk of developing temporomandibular disorders over 3 years of follow-up after controlling for the confounding factors.[50] However, the underlying mechanism of the effect of subjective sleep quality on pain is still being explored. One study showed that the poor sleeper (defined as PSQI > 5) had increased pain catastrophizing, which is a known psychosocial contributor to more intense pain and elevated pain-related emotional distress when compared to the good sleeper.[51] On the other hand, poor sleep quality has been widely considered to adversely impact individuals' physical and mental health even the overall quality of life,[52] which may influence the perceived intensity of pain. Nevertheless, our study did not find the significant associations between objective sleep quality (eg, total sleep time, sleep efficiency, stage N3) and pain. The inconsistent finding could be partly explained by the discrepancy between the evaluations of subjective and objective sleep quality. In general, PSQI estimates subjective sleep quality by individuals' perception of sleep, whereas PSG measures sleep quality based on multiple physiologic signals. As the sleep quality assessed by PSQI and pain are subjective experiences, which are easily affected by various

emotional factors. Thus, it is possible that the subjective sleep reports are more likely to influence an individual's perception of pain when compared to the objective sleep.

Mood disorder is also the prevalent comorbid condition in OSA. It has been reported that 20–35% of OSA patients have depression[53] and 14–32% have anxiety.[54] The current study found that OSA patients with chronic pain had worse mood symptoms, including depression and anxiety, compared to patients without chronic pain, and mood disorders were demonstrated as the risk factors of chronic pain and increased pain intensity. The findings were expected given the known links between depression, anxiety, and pain in non-OSA populations.[27] Pain is a complex experience encompassing both sensory and emotional dimensions. At the cognitive and behavioral level, depressive and anxiety symptoms can increase pain sensitivity by increasing social isolation and attention towards threats.[55] While at the pathophysiological level, depression and anxiety disorders share the same brain areas as the central modulation of the pain response, including the amygdala and hypothalamus, and the deficits in these areas may lead to a more severe experience of pain.[56] In addition, depression and anxiety induce stress and increase the production of proinflammatory cytokines, which could worsen pain.[57] More importantly, depressive and anxiety symptoms have been demonstrated as the mediator of the relationship between insomnia and pain.[58] Taken together, these findings suggested that mood disorders play the potential role underlying the association between OSA and pain.

Interestingly, we did not find significant associations between objective sleep parameters, especially those variables related to sleep fragmentation and nocturnal hypoxemia (eg, AHI, arousal index, minimum SaO_2, etc) and chronic pain. One previous study conducted in patients with sleep disorders (eg, insomnia, OSA, restless legs syndrome, etc) had the similar finding of no significant associations between AHI, minimum SaO_2 and pain.[4] A series of experimental and clinical studies showed inconsistent results regarding the associations of sleep fragmentation and nocturnal hypoxemia with pain.[13,18,19,22–24] It has been proposed that sleep fragmentation and nocturnal hypoxemia may differ in the effects on pain, with sleep fragmentation exacerbating pain,[19] whereas nocturnal hypoxemia ameliorating pain.[22–24] Instead, there is also some evidence to support the view of the pain-exacerbating effect due to hypoxemia.[13,18] Thus, these findings suggest that the risk of pain in OSA should be fully considered as the combined effect of different factors, instead of being influenced by a specific parameter.

The strength of the current study included both clinical and PSG variables to provide a comprehensive view of associations of mood symptoms, and subjective and objective sleep parameters with chronic pain. However, there were some limitations in this study. First, this study employed a cross-sectional design, limiting the possibility of making causal conclusions between sleep disruption, mood disorder, and pain. Second, although a power calculation was performed to calculate an appropriate sample size to detect the associations of subjective and objective sleep parameters with pain, the sample size remains relatively small. Future research with a larger sample of patients with OSA would help to verify our findings. Finally, this study was lack of the exploration of the potential biological mechanisms involved in the association between OSA and pain.

Conclusions

This study found that more than one-third (37.9%) of OSA patients had chronic pain. Subjective sleep disruption and mood disorders, but not objective sleep fragmentation or nocturnal hypoxemia, were identified as risk factors of pain in patients with OSA. These results highlight the important role of subjective sleep disruption and mood disorders on the increasing chronic pain in OSA, which are easily overlooked in clinical practice. Future longitudinal studies are needed to explore the long-term impact of these risk factors on pain and the effects of OSA treatment on pain.

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Disclosure

The authors report no conflicts of interest in this work.

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