

*Original Article*

# Relationship between Sleep-Disordered Breathing and Blood Pressure Levels in Community-Based Samples of Japanese Men

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To examine the relationship between sleep-disordered breathing (SDB) and blood pressure levels among Japanese men, we conducted a population-based cross-sectional study of 1,424 men aged 40–69 years in rural and urban communities. The 3% oxygen desaturation index (ODI) was selected as the indicator of SDB, representing the number of desaturation events per hour of recording time in which blood oxygen fell by  $\geq 3\%$  according to overnight pulse oximetry. To estimate the associations of 3% ODI levels with blood pressure levels and hypertension, multiple linear regression and logistic regression analyses were performed. The 3% ODI level was positively associated with systolic and diastolic blood pressure levels (SBP/DBP); a 5 event per hour increment of the 3% ODI level was associated with 0.8 mmHg (95% confidence interval [CI], 0.0–1.6) greater SBP and 0.7 mmHg (95% CI, 0.3–1.1) greater DBP after adjustment for age, body mass index, ethanol intake, smoking category and community. The multivariate odds ratio of hypertension for the low vs. high category of 3% ODI level was 1.63 (95% CI, 1.1–2.5). These associations were more evident among overweight than non-overweight individuals. The significant association of nocturnal oxygen desaturation with high blood pressure levels suggests that SDB plays a role in the development of hypertension among Japanese men. (*Hypertens Res* 2004; 27: 479–484)

**Key Words:** sleep-disordered breathing, oxygen desaturation, pulse-oximeter, blood pressure, community-based

## Introduction

Investigations of the relationship between sleep-disordered breathing (SDB)—*i.e.*, repetitive episodes of decreased or arrested respiratory airflow during sleep—and hypertension have mostly been limited to hospitalized patients (1, 2) or have failed to fully account for possible confounding variables (3, 4). Recently, however, several population-based

studies with large sample sizes performed in Western countries have demonstrated a positive association between SDB measured by polysomnography (PSG) and blood pressure levels/hypertension, independent of age, obesity and other confounding variables (5–8). Moreover, the Wisconsin Sleep Cohort Study reported a dose-response association between SDB severity at baseline and the incidence of newly diagnosed hypertension during a 4-year follow-up (9). This causal relationship was also supported by a study employing

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an animal model (10). Based on these findings, the Seventh Report of the Joint National Committee (JNC7) on prevention, detection, evaluation, and treatment of high blood pressure presented in the United States included sleep apnea as the first disorder on the list of identifiable causes of hypertension, and recommended a sleep study with O<sub>2</sub> saturation as a screening test (11).

To date, however, no community-based studies on the association between SDB measured by physiological parameters and blood pressure levels have been conducted in Asian countries, probably due to the difficulty in using PSG in community-based studies. Although the PSG is the gold standard for monitoring SDB in a clinical setting, it is not a practical approach for SDB screening for early detection and treatment of severe SDB in a general population. In the present population-based study of 1,424 Japanese men, we examined the association between nocturnal oxygen desaturation and blood pressure levels using pulse oximetry.

## Methods

### Subjects

A research team made up of researchers from the Osaka Medical Center for Health Science and Promotion and the University of Tsukuba has conducted annual cardiovascular risk surveys in an urban community of the district of Yao City, a suburb of Osaka, since 1963; in the rural community of Ikawa in northeast Japan since 1963; and in the rural community of Kyowa in central Japan since 1981 (12, 13). Recently, a relationship between ankle-arm systolic blood pressure (SBP) index and cardiovascular risk factors (14) and an association between angiotensinogen 174M polymorphism and high blood pressure, particularly among subjects with higher sodium intake (15), have been reported based on data from this cardiovascular risk survey.

Subjects for the present sleep investigation were recruited from among participants in the above-described annual cardiovascular surveys for the years 2000–2002. All recruited subjects were Japanese men aged 40 to 69 years, and none had been previously diagnosed with SDB. The numbers of participants were 417 from the district of Yao City (recruitment rate among the cardiovascular survey participants = 89%), 298 from Ikawa (74%), and 709 from Kyowa (86%). We restricted the subjects to men because men had a higher priority to be examined due to a higher reported prevalence of SDB in men than in women (16, 17). A total of 1,424 men, including 277 subjects using antihypertensive medication, were enrolled in the present study. 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 Blood Pressure Levels and Confounding Variables

Arterial SBP and fifth-phase diastolic blood pressure (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. Hypertension was defined as SDB  $\geq$ 160 mmHg, or DBP  $\geq$ 100 mmHg and/or use of antihypertensive medication. We measured several potential confounders (13) that might also contribute to or aggravate the incidence of SDB (17). Height in stocking feet and weight in light clothing were measured, and body mass index (BMI) was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). Interviews were conducted to determine the ethanol intake per day, number of cigarettes smoked per day, and use of antihypertensive medication. An interviewer assessed the usual weekly alcohol intake in units of *go*, a traditional Japanese unit of volume corresponding to 23 g ethanol, which was converted to g of ethanol per day. One *go* is 180 ml of sake, and corresponds to one bottle (633 ml) of beer, two single shots (75 ml) of whiskey, or two glasses (180 ml) of wine. Our previous study showed that alcohol intake was linearly associated with changes in SBP and DBP (18). Persons who smoked one or more cigarettes/day were defined as current smokers.

### Assessment of SDB

A pulse-oximeter PULSOX-3Si (Minolta Co., Osaka, Japan) was attached to the left wrist during one night of sleep at home. The sensor probe was fitted to the fourth finger and secured with tape by each subject. The internal memory of this device stores the values of blood oxygen saturation by performing a moving average for the last 5 s, updated every second; this sampling time was short enough to avoid underestimation of oxygen desaturation (19). Data were downloaded to a personal computer *via* an interface (PULSOX IF-3; Minolta) and analyzed using proprietary software supplied with the equipment (DS-3 ver. 2.0a; Minolta). We used the value of oxygen desaturation per hour (oxygen desaturation index, ODI) as an indicator of SDB. A 3% ODI was selected as an index of oxygen desaturation, representing the number of events per hour of recording time in which blood oxygen fell by  $\geq$ 3%. The 3% ODI during the estimated sleep time of more than 4 h computed for each subject was used for the analysis. Since the duration of sleep estimated by pulse oximetry is often longer than the true total sleep time, we had subjects fill out a sleep diary in order to exclude the waking time from the analysis and thereby minimize potential overestimation of the sleep duration. The criteria for SDB were defined by 3% ODI level as 5 and 15 events per hour, corresponding to mild and moderate-to-severe SDB, respectively.

Nakamata *et al.* previously reported that the validity of the pulse oximetry by synchronous overnight recording of both

**Table 1. Age-Adjusted Means (SEM) and Prevalence of Selected Cardiovascular Risk Characteristics According to 3% Oxygen Desaturation Index (ODI) Levels**

	3% ODI			<i>p</i> for trend
	0–4	5–14	≥15	
<i>N</i>	848	448	128	
Age (year)	58.1 (0.3)	58.9 (0.4)	60.3 (0.7)	0.002
BMI (kg/m <sup>2</sup> )	23.1 (0.1)	25.0 (0.1)	26.3 (0.2)	<0.0001
Current ethanol intake (g/day)	22.1 (0.8)	24.8 (1.1)	27.7 (2.1)	0.02
Current smokers (%)	44	39	32	0.004
Systolic blood pressure (mmHg)	130.9 (0.6)	133.5 (0.8)	139.9 (1.5)	<0.0001
Diastolic blood pressure (mmHg)	80.8 (0.4)	83.1 (0.5)	85.8 (0.9)	<0.0001
Use of antihypertensive medication (%)	17	22	31	<0.0001
Hypertension (%)*	21	28	41	<0.0001

\*Hypertension was defined as systolic blood pressure  $\geq 160$  mmHg or diastolic blood pressure  $\geq 100$  mmHg and/or use of antihypertensive medication. BMI, body mass index. *N*, number of subjects.

PULSOX-3Si and standard PSG among 256 consecutive patients (mean BMI, 26.8 kg/m<sup>2</sup>) who had been referred to a sleep-disordered breathing center: 80% sensitivity and 95% specificity for detecting an apnea-hypopnea index (AHI) of  $\geq 5$  by PSG using a cut-off threshold of 3% ODI = 5, and 85% sensitivity and 100% specificity for detecting an AHI of  $\geq 20$  by 3% ODI = 15 (20). To examine the reproducibility of pulse oximetry, two overnight pulse oximetry measurements were conducted in 61 men who had no habit of alcohol intake. The median values of 3% ODI on the first and the second nights were 5.4 and 4.8 per hour, respectively ( $p = 0.95$ , Wilcoxon's signed-rank test). Spearman's rank correlation coefficient was 0.81 ( $p < 0.0001$ ).

### Statistical Analysis

Age-adjusted mean values of BMI, ethanol intake, and blood pressure levels and age-adjusted prevalence of current smoking, antihypertensive medication use and hypertension were calculated according to the categories of nocturnal oxygen desaturation levels (3% ODI: <5, 5–14,  $\geq 15$ ) using analysis of covariance and the  $\chi^2$  test, and a linear trend was tested using median variables of the nocturnal oxygen desaturation categories. A predicted difference associated with a 5 event per hour increment of the 3% ODI level was calculated by multiple linear regression analysis to estimate the independent associations of the nocturnal oxygen desaturation levels with blood pressure levels, while adjusting for the potentially confounding variables of age, BMI, ethanol intake, smoking category (never-smokers, ex-smokers, current smokers), and community. A logistic regression analysis was performed to estimate the independent associations of the nocturnal oxygen desaturation levels with hypertension, adjusting for these confounding variables. A linear trend of blood pressure levels and hypertension with nocturnal oxygen desaturation levels was tested using median variables of the nocturnal oxygen desaturation categories. The analyses were also per-

formed using a stratification by age (40 to 64 and 65 to 69 years) and BMI (<25 and  $\geq 25$  kg/m<sup>2</sup>). The interactions of 3% ODI levels with age and overweight in relation to the prevalence of hypertension were examined using cross-product terms.

All statistical analyses were performed using SAS version 8.02 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 mean values and prevalences of selected cardiovascular risk characteristics among total subjects were 58.6 (SD, 7.7) years for age, 24.0 (2.9) kg/m<sup>2</sup> for BMI, 6.1 (7.1) per hour for 3% ODI, 133 (17) mmHg for SBP and 82 (10) mmHg for DBP, 73% for ethanol intake, 42% for current smoking, 19% for use of antihypertensive medication, and 25% for hypertension.

Table 1 shows the age-adjusted mean values and prevalence of risk characteristics according to the categories of nocturnal ODI levels. There were positive associations of 3% ODI levels with BMI, ethanol intake, blood pressure levels, antihypertensive medication use and hypertension, but an inverse association with current smoking.

Table 2 shows the age- and multivariate-adjusted blood pressure levels according to categories of 3% ODI levels, and predicted differences in blood pressure levels associated with a 5 event per hour increment of the 3% ODI level among 1,147 men who were not on antihypertensive medication. There were positive associations of 3% ODI levels with SBP and DBP after adjustment for age, and also again after further adjustment for other confounding variables. The predicted differences associated with a 5 event per hour increment of the 3% ODI level for SBP and DBP were 0.8 mmHg (95% confidence interval [CI], 0.0–1.6) and 0.7 mmHg (95% CI, 0.3–1.1), respectively.

**Table 2. Age-Adjusted and Multivariate-Adjusted Means (SEM) of Systolic and Diastolic Blood Pressure According to Categories of 3% Oxygen Desaturation Index (ODI) Level, and Predicted Differences (SEM) in Blood Pressure Levels Associated with 5 per Hour Increment of 3% ODI among 1,147 Subjects without Use of Antihypertensive Medication**

	3% ODI			<i>p</i> for trend	3% ODI	
	0-4	5-14	≥15		Predicted difference (SEM)	<i>p</i> value
<i>N</i>	711	350	86			
Systolic blood pressure						
Age-adjusted means (mmHg)	128.9 (0.6)	131.6 (0.9)	137.9 (1.7)	<0.0001	1.7 (0.4)	<0.0001
Multivariate adjusted means* (mmHg)	129.8 (0.6)	130.4 (0.9)	135.1 (1.7)	0.008	0.8 (0.4)	0.05
Diastolic blood pressure						
Age-adjusted means (mmHg)	80.1 (0.4)	82.6 (0.5)	86.2 (1.1)	<0.0001	1.4 (0.2)	<0.0001
Multivariate adjusted means* (mmHg)	80.8 (0.4)	81.6 (0.5)	84.2 (1.1)	0.004	0.7 (0.2)	0.004

\* Adjusted for age, body mass index, ethanol intake, smoking status, and community. *N*, number of subjects.

**Table 3. Odds Ratios\* and 95% Confidence Intervals of Hypertension According to 3% Oxygen Desaturation Index (ODI) Levels**

	<i>N</i>	3% ODI			<i>p</i> for trend
		0-4	5-14	≥15	
All subjects	1,424	1.00	1.12 (0.84, 1.49)	1.63 (1.07, 2.50)	0.01
BMI <25 kg/m <sup>2</sup>	929	1.00	0.94 (0.63, 1.40)	1.28 (0.65, 2.52)	0.46
BMI ≥25 kg/m <sup>2</sup>	495	1.00	1.36 (0.88, 2.13)	1.96 (1.09, 3.52)	0.02
Age <65 years	1,017	1.00	1.15 (0.80, 1.65)	1.61 (0.94, 2.76)	0.04
Age ≥65 years	407	1.00	1.09 (0.67, 1.76)	1.67 (0.82, 3.41)	0.11

\* Adjusted for age, body mass index (BMI), ethanol intake, smoking status, and community. *N*, number of subjects.

The prevalence of hypertension, when including men who were on antihypertensive medication, also increased with greater 3% ODI levels (Table 3). The multivariate odds ratio of hypertension was 1.63 (95% CI, 1.07–2.50) in the low vs. high categories of the 3% ODI level. The relations between 3% ODI levels and hypertension did not vary between middle-aged (40 to 64 years) and elderly (≥65 years) subjects: 1.61 (95% CI, 0.94–2.76) vs. 1.67 (95% CI, 0.82–3.41). The association tended to be more evident among overweight than among non-overweight subjects: 1.96 (95% CI, 1.09–3.52) vs. 1.28 (95% CI, 0.65–2.52), although the interaction did not reach the level of statistical significance.

## Discussion

We found a significant association between SDB severity measured by ODI and blood pressure levels among middle-aged Japanese men, independent of age, BMI, ethanol intake, and smoking status. Our results are consistent with the recent findings from the United States and Europe (5–8), and confirm the SDB-blood pressure associations among Asian populations. Furthermore, the relationship between SDB and hypertension was more obvious among overweight men than among non-overweight men, suggesting that SDB and overweight may synergistically enhance a rise in blood pressure levels.

SDB and hypertension share common risk factors, such as male gender, obesity and ethanol intake (17). In earlier studies, the independent relationship observed between SDB and hypertension was controversial because the potentially confounding factors of age and obesity were not accounted for (2, 3). Recent large cross-sectional studies have shown a positive association between polysomnographically assessed AHI and daytime hypertension with adjustment for confounding variables (5–8).

The causal relationship between SDB and hypertension has been supported by both epidemiological and animal experimental studies. A 4-year follow-up study reported the relative risk of incident hypertension as 2.89 (95% CI, 1.46–5.64) among subjects with AHI ≥15 compared with subjects with AHI = 0 (9). An animal experiment using a canine model demonstrated that daytime blood pressure increased after experimentally induced intermittent airway occlusion during nocturnal sleep and fell after a nighttime sleep with quiet breathing (10). Furthermore, two randomized clinical trials of continuous positive airway pressure intervention have demonstrated a significant reduction of nighttime and daytime blood pressure levels in hypertensive patients with obstructive sleep apnea (21, 22).

The biological mechanisms that link SDB to daytime elevation of blood pressure levels seem to be multifactorial, and probable mechanisms include high sympathetic nerve activi-

ty observed even when awake in patients with obstructive sleep apnea, which is attenuated by treatment with continuous positive airway pressure (23), increased circulating catecholamine levels associated with sympathetic nerve activity (24), enhanced vasoconstrictor sensitivity partly due to vascular remodeling by nocturnal blood pressure surges (25), and enhanced insulin resistance that is rapidly improved by treatment with continuous positive airway pressure (26).

The strengths of the present study are the use of a large community-based sample and the evaluation of SDB status during sleep at home, which has the advantage of providing a more realistic estimation of severity of SDB compared with hospital/laboratory studies because of the maintenance of regular daily habits of sleep, physical activity, diet and ethanol intake in a general population.

There are several limitations in the present study. First, because we used only a single blood pressure measurement for the analyses, the measurement variability may have weakened the SDB-blood pressure association. However, the large number of subjects in our study allowed the attainment of sufficient statistical power to detect the associations. Second, pulse oximetry inherently underestimates respiratory disturbance events during sleep compared with full-PSG, particularly in a non-obese population such as that studied here (mean BMI, 24.0 kg/m<sup>2</sup>). The sensitivity of detection of apneic/hypopneic events  $\geq 5/h$  by PSG has been reported to be 68% among subjects with BMI  $\leq 27.0$  kg/m<sup>2</sup> and 94% among those with higher BMI (20). The reasons for the lower sensitivity by pulse oximetry among lean subjects have been considered to include the functional reserve of lung volume sufficient to maintain normal blood oxygen levels, and difficulty in detecting hypopneic events that do not cause oxygen desaturation. Third, the recording time modified by self-report was regarded as the total sleep time in this study, and this value may have been longer than the real sleep time obtained only by PSG using the electroencephalogram. In any case however, these limitations would be expected to lead to an underestimation rather than an overestimation of the association between SDB and blood pressure levels. Lastly, potential dietary confounding variables such as sodium intake were not taken into account. However, there is no evidence of an association between SDB and sodium intake.

Multiple regression analysis showed that a 5 event per hour increment of the 3% ODI level corresponded to a 0.8 mmHg and 0.7 mmHg elevation of SBP and DBP, respectively. These differences in blood pressure levels seem to be small from the clinical point of view. However, even a small reduction in blood pressure levels has an important public health impact on cardiovascular morbidity and mortality. A meta-analysis of nine prospective studies demonstrated that a long-term difference of 5 mmHg in mean DBP was associated with a 34% reduction in risk of stroke and a 21% reduction in risk of coronary heart disease (27). In our previous study of Japanese, a difference of 5 mmHg in mean SBP was associated with 15% and 10% reductions of these

diseases, respectively (28). Therefore, the promotion of screening and treatment for undiagnosed SDB among populations in Japan may have a substantial impact on the prevention of cardiovascular disease.

In conclusion, the significant association of SDB with blood pressure levels suggests that SDB plays a role in the development of hypertension. Follow-up studies and clinical trials will be needed to examine the causal relationship between SDB and hypertension, and to explore the effect of the control of SDB on blood pressure reduction.

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