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Is severe obstructive sleep apnea associated with less depressive symptoms?

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ABSTRACT

Purpose: To investigate the relationship between obstructive sleep apnea (OSA) and symptoms of depression and anxiety in OSA patients.

Methods: Symptoms were assessed using the Beck Depression Inventory (BDI) and the state part of the State-Trait Anxiety Inventory (STAI-S). BDI scores of ≥10 and STAI-S scores of ≥40 were considered to indicate the presence of depression and anxiety, respectively. Apnea severities measured using polysomnography were categorized into mild, moderate, and severe subgroups bounded by the 33rd and 66th percentiles of each polysomnographic parameter. Data were stratified by age, gender, and level of daytime sleepiness.

Results: The study population comprised 795 adult patients (86.9% men). Symptoms of depression and anxiety were present in 46.2% and 49.2% of patients, respectively. Excessive daytime sleepiness was present in 40.0% of patients and did not differ depending on the level of apnea severity. Results of crude logistic regression analyses indicated that depressive symptoms were more prevalent in patients with mild OSA than those with severe OSA, regardless of the categorizing method. These results remained statistically significant following adjustment for several confounding factors. These relationships were similar but less prominent in measures of anxiety. In the sub-analyses, such negative associations between severity of OSA and depressive symptoms tended to be observed only in patients with daytime sleepiness.

Conclusions: Symptoms of depression and anxiety were found to be more prevalent in patients with mild OSA than those with severe OSA. Excessive daytime sleepiness was shown to affect the severity of depressive symptoms.

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent cessation or reduction in airflow caused by upper airway collapse during sleep. These episodes result in episodic hypoxemia, frequent arousals, and lack of refreshing sleep [1]. In a recent cohort study, the prevalence of OSA, defined by an apnea-hypopnea index (AHI) of ≥5, was 34% in men aged 30–70 years and 17% in women aged 30–70 years, respectively [2]. A recent population-based study showed that the prevalence of moderate to severe OSA (AHI ≥ 15) was 49.7% in men and 23.4% in women [3]. OSA is considered to be an independent risk factor for the development of cardiovascular diseases and depression [4–7].

Psychological disorders such as depression and anxiety are reported to be prevalent in patients with OSA. Previous reports of depression (2.9–78%) and anxiety (2.9–70%) found marked variation between patients, which was likely to be a result of methodological issues [7]. However, a recent systematic review concluded that depression is prevalent among patients with OSA, both in the community and in sleep disorder clinics [8], indicating that depression may be an under-recognized comorbid condition.

Although the high prevalence of depression in patients with OSA [7,8] and improvements in mood following continuous positive airway pressure treatment [9] suggest a direct causative link between OSA and depression, this association has not consistently been reported in the literature. In a cross-sectional study of patients with OSA [10], the prevalence of depressive symptoms was associated positively with severity of OSA. A population-based longitudinal study [11] also showed that worsening of OSA symptoms was strongly related to elevated odds for developing depression. However, other studies examining this association found little or no evidence of a positive relationship [12–16]. In a study that focused on patients with mild OSA, the prevalence of depression and anxiety was reported to be unexpectedly high (41% and 67%, respectively) [16]. Subgroups of patients, such as those experiencing rapid eye movement–related and positional OSA, have demonstrated high levels of depression despite having a substantially milder

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degree of OSA [17–19]. Furthermore, a recent Norwegian study of 3770 patients with OSA [20] reported that increased severity of OSA was associated with less anxiety and depression. Therefore, further study is warranted to elucidate the connection between severity of OSA and symptoms of depression and anxiety. The aim of the present study was to investigate this relationship in patients with newly diagnosed OSA.

2. Materials and methods

2.1. Participants

This cross-sectional study was conducted using our database which consisted of a consecutive series of patients referred to the sleep laboratory of a single university hospital with suspicion of OSA between 2009 and 2012. The database used in this study (including 795 eligible cases) was expanded from the database (including 655 eligible cases) used in our previous study of anxiety and its relationship to quality of life, independent of depression, in patients with OSA [21]. The purpose of the previous study was to determine whether anxiety is independently related to quality of life in OSA patients. However, the purpose of the current study was to determine inverse relationships between apnea severity and symptoms of depression and anxiety in OSA patients. Inclusion and exclusion criteria, method of polysomnographic recordings, and measures for anxiety and depression were similar to our previous study. Briefly, patients were included if they were older than 18 years of age and had been diagnosed with OSA, defined as an AHI of ≥5/h, following a full-night polysomnography (PSG). Exclusion criteria included a periodic limb movement index of ≥15/h, previous diagnosis of or treatment for OSA, or presence of a major medical, psychiatric, or neurological disorder. Patients who were taking regular antidepressants or anxiolytics were excluded. However, we did not exclude patients whose Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory State Scale (STAI-S) scores indicated the presence of depression and anxiety, respectively, if they had not been previously diagnosed with a psychiatric disorder or were not taking medication to treat their condition. Written informed consent was obtained from all participants included in the study. The study was approved by the Institutional Review Board of Asan Medical Center.

2.2. Polysomnography

OSA was diagnosed and the severity of sleep apnea was assessed using the full-night standard PSG, which was performed using a digital polygraph system (RemLogic ver. 2.0, Embla Systems Inc., Broomfield, CO, USA). Respiration-related events were scored according to the 2007 scoring manual of the American Academy of Sleep Medicine [22]. An episode of sleep apnea was defined as a drop in the peak thermal sensor excursion of ≥90% of the baseline value for at least 10 s. A hypopnea event was defined as a nasal-pressure signal-excursion drop of ≥30% of the baseline value for at least 10 s, accompanied by a ≥ 4% reduction in oxygen saturation from the pre-event baseline. The AHI was defined as the average number of apnea and hypopnea episodes per hour, and the respiratory distress index (RDI) was defined as the average number of apnea, hypopnea, and respiratory effort–related arousal episodes per hour. The oxygen desaturation index (ODI) was calculated as the number of desaturation events of at least 3% that occurred per hour of sleep. Minimal oxygen saturation ($MinSaO_2$) was defined as the minimum value of oxygen saturation during sleep, as recorded by oxymetry. Symptoms of OSA, as measured by AHI, RDI, ODI, and $MinSaO_2$, were categorized into mild, moderate, or severe groupings, which were bounded by the 33rd and 66th percentiles of each parameter.

2.3. Measures

On the night of the PSG, patients were asked to complete a battery of questions. Depressive symptoms were assessed using the BDI, which consists of 21 items rated on a four-point scale (0–3), with a total possible score ranging from 0 to 63 [23]. Higher scores represent a higher level of depression. BDI scores of ≥10 were considered to indicate the presence of depression. Current symptoms of anxiety (state-anxiety level) were assessed using the STAI-S [24]. The Trait Scale of the STAI, which evaluates a generalized propensity to be anxious (trait-anxiety level), was not used in this study. Individuals rated themselves for levels of anxiety associated with each statement on the questionnaire, using a Likert scale and providing responses of between 1 (not at all) and 4 (very much so) based on how they felt at the time. The range of scores was between 20 and 80; a higher score was related to an increased level of anxiety. STAI-S scores of ≥40 were considered to indicate the presence of anxiety. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), which consists of eight items rated on a four-point scale [25]. Higher scores indicate more sleepiness during daily activities. ESS scores of ≥11 were considered to indicate the presence of excessive daytime sleepiness (EDS). The Korean versions of the BDI, STAI-S, and ESS were validated [26–28].

2.4. Statistical analysis

Data are displayed as means and standard deviations for normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and numbers and percentages for nominal variables. All statistical tests were two tailed, and $p < .05$ was considered significant. Statistical comparisons of the numeric variables were conducted using the student *t*-test or Mann-Whitney *U* test, and those of the dichotomous variables were conducted using the chi-square test.

Independent relationships between the severity of OSA and symptoms of depression and anxiety were assessed with multivariable analyses using binary logistic regression. The dependent variables were the presence or absence of depression, as defined by BDI scores of ≥10, and anxiety, as defined by STAI-S scores of ≥40. The independent variables were measures of OSA severity, as determined by the AHI, RDI, ODI, and $MinSaO_2$. Levels of severity were categorized into three groups (mild, moderate, and severe), bounded by the 33rd and 66th percentiles of each parameter. The logistic analyses were adjusted by age, sex, BMI, ESS score, history of hypertension, history of diabetes mellitus, total sleep time, and total arousal index, as measured by overnight PSG. To avoid colinearity among the independent variables, each was entered separately into a multivariable model. In addition, to determine whether the statistical relationships between the data were affected by age, sex, and daytime sleepiness, logistic regression analyses with interaction term were performed after data were stratified by age (≤ 40 years, 41–50 years, 51–64 years, and ≥ 65 years), sex, and EDS (ESS scores ≥11 and ≤ 10). In the current study, the calibration power of the logistic model was assessed using the Hosmer-Lemeshow goodness-of-fit test. A well-calibrated model was indicated by $p > .05$. All statistical analyses were performed using the Statistical Package for the Social Sciences program, version 21.0 (IBM Corporation, Armonk, NY).

3. Results

3.1. Participant characteristics

Of 934 consecutive patients who met the inclusion criteria, 126 were excluded because they had comorbid medical, psychiatric, or neurological disorders. An additional 13 patients who had previously been diagnosed with or treated for OSA were also excluded. A final series of 795 patients with OSA (691 males) and a mean age of 49.0 years (SD = 11.9 years) participated in the study (Table 1). The median AHI score was 25.0/h (interquartile range 12.5–42.0/h; Table 1). The mean BDI and STAI-S scores were 10.1 (SD = 7.2) and 39.5 (SD = 10.3), respectively. The BDI score was ≥10 in 367 patients

Table 1
Participant characteristics (n = 795).

	Total (n = 795)	No depression (n = 428)	Depression (n = 367)	No anxiety (n = 404)	Anxiety (n = 391)
Age, years, mean (SD)	49.0 (11.9)	48.0 (11.9)	50.2 (11.7)**	48.6 (11.9)	49.5 (11.9)
Male, n (%)	691 (86.9)	399 (93.2)	292 (79.6)***	368 (91.1)	323 (82.6)***
BMI, kg/m^2, mean (SD)	26.0 (3.4)	25.9 (3.3)	26.0 (3.7)	26.0 (3.4)	26.0 (3.5)
Hypertension, n (%)	266 (33.5)	131 (30.6)	135 (36.8)	120 (29.7)	146 (37.3)*
Diabetes mellitus, n (%)	84 (10.6)	32 (7.5)	52 (14.2)**	26 (6.4)	58 (14.8)***
ESS, mean (SD)	9.7 (5.0)	9.1 (4.8)	10.3 (5.1)**	9.0 (4.7)	10.4 (5.1)***
ESS ≥ 10, n (%)	373 (46.9)	177 (41.4)	196 (53.4)**	161 (39.9)	212 (54.2)***
TST, h, mean (SD)	5.8 (0.9)	5.9 (0.8)	5.7 (1.0)**	5.9 (0.9)	5.8 (0.9)*
AHI, /h, median (IQR)	25.0 (12.5, 42.0)	27.3 (13.5, 45.0)	22.5 (11.9, 39.5)*	25.9 (12.7, 43.0)	24.6 (12.1, 41.0)
RDI, /h, median (IQR)	33.7 (21.7, 48.3)	35.9 (22.8, 50.0)	32.0 (20.5, 46.7)*	35.5 (22.0, 49.2)	32.5 (21.3, 48.0)
ODI, /h, median (IQR)	21.1 (10.3, 37.2)	24.0 (11.2, 39.0)	18.4 (9.8, 34.9)*	22.6 (10.5, 38.2)	19.6 (10.2, 36.0)
MinSaO$_2$, %, median (IQR)	82.0 (76.6, 86.0)	81.4 (75.6, 86.0)	83.0 (77.6, 86.1)*	81.5 (75.7, 85.6)	83.0 (77.2, 86.5)*
BDI, mean (SD)	10.1 (7.2)	4.8 (2.8)	16.2 (5.9)***	6.1 (4.5)	14.2 (7.2)***
BDI ≥ 10, n (%)	367 (46.2)	–	–	88 (21.8)	279 (71.4)***
STAI-S, mean (SD)	39.5 (10.3)	34.5 (8.1)	45.4 (9.4)***	31.5 (5.3)	47.8 (7.1)***
STAI-S ≥ 40, n (%)	391 (49.2)	112 (26.2)	279 (76.0)***	–	–

AHI: apnea-hyponea index; BDI: Beck Depression Inventory; BMI: body mass index; ESS: Epworth Sleepiness Scale; IQR: interquartile range; MinSaO$_2$: minimum arterial oxygen saturation; ODI: oxygen desaturation index; RDI: respiratory distress index; SD: standard deviation; STAI-S: State Scale of State-Trait Anxiety Inventory; TST: total sleep time.
*p < .05, **p < .01, and ***p < .001 between patients with and without depressive symptoms or between patients with and without anxiety.

(46.2%), and the STAI-S score was ≥40 in 391 patients (49.2%).

The degree of sleep apnea, as measured by AHI, RDI, ODI, and MinSaO$_2$, was significantly milder in patients with depression than in those without depression (Table 1). In contrast, patients with anxiety showed milder OSA symptoms, as measured solely by MinSaO$_2$, than those without anxiety. The scores for AHI, RDI, and ODI were the same for patients both with and without anxiety (Table 1).

Men demonstrated more severe levels of sleep apnea than women. The proportion of patients with an AHI ≥ 30 was higher in men than in women (43.7% vs. 21.2%, p < .001). However, symptoms of depression and anxiety were more common in women than in men (72.1% vs. 42.3%, p < .001 for depressive symptoms and 65.4% vs. 46.7%, p < .001 for anxiety).

Age did not differ among the subgroups of patients with different levels of sleep apnea, as categorized by clinical AHI cutoffs. Although patients with depressive symptoms were significantly older (Table 1), the proportions of patients with depressive symptoms and anxiety did not differ among the age-based subgroups.

Daytime sleepiness did not differ among the subgroups defined by apnea severity. The proportions of patients with EDS were 39.0%, 36.6%, and 43.2% in the groups of patients with mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30), and severe (AHI ≥ 30) OSA, respectively. In contrast, daytime sleepiness was significantly associated with mood. Symptoms of depression and anxiety more common in patients with EDS than in those without EDS (53.1% vs. 41.5%, p = .001 for depressive symptoms and 57.9% vs. 43.4%, p < .001 for anxiety).

3.2. The prevalence of depressed mood depending on the severity of OSA

The levels of OSA severity, as measured by AHI, RDI, ODI, and MinSaO$_2$, were categorized into mild, moderate, and severe according to the 33rd and 66th percentiles of each parameter (Table 2). The prevalence of depressive symptoms was the highest (50.4%–53.2%) in patients with mild OSA and the lowest (40.8%–42.0%) in patients with severe OSA (Table 3). Patients with mild OSA demonstrated an approximately 10% higher occurrence of depressive symptoms than those with severe OSA (Table 3).

The results from the logistic regression analyses with depressive symptoms as the dependent variable are presented in Table 4. In the crude analyses, patients with mild cases of OSA demonstrated more depressive symptoms (odds ratios [ORs] 1.412–1.660) than patients with severe cases of OSA, regardless of the categorizing method (Table 4), indicating that the prevalence of depressive symptoms is

Table 2
The boundaries of polysomnographic parameters categorizing severity of sleep apnea according to the 33rd and 66th percentiles of each parameter.

	Mild OSA	Moderate OSA	Severe OSA
AHI, /h	5≤ and < 17	17≤ and < 35	≥35
RDI, /h	< 26	26≤ and < 42	≥42
ODI, /h	< 14	14≤ and < 30	≥30
MinSaO2, %	≥85	79≤ and < 85	< 79

AHI: apnea-hyponea index; MinSaO2: minimum arterial oxygen saturation; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; RDI: respiratory distress index.

inversely associated with OSA severity. These findings remained statistically significant after controlling for age, sex, BMI, histories of hypertension and diabetes, ESS, total sleep time, and total arousal index as covariates. Patients with moderate OSA did not show any differences in depressive symptoms compared with patients who had severe OSA (Table 4). Additionally, depressive symptoms were less common in patients with moderate OSA in comparison with patients with mild OSA when measured by AHI (OR 0.668, 95% confidence interval [CI] 0.467–0.956, p = .03) and ODI (OR 0.668, 95% CI 0.464–0.961, p = .03), but not when measured by RDI (OR 0.879, 95% CI 0.611–1.265, p = .42) and MinSaO2 (OR 0.763, 95% CI 0.531–1.096, p = .12).

3.3. The prevalence of anxiety symptoms depending on the severity of OSA

The prevalence of anxiety symptoms was the highest (50.4%–53.3%) in patients with mild OSA and lowest (44.2%–47.5%) in patients with severe OSA (Table 3). The univariate logistic regression analyses did not show any differences in symptoms of anxiety between patients with severe OSA and mild or moderate OSA when measured by AHI, RDI, and ODI (Table 4). However, when measured using MinSaO$_2$, the crude model of data from patients with mild OSA demonstrated significantly higher levels of anxiety than those with severe OSA (OR 1.443, 95% CI 1.023–2.035, p = .04). This finding remained statistically significant in the adjusted model (OR 1.626, 95% CI 1.097–2.409, p = .02) (Table 4).

3.4. Interactions between OSA severity and sex, age, or daytime sleepiness

The findings that depressive symptoms occurred more frequently in

Table 3
The prevalence of anxiety and depressive symptoms depending on OSA severity (n = 795).

	Mild OSA			Moderate OSA			Severe OSA		
	n	BDI ≥ 10, n (%)	STAI ≥40, n (%)	n	BDI ≥ 10, n (%)	STAI ≥40, n (%)	n	BDI ≥ 10, n (%)	STAI ≥40, n (%)
Defined by AHI[a]	275	146 (53.1)	145 (52.7)	262	115 (43.9)	124 (47.3)	258	106 (41.1)	122 (47.3)
Defined by RDI[a]	269	136 (50.6)	137 (50.9)	257	118 (45.9)	127 (49.4)	269	113 (42.0)	127 (47.2)
Defined by ODI[a]	269	143 (53.2)	140 (52.0)	257	115 (44.7)	133 (51.8)	266	108 (40.6)	118 (44.4)
Defined by MinSaO2[a]	259	134 (51.7)	138 (53.3)	271	125 (46.1)	136 (50.2)	265	108 (40.8)	117 (44.2)
Defined by clinical AHI cutoffs[b]	236	119 (50.4)	119 (50.4)	235	113 (48.1)	118 (50.2)	324	135 (41.7)	154 (47.5)

AHI: apnea-hyponea index; BDI: Beck Depression Inventory; $MinSaO_2$: minimum arterial oxygen saturation; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; RDI: respiratory distress index; STAI-S: State Scale of State-Trait Anxiety Inventory.
[a] Polysomnographic parameters categorizing severity of sleep apnea according to the 33rd and 66th.
[b] 5 ≤ AHI < 15 mild OSA, 15 ≤ AHI < 30 moderate OSA,and AHI ≥ 30.

patients with mild OSA than in patients with severe OSA were observed only in males (ORs 1.668–2.237), patients in the age subgroup of 41–50 years (ORs 2.631–3.968), and patients with EDS (ORs 2.058–2.925) (Table 5). EDS tended to have interaction effects with OSA severity on depressive symptoms (p = .06 and 0.07 for OSA severity defined by AHI and clinical AHI cutoffs, respectively). However, there were no interaction effects between OSA severity and sex (p values = .12–0.68) or age groups (p values = .12–0.23) on depressive symptoms (Table 5). In terms of anxiety symptoms we did not find any interaction effects between OSA severity and sex (p values = .14–0.87), age groups (p values = .14–0.63), and EDS (p values = .26–0.67).

4. Discussion

In this study, depression- and anxiety-related symptoms were present in 46.2% and 49.2% of patients with OSA, respectively. Our findings were similar to those of a previous study [26], which used the Beck Anxiety Inventory and BDI to show that the proportions of OSA patients with depression and anxiety were 46.1% and 53.9%, respectively, in people who were observed in a sleep laboratory. A large sample of Chinese patients was randomly selected from a hospital database, and their survey results showed that depressive symptoms were present in 47.4% of OSA patients using Symptom Checklist 90 and the Self-Rating Depression Scale [27]. A recent meta-analysis using pooled data revealed that symptoms of depression and anxiety were prevalent in 35% and 32% of patients with OSA, respectively [7].

Relationships between the severity of OSA symptoms and depression/anxiety have not consistently been reported in the literature. Some population-based and clinical studies have found a positive association between the severity of OSA and depression [10,11], but other population-based [12,28] and clinical [13–16] studies have failed to determine such a connection. We found that signs of depression and anxiety were more prevalent in patients with mild OSA than in those with severe symptoms of OSA. These findings are consistent with those found in the recent study by Bjorvatn et al. [20]. In fact, some studies have shown that subgroups of people with milder symptoms of OSA have higher levels of depressive symptoms [17–19]. Rapid eye movement (REM)–related OSA is a typical subtype of mild OSA, in which respiratory distress occurs predominantly during REM sleep. In our previous study [18], depressive symptoms, as defined by BDI scores of ≥10, were more prevalent in patients with REM-related OSA (54.1%) than in those without REM-related OSA (42.3%). Such a high prevalence of depressive symptoms in patients with REM-related OSA remained significant (OR 1.409, 95% CI 1.039–1.911) after controlling for sex, age, obesity, and daytime sleepiness. Using a large clinical population, Conwell et al. [17] also found that patients with REM-

Table 4
Logistic regression analyses with depressive symptoms or anxiety as a dependent variable and OSA severity as covariate (n = 795).

Compared to severe OSA	BDI scores ≥ 10						STAI scores ≥ 40					
	Crude model			Adjusted model[c]			Crude model			Adjusted model[c]		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Defined by AHI[a]												
Mild	1.623	1.152–2.287	0.006	1.893	1.149–3.118	0.01	1.243	0.885–1.747	0.21	1.381	0.846–2.253	0.20
Moderate	1.122	0.792–1.589	0.52	1.244	0.798–1.939	0.34	1.002	0.710–1.413	0.99	1.128	0.730–1.745	0.59
Defined by RDI[a]												
Mild	1.412	1.005–1.984	0.047	1.561	0.923–2.638	0.10	1.160	0.827–1.628	0.39	1.205	0.719–2.019	0.48
Moderate	1.172	0.830–1.654	0.37	1.333	0.856–2.077	0.20	1.092	0.776–1.538	0.61	1.205	0.779–1.865	0.40
Defined by ODI[a]												
Mild	1.660	1.179–2.338	0.004	1.872	1.167–3.004	0.009	1.361	0.969–10,913	0.08	1.627	1.019–2.599	0.04
Moderate	1.185	0.838–1.676	0.34	1.243	0.812–1.903	0.32	1.345	0.954–1.898	0.09	1.548	1.016–2.358	0.04
Defined by MinSaO2[a]												
Mild	1.558	1.103–2.202	0.01	1.727	1.160–2.573	0.007	1.443	1.023–2.035	0.04	1.626	1.097–2.409	0.02
Moderate	1.245	0.884–1.752	0.21	1.287	0.888–1.865	0.18	1.274	0.907–1.790	0.16	1.326	0.919–1.913	0.13
Defined by clinical AHI cutoffs[b]												
Mild	1.424	1.016–1.996	0.04	1.502	0.949–2.377	0.08	1.123	0.803–1.571	0.50	1.164	0.740–1.831	0.44
Moderate	1.297	0.925–1.818	0.13	1.311	0.860–1.998	0.21	1.113	0.796–1.558	0.53	1.179	0.778–1.788	0.34

AHI: apnea-hyponea index; BDI: Beck Depression Inventory; CI: confidence interval; MinSaO2: minimum arterial oxygen saturation; ODI: oxygen desaturation index; OR: odds ratio; OSA: obstructive sleep apnea; RDI: respiratory distress index; STAI-S: State Scale of State-Trait Anxiety Inventory.
[a] Polysomnographic parameters categorizing severity of sleep apnea according to the 33rd and 66th.
[b] 5 ≤ AHI < 15 mild OSA, 15 ≤ AHI < 30 moderate OSA,and AHI ≥ 30.
[c] Adjusted by age, sex, body mass index, histories of hypertension and diabetes, a score of Epworth Sleepiness Scale, total sleep time, and total arousal index.

Table 5
Logistic regression analyses with depressive symptoms as a dependent variable and OSA severity as covariate after stratification by sex and excessive daytime sleepiness (n = 795).

Compared to severe OSA	OR (95% CI) of the BDI scores ≥ 10[c]		p value for interaction with sex	OR (95% CI) of the BDI scores ≥ 10[c]		p value for interaction with EDS
	Male (n = 691)	Female (n = 104)		EDS (n = 318)	No EDS (n = 477)	
Defined by AHI[a]			0.16			0.06
Mild	2.237 (1.319–3.796)**	0.132 (0.010–1.794)		2.426 (1.095–5.378)*	1.532 (0.793–2.962)	
Moderate	1.451 (0.911–2.312)	0.109 (0.010–1.239)		2.481 (1.207–5.097)*	0.810 (0.454–1.444)	
Defined by RDI[a]			0.68			0.22
Mild	1.661 (0.951–2.902)	0.584 (0.085–4.027)		1.970 (0.865–4.488)	1.283 (0.629–2.614)	
Moderate	1.417 (0.893–2.248)	0.531 (0.084–3.341)		1.807 (0.8761–3.726)	1.104 (0.621–1.962)	
Defined by ODI[a]			0.15			0.17
Mild	2.096 (1.274–3.449)**	0.203 (0.019–2.146)		2.925 (1.325–6.454)**	1.350 (0.738–2.468)	
Moderate	1.403 (0.899–2.192)	0.135 (0.014–1.266)		2.058 (1.015–4.174)*	0.895 (0.520–1.541)	
Defined by MinSaO2[a]			0.12			0.32
Mild	1.995 (1.300–3.061)**	0.465 (0.120–1.797)		2.506 (1.293–4.858)**	1.291 (0.776–2.148)	
Moderate	1.442 (0.973–2.137)	0.359 (0.088–1.459)		1.505 (0.842–2.691)	1.201 (0.735–1.964)	
Defined by clinical AHI cutoffs[b]			0.40			0.07
Mild	1.668 (1.029–2.703)*	0.410 (0.066–2.561)		1.608 (0.764–3.382)	1.351 (0.743–2.456)	
Moderate	1.333 (0.857–2.074)	0.590 (0.104–3.353)		2.138 (1.064–4.297)*	0.941 (0.546–1.622)	

AHI: apnea-hyponea index; BDI: Beck Depression Inventory; CI: confidence interval; EDS: excessive daytime sleepiness; MinSaO2: minimum arterial oxygen saturation; ODI: oxygen desaturation index; OR: odds ratio; OSA: obstructive sleep apnea; RDI: respiratory distress index.

[a] Polysomnographic parameters categorizing severity of sleep apnea according to the 33rd and 66th.

[b] $5 \leq AHI < 15$ mild OSA, $15 \leq AHI < 30$ moderate OSA,and $AHI \geq 30$.

[c] Adjusted by age, sex, body mass index, histories of hypertension and diabetes, total sleep time, and total arousal index.

* $p < .05$.

** $p < .01$.

related OSA had higher depressive symptomatology, despite having a substantially milder degree of OSA compared to non-stage-specific OSA. Positional OSA is a phenotype in which episodes of sleep apnea occur predominantly during sleep in the supine position. Kim et al. [19] found, using BDI-II and the Hospital Anxiety Depression Scale, that patients with supine-isolated positional OSA exhibited more symptoms of anxiety and depression despite having a milder degree of OSA compared to supine-predominant positional OSA. However, our previous study [29] did not find any differences in levels of anxiety and depression between subgroups of patients with positional OSA or between groups of patients with positional and nonpositional OSA. In addition, in a community-based study, there was a significant negative association noted between the occurrence of OSA and the presence of at least one psychiatric disorder when compared with the high-risk subjects without OSA [30].

In this study, inverse relationships between symptoms of depression and anxiety and severity of OSA were shown more prominently when using ODI or MinSaO2 to evaluate apnea severity compared with observations using AHI or RDI. This suggests that, when studying the clinical impact of OSA, the frequency or degree of oxygen desaturation may be a more appropriate PSG reading than the number and frequency of hypoxic events [31]. Macey et al. [15] proposed that distinct subgroups of patients with OSA are affected to varying degrees by apneic periods, making AHI and RDI unreliable estimates of OSA severity.

The reasons behind these findings of negative associations between the occurrence of OSA and depressive symptoms are unclear, but a potential explanation involves the protective effects of intermittent hypoxia [32–34]. A previous animal study showed that intermittent hypoxia promotes the proliferation of endogenous neuroprogenitors, which leads to neurogenesis in the adult rat hippocampus and produces antidepressant-like effects in multiple animal models [32]. In their study, hippocampal x-ray irradiation blocked both the neurogenic and behavioral effects of intermittent hypoxia, indicating that these events likely produce antidepressant-like effects by promoting neurogenesis [32]. Some animal studies have determined that the duration and intensity of intermittent bouts of hypoxia are important determinants of whether these episodes are protective or harmful [33,34]. Few studies have examined the benefits of intermittent episodes of hypoxia on mood in humans. Taken together, these findings suggest that intermittent hypoxia may have a role in protecting against mood disorders. Alternatively, selection bias may affect findings in that a misperception of mental illness as symptoms of OSA may occur [20]. In some cases, nocturnal panic attacks and daytime fatigue due to mental illness may be perceived as symptoms of OSA, and thus patients are referred to sleep laboratories for PSG. Such referral bias would contribute to a negative association between OSA and depression. Also, clinical studies usually do not include participants without OSA, and this would bias the results when the reference group has an AHI score of < 5.

Gender differences in negative associations of sleep apnea severity with depressive symptoms may exist in patients with OSA. In a population-based study, Luik et al. [35] found that severe OSA (AHI ≥ 30/h) was associated with fewer depressive symptoms than mild (5 ≤ AHI < 15 /h) or moderate (15 ≤ AHI < 15 /h) OSA in men but not in women. Similarly, the current study showed that negative associations between the severity of sleep apnea episodes and depressive symptoms were evident in men, but such interaction effects between apnea severity and sex did not show statistical significance. Such differential effects of gender were also found in a previous study [18], in which a high prevalence of depressive symptoms in patients with REM-related OSA was present in men but not in women. In contrast, McCall et al. [36] investigated correlates of depressive symptoms in patients with OSA and found that milder oxygen desaturation nadirs were associated with worse BDI scores, especially in women.

Although daytime sleepiness is not usually found to be correlated with severity of OSA, it is considered to be one of the most important consequences of the sleep disorder. It is well known that EDS is an important factor associated with depression in patients with OSA. In our current study, negative associations between the severity of OSA and symptoms of depression were observed in patients with EDS, but such interaction effects between apnea severity and EDS did not reach to statistical significance. The reasons for such potential differential effects of EDS remain unclear.

Given our findings about the negative associations between the severity of OSA and symptoms of anxiety and depression, the incomplete resolution of OSA through therapeutic trials such as mandibular advance orthotics and various surgical management procedures for OSA

could instead aggravate the mood status of patients with OSA, especially in men with sleepiness aged between 40 and 50 years. Prospective therapeutic studies are needed to explore these relationships in patients with OSA. In addition, the efficacy of antidepressants needs to be further evaluated in patients with OSA and depression.

Certain limitations should be noted when interpreting the results of the current study. First, this was a cross-sectional study and therefore could not address issues of causality. Second, our inverse correlation between the severity of OSA and the presence of depressive symptoms could not be generalized, but rather limited to a targeted population of patients with suspected OSA attending the sleep laboratory with suggestive symptoms. Also, the poor representation of women in the sample limited the generalizability of our findings. Third, continuous variables such as BDI and STAI-S were dichotomized, and OSA severity was divided into three subgroups (mild, moderate, and severe) bounded by the 33rd and 66th percentiles of each parameter. Although dichotomization or categorization of continuous variables is common in clinical research, such simplicity may result in a considerable loss of information. Thus, the statistical power required to detect a relationship between the variable and patient outcome is reduced [37]. Dichotomizing may also increase the risk of a positive result being false. Fourth, patients without OSA (AHI < 5), such as those who simply snore, were not included in the current study. These participants may have contributed useful information regarding the prevalence of depression and anxiety. Fifth, we did not collect data on insomnia and socioeconomic status, which are important predictors of mental health. Insomnia that is comorbid with OSA has been associated with an increased prevalence of depression, especially in men [38,39]. Finally, the BDI, our measurement tool for depressive symptoms, may be subject to floor effects that might confound the relationship between depression and the severity of OSA.

In conclusion, symptoms of anxiety and depression may be more prevalent in patients with mild OSA than those with severe OSA. These relationships were especially evident for depressive symptoms. There may be differential effects of excessive daytime sleepiness on negative associations of apnea severity with depressive symptoms in patients with OSA.

Conflict of interest

None.

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