Original Article

Associations of Sleep-Disordered Breathing with Excessive Daytime Sleepiness and Blood Pressure in Japanese Women

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Sleep-disordered breathing (SDB) is a recognized risk factor for excessive daytime sleepiness (EDS) and hypertension, but evidence of this association in Asian women is limited. We conducted a cross-sectional study of 3,568 women aged 30–69 years living in three Japanese communities. The 3% oxygen desaturation index (ODI) was selected as the indicator of SDB, and blood oxygen fall was estimated by overnight pulse oximetry. The prevalence of SDB was 20.2% for 3% ODI ≥ 5, 6.4% for 3% ODI ≥ 10, and 2.8% for 3% ODI ≥ 15 among Japanese women aged 30–69 years. The 3% ODI was positively associated with the prevalence of self-reported EDS and mean values of systolic and diastolic blood pressure levels. The multivariate odds ratios for 3% ODI of 5–9, 10–14, and ≥ 15 in reference to 3% ODI < 5 were 1.9 (1.2–3.0), 2.2 (1.0–4.6), and 1.8 (0.7–4.4) (*p* for trend = 0.01), respectively, for EDS and 1.1 (0.9–1.4), 1.2 (0.8–1.8), and 2.2 (1.4–3.4) (*p* for trend < 0.001), respectively, for hypertension. The severity of SDB was significantly associated with EDS and hypertension among Japanese women. (*Hypertens Res* 2008; 31: 501–506)

***Key Words*: epidemiology, sleep-disordered breathing, hypertension, excessive daytime sleepiness**

Introduction

Sleep-disordered breathing (SDB) is characterized by loud snoring and repeated episodes of complete or partial airway obstruction during sleep. Several epidemiological studies have reported that SDB correlates with hypertension (*1–5*) and other cardiovascular risk factors, such as age, body mass index (BMI), diabetes, high lipid levels (*6*), hypertension with a family history (*7*), metabolic syndrome (*8*), and the incidence of cardiovascular disease or total death (*9–11*). Previous studies have indicated a wide range of values for the prevalence of SDB in females—9–19% in American women (*2*, *12*), 28% in Spanish women (*4*), 16% in Korean women (*13*), and 30% in Chinese women living in Hong Kong (*14*)—but no data has been available for Japanese women. Several epidemiological studies using the 3% oxygen desaturation index (ODI) as an indicator of SDB reported that 3% ODI correlated with excessive daytime sleepiness (EDS) (*15*) and blood pressure levels in Japanese men (*15–17*). However, no

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This study was supported in part by a Grant-in-Aid for Scientific Research B (No. 18390194 in 2006–2008) and for Exploratory Research (No. 18659179 in 2006–2007) from the Japanese Society for the Promotion of Science, and by a Sports Research Grant (No. 17659184 in 2005–2006) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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Received April 18, 2007; Accepted in revised form October 10, 2007.

data are available on the association of 3% ODI with EDS and blood pressure levels in Japanese women.

Our *a priori* hypothesis is that women with SDB experience more severe EDS and higher blood pressure levels than those without SDB. In the present community-based study of 3,568 Japanese women, we used pulse oximetry to evaluate nocturnal oxygen desaturation and to examine the association of SDB with EDS and blood pressure levels.

Methods

Subjects

The subjects comprised 3,626 women, aged 30–69 years, who participated in a cardiovascular risk survey study and underwent a sleep investigation between 2001 and 2005, and who lived in an urban community of the district of Yao City, a suburb of Osaka ($n=1,438$; the recruitment rate among the cardiovascular survey participants = 82%), or in the two rural towns of Ikawa in northeast Japan ($n=609$; 85%) and Kyowa in central Japan ($n=1,579$; 79%). We excluded 58 women who had a history of stroke or coronary heart disease, leaving a total of 3,568 participants who were included in the analysis.

Annual cardiovascular risk surveys have been conducted since 1963 at Yao City and Ikawa, and since 1981 at Kyowa (*18–20*) by a research team of the Osaka Medical Center for Health Science and Promotion, and the University of Tsukuba. For each subject, physician epidemiologists and trained staff members explained the protocol in detail, and obtained informed consent. The study protocol was approved by the Medical Ethics Committee of the University of Tsukuba.

Measurement of Cardiovascular Risk Factors

Systolic and diastolic blood pressures (SBP and DBP) were measured by physicians using a standard mercury sphygmomanometer on the right arm while the subject was quietly seated after an at least 5-min rest. Blood pressure was measured between 8:00 AM and 4:00 PM and during the same season for each community: March in Yao, May to June in Ikawa, and October to November in Kyowa. Hypertension was defined as SBP ≥140 mmHg, or DBP ≥90 mmHg and/or use of antihypertensive medication. Height in stocking feet and weight in light clothing were measured, and BMI was calculated as weight (kg)/height^2 (m^2). Interviews were conducted to ascertain the frequency of snoring and apnea (often, sometimes, never, unknown), EDS (often, sometimes, never), morning sleepiness (often, sometimes, never), and number of cigarettes smoked per day, ethanol intake per day, treatment for sleep apnea and hypertension, and past histories of sleep apnea, stroke and coronary heart disease. Persons who reported snoring "often" over the last 3 months were labeled as exhibiting habitual snoring, those who reported having apnea "sometimes" or "often" over the last 3 months were labeled as having apnea, and those who reported having sleepiness early in the morning "often" over the last 3 months were defined as having morning sleepiness. Individuals who reported having EDS "often" over the last 3 months were defined as having EDS. Persons who smoked one or more cigarettes per day were defined as current smokers, and those who had not smoked for 3 months or more were defined as ex-smokers; both never smokers and occasional smokers were regarded as non-smokers because occasional smokers are very rare in Japan (*21*). An interviewer assessed the usual weekly alcohol intake in units of "*go*," a traditional Japanese unit of volume corresponding to 23 g ethanol, and converted it to g of ethanol per day (*22*).

Table 1. Means±SD and Prevalence of Selected Cardiovascular Risk Factors among 3,568 Women Aged 30–69 Years

Number	3,568
Age, years	54.0±9.5
Mean SpO_2	96.4±1.5
3% ODI	3.4±4.6
3% ODI ≥5, %	20.2
3% ODI ≥10, %	6.4
3% ODI ≥15, %	2.8
Excessive daytime sleepiness, %	4.2
Morning sleepiness, %	10.5
Habitual snoring, %	10.1
Apnea, %	4.3
Body mass index, kg/m^2	23.3±3.3
Systolic blood pressure, mmHg	125.2±18.0
Diastolic blood pressure, mmHg	76.5±10.4
Current ethanol intake, %	16.2
Current smokers, %	10.0
Postmenopause, %	70.5
Antihypertensive medication use, %	14.9
Hypertension, %	31.0

SpO_2, arterial oxygen saturation; ODI, oxygen desaturation index. Habitual snoring: snoring "often" over the last 3 months; apnea: apnea "sometimes" or "often" over the last 3 months; morning sleepiness: sleepiness early in the morning over the last 3 months; excessive daytime sleepiness: excessive daytime sleepiness "often" over the last 3 months; hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and/or use of antihypertensive medications.

Assessment of Sleep-Disordered Breathing

Arterial oxygen saturation (SpO_2) was measured using a pulse-oximeter (PULSOX-3Si; Minolta Co., Osaka, Japan), which was attached to the left wrist during one night of sleep at home. The ODI was calculated for ≥3% drops in SpO_2 during sleep. The 3% ODI was used as an indicator of SDB as described in previous studies (*15–18*). It represented the num-

Table 2. Age-Adjusted Means ± SEM and Prevalence of Selected Cardiovascular Risk Factors among 3,568 Women Aged 30–69 Years

	3% ODI				*p* for trend
	<5	5–9	10–14	≥15	
Number	2,848	492	127	101	
Age, years	53.6±0.2	56.0±0.4‡	54.7±0.8	54.3±0.9	0.005
Mean SpO_2	96.7±0.03	95.3±0.06‡	95.3±0.12‡	94.9±0.14‡	<0.001
Excessive daytime sleepiness, %	3.6	6.5‡	7.5*	6.3	0.004
Morning sleepiness, %	10.2	10.6	14.5	11.7	0.25
Habitual snoring, %	8.2	15.1‡	22.7‡	24.7‡	<0.001
Apnea, %	3.3	6.5†	9.9†	13.9‡	<0.001
Body mass index, kg/m^2	22.9±0.1	24.7±0.1‡	25.3±0.1‡	26.5±0.3‡	<0.001
Systolic blood pressure, mmHg	123.9±0.3	128.4±0.8‡	131.2±1.5‡	138.1±1.7‡	<0.001
Diastolic blood pressure, mmHg	75.8±0.2	78.5±0.5‡	78.3±0.9†	83.4±1.0‡	<0.001
Current ethanol intake, %	14.3	21.4‡	25.9‡	33.0‡	<0.001
Current smokers, %	9.4	12.6*	11.5	11.1	0.12
Postmenopause, %	67.0	87.8‡	85.5‡	86.0†	0.64
Antihypertensive medication use, %	12.6	19.7‡	27.8‡	39.3‡	<0.001
Hypertension, %	27.8	39.2‡	45.8‡	63.1‡	<0.001

*$p<0.05$, †$p<0.01$, ‡$p<0.001$, compared with 3% ODI <5 category. ODI, oxygen desaturation index; SpO_2, arterial oxygen saturation. The definitions of snoring, apnea, excessive daytime sleepiness, morning sleepiness, and hypertension were shown in Table 1.

ber of events per hour of recording time in which blood oxygen fell by ≥3%. The value of the 3% ODI was taken as the mean value over an at least 4-h period of sleep, as estimated by pulse oximetry. The criteria for SDB were defined by 3% ODI level as ≥5, ≥10, and ≥15 events per hour. A previous clinical validity study reported that the sensitivity was 80% and the specificity was 95% for 3% ODI ≥5 to detect an apnea-hypopnea index of ≥5 (*23*).

Statistical Analysis

Age- and multivariate-adjusted mean values and prevalence of selected SDB risk were calculated according to the categories of nocturnal oxygen desaturation levels (3% ODI: <5, 5–9, 10–14, and ≥15) using analysis of covariance and χ^2 test. The linear trend was tested by a linear regression or logistic regression model using the median variables of nocturnal oxygen desaturation categories. Adjusting for the potentially confounding variables of age (years), BMI (kg/m^2), alcohol intake category (never, former and current <23, 23 to 46 and ≥46 g/day ethanol), current smoking (yes), antihypertensive medication use (yes), menopausal status (pre- and postmenopause), and communities, a logistic regression analysis was performed to estimate the independent associations of nocturnal oxygen desaturation levels with EDS, hypertension, habitual snoring, morning sleepiness, and apnea.

All statistical analyses were performed using SAS version 9.1 software (SAS Institute Inc., Cary, USA). All probability values for statistical tests were two-tailed, and values of $p<0.05$ were regarded as statistically significant.

Results

The prevalence of SDB was 20.2% (720/3,568) for 3% ODI ≥5, 6.4% (228/3,568) for 3% ODI ≥10, and 2.8% (101/3,568) for 3% ODI ≥15 among our study population of Japanese women aged 30–69 years (Table 1).

The prevalence of SDB (3% ODI ≥5) differed among communities: it was 23.4% for Yao City, 19.9% for Ikawa, and 18.1% for Kyowa. However, the associations of SDB severity with EDS and cardiovascular risk factors did not vary by communities (p for interaction >0.05 between any two communities). Therefore, we analyzed these associations for total subjects, adjusting for communities. No subjects were being treated for sleep apnea.

Table 2 shows the mean age and age-adjusted mean values and prevalences of selected cardiovascular risk factors according to categories of nocturnal ODI levels. The 3% ODI was positively associated with each of age, BMI, SBP and DBP, and prevalence of EDS, habitual snoring, apnea, current ethanol intake, antihypertensive medication use and hypertension. The 3% ODI levels were not associated with morning sleepiness, current smoking, and postmenopause.

Table 3 shows the multivariate-adjusted mean values, odds ratios (OR) and 95% confidence intervals (95% CI) of selected cardiovascular risk factors according to the 3% ODI levels. The 3% ODI levels were positively associated with mean values of SBP. The multivariate OR for 3% ODI of 5–9, 10–14, and ≥15 in reference to 3% ODI <5 were 1.9 (1.2–3.0), 2.2 (1.0–4.6), and 1.8 (0.7–4.4) (p for trend = 0.01), respectively, for EDS and 1.1 (0.9–1.4), 1.2 (0.8–1.8), and 2.2

Table 3. Multivariate-Adjusted Means ± SEM, Odds Ratios and 95% CI of Selected Cardiovascular Risk Factors According to 3% ODI Level among 3,568 Women Aged 30–69 Years

	3% ODI				*p* for trend
	<5	5–9	10–14	≥15	
All subjects	2,848	492	127	101	
Antihypertensive medication use, %	13.5	16.8*	23.1†	32.9‡	<0.001
Mean SpO_2	96.6±0.03	95.5±0.06‡	95.6±0.12‡	95.2±0.13‡	<0.001
Systolic blood pressure, mmHg	125.0±0.3	125.3±0.7	125.4±1.5	129.5±1.6†	0.02
Diastolic blood pressure, mmHg	76.5±0.2	76.5±0.4	74.7±0.9*	78.3±1.0	0.56
Hypertension					
Number	782	202	59	64	
Odds ratio (95% CI)	1.0	1.1 (0.9–1.4)	1.2 (0.8–1.8)	2.2 (1.4–3.4)‡	<0.001
Excessive daytime sleepiness					
Number	102	30	9	6	
Odds ratio (95% CI)	1.0	1.9 (1.2–3.0)†	2.2 (1.0–4.6)*	1.8 (0.7–4.4)	0.01
Morning sleepiness					
Number	291	45	17	11	
Odds ratio (95% CI)	1.0	1.1 (0.8–1.6)	1.7 (1.0–3.0)	1.4 (0.7–2.7)	0.11
Habitual snoring					
Number	201	64	24	21	
Odds ratio (95% CI)	1.0	1.6 (1.2–2.3)†	2.3 (1.4–3.9)†	2.4 (1.4–4.2)†	<0.001
Apnea					
Number	80	27	10	11	
Odds ratio (95% CI)	1.0	1.9 (1.2–3.0)†	2.8 (1.3–5.7)†	4.2 (2.0–8.7)‡	<0.001

*$p<0.05$, †$p<0.01$, ‡$p<0.001$, compared with 3% ODI <5 category. ODI, oxygen desaturation index; SpO_2, arterial oxygen saturation; CI, confidence interval. Multivariate adjustment: age (years), body mass index (kg/m^2), alcohol intake category (never, former, current <23, 23 to 45 and ≥26 g/day ethanol), current smokers (yes), antihypertensive medication use, menopause status (pre- and postmenopause), and communities. The definitions of snoring, apnea, excessive daytime sleepiness, morning sleepiness, and hypertension were shown in Table 1.

(1.4–3.4) (*p* for trend <0.001), respectively, for hypertension. Also, the 3% ODI was positively associated with habitual snoring and apnea. The 3% ODI was not associated with morning sleepiness.

Discussion

Our study showed that the prevalence of SDB, *i.e.*, 3% ODI ≥5, was 20% in our study population of Japanese women aged 30–69 years. This prevalence did not vary materially according to the different age ranges: it was 18% for ages 30–60 years and 20% for ages 40–69 years. A similar prevalence of SDB has been reported for other Asian and Western populations, although the prevalence was approximately 30% to 70% lower for women than men (*2*, *12*, *14*, *16*). Persons with an apnea-hypopnea index (AHI) of ≥5 accounted for 16% of Korean women aged 40–69 years (*13*), 30% of Chinese women aged 30–60 years living in Hong Kong (*14*), 9–19% of American women aged 30 years or older (*2*, *12*), and 28% of Spanish women 30–70 years (*4*). The high prevalence of SDB among Asian women in spite of their low prevalence of obesity may be due to their craniofacial features compromising the upper airway (*24*).

In this study, we found a higher prevalence of EDS in women with SDB, which is consistent with the results of the Wisconsin Sleep Cohort Study (*12*) and the Sleep Heart Health Study (*25*). The positive association between 3% ODI and prevalence of habitual snoring was also consistent with the results of previous studies; the prevalence of habitual snoring was 2- to 3-fold higher in persons with an AHI of ≥5 than those with an AHI of <5 for Korean women (*13*) and American men and women (*2*).

We previously reported that the magnitude of the positive association between 3% ODI and prevalence of hypertension was not substantially different between men and women, although the prevalences of 3% ODI ≥15 and hypertension were approximately 30% to 70% lower in women than in men (*16*). The prevalence of hypertension was 2.2-fold higher for women with 3% ODI ≥15 in reference to 3% ODI <5 in the present study and 1.6 to 2.0-fold higher for Japanese men in previous studies (*15*, *16*). The Sleep Heart Health Study reported that the prevalence of hypertension was 1.5-fold higher for men and 1.2-fold higher for women with AHI ≥30 than for those with AHI <1.5 (*2*).

Experimental studies by the Toronto group using a canine model of SDB demonstrated that experimentally-induced

intermittent airway occlusion during sleep increased daytime blood pressure, and that the latter fell after sleep without repetitive airway obstruction (*26*). A prospective study reported that persons with SDB had a 3-fold higher risk of incident hypertension compared with those without it (*5*). Furthermore, a randomized clinical trial demonstrated that treatment with continuous positive airway pressure results in significant falls in both nighttime and daytime blood pressure levels in hypertensive patients with SDB (*27*). Patients with SDB had high sympathetic activation during sleep (*28*) and their blood pressure responses were associated with the magnitude of changes in heart rate and arterial O_2 saturation and the presence of arousal (*29*). Dysfunction of chemoreflex, baroreflex, and the endothelium may raise sympathetic activity and blood pressure levels (*30*).

The strengths of the present study are that we examined the status of SDB in a large community-based sample of Japanese women during sleep at home. The weaknesses of the present study are, first, that pulse oximetry underestimates respiratory disturbance events during sleep compared with full-polysomnography, particularly in a non-obese population such as the present study population (mean BMI, 23.3 kg/m^2). For the 3% ODI of >5 to screen for AHI of >5/h by polysomnography, the sensitivity was 68% and the specificity was 96% among men and women with BMI ≤27.0 kg/m^2 (*23*). Second, the self-reported sleeping time may have been longer than the real sleep time obtained by electroencephalography. However, these limitations would be expected to lead to an underestimation rather than an overestimation of the prevalence of SDB. Third, in the present study, blood pressure was measured between 8:00 AM and 4:00 PM, and we had no individual data on the exact time of measurement. However, there is some evidence that SDB shows a greater association with morning than with afternoon blood pressure levels (*27*). Thus, the positive association between SDB and blood pressure levels in the present study may have been underestimated.

In summary, the severity of SDB in our study population of Japanese women was significantly associated with EDS and hypertension. The magnitudes of these associations were similar to those reported in men in spite of the lower prevalences of sleep-disordered breathing and hypertension in women.

Acknowledgements

The authors are grateful to Ms. Yukiko Ichikawa, Ms. Miyuki Notsute, Ms. Minako Tabata, Ms. Ai Ikeda, Dr. Hiroyuki Noda, Dr. Mitsumasa Umesawa, and Dr. Isao Muraki for the excellent technical assistance and help in the data collection.

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