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【 ORIGINAL ARTICLE 】

Gender Differences in the Clinical Features of Sleep Apnea Syndrome

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Abstract:

Objective Sleep apnea syndrome is more prevalent among men than women and is frequently accompanied by metabolic syndrome (MetS). However, gender differences in the effect of sleep-disordered breathing (SDB) leading to the risk of MetS remain unclear. The aim of our study was to investigate the clinical characteristics of SDB in women and the differential influence of SDB on MetS between genders.

Methods In a single-center retrospective study, we compared the data of 1,809 consecutive SDB patients by gender to clarify the characteristics of sleep disorders in women. We also compared the prevalence of MetS and its related abnormalities by gender. A logistic regression analysis was used to determine the contributory factors for MetS.

Results The mean age and proportion of patients over 50 years of age were higher in women than in men. SDB was milder in women than in men according to polysomnography findings. Elevated Hemoglobin A1c levels and hyperlipidemia were less frequent in women than in men. The MetS prevalence was similar in women and men (30.0% vs. 35.2%). A logistic regression analysis showed that the apnea-hypopnea index (AHI) was an independent risk factor for MetS in both genders, but that female gender was independently associated with a decreased prevalence of MetS and its related abnormalities.

Conclusion Female SDB patients tend to be older with milder apnea and sleepiness than male SDB patients. A higher AHI is a significant risk factor for MetS in both genders, although female gender is an independent inhibitory factor for developing MetS in SDB patients.

Key words: sleep apnea, gender, polysomnography, metabolic syndrome

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Introduction

Sleep-disordered breathing (SDB) and sleep apnea syndrome are more prevalent among men than women. According to the Wisconsin Sleep Study in the United States, the prevalence of SDB among subjects with an apnea-hypopnea index (AHI) ≥5 was 24.0% in men and 9.0% in women (1) Those with an AHI ≥5 and accompanying symptoms of daytime drowsiness were diagnosed with SDB, the prevalence of which was 4.0% in men and 2.0% in women (1). Based on epidemiological data, the ratio of men to women with SDB was approximately 2-3:1 (2) whereas the ratio of men to women with SDB diagnosed in sleep laboratories was much more striking at approximately 8-10:1 (3).

SDB is a significant risk factor for cardio-cerebrovascular diseases, such as obesity, hypertension, hyperlipidemia, and glucose metabolic disorder. Therefore, the prevalence of metabolic syndrome (MetS) is extremely high in patients with severe SDB (4). These complications are thought to re-

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sult from insulin resistance in SDB, and SDB itself may be a cause of insulin resistance (5-8). Previous large-scale epidemiological surveys have reported a relationship between SDB and insulin resistance (9, 10). Marin et al. reported that untreated obstructive sleep apnea syndrome in men with an AHI ≥30 (average age, 50 years) increased the cardiovascular risk by 3-fold compared with healthy subjects, and 10% of patients were likely to die of cardiovascular diseases within 10 years (11). However, in women, no significant association between mortality and SDB was identified in a large-scale epidemiological study (12).

In the general Japanese adult population, the prevalence of MetS diagnosed by the Japanese Committee of the Criteria for MetS (JCCMS) is higher in men (12.0%) than in women (1.3%) (13). SDB is frequently accompanied by MetS; however, gender differences in the influence of SDB on MetS remain unclear. In addition, whether or not the influence of apnea on the development of MetS differs by gender is also unclear.

The aim of our study was to clarify the clinical features of female SDB and to investigate the gender differences in the influence of SDB on MetS.

Materials and Methods

Patients

This single-center retrospective study evaluated consecutive patients who visited Fujita Health University Hospital with symptoms suggestive of SDB between 2003 and 2012. We included patients over 20 years of age who underwent polysomnography (PSG) and were diagnosed with SDB with an AHI ≥5. We excluded patients with complications of narcolepsy, rapid eye movement (REM) sleep behavior disorders, non-REM parasomnia, and restless leg syndrome. The study protocol was approved by the Clinical Research Ethical Review Board of Fujita Health University (Fujita IRB #10-183).

Polysomnography

Each patient underwent overnight full PSG in a sleep laboratory at Fujita Health University Hospital. PSG included electroencephalography, electrooculography, electromyography of the chin, and electrocardiography, as well as assessments of the nasal and oral flows, thoracic and abdominal respiratory movements, and percutaneous arterial oxygen saturation (SpO_2). Nasal flows were recorded with thermal sensors and pressure sensors. Oral flows were recorded with thermal sensors. Thoracic and abdominal respiratory movements were measured by inductive plethysmography. SpO_2 was monitored continuously with a pulse oximeter. Respiratory events were diagnosed in accordance with the criteria of the American Academy of Sleep Medicine (14). In brief, apnea was defined as the cessation of airflow for at least 10 seconds, and hypopnea was defined as an abnormal respiratory event with a ≥30% reduction, relative to baseline, in the thoraco-abdominal movement or airflow lasting for at least 10 seconds and accompanied by >4% oxygen desaturation.

Sleep stages were scored in accordance with the international criteria proposed by Rechtschaffen and Kales (15). All of the above physiological data were recorded on one of the following three polygraphs: an Alice 3 System (Healthdyne, Atlanta, USA), a Somnostar (Carefusion, San Diego, USA), or a Sandman (Embla, Ontario, Canada). Arousals were classified according to the American Academy of Sleep Medicine criteria of 1999 (16).

Procedures and measurements

Before the start of PSG, we measured the height, weight, body mass index (BMI), systolic and diastolic blood pressures, neck circumference, abdominal circumference at the level of the umbilicus, and buttock circumference. The Epworth Sleepiness Scale (ESS) was used for the subjective analysis of daytime sleepiness. The morning after PSG, all patients underwent general blood sampling and a 75-g oral glucose tolerance test (OGTT). Patients who had already been diagnosed with diabetes were excluded from the OGTT. Plasma glucose and serum insulin levels were determined at 0, 30, 60, 90, and 120 minutes. Glucose levels <110 mg/dL at baseline and <140 mg/dL at 120 minutes in OGTT were defined as normal, and diabetes mellitus was diagnosed if the glucose levels were ≥126 mg/dL at baseline and ≥200 mg/dL at 120 minutes on the OGTT. Patients falling into neither of these categories were considered to have borderline diabetes mellitus (17). Insulin resistance was determined using the homeostasis model assessment for insulin resistance (HOMA-IR): [fasting insulin (μU/mL)×fasting plasma glucose (mg/dL)]/405 (18).

The diagnosis of MetS

The presence of MetS was determined according to the JCCMS criteria. In brief, men and women with a waist circumference of ≥85 cm and ≥90 cm, respectively, and who met at least two of the following four criteria were diagnosed with MetS: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or being treated for hypertension; triglyceride (TG) level ≥150 mg/dL or being treated for high TG; high-density lipoprotein cholesterol (HDL-C) level <40 mg/dL; and fasting blood glucose level ≥110 mg/dL, or diagnosed with diabetes mellitus.

Statistical analyses

Because data were not normally distributed according to the Shapiro-Wilk's test, the results were presented as the medians and interquartile range. The univariate analysis and comparisons between two groups were performed by the Wilcoxon test or Pearson's chi-squared test. In this study, we compared the clinical data of our SDB patients with the data from other reliable cohort studies with clearly reported sample sizes, average values, and standard deviations (19, 20). A logistic regression analysis was performed

to determine the differential contribution of multiple factors. All analyses were performed using the JMP software program, (version 9.0.2 for Windows, Japanese version; SAS Institute, Tokyo, Japan).

Results

Patient characteristics

We enrolled a total of 1,809 consecutive SDB patients (1,531 men and 278 women). The main complaints of patients in our study were heavy snoring, witnessed apnea, and excessive daytime sleepiness. Women complained of a greater variety of symptoms than men, such as interrupted sleep, insomnia, body pain, and nocturia. The median ages of the men and women were 52 and 59 years, respectively, with the age distribution by gender differing significantly (Figure). Men in their 50s were the largest group, followed by men in their 40s. In contrast, nearly 80% of women were ≥50 years of age. The male-to-female ratios of all patients, patients <50 years of age, and patients ≥50 years of age were 5.2, 8.8, and 3.8 respectively. Smoking status also differed by gender, with 32% of men and 8.1% of women being current smokers (Table 1).

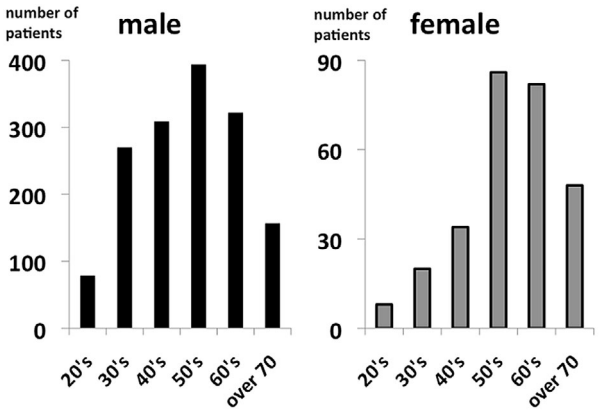

Figure. The age distribution of patients diagnosed with SDB with an AHI ≥5 and sleep-related symptoms. While men showed a relatively symmetrical distribution, with a peak occurrence in their 50's, the distribution of women deviated to ≥50 years of age. SDB: sleep-disordered breathing, AHI: apnea-hypopnea index

Table 1 summarizes the anthropometrical parameters of SDB patients in our study. The median index and distribution of BMI classification were similar between the genders. The neck and abdominal circumferences were larger in men than in women.

Different characteristics of sleep disorders and PSG findings between genders

Next, we compared the characteristics of sleep disorders in SDB patients by gender. The ESS scores and detailed PSG findings are shown in Table 2. Women had lower ESS scores than men. PSG findings showed that the apnea index (AI) and AHI were lower, the duration of time with SpO_2 <90% shorter, and the desaturation slighter in women than in men. In contrast, women had a shorter total sleep time (TST) and lower sleep efficacy and arousal index than men. Nocturnal awakening was more common in women than in men. With regard to sleep stages, the third and fourth stages comprised a greater proportion of sleep time in women than in men. The distribution of patients by SDB severity also differed between genders. More than 60% of men were categorized as having severe SDB, whereas mild, moderate, and severe SDB were evenly distributed among women.

Gender differences in the prevalence of mets and related abnormalities in SDB patients (Table 3)

We analyzed the prevalence of MetS and its related factors in our patients. The MetS prevalence did not differ significantly between men (35.2%) and women (30.0%) with SDB. While no gender differences were found in the blood pressure, the abdominal circumference was higher in men (78.1%) than in women (42.2%). An assessment of the parameters of lipid metabolism showed that a higher percentage of men had TG concentrations ≥150 mg/dL and HDL-C <40 mg/dL. Although abnormal Hemoglobin A1c (HbA1c) levels (≥5.8%) were significantly more frequent in women than in men, there were no gender differences in the prevalence of abnormalities in other factors related to glucose metabolism, including the fasting blood glucose levels, fasting insulin levels, HOMA-IR, and diabetic pattern on the 75-g

Table 1. Patients Characteristics.

		Male (n=1,531)	Female (n=278)	p value
Age	years	52.0 (41.0-61.0)	59.0 (51.0-67.0)	<0.0001
Smoking status (never : ex : current)	%	22.4: 45.6: 32.0	76.9: 15.0: 8.1	<0.0001
BMI*	≥25 kg/m^2	60.2%	59.4%	N.S.
BMI* classification				
(underweight : normal : overweight : obese)	%	1.7: 38.1: 39.9: 20.4	2.2: 38.4: 33.0: 26.5	N.S.
Neck circumference	cm	39.0 (37.5-41.5)	35.0 (33.0-37.5)	<0.0001
Abdominal circumference	cm	91.3 (85.5-98.0)	88.0 (80.0-96.5)	<0.0001
Buttock circumference	cm	97.0 (92.0-102.0)	96.0 (90.0-103.0)	N.S.

Data are expressed as median with IQR (interquartile range) except for BMI and smoking status classification.

BMI: body mass index, N.S.: not significant

Table 2. Different Characteristics of Sleep Disorders by Gender.

		Male (n=1,531)	Female (n=278)	p value
Epworth sleepiness scale		8.0 (5.0-12.0)	7.0 (4.0-12.0)	<0.01
Apnea Index	Events/h	19.3 (6.9-46.3)	8.4 (2.7-27.0)	<0.0001
Apnea Hypopnea Index	Events/h	34.5 (18.9-55.5)	22.8 (12.3-45.5)	<0.0001
3% Oxygen desaturation index	Times/h	16.5 (6.6-34.2)	12.4 (5.6-30.5)	<0.05
% Time of SpO_2<90%	%SPT	3.6 (0.6-16.4)	1.7 (0.3-9.8)	<0.001
Lowest SpO_2	%	79.0 (72.0-85.0)	81.5 (73.8-86.0)	<0.05
Total sleep time	min	469.5 (447.0-490.5)	466.0 (444.8-482.6)	<0.05
Sleep efficiency	%SPT	90.1 (81.6-95.4)	87.5 (80.0-93.1)	<0.01
Intermittent awakening	%SPT	9.4 (4.4-17.8)	12.5 (6.5-19.8)	<0.001
Rapid eye movement (REM) sleep	%TST	15.7 (10.8-19.9)	15.7 (10.0-20.7)	N.S.
Non-REM sleep 1st Stage	%TST	10.8 (5.7-19.6)	8.0 (4.5-14.7)	<0.0001
Non-REM sleep 2nd Stage	%TST	63.6 (53.9-71.6)	61.6 (50.9-70.5)	N.S.
Non-REM sleep 3rd+4th Stage	%TST	3.2 (0.0-10.0)	8.1 (1.3-15.1)	<0.0001
Arousal Index	Events/h	26.0 (14.8-43.6)	19.3 (10.3-36.8)	<0.0001
SDB severity (mild : moderate : severe)	%	19.2: 23.9: 56.9	31.6: 26.6: 41.7	<0.0001

Data are expressed as median with ICR except for SDB severity.

%SPT: % Time of sleep period time, %TST: % Time of total sleep time, N.S.: not significant

Table 3. Gender Differences in Prevalence of Metabolic Syndrome and Related Factors Abnormality in SDB Patients.

		Male (n=1,531)	Female (n=278)	p value
Metabolic syndrome		35.2	30.0	N.S.
Body mass index	≥25 kg/m^2	60.2	59.4	N.S.
Abdominal circumference*	male; ≥85 cm, female; ≥90 cm	78.1	42.2	<0.001
Blood pressure	≥130 mmHg and/or ≥85 mmHg	76.2	80.7	N.S.
Hemoglobin A1c	≥5.8%	24.8	32.3	<0.05
Fasting blood glucose level	≥110 mg/dL	29.1	32.6	N.S.
Fasting blood insulin level	≥10 μU/mL	37.6	37.2	N.S.
HOMA-IR	≥2.5	37.7	41.0	N.S.
75-g oral glucose tolerance test	Diabetic**	29.1	32.1	N.S.
Triglyceride	≥150 mg/dL	46.9	25.4	<0.001
HDL cholesterol	<40 mg/dL	17.4	9.8	<0.01

Data are expressed as percentage.

*Cut off value of waist circumference has been adjusted to East Asian standards.

**75-g oral glucose tolerance test diabetic: fasting blood glucose level ≥126 mg/dL or 2 hour OGTT glucose level ≥200 mg/dL.

HOMA-IR: homeostasis model assessment for insulin resistance, N.S.: not significant

OGTT. There were also no gender differences in the prevalence of an abnormal BMI.

Impact of female gender on the prevalence of MetS and impaired glucose tolerance in SDB patients

A multivariate logistic regression analysis showed that the AHI [adjusted odds ratio (aOR) 1.014; 95% confidence interval (CI) 1.008-1.023, p<0.0001], age (aOR 1.031; 95% CI 1.019-1.044, p<0.0001), BMI (aOR 1.276; 95% CI 1.276-1.388, p<0.0001), and smoking status (aOR 1.885; 95% CI 1.288-2.771, p=0.001) were independent risk factors for MetS (Table 4). The AHI was also an independent risk factor for indicators of impaired glucose tolerance, including HOMA-IR score (aOR 1.008; 95% CI 1.001-1.014, p<0.05) and the diabetic pattern on the 75-g OGTT (aOR 1.012; 95% CI 1.006-1.019, p<0.001) (data not shown).

Female gender was also significantly associated with a reduced prevalence of MetS (aOR 0.580; 95% CI 0.365-0.912, p=0.018) (Table 4). We therefore investigated whether or not the gender of SDB patients influenced the prevalence of abnormalities in factors related to MetS and impaired glucose tolerance, independent of the AHI, age, BMI, and smoking status. As shown in Table 5, female gender was independently associated with a decreased prevalence of abnormal serum TG levels, HDL-C levels, and abdominal circumference. Gender differences did not contribute to an abnormal

Table 4. A Multiple Regression Analysis on the Prevalence of the Metabolic Syndrome in SDB Patients.

		Adjusted odds ratio	95% CI	p value
AHI		1.014	1.076-1.023	<0.0001
Age		1.031	1.019-1.044	<0.0001
BMI		1.329	1.276-1.388	<0.0001
Never smoker	(vs. current)	1.885	1.288-2.771	0.001
Ex smoker	(vs. current)	1.617	1.156-2.264	0.005
Female gender		0.58	0.365-0.912	0.018

AHI: apnea hypopnea index, BMI: body mass index

Table 5. Impact of Female Gender on the Prevalence of the Metabolic Syndrome and Impaired Glucose Tolerance in SDB Patients.

		Adjusted odds ratio*		95% CI	p value
		Male	Female		
Metabolic syndrome prevalence		1	0.581	0.365-0.921	<0.05
Abdominal circumference	Male ≥85 cm Female ≥90 cm	1	0.026	0.014-0.048	<0.0001
Blood pressure	≥130 mmHg and/or ≥85 mmHg	1	0.955	0.618-1.498	N.S.
Fasting blood glucose level	≥110 mg/dL	1	0.943	0.647-1.437	N.S.
Triglyceride	≥150 mg/dL	1	0.478	0.329-0.687	<0.0001
HDL cholesterol	<40 mg/dL	1	0.526	0.301-0.882	<0.05
HOMA-IR	≥2.5	1	1.114	0.708-1.743	N.S.
75-g oral glucose tolerance test	Diabetic**	1	0.689	0.408-1.142	N.S.

Data are expressed as OR with 95% CI.

*Odds ratios were adjusted for age, Body mass index, and apnea hypopnea index (AHI), and smoking status (never, ex, current).

**75-g oral glucose tolerance test diabetic: fasting blood glucose level ≥126 mg/dL or 2 hour OGTT glucose level ≥200 mg/dL.

HOMA- IR: homeostasis model assessment for insulin resistance, N.S.: not significant

HOMA-IR or impaired glucose tolerance.

Finally, we evaluated the influence of SDB (AHI) on the prevalence of MetS and impaired glucose tolerance in men and women separately (Table 6). A multivariate logistic regression analysis with adjustments for the age, BMI, and smoking status showed that the AHI was independently associated with an increased prevalence of MetS (OR 1.022 95% CI 1.007-1.039 p=0.0048) and abnormalities in serum TG levels, HDL-C levels, and HOMA-IR in women. In men, the AHI was independently associated with an increased prevalence of MetS and abdominal circumference, fasting blood glucose, serum TG levels, and the diabetic pattern on the 75-g OGTT.

Discussion

The prevalence of SDB is higher in men than in women and is higher in postmenopausal women than in premenopausal women (21). Our study showed that the number of female SDB patients increased from 50 years of age, with female patients <50 years of age being rare. Although we were unable to obtain information on the menopausal status of women in this study, the mean age of natural menopause in Japanese women is 49.33 years (22). Therefore, our results suggest that the incidence of sleep disorders in women increases drastically after menopause. Furthermore, female hormones may inhibit the onset of SDB (23). Previous studies have similarly shown that progesterone increases the hypercapnic and hypoxic ventilatory responses and activates the upper airway muscles (23), leading to the suppression of SDB onset. In addition, the rates of obesity are higher in men <50 years of age and women ≥50 years of age (20), a finding that may correlate with the increased number of female SDB patients after menopause. However, our study also showed significant gender differences among SDB patients ≥50 years of age.

AHI and sleepiness have been shown to be milder in women than in men, even among older subjects, suggesting that factors other than female hormones, such as anatomical differences in the jaw, face, and upper airway structures between genders, may be related to the relative mildness of SDB in women (24). Our study found that the neck and abdominal circumferences were lower in women than in men, although no marked difference in the buttock circumference

Table 6. Impact of AHI on the Prevalence of the Metabolic Syndrome and Its Related Abnormalities in SDB Patients by Gender.

	Female		Male	
	Adjusted odds ratio* (95% CI)	p value	Adjusted odds ratio* (95% CI)	p value
Metabolic syndrome JCCMS	1.022 (1.007-1.039)	0.005§	1.010 (1.010-1.020)	0.001§
Abdominal circumference	1.001 (0.983-1.019)	0.946	1.016 (1.006-1.028)	0.002§
Hyper tension**	1.014 (0.997-1.033)	0.118	1.007 (1.000-1.014)	0.047
Fasting blood glucose level	1.012 (0.999-1.025)	0.068	1.01 (1.004-1.016)	0.002§
Triglyceride	1.015 (1.003-1.028)	0.018§	1.008 (1.002-1.013)	0.007§
HDL cholesterol	1.022 (1.004-1.041)	0.014§	1.002 (0.995-1.009)	0.556
HOMA-IR	1.019 (1.002-1.036)	0.024§	1.006 (0.999-1.013)	0.082
75 g OGTT diabetic type***	1.010 (0.994-1.028)	0.220	1.013 (1.005-1.020)	0.001§

Data are expressed as OR with 95% CI. §p<0.05.

*odds ratios were adjusted for age, Body mass index, and smoking status (never, ex, current).

**Hyper tension: systolic blood pressure ≥130 mmHg and/or diastric blood pressure ≥85 mmHg

***75 g OGTT diabetic type: fasting blood glucose level ≥126 mg/dL or 2 hour OGTT glucose level ≥200 mg/dL

was noted. While women tend to develop subcutaneous fat rather than visceral fat obesity, male body fat distributions tend to be in the upper body (25). Comparisons of age- and BMI-matched men and women have shown that the distribution of fat in the neck area is proportionately higher in men than in women (24). Thus, the pattern of fat tissue distribution may be associated with the gender-based differences in the severity of SDB.

Previous studies have found that SDB and MetS frequently accompany each other (4), with this combination further increasing the risk of cardiovascular disease based on sclerosis of the arterial walls and vasculitis (26). SDB-induced hypoxemia and its rapid recovery cause oxidative stress, inducing the activation of reactive oxygen species-sensitive transcription factors (nuclear factor-kappa B and activator protein 1) (27), followed by the production of inflammatory cytokines (tumor necrosis factor-α and interleukin-6) (28), which are presumably linked to the onset of insulin resistance (5-8) and MetS (4).

Elevated HbA1c (≥5.8%) was observed in 24.8% of male SDB patients and 32.3% of female SDB patients, with both being significantly higher than in the general population (in 16.4% of men and 10.9% of women, p<0.0001 each) (11). Our study also revealed that an increased AHI was significantly related to increased insulin resistance (abnormal HOMA-IR) and lower glucose tolerance (abnormal 75-g OGTT results) in accordance with previous reports (29). Although the MetS prevalence in the general Japanese population is higher in men than in women (12.0% vs. 1.3%) (13), the MetS prevalence among SDB patients in our study did not differ markedly between genders.

A previous study also showed that risk factors for MetS (diagnosed according to the criteria of the JCCMS) differed between Japanese men and women (30). Furthermore, the age, BMI, and AHI were independently associated with MetS in men, whereas the BMI was the only independent risk factor for MetS in women. In contrast, our analysis showed that the AHI was an independent risk factor for MetS in both genders. We found that female gender was inversely associated with MetS prevalence, i.e. apneic women may be resistant to MetS. Nevertheless, our findings indicated that the AHI was still an independent risk factor for MetS in women. The differences in these results between studies may be due to the sample size in our study being larger than in other studies (30).

Several limitations associated with the present study warrant mention. First, as all of our study subjects were Japanese, caution should be exercised when applying these results to other ethnic populations. The gender differences observed in our study may differ for other ethnicities with different physical characteristics. Second, we were unable to obtain information about the menopausal status of the women in this study. Therefore, we were unable to compare the SDB characteristics in women before and after menopause. Third, we enrolled patients who visited the outpatient clinic with symptoms or were referred from other doctors for suspicion of SDB. Asymptomatic patients and patients with atypical symptoms were not included in our study. Fourth, our study was a retrospective analysis in a single university hospital, suggesting the need for a large, prospective, multi-center study to confirm our findings.

In conclusion, female SDB patients tended to be older with milder apnea and sleepiness than male SDB patients. This study clearly demonstrates that a higher AHI is a significant risk factor for MetS in both genders. However, female gender was inversely associated with MetS prevalence independently of other factors, such as apneic severity, suggesting that apnea may make women more resistant to MetS than men. Further prospective observational studies in the entire Japanese population are warranted to confirm these findings.

The authors state that they have no Conflict of Interest (COI).

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