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Moderate to severe obstructive sleep apnea during REM sleep as a predictor of metabolic syndrome in a Korean population

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Abstract

Purpose Metabolic syndrome is a cluster of metabolic abnormalities including obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, and hyperglycemia. Obstructive sleep apnea (OSA) is known to be associated with metabolic syndrome. However, it remains uncertain which sleep parameters of OSA are associated with metabolic syndrome. We aimed to clarify the relationship between sleep variables and the presence of metabolic syndrome in patients with OSA.

Methods We prospectively recruited patients who visited the institute for the evaluation of sleep-disordered breathing. All patients underwent overnight polysomnography and sleep questionnaires. They were diagnosed with metabolic syndrome according to the 2007 consensus definition by the International Diabetes Federation. We applied multivariate logistic regression models to predict the presence of metabolic syndrome with variables related to sleep parameters.

Results A total of 85 patients (43 men) were enrolled. The mean age (± standard deviation) was 52.0 ± 14.3 years. Metabolic syndrome was diagnosed in 39 (46%) patients. Patients with metabolic syndrome had a significantly higher apnea-hypopnea index (AHI) compared with patients without metabolic syndrome. An AHI greater than 15/h during REM sleep was a significant independent predictor of metabolic syndrome (adjusted OR, 7.08; 95% CI, 1.60–31.41; $p = 0.010$) after adjusting for age, body mass index, and non-REM AHI ≥ 15/h. In partial correlation analysis, REM AHI was significantly associated with the presence of metabolic syndrome after adjusting for age and BMI ($r = 0.229$, $p = 0.042$).

Conclusion Korean patients with OSA frequently had comorbid metabolic syndrome. Moderate to severe OSA during REM sleep may be a predictor of metabolic syndrome.

Keywords Obstructive sleep apnea · Apnea-hypopnea index · Metabolic syndrome · REM sleep

Introduction

Obstructive sleep apnea (OSA) is characterized by complete or partial obstruction of the upper airway. Recurrent episodes of hypoxia or apnea cause intermittent hypoxemia, hypercapnia, microarousals, and fragmented sleep [1]. Previous studies have shown that OSA is associated with increased risks of hypertension, stroke, and type 2 diabetes mellitus [2]. OSA has been associated with various risk factors for cardiovascular and cerebrovascular risk factors including metabolic syndrome [3]. Metabolic syndrome is a cluster of metabolic abnormalities including central obesity, hypertension, hyperglycemia, and dyslipidemia [4]. The prevalence of metabolic syndrome tends to increase with the prevalence of obesity. Obesity has been considered as common risk factor for both OSA and metabolic syndrome. Conversely, it has been shown that OSA is associated with metabolic syndrome, independent of obesity [5]. OSA itself is independently associated with metabolic alterations including hypertension, dyslipidemia, and impaired glucose tolerance [2].

Apneic events can occur in both non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Sympathetic hyperactivity and cardiovascular instability are greater during REM sleep than during NREM sleep in patients with OSA [6]. OSA during REM sleep has been associated with hypertension, worsened glucose control, and neurocognitive dysfunction [7]. However, there is a lack of research focused on the impact of OSA severity during REM

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sleep on the risk of metabolic syndrome. We aimed to compare the impacts of OSA during REM and NREM sleep on the presence of metabolic syndrome.

Methods

Study participants

We screened individuals with complaints of snoring or sleep-disordered breathing prospectively at the Boramae Hospital of Seoul National University between January 2014 and May 2016. Patients with nocturnal symptoms including snoring, shortness of breath, or witnessed apnea during sleep were included. We obtained a detailed sleep history, past medical history, and body mass index (BMI) from all patients. All patients completed sleep questionnaires and overnight polysomnography (PSG). Patients comorbid with major medical problems of the cardiovascular, cerebrovascular, pulmonary, and renal systems were excluded. PSG data of insufficient total sleep time (TST; < 4 h) or less than 30 min of REM sleep were also excluded. Approval for this study was obtained from the Institutional Review Board at the Boramae Hospital of Seoul National University. Written informed consent from each patient or his/her legal representative for participation in this study was obtained.

Sleep questionnaires and polysomnography

Subjective daytime sleepiness was measured with the Epworth Sleepiness Scale (ESS) [8] and Stanford Sleepiness Scale (SSS) [9]. The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality and disturbances during the last month [10]. The subjects were instructed not to drink alcohol or caffeinated beverages and to sleep and wake up at their regular hours for a week before the study. PSG was recorded with the Twin-PSG software (Natus Neurology Incorporated, West Warwick, RI, USA) using a 6-channel electroencephalogram, a 4-channel electrooculogram, electromyogram, and electrocardiogram. A thermistor, a nasal air pressure monitoring sensor, an oximeter, piezoelectric bands, and a body position sensor were also applied to the patient. Apnea was defined as a reduction in airflow of 90% or more, lasting at least 10 s. Hypopnea was defined as a reduction in airflow of 30% or more, lasting at least 10 s and associated with ≥ 3% oxygen desaturation or an arousal [11]. OSA was graded according to the apnea-hypopnea index (AHI): AHI < 5 (events/h) was considered normal, 5 ≤ AHI < 15 was considered mild OSA, 15 ≤ AHI < 30 was considered moderate OSA, and AHI ≥ 30 was considered severe OSA. REM AHI was defined as mean AHI during total REM sleep, being at least 30 min of REM sleep.

Metabolic syndrome: diagnostic criteria and laboratory analyses

According to the modified criteria of the National Cholesterol Education Program Adult Treatment Panel guidelines III, metabolic syndrome was diagnosed if three or more of the five following factors were present: (1) waist circumference ≥ 90 cm for Asian men and ≥ 80 cm for Asian women; (2) triglycerides ≥ 150 mg/dL (or if the patient was on specific drug treatment); (3) high-density lipoprotein < 40 mg/dL for men and < 50 mg/dL for women (or if the patient was on specific drug treatment); (4) arterial blood pressure ≥ 130 or 85 mmHg, respectively, for systolic and diastolic blood pressure (or if the patient was on antihypertensive drug treatment); and (5) fasting glucose ≥ 100 mg/dL (or if the patient was on a specific drug treatment) [12]. Venous blood samples were obtained from each patient early in the morning, after PSG, with at least 8 h of fasting. Laboratory measures included glucose, total serum cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, fibrinogen, D-dimer, erythrocyte sedimentation rate, and C-reactive protein (CRP).

Statistical analysis

The participants in this study were divided into two groups based on the presence of metabolic syndrome. We used t-tests for continuous variables and Pearson's $\chi 2$ and Fisher's exact tests for categorical variables to compare the clinical, laboratory, and PSG variables between two groups. All the continuous quantitative parameters are represented as mean with standard deviation (SD). A logistic regression was applied to further evaluate risk factors for the presence of metabolic syndrome. Variables with a significant p value ($p < 0.05$) in the univariate regression were considered as candidates in the multivariate models. Several multivariate models were applied to avoid overfitting and multicollinearity. Partial correlations were calculated after controlling for possible confounding variables to estimate the relationship between the REM AHI and metabolic syndrome. Statistical analyses were performed with SPSS statistical software version 21 (SPSS Inc., Armonk, NY, USA). Two-sided p values less than 0.05 were considered statistically significant.

Results

A total of 85 patients with complaints of snoring or sleep-disordered breathing were enrolled in this analysis. The patients' age and BMI were 52.0 ± 14.3 years (mean ± standard deviation) and 24.3 ± 3.5 kg/m^2 (49% female). The mean total sleep time was 349.5 ± 64.3 min; REM sleep represented 20.0 ± 7.9% of total sleep time. Based on the AHI, 33 patients (38.8%) had an AHI of less than 5 and were diagnosed with

primary snoring. Among 52 patients with OSA, 27 patients (31.8%) were mild, 15 patients (17.6%) were moderate, and 10 patients (11.8%) were severe. Of 85 patients with snoring or OSA, 39 patients (46%) had metabolic syndrome. The presence of metabolic syndrome in patients with moderate to severe OSA was 16 (48%), which was higher than 12 (36%) in patients with primary snoring and 11 (41%) in patients with mild OSA.

The patients with metabolic syndrome were older than those without. Body mass index was increased in patients with metabolic syndrome compared to those without. Patients with metabolic syndrome had a significantly higher presence of hypertension and diabetes mellitus than those without metabolic syndrome ($p < 0.001$ and $p = 0.003$, respectively). Among the laboratory variables, CRP was increased in patients with metabolic syndrome compared to those without. In PSG parameters, patients with metabolic syndrome had a substantially higher AHI compared to those without. Interestingly, REM AHI in patients with metabolic syndrome was significantly higher than that in patients without ($p = 0.001$), but not AHI during non-REM sleep ($p = 0.053$). Patients with metabolic syndrome showed worse hypoxic conditions, with increased length of longest sleep apnea and time below 90% of oxygen saturation, compared to those without metabolic syndrome ($p = 0.029$ and $p = 0.001$, respectively). Table 1 summarizes the clinical, laboratory, and PSG features of patients with and without metabolic syndrome.

Univariate logistic regressions are applied to estimate the risk of metabolic syndrome. Age, BMI, hypertension, dyslipidemia, AHI, REM AHI, and time below 90% oxygen saturation had significant associations with the risk for metabolic syndrome (Table 2). Interestingly, moderate to severe OSA during REM sleep (REM AHI ≥ 15/h) was a significant predictor for the presence of metabolic syndrome (odds ratio [OR], 5.91; 95% CI, 2.24–15.56). NREM AHI ≥ 15/h also revealed increased risk for the metabolic syndrome (OR, 2.38; 95% CI, 0.86–6.54), but this was not statistically significant due to limited sample size ($p = 0.053$). We have reduced the number of covariates in the multivariate models, due to concerns about overfitting. In the model with multivariate analysis including AHI ≥ 15/h as a covariate, age and AHI greater than 15/h showed higher odds for metabolic syndrome ($p = 0.005$ and $p = 0.034$; Model 1 in Table 3). In multivariate analysis with REM AHI and NREM AHI as continuous variables (Model 2 in Table 3), age, BMI, and REM AHI revealed higher risk for the presence of metabolic syndrome ($p = 0.024$, $p = 0.045$, and $p = 0.047$, respectively; Model 2 in Table 3). In the multivariate model with REM AHI ≥ 15/h, moderate to severe REM AHI was a significant independent predictor of the presence of metabolic syndrome after controlling for age, BMI, and NREM AHI ≥ 15/h (adjusted OR, 7.08; 95% CI, 1.60–31.41; $p = 0.010$; Model 3 in Table 3). In partial correlation analysis, REM AHI was significantly associated with the presence of metabolic syndrome after adjusting for age and BMI ($r = 0.229$, $p = 0.042$).

Discussion

This prospective observational study has demonstrated that the presence of metabolic syndrome was 54% in non-obese patients with the symptoms of sleep-disordered breathing. Moderate to severe REM AHI was an independent predictor of metabolic syndrome after adjusting for other prognostic variables including age and BMI. To the best of our knowledge, this is the first report to demonstrate the association between REM AHI and cormobid metabolic syndrome in non-obese patients with snoring or OSA.

OSA and metabolic syndrome are highly prevalent in middle-aged adults. The prevalence of OSA in general population is 9–14% in men and 4–7% in women and increases with age [2]. In a general population-based study of 2074 subjects with home PSG, REM-related sleep-disordered breathing is independently associated with metabolic syndrome [13]. The prevalence of metabolic syndrome among Asians ranges from 21 to 41% in population-based studies [14]. In our study, 52% of patients with OSA (AHI ≥ 5/h) had metabolic syndrome, while 36% of patients with primary snoring had metabolic syndrome. On the contrary, 69% of patients with metabolic syndrome presented OSA. Our finding was consistent with that of previous studies that OSA is highly associated with metabolic syndrome [5].

Obesity has been considered as a major risk factor for metabolic syndrome as well as OSA [15]. In a 4-year follow-up study with obese patients [16], weight loss program revealed greater decrease of REM AHI than non-REM AHI although the initial REM AHI was higher than non-REM AHI. Losing weight could result in the improvements of both REM AHI and metabolic syndrome in obese patients. However, in non-obese patients, OSA is an independent risk factor for predisposition to some components of metabolic syndrome independently of obesity [17]. Several possible mechanisms leading to metabolic syndrome include intermittent hypoxia, oxidative stress, cytokines, and inflammation resulting from OSA [2]. Increased reactive oxygen species and oxidative stress from repeated intermittent hypoxia and consequent reoxygenation during OSA can result in impaired glucose control, insulin resistance, and dyslipidemia. Increased inflammatory cytokines from repetitive intermittent hypoxia and sleep fragmentation may also increase hypertension, insulin resistance, and dyslipidemia [18].

REM sleep accounts for approximately 20% of total sleep time and is mostly concentrated in the second half of sleep time. REM sleep is more highly associated with marked fluctuation of sympathovagal balance and cardiovascular instability than non-REM sleep [19]. The collapsing tendency of

Table 1 Clinical and polysomnographic characteristics between two groups with or without metabolic syndrome

	MS group	Non-MS group	*p* value
Clinical factors			
Subjects, no. (%)	39 (45.9)	46 (54.1)	
Age, years, mean (SD)	56.5 (10.8)	48.3 (15.9)	0.006
Men, no. (%)	21 (53.8)	22 (47.8)	0.582
BMI, kg/m^2, mean (SD)	25.5 (4.0)	23.1 (2.6)	0.002
ESS score, mean (SD)	2.5 (0.8)	2.7 (0.9)	0.562
SSS score, mean (SD)	5.7 (4.1)	5.8 (5.0)	0.853
Global PSQI score, mean (SD)	10.8 (3.4)	10.2 (3.3)	0.570
Hypertension, no. (%)	21 (53.8)	2 (4.3)	< 0.001
Diabetes mellitus, no. (%)	7 (17.9)	0 (0.0)	0.003
Cardiovascular disease, no. (%)	4 (10.3)	1 (2.2)	0.117
Stroke, no. (%)			0.057
Smoking, no. (%)	3 (7.7)	0 (0.0)	0.759
Alcohol, no. (%)	10 (25.6)	12 (26.1)	0.963
Biochemical markers			
WBC, × 10^3/ul, mean (SD)	6.7 (2.1)	5.9 (1.5)	0.116
RBC, × 10^6/ul, mean (SD)	4.7 (0.6)	4.6 (0.4)	0.445
Hemoglobin, g/dL, mean (SD)	14.7 (1.6)	14.2 (1.3)	0.189
Hematocrit, %, mean (SD)	44.3 (8.9)	42.2 (3.2)	0.306
Platelet, ×10^3/ul, mean (SD)	241.1 (48.7)	243.7 (50.2)	0.846
Fibrinogen, mg/dL, mean (SD)	275.2 (56.8)	267.0 (48.8)	0.478
D-dimer, mg/L, mean (SD)	0.4 (0.5)	0.4 (0.6)	0.985
CRP, mg/dL, mean (SD)	0.3 (0.5)	0.1 (0.2)	0.007
ESR, mm/h, mean (SD)	9.1 (8.6)	8.6 (6.3)	0.804
Polysomnographic parameters			
Time in bed, min, mean (SD)	433.7 (26.6)	425.1 (44.8)	0.609
Total sleep time, min, mean (SD)	355.4 (54.0)	344.6 (72.2)	0.637
N1 sleep, %, mean (SD)	19.4 (9.1)	15.8 (10.9)	0.025
N2 sleep, %, mean (SD)	45.6 (7.9)	46.5 (8.7)	0.525
N3 sleep, %, mean (SD)	14.6 (7.4)	18.0 (8.7)	0.052
REM sleep, %, mean (SD)	20.4 (7.9)	19.7 (8.0)	0.965
Sleep latency, min, mean (SD)	8.0 (8.2)	12.5 (16.4)	0.351
REM sleep latency, min, mean (SD)	115.5 (68.9)	116.8 (61.3)	0.650
Sleep efficiency, %, mean (SD)	81.9 (11.1)	81.3 (13.5)	0.850
Arousal index, events/h, mean (SD)	23.5 (15.5)	18.0 (10.9)	0.078
PLMS index, events/h, mean (SD)	8.4 (17.9)	2.7 (9.7)	0.069
AHI, events/h, mean (SD)	17.8 (19.5)	9.8 (13.2)	0.017
Normal, no. (%)	12 (30.8)	21 (45.7)	
Mild no. (%)	11 (28.2)	16 (34.8)	
Moderate, no. (%)	9 (23.1)	6 (13.0)	
Severe, no. (%)	7 (17.9)	3 (6.5)	
AHI during NREM sleep, mean (SD)	16.4 (20.9)	9.6 (14.2)	0.053
AHI during REM sleep, mean (SD)	22.6 (18.8)	10.0 (12.5)	0.001
Supine position, % of TST, mean (SD)	58.4 (28.3)	62.3 (23.8)	0.517
Apnea index, events/h, mean (SD)	3.1 (6.3)	2.9 (8.7)	0.025
Mixed apnea index, events/h, mean (SD)	1.2 (4.0)	0.0 (0.1)	0.095
Hypopnea index, events/h, mean (SD)	13.2 (14.3)	7.9 (10.7)	0.022
Longest sleep apnea, sec, mean (SD)	23.7 (19.3)	16.6 (22.8)	0.029
Time below 90% SpO2, % of TST, mean (SD)	5.5 (14.1)	1.2 (2.7)	0.001

MS metabolic syndrome; *SD* standard deviation; *BMI* body mass index; *ESS* Epworth Sleepiness Scale; *SSS* Stanford Sleepiness Scale; *PSQI* Pittsburgh Sleep Quality Index; *CRP* C-reactive protein; *ESR* erythrocyte sedimentation rate; *N1* stage 1; *N2* stage 2; *N3* stage 3; *REM* rapid eye movement; *PLMS* periodic limb movement during sleep; *AHI* apnea-hypopnea index; *SpO2* peripheral oxygen saturation; *TST* total sleep time

Table 2 Univariate logistic regression for clinical and polysomnographic predictors of metabolic syndrome

	Odds ratio	95% confidence interval	*p* value
Clinical variables			
Age	1.05	1.01–1.08	0.011
Men	0.79	0.33–1.85	0.580
BMI	1.29	1.09–1.53	0.004
ESS	0.77	0.45–1.32	0.343
PSQI	1.05	0.92–1.20	0.485
Hypertension	25.67	5.44–121.00	< 0.001
Diabetes mellitus			
Dyslipidemia	18.86	4.00–88.90	< 0.001
Cardiovascular disease	5.14	0.55–48.09	0.151
Smoking	1.21	0.36–4.11	0.758
Alcohol	0.98	0.37–2.59	0.963
Polysomnographic variables			
Total sleep time	1.00	0.99–1.01	0.441
Proportion of N1 sleep	1.04	0.99–1.08	0.112
Proportion of N2 sleep	0.99	0.94–1.04	0.644
Proportion of N3 sleep	0.95	0.90–1.00	0.061
Proportion of REM sleep	1.01	0.96–1.07	0.689
Sleep latency	0.97	0.93–1.01	0.143
REM sleep latency	1.00	0.99–1.01	0.925
Sleep efficiency	1.00	0.97–1.04	0.805
Arousal index	1.03	1.00–1.07	0.072
PLMS index	1.03	0.99–1.08	0.097
AHI	1.03	1.00–1.06	0.038
AHI during NREM sleep	1.02	0.99–1.05	0.091
AHI during NREM sleep ≥ 15/h	2.38	0.86–6.54	0.094
AHI during REM sleep	1.06	1.02–1.09	0.002
AHI during REM sleep ≥ 15/h	5.91	2.24–15.56	< 0.001
Supine position	0.99	0.98–1.01	0.487
Apnea index	1.00	0.95–1.06	0.925
Hypopnea index	1.04	0.99–1.08	0.071
Longest sleep apnea	1.02	0.99–1.04	0.139
Time below 90% SpO2	1.16	1.02–1.31	0.026

BMI body mass index; *ESS* Epworth Sleepiness Scale; *SSS* Stanford Sleepiness Scale; *PSQI* Pittsburgh Sleep Quality Index; *N1* stage 1; *N2* stage 2; *N3* stage 3; *REM* rapid eye movement; *PLMS* periodic limb movement during sleep; *AHI* apnea-hypopnea index; *SpO2* peripheral oxygen saturation

upper airway increases during REM sleep due to decreased muscle tone of genioglossus from the cholinergic-mediated inhibition of the hypoglossal nerve [20, 21]. Obstructive apneas and hypopneas during REM sleep were of longer duration and led to greater oxygen desaturation compared to those of non-REM sleep [22–24].

Mokhlesi et al. demonstrated that OSA during REM sleep is independently associated with the higher prevalence and incidence of hypertension. Increasing quartiles of REM AHI were strongly associated with hypertension as a dose relationship between REM AHI and hypertension [25]. A recent report from a population-based longitudinal cohort from Australia revealed that severe REM OSA (REM AHI ≥ 30/h) was independently associated with prevalent and recent onset hypertension [odds ratio (OR) 2.4, 95% confidence interval (CI) 1.42–4.06; and OR 2.24, 95% CI 1.04–4.81, respectively] [26]. Blood pressure (BP) normally declines by more than 10–20% at nighttime during sleep compared to waking BP. Non-dipping BP, which may be a marker for the development of hypertension, has been associated with worsened cardiovascular outcome and increased target organ damage [27]. In another longitudinal analysis from WSCS, OSA in REM sleep, independent of NREM OSA, was significantly associated with incidental nocturnal non-dipping of BP [28].

OSA has been considered to be associated with impaired glucose metabolism such as fasting hyperglycemia, insulin

Table 3 Multivariate logistic regression model for the predictors of metabolic syndrome

Model	Odds ratio	95% confidence interval	*p value*
Model 1			
Age	1.09	1.03–1.16	0.005
Body mass index	1.24	0.99–1.55	0.063
AHI ≥ 15/h	1.54	1.09–2.04	0.034
Model 2			
Age	1.05	1.01–1.09	0.028
Body mass index	1.27	1.03–1.56	0.027
AHI during REM sleep	1.45	1.21–1.76	0.026
AHI during NREM sleep	0.97	0.93–1.02	0.231
Model 3			
Age	1.05	1.01–1.09	0.022
Body mass index	1.22	1.01–1.48	0.042
AHI ≥ 15/h during REM sleep	7.08	1.60–31.41	0.010
AHI ≥ 15/h during NREM sleep	2.16	0.40–11.76	0.372

REM rapid eye movement; *NREM* non-REM; *AHI* apnea-hypopnea index

resistance, and impaired glucose tolerance [29, 30]. In a community-based study with 3310 participants, AHI during REM sleep was associated with insulin resistance, even in the absence of NREM AHI [31]. Increasing severity of OSA during REM sleep was shown to be associated with worsened glycemic control in type 2 diabetes [32]. In a study with continuous positive airway pressure (CPAP) treatment, CPAP usage during the entire 8-h sleep period (covering all REM sleep) improved glycemic control without increasing serum insulin levels, which suggests that restoration of OSA decreases insulin resistance [33].

In the current study, patients with a REM AHI at least 15/h had an approximately 7-fold greater OR of the presence of metabolic syndrome after adjusting for age, BMI, and NREM AHI. Our unique findings from Asian patients are evidence for the necessity to treat moderate to severe OSA during REM sleep. In a European population-based study, REM AHI ≥ 20/h was independently associated with metabolic syndrome (OR 1.94) [13], which was lower than that (OR 7.08) of our Korean population. White Europeans were more obese based on BMI and waist circumference in comparison with Asians [34]. Ethnic difference of obesity might contribute to the different risks of obesity for metabolic syndrome. Our findings suggest that metabolic syndrome in Asians could be more affected by other factors such as REM AHI than Europeans. Wen et al. reported that Asian population showed significant mortality risks started at BMI ≥ 25.0 kg/m^2, rather than BMI ≥ 30.0 kg/m^2 [35]. Country-specific and ethnic-specific BMI cut-off points should be applied in the future studies [36], although obesity might be less contributable to the risk for metabolic syndrome in our study of Asians in comparison with Europeans or Caucasians.

In the perspective of pathophysiology in apneic events during REM sleep, several plausible mechanisms may act to lower the threshold for the development of metabolic syndrome. There is an increased risk of upper airway collapse, elevated sympathetic activity, and a higher tendency of blood pressure increase during REM sleep than during NREM sleep [6, 21]. Furthermore, longer duration of sleep apnea or hypopnea, greater oxygen desaturation, and impaired hypoxic and hypercapnic respiratory drive occur during REM sleep [22, 23]. These multiple mechanistic changes could intermediately increase the risk of each diagnostic component of metabolic syndrome, including hypertension, diabetes, and dyslipidemia.

In conclusion, metabolic syndrome is frequently present in patients with OSA. Moderate to severe OSA during REM sleep is common, and REM AHI can be a predictor for metabolic syndrome. Especially in patients with REM AHI greater than 15/h, the risk of comorbid metabolic syndrome should not be overlooked, and each component of metabolic syndrome should be diagnosed and treated simultaneously with OSA therapy. Because REM sleep primarily or usually occurs in the latter half of the patients' sleeping period, both diagnostic studies and CPAP titration studies should include early morning hours before awakening. Further studies need to be performed to elucidate the differential mechanisms by which sleep-disordered breathing in REM sleep contributes to the metabolic syndrome in both Asian and other ethnic populations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict(s) of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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Comment This study finds an association between the metabolic syndrome and OSA during REM sleep, with an adjusted OR of 7.08, but no significant association with non-REM OSA. This study adds to the growing body of literature finding REM OSA to be associated with cardiometabolic outcomes. A study in a Caucasian population (HypnoLaus cohort) also found an association between REM OSA and metabolic syndrome. The lower OR in that study may have been due to the different ethnicity of participants but also to the population-based rather than clinical-based study design. Several particularities of REM OSA may account for greater impact on outcomes as discussed by authors, notably, often more marked hypoxemia.

Although analyses were adjusted for body mass index, BMI is a poor predictor of metabolic and cardiovascular complications. Rather, waist circumference, which reflects visceral fat, is much more predictive but was not adjusted for and remains a possible confounder in this study. Further studies in different populations will need to more clearly delineate the role of OSA itself, including related intermittent hypoxemia, sleep fragmentation and deprivation, autonomic activation, etc., on metabolic dysregulation. Could an interaction exist between increased visceral fat and intermittent hypoxemia? Treatment studies will be particularly important to help guide clinical practice. Should we be more aggressive in treating patients with lower overall AHI if REM AHI is ≥ 15/h?

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