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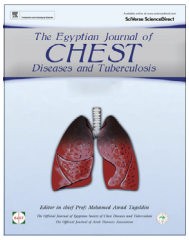

ORIGINAL ARTICLE

Predictors of anxiety and depression in patients with obstructive sleep apnea

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KEYWORDS

Obstructive sleep apnea;
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Quality of life

Abstract *Background and objective:* Several studies have investigated the association of obstructive sleep apnea syndrome (OSAS) with depression and anxiety; however, the relationship is still poorly understood. Therefore, we aimed to assess anxious and depressive symptoms in OSA, and evaluate their association with potentially related variables of OSAS.

Subjects and methods: This study included 72 patients newly diagnosed with obstructive sleep apnea and 30 controls. Patients underwent an overnight polysomnography and were assessed using the Epworth sleepiness scale (ESS) for excessive daytime sleepiness (EDS), hospital anxiety and depression scale (HAD) for anxious and depressive symptoms, and Maugeri obstructive sleep apnea syndrome (MOSAS) questionnaire for quality of life (QOL).

Results: 72 OSA patients (60 men and 12 women) whose mean age was 48.8 ± 11.73 yr and mean apnea and hypopnea index (AHI) was 64 ± 21.86, were compared with 30 controls according to their HAD scores. We found that the HAD score for anxiety and depression was higher in OSA patients than in the control group (p = 0.001 and 0.002 respectively). Moreover, the prevalence of symptoms of anxiety in patients with OSA was 33% while that of depression was 51%. Linear regression analysis revealed that daytime sleepiness and reduced QOL were strong predictors of depressive symptoms in OSA patients (P = 0.001 and 0.002 respectively), while reduced QOL was the only predictor of anxious symptoms (p = 0.035). No significant relations were found between severity of psychological symptoms and AHI or nocturnal hypoxemia in OSA patients.

Conclusion: Anxious and depressive symptoms are highly prevalent in patients with moderate to severe untreated OSAS. The severity of depressive symptoms maybe more related to excessive

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daytime sleepiness than to nocturnal hypoxemia. The reduced QOL is a strong predictor of psychiatric symptoms in OSAS patients. Therefore, patients with OSAS should be routinely screened for psychiatric symptoms to improve QOL and optimize diagnosis and therapy in these patients.

Introduction

Obstructive sleep apnea (OSA) is by far the most common form of sleep-disordered breathing, which is associated with increased morbidity and mortality and diminished quality of life [1]. It is characterized by recurrent episodes of upper airway obstruction during sleep, which induces nocturnal hypoxemia, hypercapnia and sleep fragmentation [2]. It subsequently results in excessive daytime sleepiness, mood problems, poor neurocognitive performance as well as serious organ system dysfunction [3]. Fatigue, daytime sleepiness, lack of energy, irritability, headache and insomnia are common symptoms of OSAS, some of which resembles symptoms associated with anxious and depressive conditions. However, clinicians may have problems differentiating psychiatric disease from symptoms related to organic disease [4]. Over the past few years, the burgeoning interest in psychopathological changes in patients with sleep-disordered breathing (SDB) has resulted in a large increase in the number of published studies on this topic [5]. Several studies have investigated the association of OSAS with depression and anxiety; however, the relationship is still poorly understood [4,6–9]. Increased awareness of the relationship between these psychiatric comorbidities and OSAS might significantly improve diagnostic accuracy as well as treatment outcome for both disorders [10]. The hospital anxiety and depression scale (HAD) is a well-documented instrument for assessing symptoms of anxiety and depression in patients with somatic diseases [11]. Therefore, we aimed to assess anxious and depressive symptoms as the most prevalent psychological disturbances in OSAS using the HAD scale, and evaluate their association with potentially related variables in patients with newly diagnosed OSAS.

Subjects and methods

This study included 72 patients newly diagnosed with obstructive sleep apnea, as well as 30 controls who had no personal histories of psychiatric diseases, snoring and/ or other sleep disorders.

Patients' exclusion criteria were; CPAP/BiPAP therapy, the presence of other sleep disorders, presence of obstructive lung disease, the presence of a significant comorbidity such as malignancy, severe heart failure or stroke, or refusal to fill out psychological questionnaires.

Data were collected regarding anthropometric measurements, demographic factors, smoking, clinical parameters like observed apnea by partner and co-morbid conditions as diabetes or hypertension.

Nocturnal sleep studies

All patients underwent overnight polysomnography using Respironics Alice 5 system (RESMED, Germany Inc). It is a level I device that records parameters such as body position, effort (thorax and abdomen), nasal flow (canula and/or thermistor), snoring (canula and/or microphone), SpO_2, plethysmogram, pulse rate, ECG, CPAP/BiPAP, and PLM overnight in hospital. Recordings of at least 5 h were required to validate the sleep study. The analysis was carried out automatically and manually. Respiratory events were scored using standard criteria [12,13]. The apnea hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of sleep. As indices of nocturnal hypoxemia we considered the oxygen desaturation index (this is the number of times that the oxygen saturation falls by more than 3 or 4 percent per hour of sleep), T90 (the fraction of sleep time spent below an oxygen saturation of 90 percent) and the minimal value recorded during sleep (minimal SaO2) [12,13].

The study inclusion criteria were an age of >18 years and a confirmed diagnosis of OSAS based on the AHI: AHI $\geqslant 15$ events per hour or AHI $\geqslant 5$ and $\leqslant 14$ events per hour with documented sleep symptoms or documented hypertension, ischemic heart disease, or a history of stroke [13].

Assessment of daytime sleepiness

The Epworth sleepiness scale (ESS) was used for assessing daytime sleepiness. This is a commonly used self-administered scale with eight items about how easily the respondent would fall asleep in different situations. The items are scored on a 0–3 scale, which are added to give an overall score of 0–24. Higher scores indicate more sleepiness. ESS score 2–10 is considered 'normal' and >10 indicative of pathological sleepiness [14].

Assessment of anxiety and depression

Symptoms of anxiety and depression were measured with the hospital anxiety and depression scale (HADS). The HADS is a validated and reliable psychological measure widely used in both hospitalized and primary care patients with chronic diseases. The HADS is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D) both containing seven items, rated 0–3, giving a possible maximum score for anxiety and depression of 21. The scores range from 0 to 21 for each subscale, with a score of 0–7 denoting a noncase, 8–10 a possible case, and 11 or higher a probable case [11].

Assessment of quality of life (QOL)

We used the new validated Maugeri obstructive sleep apnea syndrome (MOSAS) questionnaire which is used to assess the psychological and physical impact of OSAS as well as the adherence to the CPAP device. Its items cover the domains of normal daily routine, social interactions emotional functioning, and symptoms. It is composed of 2 sections; section A consists of 16 items, scored on a 1–4 scale, divided into two factors: sleep apnea Psychological Impact (10 items) and

sleep apnea Physical Impact (4 items), with two clinically appropriate filler items., and section B measures the discomfort and nuisance caused by CPAP use (7 items) and therefore was not applied in our patients. Higher score means greater psychological or physical impact [15].

All subjects were enrolled in the study after a written informed consent according to the protocol approved by the Ethics Committee of the Hospital.

Statistical analysis

Data were collected, tabulated, then analyzed using SPSS Version13. Qualitative data were presented as numbers and percentage. Quantitative data were expressed as means and standard deviation. Groups were compared for demographic and clinical characteristics and scores on the questionnaire measures using unpaired t-test. Pearson correlation coefficient (r) was used to assess the relation between HAD anxiety and depression scores and numeric variables. Linear regression analysis was used to examine the influence of confounding factors affecting depression and anxiety scores. For all statistical tests, a p-value of $\leqslant 0.05$ was considered significant.

Results

72 newly diagnosed OSAS patients were enrolled in this study; they were 60 men and 12 women and their mean age was 48.8 ± 11.73 yr. Their mean AHI was 64 ± 21.86 indicating that they were on average suffering from severe obstructive sleep apnea. The patients' characteristics are shown in Table 1. HAD scores of the patient group were compared with a control group including 30 healthy adults (24 men and 8 women, mean age 50.0 ± 1.22 yr) randomly selected and age- and sex-matched (Table 2 and Fig. 1).

Table 1 Patients Characteristics.

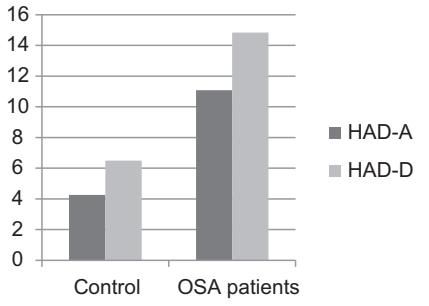
Gender, *n* (%)	
Male	60 (83)
Female	12 (17)
Age	48.8 ± 11.73
BMI	42.8 ± 6.51
Smoking status, *n* (%)	
Current smoker	25 (35)
Ex-smoker	12 (17)
Never smoker	35 (49)
ESS	17.8 ± 4.07
Observed apnea by partner, n (%)	54 (75)
Comorbities, *n* (%)	
HTN	36 (50)
DM	18 (25)
Others	15 (21)
AHI	64 ± 21.86
ODI	50.4 ± 18.71
T90	48.8 ± 18.76
Minimum SaO_2	65.2 ± 11.02
MOSAS-A	42.1 ± 6.11

Results are expressed as mean + standard deviation unless otherwise specified. Definition of abbreviations: *n*: number of patients, BMI:body mass index, ESS:Epworth sleepiness scale, HTN:hypertension, DM:diabetes mellitus, AHI: apnea hypopnea index, ODI:oxygen desturation index, T90: fraction of sleep time spent below an oxygen saturation of 90 percent, SaO_2: arterial oxygen saturation, MOSAS:Maugeri obstructive sleep apnea syndrome questionnaire.

Table 2 Comparison of the HAD anxiety and depression scales in the patients and control group.

	OSA patients	Control	P
HADS-A	11.1 ± 3.09	4.25 ± 2.63	0.001*
HADS-D	14.8 ± 4.11	6.5 ± 2.65	0.002*

p:*p* value for Student t-test.
HADS-A: hospital anxiety and depression subscale for anxiety.
HADS-D: hospital and depression subscale for depression.
* Statistically significant at $p \leqslant 0.05$.



HAD-A: Hospital anxiety and depression scale for anxiety
HAD-D: Hospital and depression scale for depression

Figure 1 Comparison of the HAD anxiety and Depression scales in the patients and control group. HAD-A: hospital anxiety and depression scale for anxiety HAD-D: Hospital and depression scale for depression.

Twenty-four patients (33%) had an anxiety score of $\geqslant 11$ (probable anxiety), and 37 patients (51%) had a depression score of $\geqslant 11$ (probable depression). The characteristics of patients with and without anxiety and/or depression are shown in Tables 3 and 4.

Depressed patients had more daytime sleepiness, measured by the Epworth sleepiness scale, as compared with non-depressed patients, However, depressed patients showed no significant differences as regards sex, age, BMI, smoking, comorbidities, respiratory sleep parameters and QOL.

In addition, anxious patients showed no significant difference from non-anxious patients regarding the different demographic, clinical and respiratory sleep parameters as well as QOL (Tables 3 and 4).

Correlation analysis of the HAD anxiety and depression scores with other parameters

Correlation analyses of the HAD scores and numeric parameters (demographic, clinical, respiratory sleep parameters, and QOL) showed that the HAD depression score was significantly correlated with daytime sleepiness and reduced QOL ($p = 0.002$ for both), while the HAD anxiety score was significantly correlated with QOL only ($p = 0.035$). Moreover,

Table 3 Descriptive statistics according to HAD anxiety score.

	Anxious Score < 11 $N = 24$	Not anxious Score ⩾ 11 $N = 48$	*P* value
Gender, *n*(%)			
Male	21 (88)	39 (81)	NS
Female	3 (13)	9 (19)	
Age	45.3 ± 9.25	50.5 ± 13.01	NS
BMI	42.5 ± 6.66	42.9 ± 6.9	NS
Smoking status, *n* (%)			
Current smoker	7 (29)	18 (38)	NS
Ex-smoker	9 (38)	3 (6)	
Never smoker	8 (33)	27 (56)	
ESS	19.8 ± 2.63	16.8 ± 4.43	NS
Observed apnea by partner, number (%)	20 (83)	34 (71)	NS
Comorbities (*n*)			
HTN	12 (50)	24 (50)	NS
DM	4 (21)	13 (27)	
Others	6 (25)	9 (19)	
AHI	67.8 ± 18.41	64.0 ± 24.51	NS
ODI	58.3 ± 16.90	48.8 ± 19.83	NS
T90	51.8 ± 13.07	47.9 ± 21.88	NS
Minimum SO_2	71.3 ± 2.50	64.3 ± 16.11	
MOSAS-A	45.3 ± 1.89	40.5 ± 6.97	NS
HADS-D	16.5 ± 4.04	14.0 ± 4.4	NS

Results are expressed as mean + standard deviation unless otherwise specified. *p*:*p* value for Student t-test, *n*: number of patients, BMI:body mass index, ESS:Epworth sleepiness scale, HTN:hypertension, DM:diabetes mellitus, AHI:apnea hypopnea index, ODI:oxygen desturation index, T90: fraction of sleep time spent below an oxygen saturation of 90 percent, SaO_2: arterial oxygen saturation.
MOSAS:Maugeri obstructive sleep apnea syndrome questionnaire, HADS-D: Hospital and depression scale for depression.

there was a significant positive correlation between the HAD anxiety and depression scores (see Table 5).

Linear regression analysis was done to control for potentially confounding factors affecting the depression and anxiety scores. A regression analysis model was done for each score separately with the HAD score as the dependant variable and with all the demographic, clinical, respiratory sleep parameters well as QOL measured by the MOSAS questionnaire as the independent variables. Reduced QOL, measured by the MOSAS questionnaire, was a significant predictor of both anxiety and depression. In addition, daytime sleepiness measured by the ESS was additional significant predictor of depression only Table 6.

Discussion

In this study, we aimed to determine the prevalence of anxious and depressive symptoms in treatment-naïve moderate to severe OSA patients, and their relation with different variables of obstructive sleep apnea syndrome. During the study period, the majority of patients referred for assessment for possible OSA were male patients (60 males and 12 females), this discrepancy might reflect the increased incidence of OSA in males reported in several studies [2], but could also be due to bias in referral with more male patients referred for the sleep study.

We found that the prevalence of symptoms of anxiety in patients with OSA was 33% while that of depression was 51%. Moreover, the HAD score for anxiety and depression was higher in OSA patients than in the control group ($p = 0.001$ and 0.002 respectively). This high prevalence is in line with findings reported in some studies in which OSA was highly associated with anxiety and/or depression [2,4,8,9]. Prevalence figures for depression and anxiety varied widely, even between studies using the same method of assessment, showing a marked variety in the prevalence of both depression (7–63%) and anxiety (11–70%) [16].

Several studies have investigated the association of OSAS with depression and anxiety; however, the relationship is still poorly understood. In untreated OSAS, rates of depression are elevated compared with general populations [8,9], although not necessarily at a pathological level [7]. In contrast, some other studies have been unable to confirm this association between OSAS and anxiety or depression [4]. Some of the mixed findings among studies can be explained by differences in sample size, study population, gender distribution, age, variability in scales used to assess anxiety and depression and the overlap between mood alteration and OSAS-related symptoms [3,10].

This high prevalence of depressive symptoms in OSA patients can be explained by several possible underlying mechanisms. The two main factors suspected to be responsible for depressive symptoms in OSAS are sleep fragmentation and oxygen desaturation during sleep. Sleep fragmentation is a direct consequence of the recurrent microarousals associated with the apneas and hypopneas, and the nocturnal hypoxemia

Table 4 Descriptive statistics according to HAD depression score.

	Depressed Score < 11 $N = 37$	Not depressed Score ⩾ 11 $N = 35$	*P* value
Gender (*n*)			
Male	30 (81)	30 (86)	NS
Female	7 (19)	5 (14)	
Age	45.3 ± 9.25	50.5 ± 13.01	0.06
BMI	44.2 ± 4.45	41.3 ± 8.29	NS
Smoking status, *n*(%)			
Current smoker	18 (49)	7 (20)	NS
Ex-smoker	7 (19)	5 (14)	
Never smoker	12 (32)	23 (66)	
ESS	20.3 ± 1.97	15.2 ± 4.07	0.019*
Observed apnea by partner, number (%)	30 (81)	24 (68)	NS
Comorbities (*n*)			
HTN	20 (54)	16 (46)	NS
DM	10 (27)	8 (23)	NS
Others	7 (19)	8 (23)	
AHI	72.2 ± 13.01	58.3 ± 19,9	NS
ODI	56.5 ± 13.72	47.3 ± 20.14	NS
T90	54.8 ± 20.64	46.5 ± 14.74	NS
Minimum SO2	62.2 ± 12.34	67.3 ± 8.7	NS
MOSAS-A	45.17 ± 2.99	39 ± 7.10	0.078
HADS-A	12.17 ± 2.04	10.0 ± 3.74	NS

Results are expressed as mean + standard deviation unless otherwise specified. *p*:*p* value for Student t-test, *n*: number of patients, BMI:body mass index, ESS:Epworth sleepiness scale, HTN:hypertension, DM:diabetes mellitus, AHI:apnea hypopnea index, ODI:oxygen desturation index, T90: fraction of sleep time spent below an oxygen saturation of 90 percent, SaO_2: arterial oxygen saturation, MOSAS:Maugeri obstructive sleep apnea syndrome questionnaire, HADS-A: Hospital and depression scale for anxiety.
* Statistically significant at $p \leqslant 0.05$.

Table 5 Correlation of the HAD anxiety and depression scores with the Epworth sleepiness scale (ESS) and quality of life.

	ESS		MOSAS		HADS-A	
	r	*p*	*r*	*p*	*r*	*p*
HADS-D	0.80	0.002*	0.79	0.002*	0.65	0.023*
HADS-A	0.41	NS	0.61	0.035*	–	–

r: Pearson correlation coefficient, * Statistically significant at $p \leqslant 0.05$, HADS-A: Hospital anxiety and depression scale for anxiety, HADS-D: Hospital and depression scale for depression, MOSAS :Maugeri obstructive sleep apnea syndrome questionnaire.

Table 6 Linear regression model of factors predictive of HAD anxiety and depression scores.

		β^*	*P*	R^2
Model A			0.022*	0.459
HAD-A	MOSAS	0.678	0.022*	
Model B			0.001*	0.727
HAD-D	ESS	0.853	0.001*	
	MOSAS	0.779	0.005*	

A and B are 2 different linear regression models for the hospital anxiety and depression subscale for anxiety and depression respectively. $\beta^{\#}$: the regression cooefficient MOSAS:Maugeri obstructive sleep apnea syndrome questionnaire.
* Statistically significant at $p \leqslant 0.05$.

is due to the intermittent drops in oxygen saturation caused by the respiratory events [10]. Sleep fragmentation is the primary cause of excessive daytime sleepiness (EDS) in OSA patients, and is suggested to result in the depressive symptomatology. This last perspective gains support from our finding that EDS as measured by the Epworth sleepiness scale (ESS) was the main predictor for the HAD depression score in the linear regression analysis ($p = 0.001$). Many other studies have reported similar correlation with the EDS [4,5,17]. However, with respect to hypoxemia despite the fact that the AHI and the ODI were more in depressed patients, it didn't reach statistical significance, suggesting that the severity of depressive symptoms maybe more related to excessive daytime sleepiness than to nocturnal hypoxemia.

However, Engleman et al. noted that the effect of depression in OSA correlated highly with the severity of hypoxic events measured with AHI [18]. Moreover, recently, preliminary imaging data suggests that hypoxemia related to OSA might also play a role in impacting mood. Cerebral metabolic impairment resulting from recurrent nocturnal hypoxemia in OSA had previously been observed in several imaging investigations on OSA [19–21]; independently, white matter hyperintensities (WMH) have been linked to depressive symptomatology in

studies on affective disorders [22–26]. Aloia et al. reported in a small sample of older patients with OSA more subcortical WMH in the brain MRI of patients with a severe OSA as compared to those with minimal OSA, and a tendency for a positive correlation between these subcortical hyperintensities and depression scores on the Hamilton Depression Scale [27].

The high comorbidity of OSA and depression also suggests that both disorders may share a common neurobiological risk factor. On the neurotransmitter level, the serotoninergic system has a central role as a neurobiological substrate underlying impairments in the regulations of mood, sleep-wakefulness cycle, and upper airway muscle tone control during sleep. Depression is associated with a functional decrease of serotoninergic neurotransmission, and is mostly responsible for the alterations in sleep [28]. The physiopathology of OSA involves numerous factors, among which the abnormal pharyngeal collapsibility during sleep is one of the most compelling. Serotonin delivery to upper airway dilatator motor neurons has been shown to be reduced in dependency of the vigilance state [29]. This leads to reductions in dilator muscle activity specifically during sleep, which may contribute to sleep apnea. However, whereas the role of serotonin in mood disorders has been largely documented, its involvement in the pathophysiology of sleep apnea remains to be clarified [10].

Moreover, OSA and depression share other common risk factors, as both have independently been shown to be associated with metabolic syndrome, and also with the development of cardiovascular disease [30,31].

Several previous investigations examining the covariation between depression score of patients with SDB and nocturnal variables (AHI and nocturnal hypoxemia) found little [8,32] or no evidence of a linear relation [33,34], suggesting that the presence of OSA and its severity is not the primary cause of psychopathological changes in SDB patients. Similarly, in a regression analysis of variables associated with sleep apnea, we found no association between AHI or other sleep parameters and HAD anxiety or depression score. Nevertheless, a strong relationship was found between HAD depression score and sleepiness, using the ESS. This finding further supports the suggestion of a possible shared pathway between these conditions. As several studies found that obstructive sleep apnea is associated with elevated levels of the cytokines IL6 and tumor necrosis factor [35,36]. These cytokines have been proposed as the mediators of daytime sleepiness in this condition. Major depression has also been shown to be associated with an immune response involving pro-inflammatory cytokines; IL 1, IL 6 and interferon [37].

Reports of anxiety in the context of OSAS are less common than depression but are nevertheless not unusual. Moreover, many research literatures concerned themselves mainly with whether or not there are clinical levels of depression. Thus, the full complex array of psychopathology may not have been adequately acknowledged in quantity and quality [38]. Since we have demonstrated a high prevalence of anxiety in addition to depression in the patients' group, in addition to the positive correlation found between the two psychiatric comorbidities in these patients ($p = 0.023$), this represents an oversight in the investigation into the relationship between OSAS and mental health, as recent evidence suggests that when depression is considered in conjunction with other symptoms it is more closely tied to the biological markers of OSAS [39].

Another important finding is that the QOL, measured by MOSAS questionnaire, was a strong predictor for both; the HAD anxiety and depression scores ($p = 0.022$ and 0.005 respectively). Very few published reports have examined the relationship between the QOL and mood [40]. The findings that the QOL may play an important role in anxious or depressive state is reasonable because this reduced QOL reflects deficits in functioning across a number of areas [41]. Such difficulties may be so severe that job performances and family life may be affected, leading in turn to emotional disturbances and personality changes. These findings support the hypothesis that some of the psychopathological changes described in patients with OSAS are likely to reflect the reduced alertness and the reduced vigor and QOL related to breathing disorders [5].

Moreover, the reduced QOL present in SDB patients may affect their general health perception and their functional and emotional well-being inducing, in turn, personality changes such as aggressiveness, irritability, anxiety or depression, all expressing adaptation of the patients to their worsening life condition [42].

This study has its own limitations; first, the unequal number of males and females, as the gender of subjects may have a significant impact on mood; since women are more vulnerable to mood alterations. Also, it is important to take note of the limitations of mood scales, which are not proper diagnostic tools for the detection of depression or anxiety; they only represent depressive and anxious symptoms, however diagnosis of the clinical entity requires a psychiatric consultation.

In conclusion, our study demonstrated that anxious and depressive symptoms are highly prevalent in patients with moderate to severe untreated obstructive sleep apnea. The severity of depressive symptoms maybe more related to excessive daytime sleepiness than to nocturnal hypoxemia. The reduced QOL is a strong predictor of psychiatric symptoms in OSA patients.

Therefore, in clinical practice we think it is feasible to be alert to psychiatric symptoms in patients with OSAS and routine screening with instruments like the HAD scale should be encouraged, to improve QOL and optimize diagnosis and therapy in these patients.

Future research is needed to investigate the causal relationship between psychiatric symptoms and OSAS, as well as the appropriate treatment for these comorbidities.

Declaration of interest

The authors have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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