Original Article

Nocturnal Intermittent Hypoxia and Metabolic Syndrome; the Effect of being Overweight: the CIRCS Study

Isao Muraki^{1,2}, Takeshi Tanigawa³, Kazumasa Yamagishi⁴, Susumu Sakurai³, Tetsuya Ohira¹, Hironori Imano², Masahiko Kiyama², Akihiko Kitamura², Shinichi Sato^{2,5}, Takashi Shimamoto², Masamitsu Konishi², and Hiroyasu Iso¹, for the CIRCS Investigators

¹Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Suita, Japan

²Osaka Medical Center for Health Science and Promotion, Osaka, Japan

³Department of Public Health, Doctoral Program in Social Medicine, Graduate School of Medicine, Ehime University, Toon, Japan

⁴Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences, and Institute of Community Medicine, University of Tsukuba, Tsukuba, Japan

⁵Chiba Prefectural Institute of Public Health, Chiba, Japan

Aim: We investigated whether nocturnal intermittent hypoxia, a surrogate marker for obstructive sleep apnea, is associated with metabolic syndrome and its components among Japanese.

Methods: We examined 1,710 male and 2,896 female community-dwelling Japanese aged 40 to 69, who participated in annual cardiovascular examinations and investigations of sleep. Nocturnal intermittent hypoxia was estimated based on a 3% oxygen desaturation index measured with pulse-oximetry during sleep. No, mild and moderate-to-severe nocturnal intermittent hypoxia were defined by <5, 5 to <15 and ≥ 15 events/hour, respectively. Metabolic syndrome was defined by modified criteria of the Adult Treatment Panel III guidelines.

Results: Compared with no nocturnal intermittent hypoxia, the multivariable odds ratio of metabolic syndrome was 1.9 (95% confidence interval: 1.6–2.4) for mild and 3.2 (2.2–4.7) for moderate-to-severe nocturnal intermittent hypoxia among men; 2.6 (2.1–3.4) and 5.8 (3.4–9.8) among women, respectively. When stratified by overweight status (body mass index ≥ 25 kg/m²), the multivariable odds ratio of two or more metabolic risk factors (other than overweight) associated with moderate-to-severe nocturnal intermittent hypoxia was 1.9 (1.2–3.1) among non-overweight subjects and 1.4 (0.9–2.1) among overweight subjects (p for interaction = 0.002).

Conclusions: Nocturnal intermittent hypoxia was associated with the accumulation of metabolic risk factors, especially among non-overweight individuals.

J Atheroscler Thromb, 2010; 17:369-377.

Key words; Metabolic syndrome, Intermittent hypoxia, Sleep-disordered breathing, Overweight, Cross-sectional study

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction

Address for correspondence: Hiroyasu Iso, Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

E-mail: iso@pbhel.med.osaka-u.ac.jp

Received: July 20, 2009

Accepted for publication: October 6, 2009

during sleep, which cause enhanced sympathetic activity, elevated intrathoracic pressure, increased cytokine levels, increased oxidative stress and sleep deprivation¹. OSA is associated with hypertension, dyslipidemia and glucose abnormality, independent of traditional confounding factors (e.g. age, sex and body mass index (BMI))². In addition, prospective studies have shown that OSA increases the risk of cardiovascular disease, independently of traditional confounding factors³. Therefore, OSA has been noted as a new cardiovascular risk factor.

Metabolic syndrome (MetS) reflects high cardiovascular risk conditions^{4,6}. The prevalence of MetS defined by the Adult Treatment Panel III guidelines of the National Cholesterol Education Program (NCEP/ATPIII) was 2-fold higher among patients with an apnea-hypopnea index (AHI) ≥ 5 than among those with AHI < 5 ^{7, 8}, 2- to 4-fold higher among those with AHI ≥ 15 than among those with AHI < 15 ^{8, 9}, and 9-fold higher among those with AHI ≥ 15 and OSA-related symptoms (e.g. excessive daytime sleepiness) than among those without either¹⁰. Vgontzas and colleagues suggested that MetS manifests as OSA, because of the association of MetS with increased oxidative stress, insulin resistance and increased levels of cytokines, which are also associated with OSA^{11, 12}. However, since most previous studies recruited mainly obese or overweight subjects (body mass index, BMI; 25.9–38.4 kg/m²)^{7–11}, and both OSA and MetS were strongly associated with BMI, prior findings may not be applicable to non-overweight populations.

To examine whether these associations were extrapolated in a lean population, we examined the association between nocturnal intermittent hypoxia and MetS among community-dwelling Japanese, which consisted mainly of non-overweight subjects.

Methods

The Circulatory Risk in Communities Study (CIRCS) is a prospective community-based study that has been launched to prevent stroke in five communities across Japan since 1963, described in detail elsewhere^{6, 13, 14}. Annual cardiovascular risk surveys and monitoring of cardiovascular events are systematically conducted by a research team of the Osaka Medical Center for Health Science and Promotion, the Osaka University and the University of Tsukuba. An investigation of sleep as part of the annual cardiovascular surveys was started in three communities (Ikawa; a northeast rural community, Yao; a mid-west suburban community, and Kyowa; a mid-east rural community) in 2000¹⁵. The study protocol was approved by the Institutional Review Board of the Osaka Medical Center for Health Science and Promotion, Osaka University and the University of Tsukuba.

Subjects

The participants in the 2001 to 2005 annual cardiovascular surveys aged 40 to 69 years were recruited for the present investigation. The numbers of participants were 448 men and 853 women from Yao (recruitment rate among the cardiovascular survey participants = 95% for men and 77% for women), 397

men and 571 women from Ikawa (93% and 88%), and 917 men and 1,507 women from Kyowa (89% and 87%). No subject had a history of OSA diagnosed by a physician. Subjects who had a history of stroke ($n=55$) or a history of heart disease ($n=33$) were excluded. A total of 1,710 men and 2,896 women were enrolled in the present study. For each subject, a physician and trained staff explained the protocol in detail, and obtained informed consent.

Measurement of Metabolic Risk Factors and Confounding Variables

Height in stocking feet and weight in light clothing were measured and BMI was calculated as weight (kg) divided by the square of height (m). 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 at least 5 min of rest.

For the measurement of serum lipids and glucose, venous blood was drawn from seated participants into a plain, siliconized glass tube and serum was separated within 30 min. The serum sample was transported on dry ice to the Osaka Medical Center for Health Science and Promotion, and stored at -70°C prior to analysis. Serum total cholesterol, HDL-cholesterol, triglyceride and glucose levels were measured using enzymatic methods for lipids and the hexokinase method for glucose with an automatic analyzer (AU2700, Olympus Co., Tokyo, Japan) at the Osaka Medical Center for Health Science and Promotion, whose laboratory is an international member of the US National Cholesterol Reference Method Laboratory Network¹⁶.

We measured several potential confounders that might also contribute to or aggravate OSA². Interviews were conducted to determine alcohol intake per day, number of cigarettes smoked per day, time since last meal, use of antihypertensive and diabetes medication, and for women, menopausal status. An interviewer assessed normal weekly alcohol intake which was converted to grams of ethanol per day. Persons who smoked ≥ 1 cigarette/day were defined as current smokers. The distribution of time since the last meal did not differ between men and women; < 2 hours (8% for men, 5% for women), 2 hours (9%, 7%), 3–7 hours (35%, 30%) and ≥ 8 hours (52%, 53%).

A modified definition of NCEP/ATPIII¹⁷ was used to categorize subjects according to metabolic risk factors. Since waist circumference was not available in the present study, BMI was used for the assessment of obesity. The Asian criterion of obesity is a BMI ≥ 25.0 kg/m², or waist circumference ≥ 80 cm for women and

≥ 90 cm for men¹⁸). MetS was defined as three or more of the following metabolic risk factors: 1) BMI ≥ 25.0 kg/m², 2) fasting plasma glucose concentration ≥ 110 mg/dL (6.11 mmol/L) or non-fasting glucose concentration ≥ 140 mg/dL (7.77 mmol/L) or on medication, 3) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or on medication, 4) HDL-cholesterol concentration < 40 mg/dL (1.03 mmol/L) for men and < 50 mg/dL (1.29 mmol/L) for women, and 5) fasting or non-fasting triglyceride concentration ≥ 150 mg/dL (1.69 mmol/L). The presence of ≥ 2 metabolic risk factors was also defined as two or more metabolic risk factors other than overweight. We previously reported that MetS defined by these criteria was associated with incident ischemic stroke and heart disease⁶.

Assessment of Nocturnal Intermittent Hypoxia

Nocturnal intermittent hypoxia was measured by Pulse-oximetry during one night's sleep using a pulse-oximeter (PULSOX-3Si, Minolta Co., Osaka, Japan) at the participants' own home¹⁵. The sensor probe was fitted to the fourth or fifth finger with tape. The device stores values of peripheral blood oxygen saturation by performing a moving average for the last 5 seconds, updated every second; this sampling time was short enough to avoid underestimation of oxygen desaturation¹⁹. Data were downloaded to a personal computer via an interface (PULSOX IF-3, Minolta) and analyzed by proprietary software (DS-3 ver. 2.0a, Minolta). Because the measurement time of pulse-oximetry is often longer than the true total sleep time, we used a single night's sleep log to exclude waking time from the analysis to minimize the potential for overestimating total sleep time. We used oxygen desaturation of 3% or more per hour of the adjusted measurement time (the 3% oxygen desaturation index, 3%ODI) as the indicator for nocturnal intermittent hypoxia. The severity of nocturnal intermittent hypoxia was defined by the 3%ODI level as 5 or 15 events per hour, corresponding to mild or moderate-to-severe nocturnal intermittent hypoxia, respectively.

The validity of pulse-oximetry using synchronous overnight recordings of both PULSOX-3Si and standard polysomnography (PSG) was confirmed previously among 256 consecutive patients in a sleep-disordered breathing center (mean body mass index, 26.8 kg/m²). The sensitivity and specificity were 80% and 95%, respectively, for detecting an apnea-hypopnea index (AHI) of ≥ 5 by PSG using a cut-off threshold of 3%ODI = 5. Similarly, the sensitivity and specificity for detecting AHI of ≥ 20 by PSG using a cut-off threshold of 3%ODI = 15 were 85% and 100%, respectively²⁰. To examine the reproducibility, pulse-oxime-

try was conducted for two nights among 61 men in the present study. The median values of 3%ODI were 5.4 on the first night and 4.8 on the second night (p for difference = 0.95, Wilcoxon's signed-rank test). Spearman's rank correlation coefficient was 0.81 ($p < 0.001$).

Statistical Analysis

Age and multivariable-adjusted mean values and prevalence of cardiovascular characteristics were calculated and tested by analysis of covariance according to 3%ODI. We used the logistic regression analysis to evaluate age- and multivariable-adjusted Odds ratios (ORs) of MetS according to 3%ODI. A trend test was performed with a regression model for mean values, and a logistic regression model for proportion and odds ratios, using median values of 3%ODI as representative of nocturnal intermittent hypoxia severity. The interactions of 3%ODI with sex, overweight and BMI in relation to MetS and its components were tested using cross-product terms of these variables in the logistic regression model. We included age (year), sex, smoking status (nonsmoker and current smoker), current ethanol intake (g/day), time since last meal (< 2 , 2, 3–7 and ≥ 8 hours) and for women, menopausal status (pre- and post-menopause), into the multivariable models. All analyses were conducted using the SAS statistical package, version 9.13 (SAS Institute Inc., Cary, NC). All p -values for statistical tests were two-tailed and $p < 0.10$ to 0.05 and $p < 0.05$ was regarded as borderline significance and statistical significance, respectively.

Results

The age-adjusted prevalence of mild and moderate-to-severe nocturnal intermittent hypoxia essentially did not differ among these three communities; the prevalence was 29 to 35% for mild and 8 to 9% for moderate-to-severe nocturnal intermittent hypoxia among men, and 15 to 17% for mild and 2 to 3% for moderate-to-severe nocturnal intermittent hypoxia among women.

Sex-specific age-adjusted distributions of cardiovascular risk factors according to 3%ODI are shown in **Table 1**. Mean values of age, BMI, SBP, DBP, serum glucose, triglyceride, and the proportion of anti-hypertensive medication use were higher, and mean values of HDL-cholesterol were lower, with increased 3%ODI among both sexes. Current ethanol intake and currently smoking were positively associated with 3%ODI among men. Mean values of serum total cholesterol were positively associated with 3%ODI among

Table 1. Sex-specific age-adjusted mean values (standard error) and prevalence of cardiovascular risk factors according to a 3% oxygen desaturation index

	Men				Women			
	3%ODI			<i>p</i> for trend	3%ODI			<i>p</i> for trend
	0 to <5	5 to <15	≥15		0 to <5	5 to <15	≥15	
No.	1,031	527	152		2,358	473	65	
Age, year	57.5 (0.2)	58.4 (0.3)	59.6 (0.6)	<0.001	55.8 (0.2)	59.5 (0.4)	60.7 (1.0)	<0.001
Body mass index, kg/m ²	23.2 (0.1)	25.0 (0.1)	26.4 (0.2)	<0.001	22.9 (0.1)	25.0 (0.1)	26.9 (0.4)	<0.001
Current ethanol intake, g/day	22.3 (0.7)	25.1 (1.0)	28.5 (1.9)	<0.001	1.7 (0.1)	1.9 (0.3)	2.4 (0.9)	0.36
Current smoker, %	46	40	36	<0.001	5	4	2	0.15
Systolic blood pressure, mmHg	130 (0)	133 (1)	137 (1)	<0.001	125 (0)	127 (1)	135 (2)	<0.001
Diastolic blood pressure, mmHg	81 (0)	83 (0)	85 (1)	<0.001	76 (0)	77 (0)	81 (1)	<0.001
Serum blood glucose, mg/dL	108.0 (1.0)	107.3 (1.4)	113.9 (2.6)	0.08	99.6 (0.4)	101.1 (0.9)	106.2 (2.4)	0.002
Serum total cholesterol, mg/dL	201.9 (1.1)	209.1 (1.5)	213.6 (2.7)	<0.001	218.0 (0.7)	216.5 (0.9)	211.5 (4.4)	0.11
HDL-cholesterol, mg/dL	56.6 (0.5)	54.0 (0.6)	52.8 (1.2)	<0.001	63.9 (0.3)	59.1 (0.7)	58.1 (1.8)	<0.001
Triglyceride, mg/dL	134.1 (3.7)	156.8 (5.1)	168.8 (9.6)	<0.001	103.5 (1.9)	119.5 (4.3)	136.9 (11.5)	<0.001
Fasting blood drawing, %	52	53	51	0.84	54	46	59	0.17
Use of antihypertensive medication, %	16	23	33	<0.001	15	24	38	<0.001
Use of diabetic medication, %	5	4	6	0.95	2	4	2	0.03

men, but inversely associated among women.

Table 2 shows the age- and multivariable-adjusted ORs of MetS and its components according to the severity of nocturnal intermittent hypoxia. Overweight, high blood pressure, a low HDL-cholesterol level and a high triglyceride level were positively associated with the severity of nocturnal intermittent hypoxia after adjustments for the confounding factors among both sexes. Glucose abnormality was associated with moderate-to-severe nocturnal intermittent hypoxia among men, but not among women. After further adjustment for BMI, the association of nocturnal intermittent hypoxia with each of these metabolic risk factors was weakened except for glucose abnormality. The age-adjusted prevalence of MetS was 2-fold and 4-fold higher for mild and moderate-to-severe nocturnal intermittent hypoxia, respectively among men, and 3-fold and 5-fold higher for mild and moderate-to-severe nocturnal intermittent hypoxia, respectively among women. After adjustments for the confounding factors, these associations did not change materially. The interaction of mild and moderate-to-severe nocturnal intermittent hypoxia with sex in relation to MetS was statistically significant (*p* for interaction=0.03 for mild and 0.04 for moderate-to-severe nocturnal intermittent hypoxia).

Since the impact of being overweight on both nocturnal intermittent hypoxia and metabolic risk factors seemed to be large, we further examined associations between nocturnal intermittent hypoxia and

metabolic risk factors stratified by overweight status (**Table 3**). The associations did not vary with the presence and absence of this factor although they tended to be stronger for high blood pressure and high triglyceride among overweight individuals. After further adjustment for BMI, the associations for high blood pressure and high triglyceride were weakened, but remained statistically significant among non-overweight subjects. The interaction between nocturnal intermittent hypoxia and BMI in relation to high blood pressure, a high triglyceride level, and the presence of 2 or more metabolic risk factors was statistically significant or borderline significant (*p* for interaction=0.006 for high blood pressure, 0.08 for high triglyceride and 0.002 for the presence of 2≥ metabolic risk factors).

Discussion

Nocturnal intermittent hypoxia was positively associated with MetS and its components among both men and women. The prevalence of MetS associated with nocturnal intermittent hypoxia was 2 to 3-fold higher for persons with a ODI of 5 to <15 and 4 to 5-fold higher for persons with an ODI of ≥15 compared with those with an ODI of <5. The magnitude of these associations was similar to those in previous studies of American and Chinese⁷⁻⁹). As for the components of MetS, previous studies reported that nocturnal intermittent hypoxia was associated with

Table 2. Sex-specific age- and multivariable-adjusted odds ratios (95% confidence intervals) of metabolic risk factors and MetS according to the 3% oxygen desaturation index

	Men			Women			<i>p</i> for interaction	
	3%ODI			3%ODI			Mild SDB × Sex	Moderate-to-severe SDB × Sex
	0 to <5	5 to <15	≥15	0 to <5	5 to <15	≥15		
No. at risk	1,031	527	152	2,358	473	65		
Overweight								
No. of cases (%)	234 (23)	256 (49)	97 (64)	507 (22)	234 (49)	42 (65)		
Age-adjusted OR	1.0	3.2 (2.6, 4.1)	6.1 (4.3, 8.8)	1.0	3.5 (2.8, 4.3)	6.5 (3.8, 10.9)		
Multivariable-adjusted OR	1.0	3.3 (2.6, 4.1)	6.1 (4.2, 8.8)	1.0	3.5 (2.9, 4.4)	7.2 (4.2, 12.1)	0.46	0.63
High blood pressure								
No. of cases (%)	625 (61)	378 (72)	125 (82)	1,033 (44)	284 (60)	52 (80)		
Age-adjusted OR	1.0	1.6 (1.3, 2.0)	2.8 (1.8, 4.3)	1.0	1.5 (1.2, 1.9)	3.9 (2.1, 7.3)		
Multivariable-adjusted OR	1.0	1.5 (1.2, 1.9)	2.6 (1.6, 4.0)	1.0	1.5 (1.2, 1.9)	4.0 (2.1, 7.5)	0.84	0.33
Further adjustment for BMI	1.0	1.2 (1.0, 1.5)	1.7 (1.0, 2.6)	1.0	1.1 (0.8, 1.4)	2.2 (1.1, 4.2)		
Glucose abnormality								
No. of cases (%)	202 (20)	96 (18)	46 (30)	197 (8)	63 (13)	13 (20)		
Age-adjusted OR	1.0	0.9 (0.7, 1.2)	1.7 (1.2, 2.5)	1.0	1.4 (1.0, 1.9)	2.1 (1.1, 3.9)		
Multivariable-adjusted OR	1.0	0.9 (0.7, 1.2)	1.7 (1.2, 2.6)	1.0	1.5 (1.1, 2.1)	1.9 (1.0, 3.7)	0.009	0.78
Further adjustment for BMI	1.0	0.9 (0.7, 1.2)	1.7 (1.1, 2.5)	1.0	1.2 (0.9, 1.6)	1.2 (0.6, 2.3)		
Low HDL cholesterol								
No. of cases (%)	110 (11)	64 (12)	18 (12)	394 (17)	126 (27)	17 (26)		
Age-adjusted OR	1.0	1.3 (0.8, 1.6)	1.1 (0.6, 1.8)	1.0	1.7 (1.3, 2.1)	1.5 (0.9, 2.7)		
Multivariable-adjusted OR	1.0	1.3 (0.9, 1.8)	1.3 (0.8, 2.2)	1.0	1.7 (1.3, 2.2)	1.2 (0.6, 2.3)	0.28	0.70
Further adjustment for BMI	1.0	1.2 (0.8, 1.6)	1.1 (0.6, 2.0)	1.0	1.3 (1.0, 1.7)	1.0 (0.6, 1.9)		
High triglyceride								
No. of cases (%)	294 (29)	197 (37)	60 (39)	363 (15)	110 (23)	28 (43)		
Age-adjusted OR	1.0	1.5 (1.2, 1.9)	1.8 (1.2, 2.5)	1.0	1.5 (1.2, 1.9)	3.6 (2.2, 6.1)		
Multivariable-adjusted OR	1.0	1.6 (1.3, 2.1)	1.8 (1.3, 2.6)	1.0	1.5 (1.1, 1.9)	3.8 (2.3, 6.5)	0.64	0.02
Further adjustment for BMI	1.0	1.1 (0.9, 1.5)	1.1 (0.7, 1.5)	1.0	1.1 (0.9, 1.4)	2.3 (1.3, 4.0)		
Metabolic syndrome								
No. of cases (%)	178 (17)	145 (28)	61 (40)	243 (10)	121 (26)	28 (43)		
Age-adjusted OR	1.0	1.8 (1.6, 2.3)	3.2 (2.2, 4.6)	1.0	2.6 (2.0, 3.4)	5.5 (3.3, 9.3)		
Multivariable-adjusted OR	1.0	1.9 (1.6, 2.4)	3.2 (2.2, 4.7)	1.0	2.6 (2.1, 3.4)	5.8 (3.4, 9.8)	0.03	0.04

Multivariable-adjusted OR was adjusted for age (year), smoking status (nonsmoker and current smoker), current ethanol intake (g/day), time since last meal (<2, 2, 3–7 and ≥8 hours) and for women, menopausal status (pre- and post-menopause).

MetS^{7–10}) as well as obesity, hypertension, glucose abnormality and high triglyceride levels²). Our results generally confirmed these previous findings.

OSA and MetS were each associated strongly with BMI. Then, we examined the association between the severity of nocturnal intermittent hypoxia and each metabolic risk factor after stratification by overweight status. The associations with high blood pressure, a high triglyceride level and the presence of two or more metabolic risk factors were modified by overweight and BMI. To our knowledge, this study is the first to show significant interaction between nocturnal intermittent hypoxia and BMI in relation to metabolic

risk factors.

Several mechanisms, other than being overweight, for nocturnal intermittent hypoxia affect metabolic risk factors. First, reduced blood oxygen saturation stimulates peripheral arterial chemoreceptors, especially carotid bodies, and enhances sympathetic drive, an effect which appears to be carried over into normal waking hours, leading to elevated blood pressure²¹). This mechanism was supported by reports that nasal continuous positive pressure reduced baroreceptor sensitivity²²) and ambulatory blood pressure²³). Second, increased sympathetic tone also raised serum catecholamine levels, leading to elevated serum glu-

Table 3. Age, sex- and multivariable-adjusted odds ratios (95% confidence intervals) of metabolic risk factors and the presence of ≥ 2 metabolic risk factors according to the 3% oxygen desaturation index, stratified by overweight

	Not overweight			Overweight			<i>p</i> for interaction	
	3%ODI			3%ODI			Moderate-to-severe SDB $\times$ Overweight	Moderate-to-severe SDB $\times$ BMI
	0 to <5	5 to <15	≥ 15	0 to <5	5 to <15	≥ 15		
No. at risk	2,645	510	78	740	490	139		
High blood pressure								
No. of cases (%)	1,185 (45)	293 (58)	63 (81)	472 (64)	369 (75)	114 (82)		
Age, sex-adjusted OR	1.0	1.2 (1.0, 1.4)	3.2 (1.8, 5.8)	1.0	1.5 (1.1, 1.9)	1.9 (1.2, 3.1)		
Multivariable-adjusted OR	1.0	1.1 (0.9, 1.4)	2.9 (1.6, 5.3)	1.0	1.5 (1.1, 1.9)	2.0 (1.2, 3.2)	0.16	0.006
Further adjustment for BMI	1.0	1.0 (0.8, 1.3)	2.5 (1.4, 4.6)	1.0	1.4 (1.0, 1.8)	1.5 (0.9, 2.4)		
Glucose abnormality								
No. of cases (%)	288 (11)	74 (15)	19 (24)	110 (15)	85 (17)	40 (29)		
Age, sex-adjusted OR	1.0	1.1 (0.7, 1.3)	1.5 (0.9, 2.6)	1.0	1.1 (0.8, 1.5)	1.9 (1.2, 2.9)		
Multivariable-adjusted OR	1.0	1.0 (0.7, 1.4)	1.5 (0.9, 2.7)	1.0	1.2 (0.8, 1.6)	1.9 (1.2, 3.1)	1.00	0.56
Further adjustment for BMI	1.0	1.0 (0.7, 1.3)	1.4 (0.8, 2.5)	1.0	1.1 (0.8, 1.5)	1.6 (1.0, 2.6)		
Low HDL cholesterol								
No. of cases (%)	349 (13)	80 (16)	12 (15)	155 (21)	110 (22)	23 (17)		
Age, sex-adjusted OR	1.0	1.3 (1.0, 1.7)	1.4 (0.7, 2.6)	1.0	1.2 (0.9, 1.6)	0.9 (0.6, 1.5)		
Multivariable-adjusted OR	1.0	1.4 (1.0, 1.8)	1.6 (0.8, 3.0)	1.0	1.3 (1.0, 1.8)	1.1 (0.7, 1.9)	0.34	0.11
Further adjustment for BMI	1.0	1.2 (0.9, 1.6)	1.3 (0.7, 2.6)	1.0	1.3 (1.0, 1.7)	1.0 (0.6, 1.8)		
High triglyceride								
No. of cases (%)	433 (16)	131 (26)	29 (37)	224 (30)	176 (36)	59 (42)		
Age, sex-adjusted OR	1.0	1.5 (1.0, 1.7)	2.3 (1.4, 3.7)	1.0	1.1 (0.9, 1.5)	1.3 (0.9, 2.0)		
Multivariable-adjusted OR	1.0	1.5 (1.0, 1.8)	2.2 (1.4, 3.7)	1.0	1.2 (0.9, 1.6)	1.4 (0.9, 2.1)	0.12	0.08
Further adjustment for BMI	1.0	1.2 (1.0, 1.6)	1.7 (1.0, 2.8)	1.0	1.1 (0.9, 1.5)	1.2 (0.8, 1.9)		
The presence of ≥ 2 metabolic risk factors								
No. of cases (%)	538 (19)	149 (29)	38 (49)	288 (39)	222 (45)	77 (55)		
Age, sex-adjusted OR	1.0	1.3 (1.0, 1.6)	2.6 (1.6, 4.1)	1.0	1.1 (0.9, 1.5)	1.6 (1.1, 2.3)		
Multivariable-adjusted OR	1.0	1.3 (1.0, 1.6)	2.5 (1.5, 4.0)	1.0	1.2 (1.0, 1.6)	1.7 (1.1, 2.5)	0.09	0.002
Further adjustment for BMI	1.0	1.1 (0.9, 1.4)	1.9 (1.2, 3.1)	1.0	1.2 (0.9, 1.5)	1.4 (0.9, 2.1)		

Multivariable-adjusted OR was adjusted for age (year), sex, body mass index (kg/m^2), smoking status (nonsmoker and current smoker), current ethanol intake (g/day), time since last meal (< 2, 2, 3–7 and ≥ 8 hours) and for women, menopausal status (pre- and post-menopause).

cose levels²⁴). Third, oxidative stress owing to repetitive hypoxia elevated cytokine levels (e.g. tumor necrosis factor- α ; TNF- α and interleukin-6; IL-6)²⁵, which led to increased insulin resistance²⁶. Fourth, sleep deprivation and the stress there from inhibited slow wave sleep and activated the hypothalamic-pituitary-adrenal axis²⁷. Inhibition of slow wave sleep decreased growth hormone levels, leading to a reduction in metabolism, and serum leptin levels and increased serum ghrelin levels, leading to the stimulation of appetite. Activation of the hypothalamic-pituitary-adrenal axis increased serum cortisol levels²⁸, leading to hyperglycemia and insulin resistance²⁹. Lastly, an experimental study has shown that intermittent

hypoxia caused an increase in hepatic levels of triglyceride and phospholipid, and upregulated the expression of genes involved in lipid biosynthesis in mice³⁰. Therefore, nocturnal intermittent hypoxia may increase serum triglyceride levels.

To explain the interaction between nocturnal intermittent hypoxia and BMI in relation to high blood pressure and high triglyceride levels, we considered whether BMI affects metabolic risk factors both directly and indirectly. Being overweight is associated with the accumulation of fat, which increases levels of free fatty acids and adipokines (e.g. TNF- α and IL-6)^{31, 32}. An increase in adipokines causes elevated blood pressure³³. An increase in free fatty acids causes

lipoprotein synthesis in the liver and raises serum triglyceride levels³⁴). Being overweight may also be associated with metabolic risk factors indirectly, mediated by nocturnal intermittent hypoxia. For example, reduced oxygen saturation enhances sympathetic activity to raise blood pressure²³) and the production of VLDL in liver, and raises blood triglyceride levels³⁰), common pathways in overweight individuals. Therefore, being overweight may weaken the effect of nocturnal intermittent hypoxia on high blood pressure and high triglyceride levels.

The strengths of the present study were the large sample size ($n \approx 4,000$), and community-based approach. Another strength was that we investigated lean persons in Asia, whereas previous large studies were mainly of obese or overweight persons in the United States.

Several limitations of the present study need to be discussed. First, the study had a cross-sectional design. Therefore, we cannot prove the causality between nocturnal intermittent hypoxia and MetS. Second, we measured oxygen desaturation during sleep by pulse-oximetry to estimate OSA. Since apneic episodes do not always cause oxygen desaturation, we could not accurately estimate very mild OSA. However, the specificity of the screening remained high²⁰). Third, we used BMI as the definition of MetS. Some studies reported that abdominal obesity had a stronger association with OSA than did high BMI³⁵). Therefore, there may be some, though not substantial, misclassification because a previous study reported that BMI was highly correlated with abdominal fat as well as waist circumference ($r = 0.87$ for BMI and $r = 0.91$ for waist circumference)³⁶). Fourth, the same cutoff point of serum triglycerides was used for fasting and non-fasting data as the criterium for high triglyceride levels. Although justification of the use of the same cutoff point as fasting status is under debate, the data of non-fasting triglycerides can be used because it is a significant predictor for ischemic heart disease¹⁴). Fifth, we used a non-fasting glucose concentration ≥ 140 mg/dL (7.77 mmol/L) as a component of MetS. Although we defined fasting status as more than 8 hours after the last meal, plasma glucose levels returned to pre-prandial levels in 2–3 hours after the last meal among subjects with normal glucose tolerance³⁷). The proportion of participants with glucose abnormality for each definition of fasting status (more than 8 hours after the last meal vs. more than 3 hours after the last meal) was 14% vs. 25% for non-fasting and 26% vs. 24% for fasting in men, and in women, 14% vs. 11% and 12% vs. 12%, respectively. Therefore, we may have underestimated the number of participants

with glucose abnormality among men. However, there was no difference change in our results between definitions of fasting status.

Mean BMI is much lower in Asia³⁸), and the prevalence of OSA was reported to be less than half that in the United States³⁹). However, our findings suggest that OSA affects cardiovascular risk factors more strongly among lower BMI populations. Therefore, the impact of OSA on cardiovascular risk factors may be potentially large in Asia.

Acknowledgements

We thank Dr. Mitsumasa Umesawa, MD, PhD, Ms. Yukiko Ichikawa and Ms. Miyuki Notsute for technical assistance, and Ms. Minako Kudo, Ms. Kazuyo Kamei and staff of the Osaka Medical Center for Health Science and Promotion, Osaka University and the University of Tsukuba for data collection.

Notice of Grant Support

This was not an industry supported study. This study was supported in part by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Grant-in-Aid for research B: 14370132) and the Health and Labor Sciences Research Grant (Clinical Research for Evidence Based Medicine), Ministry of Health, Welfare and Labor, the FULLHAP, Japan, and the University Research Project Research Grant (B), University of Tsukuba. Drs. Muraki, Tanigawa, Yamagishi, Sakurai, Cui, Imano, Sato, Kitamura, Shimamoto, Konishi and Iso have indicated no conflicts of interest.

References

- 1) Caples SM, Garcia-Touchard A, Somers VK: Sleep-disordered breathing and cardiovascular risk. *Sleep*, 2007; 30: 291-303
- 2) Young T, Peppard PE, Gottlieb DJ: Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*, 2002; 165: 1217-1239
- 3) Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T: Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol*, 2008; 52: 686-717
- 4) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T,

- Yokote K, Yokode M: Metabolic syndrome. *J Atheroscler Thromb*, 2008; 15: 1-5
- 5) Teramura M, Emoto M, Araki T, Yokoyama H, Motoyama K, Shinohara K, Mori K, Koyama H, Shoji T, Inaba M, Nishizawa Y: Clinical impact of metabolic syndrome by modified NCEP-ATP III criteria on carotid atherosclerosis in Japanese adults. *J Atheroscler Thromb*, 2007; 14: 172-178
 - 6) Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, Cui R, Tanigawa T, Shimamoto T: Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. *Stroke*, 2007; 38: 1744-1751
 - 7) Lam JC, Lam B, Lam CL, Fong D, Wang JK, Tse HF, Lam KS, Ip MS: Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong. *Respir Med*, 2006; 100: 980-987
 - 8) Parish JM, Adam T, Facchiano L: Relationship of metabolic syndrome and obstructive sleep apnea. *J Clin Sleep Med*, 2007; 3: 467-472
 - 9) Sasanabe R, Banno K, Otake K, Hasegawa R, Usui K, Morita M, Shiomi T: Metabolic syndrome in Japanese patients with obstructive sleep apnea syndrome. *Hypertens Res*, 2006; 29: 315-322
 - 10) Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP: Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J*, 2004; 25: 735-741
 - 11) Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP: Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab*, 2000; 85: 1151-1158
 - 12) Vgontzas AN, Bixler EO, Chrousos GP: Sleep apnea is a manifestation of the metabolic syndrome. *Sleep Med Rev*, 2005; 9: 211-224
 - 13) Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, Yamagishi K, Noda H, Tanigawa T, Iso H, Shimamoto T: Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: the Circulatory Risk in Communities Study (CIRCS). *Stroke*, 2009; 40: 1571-1577
 - 14) Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, Shimamoto T, Iida M, Komachi Y: Serum triglycerides and risk of coronary heart disease among Japanese men and women. *Am J Epidemiol*, 2001; 153: 490-499
 - 15) Tanigawa T, Tachibana N, Yamagishi K, Muraki I, Umesawa M, Shimamoto T, Iso H: Usual alcohol consumption and arterial oxygen desaturation during sleep. *JAMA*, 2004; 292: 923-925
 - 16) Nakamura M, Sato S, Shimamoto T: Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US cholesterol reference method laboratory network. *J Atheroscler Thromb*, 2003; 10: 145-153
 - 17) National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*, 2002; 106: 3143-3421
 - 18) World Health Organization Western Pacific Region, International Association for the Study of Obesity and the International Obesity Task Force. The Asia-Pacific perspective: Redefining obesity and its treatment. Health Communications Australia Pty Limited: Australia; 2000
 - 19) Clark JS, Votteri B, Ariagno RL, Cheung P, Eichhorn JH, Fallat RJ, Lee SE, Newth CJ, Rotman H, Sue DY: Noninvasive assessment of blood gases. *Am Rev Respir Dis* 1992; 145: 220-232
 - 20) Nakamata M, Kubota Y, Sakai K, Kinebuchi S, Nakayama S, Ohira T, Sato S, Shinoda S, Kawano S: The limitation of screening test for patients with sleep apnea syndrome using pulse oximetry. *J Jpn Soc Respir Care*, 2003; 12: 401-406 (in Japanese)
 - 21) Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK: Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. *Circulation*, 1998; 97: 943-945
 - 22) Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM: Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J*, 2007; 29: 720-727
 - 23) Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ: Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet*, 2002; 359: 204-210
 - 24) Nonogaki K: New insights into sympathetic regulation of glucose and fat metabolism. *Diabetologia*, 2000; 43: 533-549
 - 25) Ciftci TU, Kokturk O, Bukan N, Bilgihan A: The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. *Cytokine*, 2004; 28: 87-91
 - 26) Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS: Protection from obesity-induced insulin resistance in mice lacking TNF- α function. *Nature*, 1997; 389: 610-614
 - 27) Van Cauter E, Spiegel K, Tasali E, Leproult R: Metabolic consequences of sleep and sleep loss. *Sleep Med*, 2008; 9 Suppl 1: S23-S28
 - 28) Spiegel K, Leproult R, Van Cauter CE: Impact of sleep debt on metabolic and endocrine function. *Lancet*, 1999; 354: 1435-1439
 - 29) Follenius M, Brandenberger G, Bandesapt JJ, Libert JP, Ehrhart J: Nocturnal cortisol release in relation to sleep structure. *Sleep*, 1992; 15: 21-27
 - 30) Li J, Nanayakkara A, Jun J, Savransky V, Polotsky VY: Effect of deficiency in SREBP cleavage-activating protein on lipid metabolism during intermittent hypoxia. *Physiol Genomics*, 2007; 31: 273-280
 - 31) Chudek J, Wiecek A: Adipose tissue, inflammation and endothelial dysfunction. *Pharmacol Rep*, 2006; 58 Suppl: 81-88
 - 32) Zimmermann R, Strauss JG, Haemmerle G, Schoiswohl G, Birner-Gruenberger R, Riederer M, Lass A, Neuberger G, Eisenhaber F, Hermetter A, Zechner R: Fat mobiliza-

- tion in adipose tissue is promoted by adipose triglyceride lipase. *Science*, 2004; 306: 1383-1386
- 33) Guzik TJ, Mangalat D, Korbout R: Adipocytokines - novel link between inflammation and vascular function? *J Physiol Pharmacol*, 2006; 57: 505-528
- 34) Jensen MD, Haymond MW, Rizza RA, Cryer PE, Miles JM: Influence of body fat distribution on free fatty acid metabolism in obesity. *J Clin Invest*, 1989; 83: 1168-1173
- 35) Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP: Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab*, 2000; 85: 1151-1158
- 36) Hwang MJ, Chung WS, Gallagher D, Kim DY, Shin HD, Song MY: How useful is waist circumference for assessment of abdominal obesity in Korean pre-menopausal women during weight loss? *Asia Pac J Clin Nutr*, 2008; 17: 229-234
- 37) American Diabetes Association. Postprandial blood glucose. American Diabetes Association. *Diabetes Care*, 2001; 24: 775-778
- 38) Balkau B, Deanfield JE, Després JP, Bassand JP, Fox KA, Smith SC Jr, Barter P, Tan CE, Van Gaal L, Wittchen HU, Massien C, Haffner SM: International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation*, 2007; 116: 1942-1951
- 39) Lam B, Lam DC, Ip MS: Obstructive sleep apnoea in Asia. *Int J Tuberc Lung Dis*, 2007; 11: 2-11