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Early View

Original article

Sleep disordered breathing and metabolic comorbidities across gender and menopausal status in East Asians; the Nagahama Study

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Title

Sleep disordered breathing and metabolic comorbidities across gender and menopausal status in East Asians; the Nagahama Study.

Short running title

SDB and metabolic comorbidities in East Asians

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Abstract

It is well known that the prevalence of sleep disordered breathing (SDB) is increased in patients with obesity or metabolic comorbidities. However, the way in which the prevalence of SDB increases in relation to comorbidities according to the severity of obesity remains unclear.

This cross-sectional study evaluated 7,713 community participants with nocturnal oximetry ≥2 nights. SDB was assessed by the 3% oxygen desaturation index corrected for sleep duration obtained by wrist actigraphy (Acti-ODI3%). SDB severity was defined by Acti-ODI3%. Obesity was defined as body mass index ≥25 kg/m^2.

The prevalence of SDB was 41.0% (95% CI 39.9-42.1), 46.9% (45.8-48.0), 10.1% (9.5-10.8), and 2.0% (1.7-2.3) in normal, mild, moderate, and severe SDB, respectively, with notable sex differences evident (men >post-menopausal women >pre-menopausal women). Comorbidities such as hypertension, diabetes, and metabolic syndrome were independently associated with the prevalence of moderate-to-severe SDB, and coincidence of any one of these with obesity was associated with a higher probability of moderate-to-severe SDB (OR 8.2, 95% CI 6.6-10.2; 7.8, 5.6-10.9; 6.7, 5.2-8.6, respectively). Dyslipidemia in addition to obesity was not

additively associated with the prevalence of moderate to-severe SDB. The number of antihypertensive drugs was associated with SDB (P for trend <0.001). Proportion of a high cumulative percentage of sleep time with SpO_2 <90% increased even among moderate-to-severe SDB with increases in obesity.

Metabolic comorbidities contribute to SDB regardless of the degree of obesity. We should recognize the extremely high prevalence of moderate-to-severe SDB in patients with obesity and metabolic comorbidities.

Keywords

Sleep disordered breathing; obesity; hypertension; diabetes; dyslipidemia; metabolic syndrome; sex difference; menopause; general population.

Introduction

Obesity is one of the most important factors related to health, and its prevalence is increasing[1, 2]. Sleep disordered breathing (SDB) is a major health problem in those with obesity[3]. The prevalence of SDB has increased in comparison with past decades, and recent studies of general populations showed a prevalence of SDB as high as 60-80%[4, 5]. One reason for this change is assumed to be the increased rate of obesity[6, 7].

Although some study results have not been definitive, the associations between SDB and metabolic comorbidities such as hypertension[8], diabetes[9, 10], dyslipidemia[11, 12], and metabolic syndrome (MetS)[13, 14] are well known. These metabolic comorbidities were reported to be associated with high percentages of SDB in hospital or laboratory-based studies[13, 15, 16]; however, the percentage of SDB in terms of comorbidities is not fully understood, especially in general populations. When we think in terms of cardiometabolic diseases, it is well accepted that obesity has a strong impact. In addition, obesity is a definite risk factor for SDB[3, 17]. Therefore, the association between SDB and metabolic comorbidities should be investigated considering the strong confounding factor of obesity; nonetheless, details of the associations according to the severity of obesity remain unclear.

The intermittent hypoxemia caused by SDB is important in inducing systemic inflammation[18]. Recently, not only intermittent hypoxia but the hypoxic burden in patients with SDB was reported to be a factor in inducing cardiovascular diseases[19].

Obesity, SDB, and metabolic comorbidities are common conditions and moreover have unignorable effects on public health; therefore, it is important to investigate the associations among these risk factors and SDB. Also, because there are significant sex differences in the prevalence of SDB[20, 21], investigating differences according to sex as well as menopausal status is important.

We hypothesized that obesity and metabolic comorbidities independently increase the prevalence of SDB. This study aimed to investigate the relationships among obesity, SDB, and metabolic comorbidities according to sex differences and menopausal status. Using simple measurements of nighttime oxygen desaturation, SDB can be underestimated because data are not based on actual sleep duration but on the duration of measurements by oximetry. Therefore, we performed a population-based study (the Nagahama Study) and examined oxygen saturation during sleep by pulse oximetry, which was adjusted by objective sleep duration generated from actigraphy in men, pre-menopausal women, and post-menopausal women.

Methods

Study participants

Participants in the Nagahama study were recruited between 2013 and 2016 from the general population of Nagahama, a rural city of 125,000 inhabitants located in central Japan.

Community residents between 34 and 80 years of age and living independently without any physical impairments or dysfunctions were eligible to participate. A total of 9,850 individuals participated in the investigation[5]. Menopausal status was surveyed by a questionnaire and we categorized women according to pre-menopausal (questionnaire answer "no") and post-menopausal (questionnaire answer "yes" for whatever reasons) status. The ethics committee of Kyoto University Graduate School of Medicine approved this study, and we obtained written informed consent from all participants.

Assessments of SDB

A pulse oximeter (PULSOX-Me300; Konica Minolta Inc., Tokyo, Japan) was put on the nondominant wrist during 4 nights of sleep. Data without oxygen-saturation signals or incomprehensible recordings were excluded from analysis. For selected data, we decided the onset and completion of sleep based on the results of actigraphy (Actiwatch 2 or the Actiwatch Spectrum Plus; Philips Respironics, Murrysville, PA, USA) and used the actual sleep duration for calculations[5]. We used averaged data from a minimum of 2 days for analysis.

A 3% oxygen desaturation index (ODI) was constructed based on increments of ≥3% of drops in oxygen saturation from baseline per h during measured sleep time by actigraphy. We used the actigraphy-modified ODI3% (Acti-ODI3%) as an indicator of SDB that mimicked sleep

apnea, and defined the severity of SDB by Acti-ODI3% levels as follows: normal, <5 /h; mild, 5-<15 /h; moderate, 15-<30 /h; and severe, ≥30 /h. We also measured the actigraphy-modified cumulative percentage of sleep time with SpO_2 <90% (Acti-CT90) as a surrogate marker for continuous hypoxia, mean SpO_2, and minimum SpO_2 during sleep. In our preliminary data, Acti-ODI3% was more comparable to the apnea-hypopnea index (AHI) derived from attended polysomnography in 32 patients ($r = 0.99$, $P < 0.001$; AHI = Acti-ODI3%*1.04 + 1.45) than simply-measured ODI3% without actigraphy-modification ($r = 0.92$, $P < 0.001$; AHI = usual ODI3%*1.27 + 2.06) (Figure S1).

Assessment of obesity

We assessed three parameters of obesity: body mass index (BMI) [22], waist circumference (WC) [23], and body fat percentage [24]. BMI was calculated using the obtained height and weight data. WC was measured at the umbilical point in the standing position. Body fat percentage was calculated by bioelectrical impedance analysis (BIA).

Definition of comorbidities

Hypertension was defined as follows: ongoing treatment with antihypertensive agents or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Data on the number of antihypertensive drugs were obtained by the following item on the questionnaire:

"How many kinds of antihypertensive drugs do you take for hypertension?" Resistant hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg with the use of ≥3 antihypertensive medications or the use of ≥4 antihypertensive medications regardless of blood pressure level. Otherwise, hypertension was defined as non-resistant hypertension. Diabetes was defined as follows: ongoing treatment with oral antihyperglycemic agents and/or insulin or hemoglobin A1c ≥6.5%.

The analysis of dyslipidemia and metabolic syndrome was performed in participants in a fasting state (≥10 h). Dyslipidemia was defined as follows: ongoing treatment with antihyperlipidemic agents or low-density lipoprotein ≥140 mg/dL, high-density lipoprotein <40 mg/dL, or triglycerides ≥150 mg/dL. Metabolic syndrome was defined according to the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome [25]: WC ≥85 cm in men or ≥90 cm in women and at least two of the following: 1) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or the use of antihypertensive drugs, 2) fasting plasma glucose ≥110 mg/dL or the use of drugs for diabetes, and 3) high-density lipoprotein <40 mg/dL or triglycerides ≥150 mg/dL or the use of antihyperlipidemic drugs.

Statistics

Values are expressed as mean ± standard deviation, frequency (95% confidence interval), or medians [interquartile range]. Multiple logistic regression analyses were performed to assess

the relationships among SDB and obesity parameters and/or comorbidities. The models were adjusted by age, sex, alcohol status, and smoking status. The Cochrane-Armitage test was used as a trend test. A two-tailed P value <0.05 was deemed statistically significant. We conducted statistical analyses using JMP Pro 13.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

Study participants

Figure S2 is a flowchart of study enrollment. The total sample for the analysis was comprised of 7,713 individuals from the 9,850 initial participants. Table 1 summarizes the clinical characteristics of study participants. The differences between included and not-included participants were as follows: age (57.9 ± 12.1 vs. 58.5 ± 13.5 y, P = 0.03), sex (32.5/23.4/44.2 vs. 33.7/23.6/42.8% in men/pre-menopausal women/post-menopausal women, P = 0.40), and BMI (22.3 ± 3.3 vs. 22.2 ± 3.4 kg/m^2, P = 0.59). Mean BMI was in descending order for men >post-menopausal women and >pre-menopausal women. A similar tendency was seen in WC, while the order of body fat percentage was post-menopausal women >pre-menopausal women >men. As to complications, men had the highest percentages of hypertension, diabetes, and MetS, while post-menopausal women had the highest percentage of dyslipidemia. The associations among obesity parameters are shown for men, premenopausal women, and postmenopausal women in Table S1**.** As shown in Table S1, significant correlations were seen

among BMI and WC, WC and body fat percentage, and BMI and body fat percentage.

SDB prevalence

SDB parameters in men (n = 2,491) and women according to menopausal status (n = 1,794 pre-menopausal women, n = 3,388 post-menopausal women) are shown in Table 2. The prevalence of SDB was 41.0% (95% CI 39.9-42.1), 46.9% (45.8-48.0), 10.1% (9.5-10.8), and 2.0% (1.7-2.3) in normal, mild, moderate, and severe SDB, respectively. There was a notable sex difference in prevalence: men >post-menopausal women >pre-menopausal women. The prevalence of SDB in East Asians was not much different from that reported in studies of Caucasian or Hispanic/Latino participants[4, 26, 27] (Figure S3). For the sensitivity analysis, we included continuous positive airway pressure (CPAP) users (n = 41) into the moderate-to-severe SDB group and then calculated the prevalence of SDB. The prevalence of SDB then changed to be 40.8% (95% CI 39.7-41.9), 46.6% (45.5-47.8), and 12.6% (11.9-13.3) in normal, mild, and moderate-to-severe SDB, respectively. A slight increase in the prevalence of moderate-to-severe SDB was then noted.

Association between obesity parameters and SDB

The prevalence of moderate-to-severe SDB according to age and BMI categories is shown in Figure 1. Increased age and BMI were both related to a greater presence of

moderate-to-severe SDB. Those <40 years old were much more susceptible to SDB when they were obese (BMI ≥25 kg/m^2; unadjusted odds ratio 40.6 (95% CI 14.9-110.5) compared to non-obese). When the impact of specific obesity parameters was investigated, a significant association was seen for each obesity parameter (Table S2). Given the values of point estimation of odds ratio, in all obesity parameters, the association between the obesity parameter and SDB was the strongest in pre-menopausal women, followed by men and post-menopausal women.

Association between comorbidities and SDB according to severity of obesity

Prevalence of moderate-to-severe SDB according to BMI and the presence of hypertension or diabetes in the whole cohort, and men, pre-menopausal women, and post-menopausal women subgroups is shown in Figure 2. In the whole cohort and all subgroups, moderate-to-severe SDB was found in those with comorbidities, and the presence of diabetes rather than hypertension was more closely related to the presence of moderate-to-severe SDB. In particular, pre-menopausal women with diabetes had the highest prevalence of moderate-to-severe SDB. For hypertension, when analyzed by the number of antihypertensive drugs, the prevalence of moderate-to-severe SDB was significantly increased according to the number of drugs used regardless of blood pressure level (P for trend <0.001) (Figure 3A). In addition, resistant hypertension, although it was a small number (n = 110), was significantly

associated with a high prevalence of moderate-to-severe SDB (Figure 3B).

When obesity was defined as BMI ≥25 kg/m^2, coincidence of both obesity and any comorbidity with the exception of dyslipidemia, compared to a single factor resulted in a high prevalence of moderate-to-severe SDB (Figure 4). After adjusting for covariates, coincidence of both obesity and comorbidities resulted in a high prevalence of moderate-to-severe SDB (OR 8.2, 95% CI 6.6-10.2 in hypertension; OR 7.8, 95% CI 5.6-10.9 in diabetes; OR 5.8, 95% CI 4.6-7.4 in dyslipidemia; OR 6.7, 95% CI 5.2-8.6 in MetS). These ORs were compared with those of participants with neither hypertension nor obesity, with neither diabetes nor obesity, with neither dyslipidemia nor obesity, and with neither metabolic syndrome nor obesity, respectively. Although obesity was a strong factor for the presence of moderate-to-severe SDB, the presence of comorbidities was also an independent factor for the presence of moderate-to-severe SDB, even in the absence of obesity (OR 2.3, 95% CI 1.8-2.8 in hypertension; OR 1.5, 95% CI 1.1-2.1 in diabetes; OR 1.5, 95% CI 1.2-1.9 in dyslipidemia; OR 2.2, 95% CI 1.6-3.0 in MetS). However, dyslipidemia in addition to obesity was not additively associated with SDB (Figure 5). For sensitivity analyses, we changed the cutoff level of SDB to Acti-ODI3% 5 or 20 and showed the percentages and odd ratios in Figure S4-S7. The results were similar to the original analyses in that the impact was higher in the order of doubly negative, only comorbidity present, only obesity present, and doubly positive, and dyslipidemia in addition to obesity was not additively associated with SDB.

Association between SDB and clinical symptoms

Excessive daytime sleepiness (EDS) was not related to the presence of moderate-to-severe SDB (EDS +, 11.7% (95% CI 9.9-13.7) vs. EDS -, 12.2% (11.4-13.0), P = 0.65). When the effect of the combination of metabolic comorbidities or obesity with EDS was evaluated, metabolic comorbidities or obesity rather than EDS was associated with a higher prevalence of SDB (Figure S8). Poor sleep quality was also not related to the presence of moderate-to-severe SDB (poor sleep quality +, 13.0% (95% CI 11.8-14.4) vs. poor sleep quality -, 11.6% (10.7-12.5), P = 0.61), and metabolic comorbidities or obesity rather than poor sleep quality was associated with a higher prevalence of SDB (Figure S9).

Association between Acti-ODI3% and Acti-CT90 according to severity of obesity

The prevalence of high Acti-CT90 among participants with moderate-to-severe SDB according to BMI is shown in Figure 6. In accordance with increases in BMI, percentages of high Acti-CT90 increased among those with moderate-to-severe SDB. This tendency was not evident among those without SDB and with mild SDB (Figures S10 and S11, respectively).

Discussion

In terms of gender and menopausal status, current study shows notable epidemiological evidence about the contribution to SDB by obesity and comorbidities. The prevalence of SDB

in East Asians was 41.0% (95% CI 39.9-42.1), 46.9% (45.8-48.0), 10.1% (9.5-10.8), and 2.0% (1.7-2.3) in normal, mild, moderate, and severe SDB, respectively, with notable sex differences evident (men >post-menopausal women >pre-menopausal women). These results did not differ greatly from other studies in Caucasian or Hispanic/Latino participants. BMI, WC, and body fat percentage were contributors to SDB, but the degrees of the contributions were different by sex. Pre-menopausal women were the most susceptible to obesity in the context of SDB prevalence. Comorbidities such as hypertension, diabetes, and MetS with and without obesity were independently associated with SDB, and their coincidence increased the probability of SDB. As to hypertension, the number of antihypertensive drugs was associated with SDB. However, dyslipidemia in addition to obesity was not additively associated with SDB. Percentages of high Acti-CT90 increased among those with moderate-to-severe SDB according to increases in obesity.

In this study, we showed the percentages of SDB in the presence or absence of hypertension and diabetes according to sex and menopausal status in relation to BMI (Figure 2). Previously, SDB was reported to be associated with various comorbidities such as hypertension[8], diabetes [9, 10], dyslipidemia[11, 12], and MetS[13, 14]. However, the reverse viewpoint was hardly discussed, although the direction of the causal relationship would be from SDB to comorbidities[18]. Not surprisingly, a positive association was observed, but we showed the real-world percentages of SDB for each comorbidity examined, especially according to sex

and menopausal status groupings and BMI values. To our knowledge, this is the first study to evaluate these specific aspects. Clinically, real-world data on SDB for various comorbidity and obesity groupings are of practical value and would be helpful in formulating public health policies. In particular, the number of antihypertensive drugs was associated with SDB (Figure 3). When a number of antihypertensive drugs are required, the degree of hypertension would be severe, which could explain these results on the prevalence of SDB. Questioning a patient on the number of antihypertensive drugs is very simple and would be helpful for detecting SDB in daily clinical settings. The percentage of moderate-to-severe SDB in those with hypertension was previously reported to be about 30%[28]. In this study, the result was 22.9%. Also, the percentage of moderate-to-severe SDB in those with resistant hypertension was reported to be as high as 80%[15]. However, it was 39.1% in our study. This discrepancy was probably due to characteristics of the participants; that is, participants in this study were from a general population and were East Asians. Therefore, in a general population, the percentage might not be as high as previously reported; however, educational efforts on this issue are important because the result of 40% is sufficiently high to warrant attention.

In examining the impact of combinations of comorbidities and obesity on SDB (Figures 4-5) the impact was higher in the order of doubly negative, only comorbidity present, only obesity present, and doubly positive. Therefore, a comorbidity without obesity was a risk factor for SDB, although it was reported that obesity was a strong confounding factor between SDB and

metabolic comorbidities[29]. In particular, pre-menopausal women were more affected by obesity than the other groups, indicating the need for treating obesity in that group as body weight control has been shown to be important[30]. In addition, the predictive value of clinical symptoms such as EDS or poor sleep quality was, if any, slight, and comorbidities or obesity had a greater impact on the presence of SDB, which may reinforce the importance of identifying metabolic comorbidities.

The association of dyslipidemia was not additive to obesity in relation to SDB, differing from the other comorbidities examined. There have been reports that dyslipidemia was not associated with SDB[29, 31]. On the other hand, CPAP therapy was reported to reduce postprandial lipidemia[32], while weight loss rather than CPAP therapy was more effective in improving dyslipidemia[30]. Therefore, the impact of obesity may be strong for dyslipidemia compared to other metabolic comorbidities.

Although many studies showed an association between obesity and SDB[3, 17], there were few reports of differences among obesity parameters[33]. In this study, we firstly presented the comprehensive association between obesity parameters and SDB in a large community cohort according to sex differences and menopausal status (n = 7,713). Not surprisingly, the more severe the obesity parameters were, the more SDB participants were detected; and each obesity parameter was independently associated with SDB (Table S2). However, these three parameters were well correlated with each other (Table S1). Therefore, it might be better to

use only one of them in a population-based study for fear of collinearity. Also, associations between SDB and obesity parameters substituted by odds ratios were different among groups (post-menopausal women< men< pre-menopausal women). A strong impact of obesity on pre-menopausal women was previously suggested[34]. Therefore, among the groups examined, pre-menopausal women may be the most susceptible to obesity in the context of SDB development.

Previously it was shown that those who met the cutoff BMI of 32.3 kg/m^2 had a 6-fold increase in the prevalence of moderate SDB in the United States[35]. However, in this study, the cutoff of BMI 25 kg/m^2 was the point at which the prevalence of SDB was increased. This value was much lower than previously reported. BMI $\geq$25 kg/m^2 is considered as obesity in Japan (definition by Japan Society for the Study of Obesity). Although obesity is defined by BMI $\geq$30 kg/m^2 in Westerners, only 4% of Japanese meet this criterion, while about 30% of men and 20% of women have BMI $\geq$25 kg/m^2[36]. Therefore, in East Asians, we may need to pay attention to the presence of moderate-to-severe SDB at lower BMIs than among Westerners[37].

Lastly, we showed a specific association between intermittent and continuous hypoxia according severity of obesity (Figure 6, S10-S11). When obesity developed, continuous hypoxia accordingly deteriorated even in moderate-to-severe intermittent hypoxia (Acti-ODI3% $\geq$15). Intermittent hypoxia was reported to enhance sympathetic responses to

continuous hypoxia[38], so the double negative effects may contribute to a poor prognosis especially in obese patients with moderate-to-severe SDB[39].

Several limitations should be mentioned. First, as this study was cross-sectional, it remains unresolved about causality. Also, as data were from only East Asian participants, the results of this study might not be generalized to other ethnic groups[37]. Nonetheless, these are the first such results from a large East Asian cohort, and these findings would be valuable in assessing worldwide data. Second, SDB was evaluated by pulse oximetry. Previous studies using simple ODI without adjusting for objective sleep duration had drawbacks in the diagnosis of SDB. Indeed, it is better to use polysomnography for diagnosing SDB. However, polysomnography is burdensome, requiring much effort. In this study, as ODI was adjusted for objective sleep duration by actigraphy, which is similar to sleep duration by polysomnography, this Acti-ODI might not deviate from information obtained with polysomnography as shown in Methods. Third, a certain level of participants were non-fasting and non-fasting participants were excluded from the analysis of dyslipidemia and MetS so that these participants differed from those included in the analysis of hypertension and diabetes. However, random selection of participants with a fasting state would minimize the bias. The large number of those with a fasting state (n = 6,051) would be sufficient for statistical power.

In conclusion, metabolic comorbidities such as hypertension, diabetes, dyslipidemia, MetS,

and obesity were independently associated with SDB, and their coincidence increased the probability of SDB. However, dyslipidemia in addition to obesity was not additively associated with SDB. Not only obesity but also metabolic comorbidities should be given attention in terms of the presence of SDB.

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Disclosure Statement

Contributions of each author:

Study design: T. Matsumoto and K.C.; Data collection: T. Matsumoto, K.M., Yasuharu T., T. Minami, O.K., H.T., N.T., S.H., K.T., T.O., T.W., N.K., K.S., T.K., T.T., Yoshimitsu T., T.N., T.H., F.M., and K.C.; Data analysis and interpretation: T. Matsumoto and K.C.; Manuscript drafting: T. Matsumoto and K.C.; Critical revision: K.M., Yasuharu T., T. Minami, O.K., H.T., N.T., S.H., K.T., T.O., T.W., N.K., K.S., T.K., T.T., S.M., Yoshimitsu T., T.N., T.H., and F.M.; Approval of the final version of manuscript: T. Matsumoto, K.M., Yasuharu T., T. Minami, O.K., H.T., N.T., S.H., K.T., T.O., T.W., N.K., K.S., T.K., T.T., S.M., Yoshimitsu T., T.N., T.H., F.M., and K.C.

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References

1. Cefalu WT, Bray GA, Home PD, Garvey WT, Klein S, Pi-Sunyer FX, Hu FB, Raz I, Van Gaal L, Wolfe BM, Ryan DH. Advances in the Science, Treatment, and Prevention of the Disease of Obesity: Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care* 2015: 38(8): 1567-1582.

2. Rahmouni K. Obesity-associated hypertension: recent progress in deciphering the pathogenesis. *Hypertension* 2014: 64(2): 215-221.

3. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014: 383(9918): 736-747.

4. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P, Tafti M, Haba-Rubio J. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015: 3(4): 310-318.

5. Matsumoto T, Murase K, Tabara Y, Gozal D, Smith D, Minami T, Tachikawa R, Tanizawa K, Oga T, Nagashima S, Wakamura T, Komenami N, Setoh K, Kawaguchi T, Tsutsumi T, Takahashi Y, Nakayama T, Hirai T, Matsuda F, Chin K. Impact of sleep characteristics and obesity on diabetes and hypertension across genders and menopausal status: the Nagahama study. *Sleep* 2018: 41(7): zsy071.

6. Namen AM, Chatterjee A, Huang KE, Feldman SR, Haponik EF. Recognition of

Sleep Apnea Is Increasing. Analysis of Trends in Two Large, Representative Databases of Outpatient Practice. *Ann Am Thorac Soc* 2016: 13(11): 2027-2034.

7. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013: 177(9): 1006-1014.

8. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000: 342(19): 1378-1384.

9. Aronsohn RS, Whitmore H, Van Cauter E, Tasali E. Impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes. *Am J Respir Crit Care Med* 2010: 181(5): 507-513.

10. Kendzerska T, Gershon AS, Hawker G, Tomlinson G, Leung RS. Obstructive sleep apnea and incident diabetes. A historical cohort study. *Am J Respir Crit Care Med* 2014: 190(2): 218-225.

11. Toyama Y, Chin K, Chihara Y, Takegami M, Takahashi KI, Sumi K, Nakamura T, Nakayama-Ashida Y, Minami I, Horita S, Oka Y, Wakamura T, Fukuhara SI, Mishima M, Kadotani H. Association between sleep apnea, sleep duration, and serum lipid profile in an urban, male, working population in Japan. *Chest* 2013: 143(3): 720-728.

12. Wu WT, Tsai SS, Shih TS, Lin MH, Chou TC, Ting H, Wu TN, Liou SH. The Association between Obstructive Sleep Apnea and Metabolic Markers and Lipid Profiles.

PLoS One 2015: 10(6): e0130279.

13. Chin K, Oga T, Takahashi K, Takegami M, Nakayama-Ashida Y, Wakamura T, Sumi K, Nakamura T, Horita S, Oka Y, Minami I, Fukuhara S, Kadotani H. Associations between obstructive sleep apnea, metabolic syndrome, and sleep duration, as measured with an actigraph, in an urban male working population in Japan. *Sleep* 2010: 33(1): 89-95.

14. Akahoshi T, Uematsu A, Akashiba T, Nagaoka K, Kiyofuji K, Kawahara S, Hattori T, Kaneita Y, Yoshizawa T, Takahashi N, Uchiyama M, Hashimoto S. Obstructive sleep apnoea is associated with risk factors comprising the metabolic syndrome. *Respirology* 2010: 15(7): 1122-1126.

15. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, Leung RS, Bradley TD. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens* 2001: 19(12): 2271-2277.

16. Lam DC, Lui MM, Lam JC, Ong LH, Lam KS, Ip MS. Prevalence and recognition of obstructive sleep apnea in Chinese patients with type 2 diabetes mellitus. *Chest* 2010: 138(5): 1101-1107.

17. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care* 2008: 31 Suppl 2: S303-309.

18. Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI. Molecular signatures of obstructive sleep apnea in adults: a review and perspective. *Sleep* 2009: 32(4): 447-470.

19. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, Ancoli-Israel S, Ensrud K, Purcell S, White DP, Redline S, Wellman A. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019: 40(14): 1149-1157.

20. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med* 2003: 167(9): 1181-1185.

21. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 2001: 163(3 Pt 1): 608-613.

22. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013: 309(1): 71-82.

23. Lean MJ, Han TS. Waist worries. *Am J Clin Nutr* 2002: 76(4): 699-700.

24. Roubenoff R. Applications of bioelectrical impedance analysis for body composition to epidemiologic studies. *Am J Clin Nutr* 1996: 64(3 Suppl): 459s-462s.

25. Matsuzawa Y. Metabolic syndrome--definition and diagnostic criteria in Japan. *J Atheroscler Thromb* 2005: 12(6): 301.

26. Arnardottir ES, Bjornsdottir E, Olafsdottir KA, Benediktsdottir B, Gislason T.

Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms. *Eur Respir J* 2016: 47(1): 194-202.

27. Redline S, Sotres-Alvarez D, Loredo J, Hall M, Patel SR, Ramos A, Shah N, Ries A, Arens R, Barnhart J, Youngblood M, Zee P, Daviglus ML. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds. The Hispanic Community Health Study/Study of Latinos. *Am J Respir Crit Care Med* 2014: 189(3): 335-344.

28. 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. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008: 118(10): 1080-1111.

29. Wakabayashi Y, Oka R, Nakaya M, Karashima S, Kometani M, Sakurai M, Yoshimura K, Yoneda T. Associations between Sleep-Disordered Breathing and Metabolic Risk Factors beyond Obesity. *J Diabetes Res* 2018: 2018: 1567683.

30. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, Foster GD, Maislin G, Saif H, Broderick P, Chittams J, Hanlon AL, Pack AI. CPAP, weight loss, or

both for obstructive sleep apnea. *N Engl J Med* 2014: 370(24): 2265-2275.

31. Ozol D, Turkay C, Kasapoglu B, Karamanli H, Yildirim Z. Relationship between components of metabolic syndrome and polysomnographic findings in obstructive sleep apnea. *Metab Syndr Relat Disord* 2011: 9(1): 13-18.

32. Phillips CL, Yee BJ, Marshall NS, Liu PY, Sullivan DR, Grunstein RR. Continuous positive airway pressure reduces postprandial lipidemia in obstructive sleep apnea: a randomized, placebo-controlled crossover trial. *Am J Respir Crit Care Med* 2011: 184(3): 355-361.

33. Ogretmenoglu O, Suslu AE, Yucel OT, Onerci TM, Sahin A. Body fat composition: a predictive factor for obstructive sleep apnea. *Laryngoscope* 2005: 115(8): 1493-1498.

34. Ross R, Freeman J, Hudson R, Janssen I. Abdominal obesity, muscle composition, and insulin resistance in premenopausal women. *J Clin Endocrinol Metab* 2002: 87(11): 5044-5051.

35. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol (1985)* 2005: 99(4): 1592-1599.

36. the Japanese Ministry of Health, Labour and Welfare (available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/eiyou/h29-houkoku.html; accessed September 16, 2019). [cited; Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/eiyou/h29-houkoku.

html.

37. Chen X, Wang R, Lutsey PL, Zee PC, Javaheri S, Alcantara C, Jackson CL, Szklo M, Punjabi N, Redline S, Williams MA. Racial/ethnic differences in the associations between obesity measures and severity of sleep-disordered breathing: the Multi-Ethnic Study of Atherosclerosis. *Sleep Med* 2016: 26: 46-53.

38. Leuenberger UA, Hogeman CS, Quraishi SA, Linton-Frazier L, Gray KS. Short-term intermittent hypoxia enhances sympathetic responses to continuous hypoxia in humans. *J Appl Physiol (1985)* 2007: 103(3): 835-842.

39. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol* 2013: 62(7): 569-576.

Figure Legends

Figure 1. Prevalence of moderate-to-severe SDB according to age and body mass index groupings.

Body mass index (mg/m^2) and age (years) are categorized from <20 to ≥25 in 2.5 units and from <40 to ≥70 in 10 units, respectively. The number above each bar graph represents the raw estimate of the percentage of moderate-to-severe SDB.

Moderate-to-severe SDB is defined by ≥15 /h of the 3% oxygen desaturation index by actigraphy.

SDB, sleep disordered breathing.

Figure 2. Prevalence of moderate-to-severe SDB in men and women according to menopausal status in relation to hypertension and/or diabetes.

(A) Total population, men and women according to menopausal status. (B) Presence or absence of hypertension/diabetes in all participants, (C) Presence or absence of hypertension/diabetes in men, (D) Presence or absence of hypertension/diabetes in pre-menopausal women, (E) Presence or absence of hypertension/diabetes in post-menopausal women.

Data on dyslipidemia and metabolic syndrome were limited to participants with a fasting state.

HTN, hypertension; DM, diabetes; Pre-Women, pre-menopausal women; Post-Women, post-menopausal women; SDB, sleep disordered breathing.

Figure 3. Prevalence of moderate-to-severe SDB according to the number of antihypertensive drugs and the presence or absence of resistant hypertension.

(A) Prevalence of moderate-to-severe SDB according to the number of antihypertensive drugs.

(B) Prevalence of moderate-to-severe SDB according to the presence or absence of resistant hypertension.

The number below each bar graph represents the sample size of that group. Point estimates value and 95% confidence interval are shown in the Figure. Hypertension is considered present according to ongoing pharmacological treatment with antihypertensive drugs or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Resistant hypertension is defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg with the use of ≥3 antihypertensive medication or use of ≥4 antihypertensive medication regardless of blood pressure level. Otherwise, hypertension is defined as non-resistant hypertension.

HTN, hypertension; SDB, sleep disordered breathing.

Figure 4. Percentages of moderate-to-severe SDB according to comorbidity and/or

obesity.

(A) Presence or absence of hypertension and/or obesity, (B) Presence or absence of diabetes and/or obesity, (C) Presence or absence of dyslipidemia and/or obesity, (D) Presence or absence of metabolic syndrome and/or obesity.

The number below each bar graph represents the sample size of that group. Point estimates value and 95% confidence interval are shown in the Figure. Data on dyslipidemia and metabolic syndrome were limited to participants in a fasting state.

HTN, hypertension; DM, diabetes; DL, dyslipidemia, MetS, metabolic syndrome; SDB, sleep disordered breathing.

Figure 5. Odds ratios for moderate-to-severe SDB according to comorbidity and/or obesity.

(A) Presence or absence of hypertension and/or obesity, (B) Presence or absence of diabetes and/or obesity, (C) Presence or absence of dyslipidemia and/or obesity, (D) Presence or absence of metabolic syndrome and/or obesity.

Point estimates value and 95% confidence interval are shown in the Figure. Vertical lines are shown as the log-transformed scale.

The results were adjusted for age, sex, smoking, and alcohol status.

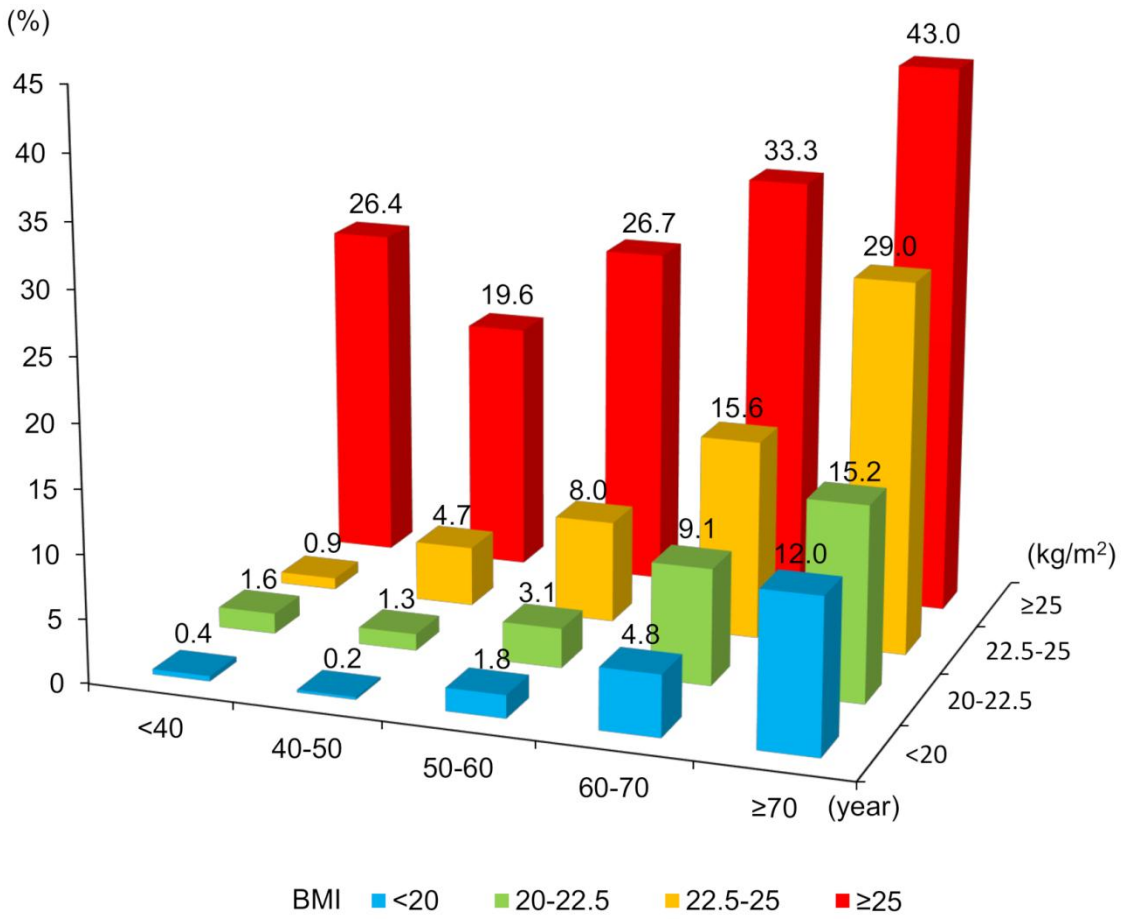
Data on dyslipidemia and metabolic syndrome were limited to participants in a fasting state.

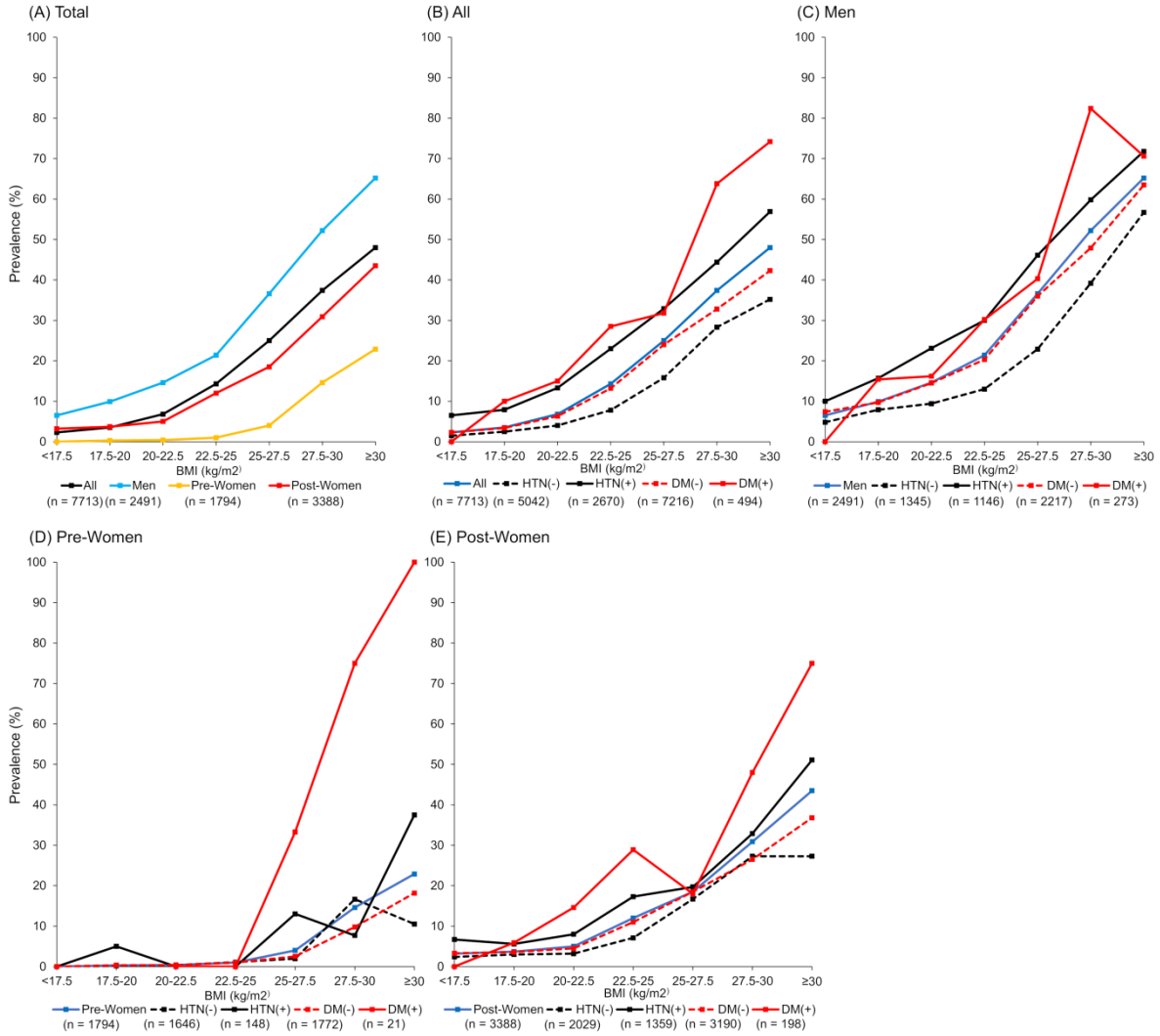
HTN, hypertension; DM, diabetes; DL, dyslipidemia, MetS, metabolic syndrome; SDB, sleep disordered breathing.

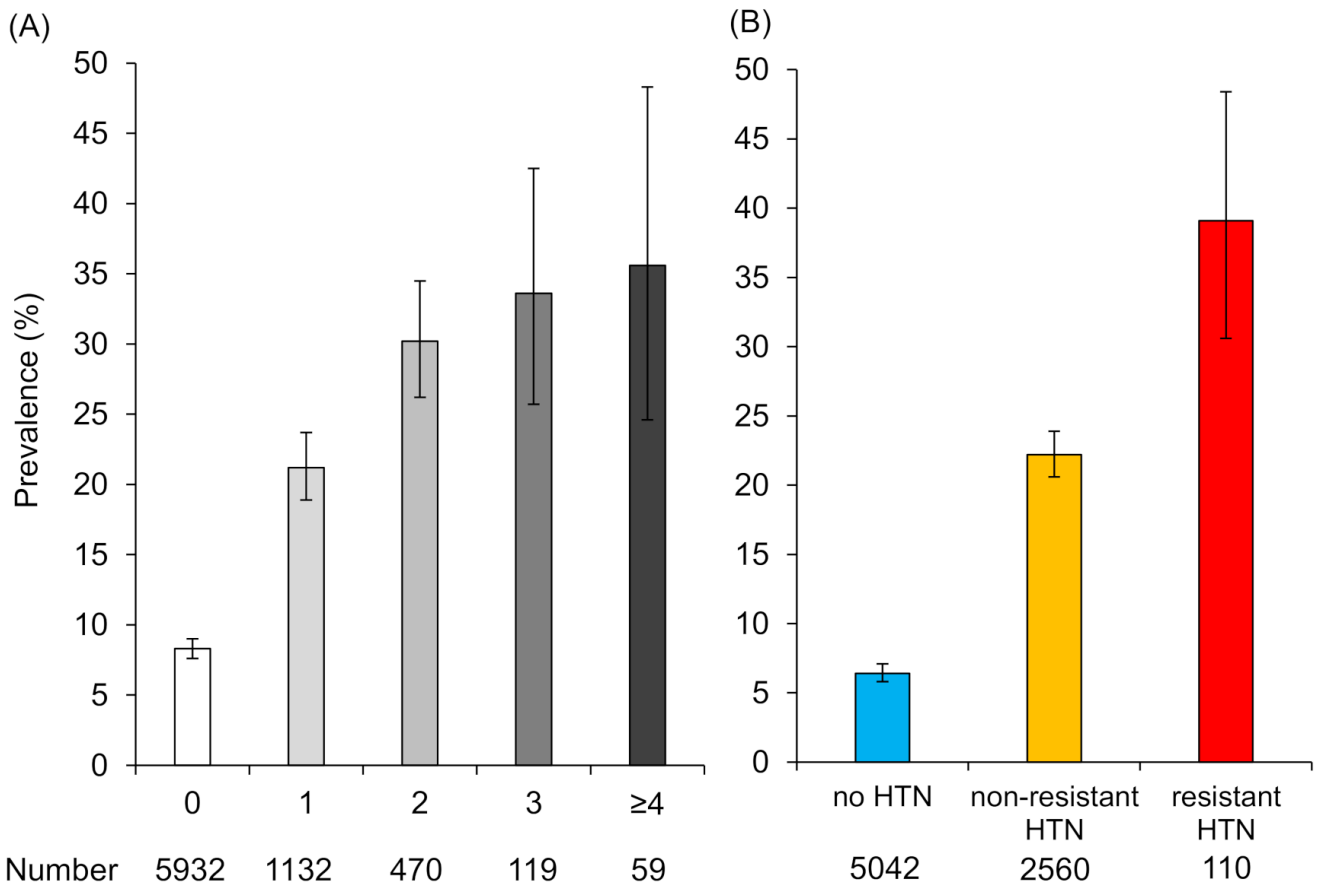
Figure 6. Percentages of high Acti-CT90 among moderate-to-severe SDB according to severity of obesity

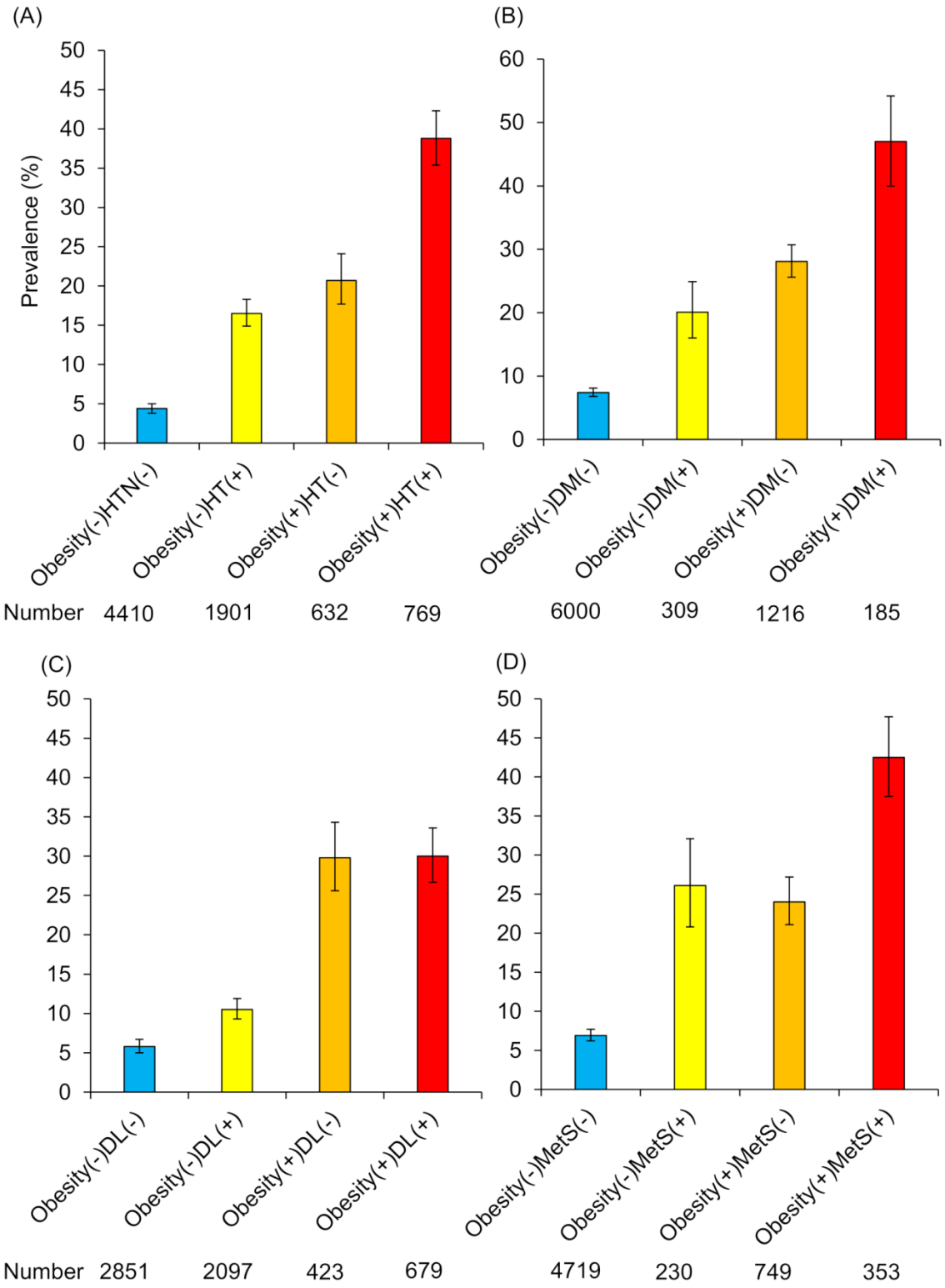
Point estimates value and 95% confidence interval are shown in the Figure.

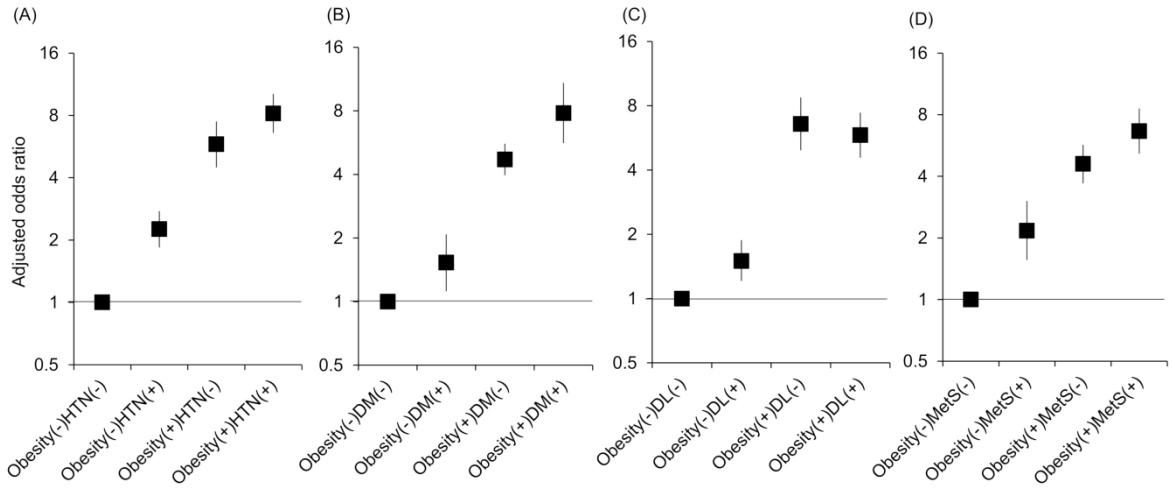
Acti-CT90, actigraphy-modified cumulative percentage of sleep time with SpO_2 <90%; SDB, sleep disordered breathing; BMI, body mass index.


(%)
45
40
35
30
25
20
15
10
5
0
26.4
19.6
26.7
33.3
43.0
0.9
4.7
8.0
15.6
29.0
1.6
1.3
3.1
9.1
15.2
0.4
0.2
1.8
4.8
12.0
<40
40-50
50-60
60-70
≥70
(year)
(kg/m2)
≥25
22.5-25
20-22.5
<20
BMI
<20
20-22.5
22.5-25
≥25


(A) Total
Prevalence (%)
BMI (kg/m2)
All (n = 7713)
Men (n = 2491)
Pre-Women (n = 1794)
Post-Women (n = 3388)
(B) All
BMI (kg/m2)
All (n = 7713)
HTN(-) (n = 5042)
HTN(+) (n = 2670)
DM(-) (n = 7216)
DM(+) (n = 494)
(C) Men
BMI (kg/m2)
Men (n = 2491)
HTN(-) (n = 1345)
HTN(+) (n = 1146)
DM(-) (n = 2217)
DM(+) (n = 273)
(D) Pre-Women
Prevalence (%)
BMI (kg/m2)
Pre-Women (n = 1794)
HTN(-) (n = 1646)
HTN(+) (n = 148)
DM(-) (n = 1772)
DM(+) (n = 21)
(E) Post-Women
BMI (kg/m2)
Post-Women (n = 3388)
HTN(-) (n = 2029)
HTN(+) (n = 1359)
DM(-) (n = 3190)
DM(+) (n = 198)


(A)
Prevalence (%)
50
45
40
35
30
25
20
15
10
5
0
0
1
2
3
≥4
Number
5932
1132
470
119
59
(B)
no HTN
non-resistant HTN
resistant HTN
5042
2560
110


(A)
Prevalence (%)
50
45
40
35
30
25
20
15
10
5
0
Obesity(-)HTN(-)
Obesity(-)HT(+)
Obesity(+)HT(-)
Obesity(+)HT(+)
Number 4410 1901 632 769
(B)
60
50
40
30
20
10
0
Obesity(-)DM(-)
Obesity(-)DM(+)
Obesity(+)DM(-)
Obesity(+)DM(+)
6000 309 1216 185
(C)
50
45
40
35
30
25
20
15
10
5
0
Obesity(-)DL(-)
Obesity(-)DL(+)
Obesity(+)DL(-)
Obesity(+)DL(+)
Number 2851 2097 423 679
(D)
50
45
40
35
30
25
20
15
10
5
0
Obesity(-)MetS(-)
Obesity(-)MetS(+)
Obesity(+)MetS(-)
Obesity(+)MetS(+)
4719 230 749 353


(A)
(B)
(C)
(D)
Adjusted odds ratio
16
8
4
2
1
0.5
Obesity(-)HTN(-)
Obesity(-)HTN(+)
Obesity(+)HTN(-)
Obesity(+)HTN(+)
Obesity(-)DM(-)
Obesity(-)DM(+)
Obesity(+)DM(-)
Obesity(+)DM(+)
Obesity(-)DL(-)
Obesity(-)DL(+)
Obesity(+)DL(-)
Obesity(+)DL(+)
Obesity(-)MetS(-)
Obesity(-)MetS(+)
Obesity(+)MetS(-)
Obesity(+)MetS(+)

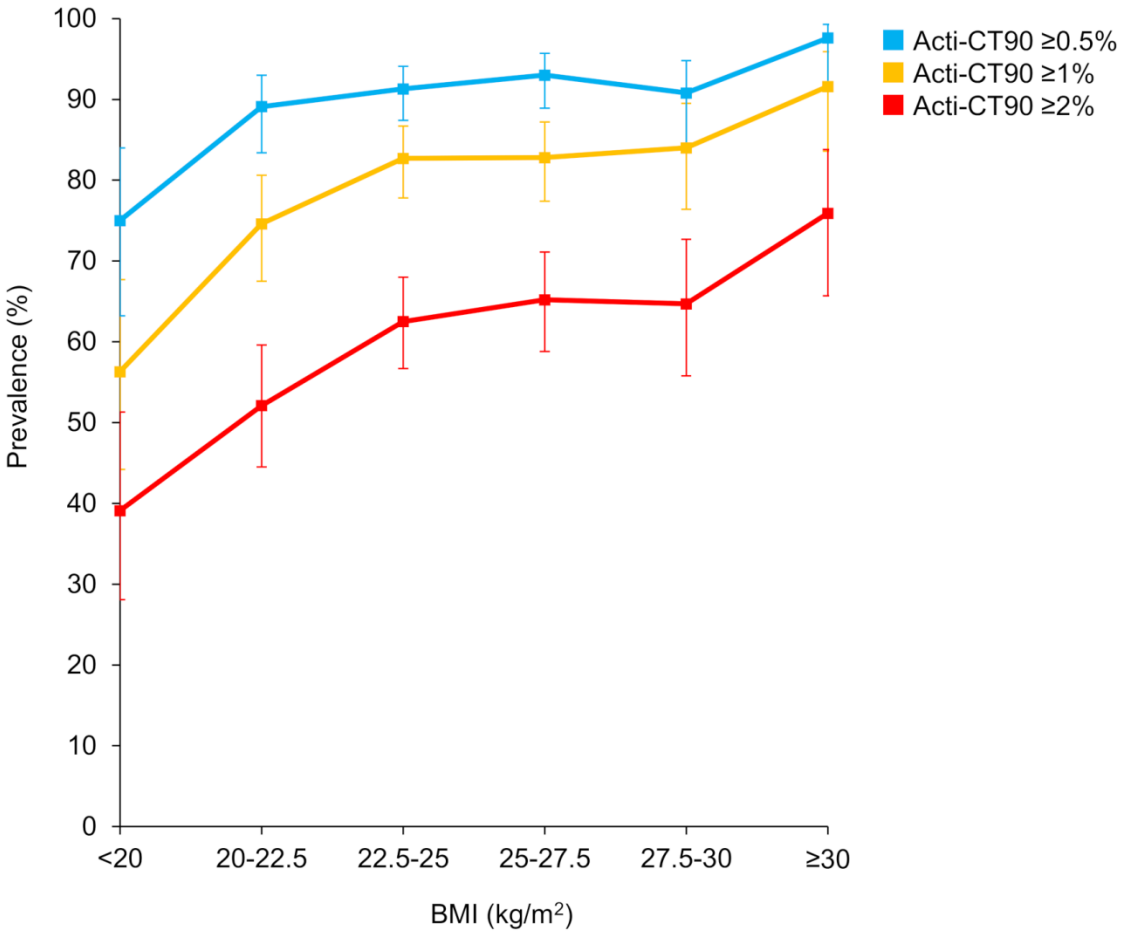

Acti-CT90 ≥0.5%
Acti-CT90 ≥1%
Acti-CT90 ≥2%
Prevalence (%)
100
90
80
70
60
50
40
30
20
10
0
<20
20-22.5
22.5-25
25-27.5
27.5-30
≥30
BMI (kg/m2)

Table 1. Baseline characteristics of study participants

	All	Men	Women (pre-menopausal)	Women (post-menopausal)	*P*
N	7,713	2,491 (32.5%)	1,794 (23.4%)	3,388 (44.2%)	
Descriptive information					
Age (y)	57.9 ± 12.1	59.9 ± 12.5	43.7 ± 5.1[*]	63.8 ± 7.6[*, †]	<0.001
Sex (male, %)	32.3				-
Body mass index (kg/m^2)	22.3 ± 3.3	23.3 ± 3.1	21.3 ± 3.3[*]	22.0 ± 3.2[*, †]	<0.001
Waist circumference (cm)	81.8 ± 9.4	85.1 ± 8.7	77.5 ± 9.0[*]	81.8 ± 9.2[*, †]	<0.001
Current smoker (%)	9.7	22.3	6.4	2.3	<0.001
Alcohol intake[‡] (Go/w)	0.28 [0-3.89]	4.55 [0.28-12.73]	0.23 [0-1.36][*]	0 [0-0.57][*, †]	<0.001
Fasting status (%)	78.5	77.8	79.3	78.7	0.477
BIA data					
Body fat percentage (%)	25.3 ± 7.4	21.0 ± 6.1	25.8 ± 6.8[*]	28.3 ± 7.0[*, †]	<0.001
Comorbidity					
Hypertension (%)	34.6	46.0	8.3	40.1	<0.001
Diabetes (%)	6.4	11.0	1.2	5.8	<0.001
Dyslipidemia[§] (%)	45.9	49.4	18.7	57.7	<0.001
Metabolic syndrome[§] (%)	9.6	19.3	1.5	7.0	<0.001
Sleep questionnaire					
Epworth Sleepiness Scale	6.2 ± 4.1	5.8 ± 4.1	7.1 ± 4.4[*]	6.1 ± 3.8[*, †]	<0.001
Excessive daytime sleepiness (%)	14.2	12.6	19.6	12.5	<0.001
Pittsburgh Sleep Quality Index	5.0 ± 2.8	4.8 ± 2.8	4.6 ± 2.4[*]	5.4 ± 3.0[*, †]	<0.001
Poor sleep quality (%)	35.5	34.0	29.0	40.1	<0.001

Abbreviations: BIA, bioelectrical impedance analysis.

Data are expressed as means ± SD, percentages, or medians [interquartile range].

Alcohol consumption was calculated by multiplying the amount consumed in a single day and number of drinking days per week and was represented using Japanese traditional units of alcohol (Go), where 1 Go corresponds to 22 g of ethanol.

Last meal ≥10 h were defined as fasting status.

Hypertension was considered present when the patient was treated for systemic hypertension or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Diabetes was considered present when the patient was treated for diabetes or hemoglobin A1c ≥6.5%.

Data on menopause were unavailable for 40 women.

Data on hypertension, diabetes, dyslipidemia, and metabolic syndrome were unavailable for 1, 3, 3, and 1 participant, respectively.

Those with an Epworth Sleepiness Score >10 were defined as having excessive daytime sleepiness.

Those with a Pittsburgh Sleep Quality Index ≥6 were defined as having poor sleep quality.

*: P <0.05 vs Men; †: P <0.05 vs Women (pre-menopausal).

‡: Kruskal-Wallis test was used. Other continuous variables were calculated by analysis of variance.

§: Data were analyzed by 6,051 participants, 1,937 men, 1,422 pre-menopausal women, and 2,665 post-menopausal women in fasting status.

Table 2. SDB parameters in men and women according to menopausal status

		All	Men	Women (pre-menopausal)	Women (post-menopausal)	*P*
N		7,713	2,491 (32.5%)	1,794 (23.4%)	3,388 (44.2%)	
SDB category (%)	Normal	41.0 (39.9-42.1)	19.0 (17.5-20.6)	73.6 (71.5-75.6)	39.8 (38.2-41.4)	<0.001
	Mild	46.9 (45.8-48.0)	57.5 (55.6-59.5)	24.8 (22.9-26.9)	50.8 (49.1-52.5)	
	Moderate	10.1 (9.5-10.8)	18.9 (17.4-20.5)	1.6 (1.1-2.2)	8.2 (7.4-9.2)	
	Severe	2.0 (1.7-2.3)	4.5 (3.8-5.4)	0	1.2 (0.9-1.6)	
Actigraphy-modified ODI3%[§] (events/h)		5.9 [3.6-10.1]	9.0 [5.7-14.4]	3.5 [2.5-5.1][*]	6.0 [3.8-9.5][*, †]	<0.001
Actigraphy-modified CT90[§] (%)		0.18 [0.05-0.75]	0.44 [0.11-1.54]	0.05 [0.02-0.15][*]	0.19 [0.06-0.69][*, †]	<0.001
Mean SpO_2 (%)		96.8 [95.9-97.6]	96.2 [95.3-96.9]	97.9 [97.3-98.4][*]	96.7 [95.8-97.3][*, †]	<0.001
Minimum SpO_2 (%)		84.8 [81.2-87.6]	83.7 [79.4-86.7]	86.4 [83.3-88.9][*]	84.7 [81.4-87.3][*, †]	<0.001

Abbreviations: SDB, sleep disordered breathing; ODI, oxygen desaturation index; CT90, cumulative percentage of sleep time with SpO_2 <90%.

Data about SDB category are expressed as percentages (95% confidence interval), and others are as medians [interquartile range].

Total sleep duration (from sleep onset time to wake-up time) by actigraphy and actual sleep duration (sleep duration after exclusion of wake-time after sleep onset from total sleep duration) were determined using the standard factory-default algorithm. The ODI3% adjusted for actual sleep duration was used as an indicator of SDB, and the severity of SDB was defined by ODI3% levels as follows: normal, <5 /h; mild, 5-<15 /h; moderate, 15-<30 /h; and severe, ≥30 /h.

Continuous variables were calculated by the Kruskal-Wallis test.

*: *P* <0.05 vs Men; †: *P* <0.05 vs Women (pre-menopausal).

Online Supplemental Material

Sleep disordered breathing and metabolic comorbidities across gender and menopausal status in East Asians; the Nagahama Study

Takeshi Matsumoto, MD, PhD, Kimihiko Murase, MD, PhD, Yasuharu Tabara, PhD, Takuma Minami, MD, Osamu Kanai, MD, Hirofumi Takeyama, MD, Naomi Takahashi, MPH, Satoshi Hamada, MD, PhD, Kiminobu Tanizawa, MD, PhD, Tomoko Wakamura, PhD, Naoko Komenami, PhD, Kazuya Setoh, PhD, Takahisa Kawaguchi, MSc, Takanobu Tsutsumi, PhD, Satoshi Morita, PhD, Yoshimitsu Takahashi, PhD, Takeo Nakayama, MD, PhD, Toyohiro Hirai, MD, PhD, Fumihiko Matsuda, PhD, Kazuo Chin, MD, PhD

Detailed Methods

Assessments of SDB

A pulse oximeter (PULSOX-Me300; Konica Minolta Inc., Tokyo, Japan) was attached to the nondominant wrist during 4 nights of sleep. The sensor probe was fitted to the index or middle finger and secured with tape and a cap by the participant. The internal memory of this device stores the blood oxygen saturation values by performing a moving average for the previous 3 seconds, updated every second. Data were analyzed by DS-Me version 2.1.0 software (Konica Minolta Inc.). To minimize erroneous minimum oxygen saturation values, each oximetry tracing was reviewed by trained staff members to remove potential artifacts and to verify the minimum oxygen saturation value reported. Data without oxygen-saturation signals or incomprehensible recordings were excluded from analysis. Data recorded for less than 2 h were also excluded because Medicare guidelines require at least 2 h of documented sleep time[1]. For selected data, the start and end times of sleep were set according to the results of actigraphy (Actiwatch 2 or the Actiwatch Spectrum Plus; Philips Respironics, Murrysville, PA, USA) and the actual sleep duration was used for calculations[2]. Data from a minimum of 2 days were required for analysis, and then averaged.

Oximetry data were subjected to a computerized algorithm to identify oxygen desaturations of ≥3%. A 3% oxygen desaturation index (ODI) was constructed based on increments of ≥3% of drops in oxygen saturation from baseline per h during measured sleep time by actigraphy. We used the actigraphy-modified ODI3% (Acti-ODI3%) as an indicator of SDB that mimicked sleep apnea, and the severity of SDB was defined by Acti-ODI3% levels as follows: normal, <5 /h; mild, 5-<15 /h; moderate, 15-<30 /h; and severe, ≥30 /h. We also measured the actigraphy-modified cumulative percentage of sleep time with SpO_2 <90% (Acti-CT90) as a surrogate marker for continuous hypoxia, mean SpO_2, and minimum SpO_2 during sleep. In our preliminary data, Acti-ODI3% was more comparable to the apnea-hypopnea index (AHI) derived from attended polysomnography in 32 patients ($r = 0.99$, $P < 0.001$; AHI = Acti-ODI3%*1.04 + 1.45) than simply-measured ODI3% without actigraphy-modification ($r = 0.92$, $P < 0.001$; AHI = usual ODI3%*1.27 + 2.06) (Figure S1).

Assessment of obesity

We assessed three parameters of obesity: body mass index (BMI)[3], waist circumference (WC)[4], and body fat percentage[5]. Height and weight measurements were determined with calibrated scales and BMI was calculated using the obtained height and weight data. WC was measured at the umbilical point in the standing position. Body fat percentage was calculated by bioelectrical impedance analysis (BIA). For measurements by BIA, patients were assessed in the supine position by a body composition analyzer (InBody 430; InBody Co., Ltd., Seoul, Korea). Body fat percentage was expressed as a percentage of total body weight.

Definition of comorbidities

Brachial blood pressure was measured twice using an automatic cuff-oscillometric device (HEM9000-AI, Omron Healthcare, Kyoto, Japan) in the sitting position, and mean values were used in the analysis. Before measurements of blood pressure, participants rested a few minutes or more. Hypertension was considered present according to ongoing pharmacological treatment with antihypertensive drugs or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Data on the number of antihypertensive drugs was collected with a questionnaire, "how many kinds of antihypertensive drugs do you take for hypertension?". Resistant hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg with the use of ≥3 antihypertensive medications or the use of ≥4 antihypertensive medications regardless of blood pressure level. Otherwise, hypertension was defined as non-resistant hypertension. Diabetes was considered present according to ongoing pharmacological treatment with oral antihyperglycemic drugs and/or insulin or hemoglobin A1c ≥6.5% because not all participants underwent fasting tests.

The analysis of dyslipidemia and metabolic syndrome was performed in participants in a fasting state (≥10 h). Dyslipidemia was considered present according to ongoing pharmacological treatment with antihyperlipidemic drugs or low-density lipoprotein ≥140 mg/dL, high-density lipoprotein <40 mg/dL, or triglycerides ≥150 mg/dL. Metabolic syndrome was considered present according to the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome[6]: WC ≥85 cm in men or ≥90 cm in women and at least two of the following: 1) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or the use of antihypertensive drugs, 2) fasting plasma glucose ≥110 mg/dL or the use of drugs for diabetes, and 3) high-density lipoprotein <40 mg/dL or triglycerides ≥150 mg/dL or the use of antihyperlipidemic drugs.

Assessment of excessive daytime sleepiness

The Epworth Sleepiness Scale (ESS) was employed to identify study participants manifesting excessive daytime sleepiness (EDS)[7] with an ESS score >10 corresponding to the presence of EDS.

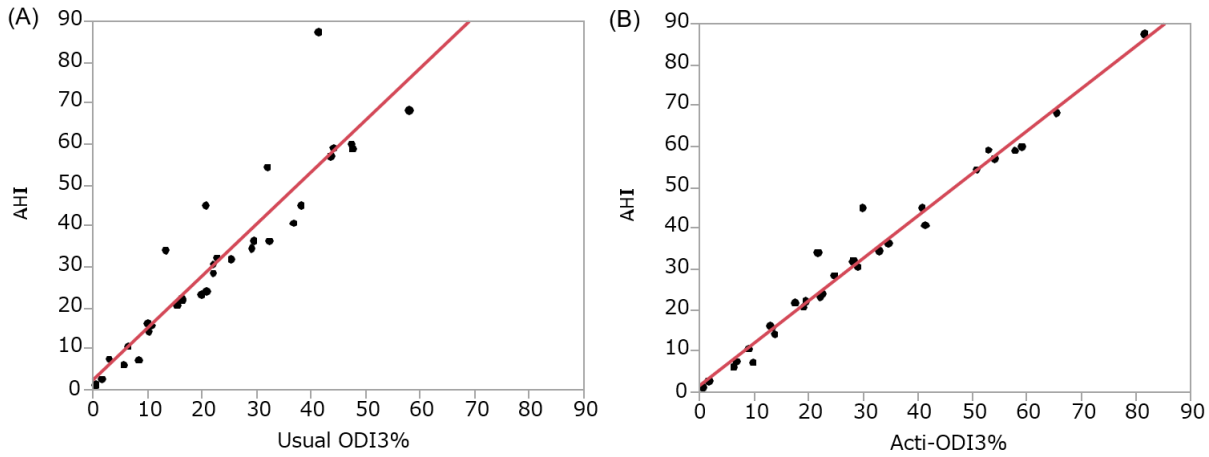
Assessment of sleep quality

We assessed subjective sleep quality by the Pittsburgh Sleep Quality Index (PSQI)[8]. Those with a PSQI score ≥6 were considered to have poor sleep quality.

References

1. Chesson AL, Jr., Berry RB, Pack A. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. *Sleep* 2003: 26(7): 907-913.
2. Matsumoto T, Murase K, Tabara Y, Gozal D, Smith D, Minami T, Tachikawa R, Tanizawa K, Oga T, Nagashima S, Wakamura T, Komenami N, Setoh K, Kawaguchi T, Tsutsumi T, Takahashi Y, Nakayama T, Hirai T, Matsuda F, Chin K. Impact of sleep characteristics and obesity on diabetes and hypertension across genders and menopausal status: the Nagahama study. *Sleep* 2018: 41(7).
3. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013: 309(1): 71-82.
4. Lean MJ, Han TS. Waist worries. *Am J Clin Nutr* 2002: 76(4): 699-700.
5. Roubenoff R. Applications of bioelectrical impedance analysis for body composition to epidemiologic studies. *Am J Clin Nutr* 1996: 64(3 Suppl): 459s-462s.
6. Matsuzawa Y. Metabolic syndrome--definition and diagnostic criteria in Japan. *J Atheroscler Thromb* 2005: 12(6): 301.
7. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep* 1992: 15(4): 376-381.
8. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989: 28(2): 193-213.
9. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P, Tafti M, Haba-Rubio J. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015: 3(4): 310-318.
10. Arnardottir ES, Bjornsdottir E, Olafsdottir KA, Benediktsdottir B, Gislason T. Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms. *Eur Respir J* 2016: 47(1): 194-202.
11. Redline S, Sotres-Alvarez D, Loredo J, Hall M, Patel SR, Ramos A, Shah N, Ries A, Arens R, Barnhart J, Youngblood M, Zee P, Daviglus ML. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds. The Hispanic Community Health Study/Study of Latinos. *Am J Respir Crit Care Med* 2014: 189(3): 335-344.

Figure S1. Comparison between apnea-hypopnea index derived from attended polysomnography and oxygen desaturation index with or without actigraphy modification.

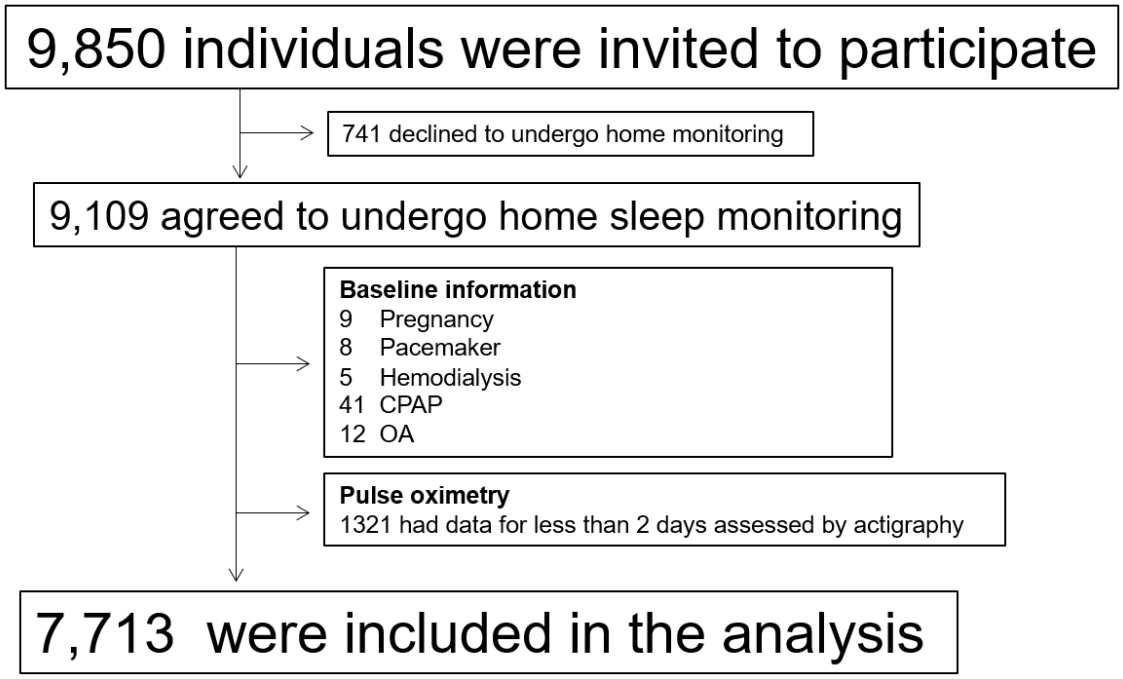


(A) Comparison between AHI and usual ODI3%. (B) Comparison between AHI and Acti-ODI3%.

Acti-ODI3% was more comparable to the AHI derived from attended polysomnography in 32 patients ($r = 0.99$, $P < 0.001$; AHI = Acti-ODI3%*1.04 + 1.45) than simply-measured ODI3% without actigraphy modification ($r = 0.92$, $P < 0.001$; AHI = usual ODI3%*1.27 + 2.06).

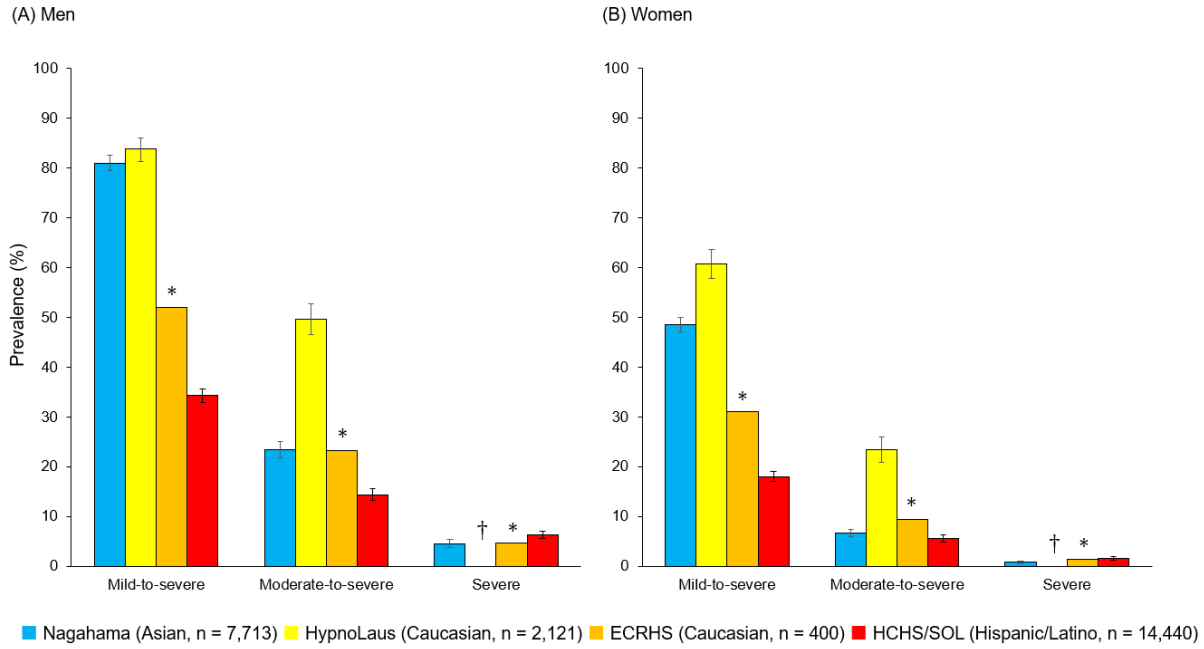
AHI, apnea-hypopnea index; oxygen desaturation index, ODI.

Figure S2. Flowchart of study participants.



CPAP, continuous positive airway pressure; OA, oral appliance.

Figure S3. Comparison of the prevalence of SDB among population-based studies.



The prevalence of SDB in recent population-based studies is shown according to SDB severities. Mild-to-severe means AHI/ODI ≥5, moderate-to-severe means AHI/ODI ≥15, and severe means AHI/ODI ≥30.

Point estimates value and 95% confidence interval are shown in the Figure.

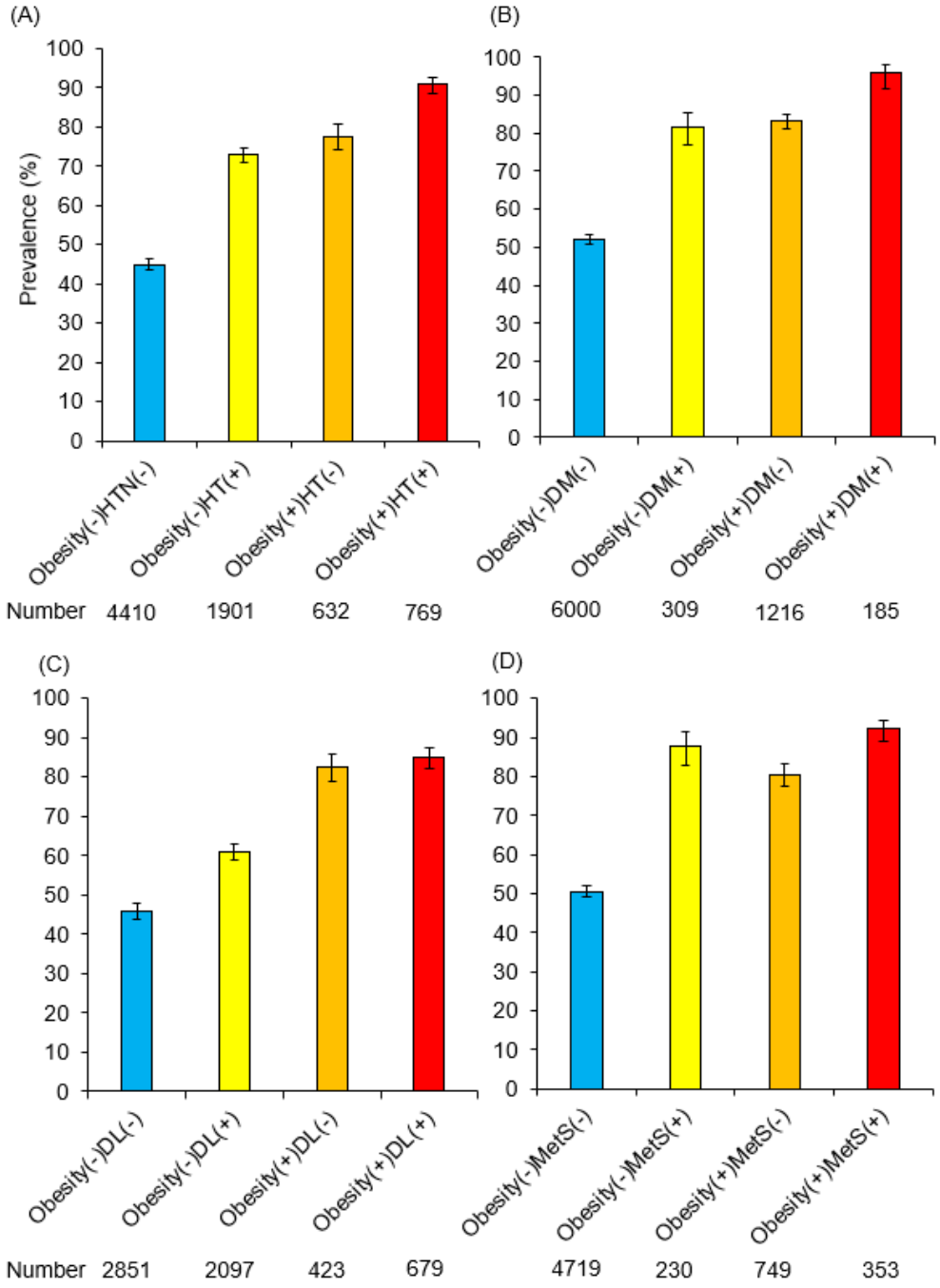
Nagahama study is shown as the representative of East Asians (age 59.9 ± 12.5 y, BMI 23.3 ± 3.1 kg/m^2 in men; age 56.9 ± 11.8 y, mean BMI 21.8 ± 3.3 kg/m^2 in women), HypnoLaus study is shown as the representative of Caucasians (age 56 [49-67] y, BMI 26.2 ± 3.7 kg/m^2 in men; age 58 [50-69] y, mean BMI 25.1 ± 4.6 kg/m^2 in women)[9], ECRHS is shown as another representative of Caucasians (age 54.8 ± 6.9 y, BMI 28.6 ± 4.4 kg/m^2 in men; age 54.6 ± 6.8 y, mean BMI 27.8 ± 5.4 kg/m^2 in women)[10], and HCHS/SOL is shown as the representative of Hispanics/Latinos (adjusted to mean age 41.1 y and mean BMI 29.3 kg/m^2 in both sexes)[11].

*: Data on 95% confidence intervals in ECRHS are not available.

†: Data on the prevalence of severe SDB in the HypnoLaus study are not available.

AHI, apnea hypopnea index; ODI, oxygen desaturation index; BMI, body mass index; ECRHS, European Community Respiratory Health Survey; HCHS/SOL, Hispanic Community Health Study/Study of Latinos.

Figure S4. Percentages of mild SDB according to comorbidity and/or obesity.

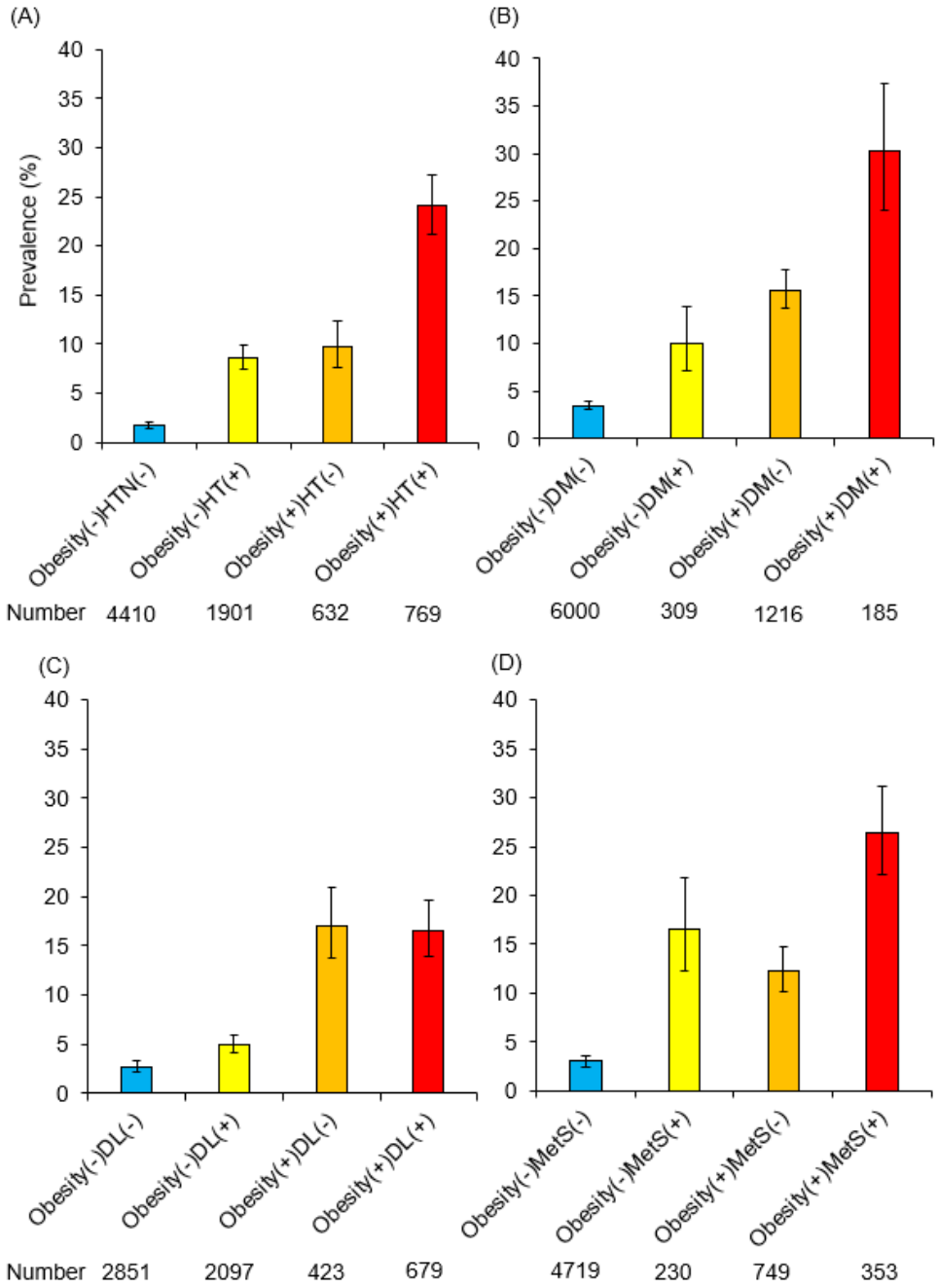


(A) Presence or absence of hypertension and/or obesity, (B) Presence or absence of diabetes and/or obesity, (C) Presence or absence of dyslipidemia and/or obesity, (D) Presence or absence of metabolic syndrome and/or obesity.

The number below each bar graph represents the sample size of that group. Point estimates value and 95% confidence interval are shown in the Figure. Data on dyslipidemia and metabolic syndrome were limited to participants in a fasting state.

HTN, hypertension; DM, diabetes; DL, dyslipidemia, MetS, metabolic syndrome; SDB, sleep disordered breathing.

Figure S5. Percentages of SDB with Acti-ODI3%≥20 according to comorbidity and/or obesity.

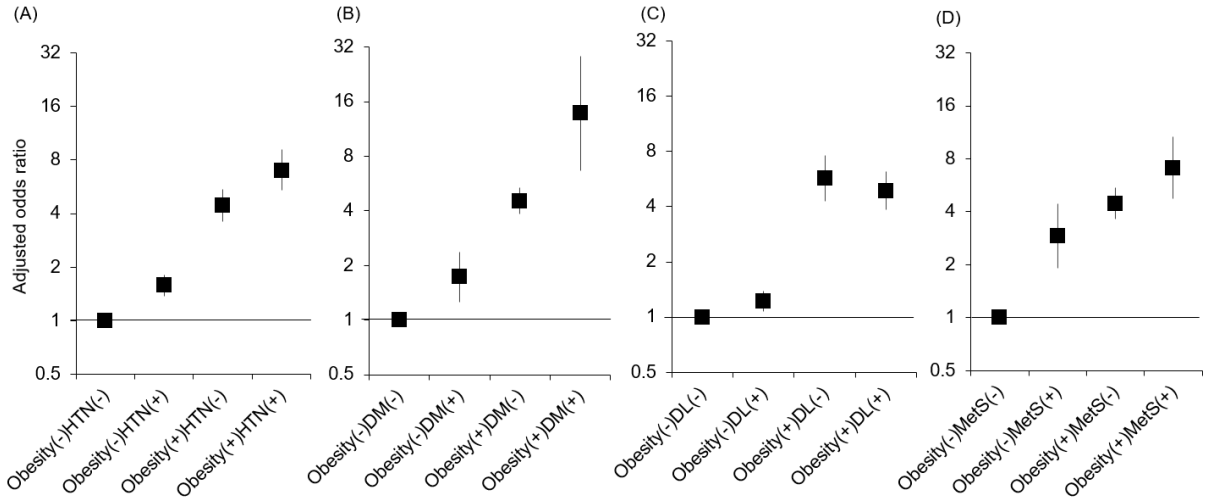


(A) Presence or absence of hypertension and/or obesity, (B) Presence or absence of diabetes and/or obesity, (C) Presence or absence of dyslipidemia and/or obesity, (D) Presence or absence of metabolic syndrome and/or obesity.

The number below each bar graph represents the sample size of that group. Point estimates value and 95% confidence interval are shown in the Figure. Data on dyslipidemia and metabolic syndrome were limited to participants in a fasting state.

HTN, hypertension; DM, diabetes; DL, dyslipidemia, MetS, metabolic syndrome; SDB, sleep disordered breathing.

Figure S6. Odds ratios for mild SDB according to comorbidity and/or obesity.



(A) Presence or absence of hypertension and/or obesity, (B) Presence or absence of diabetes and/or obesity, (C) Presence or absence of dyslipidemia and/or obesity, (D) Presence or absence of metabolic syndrome and/or obesity.

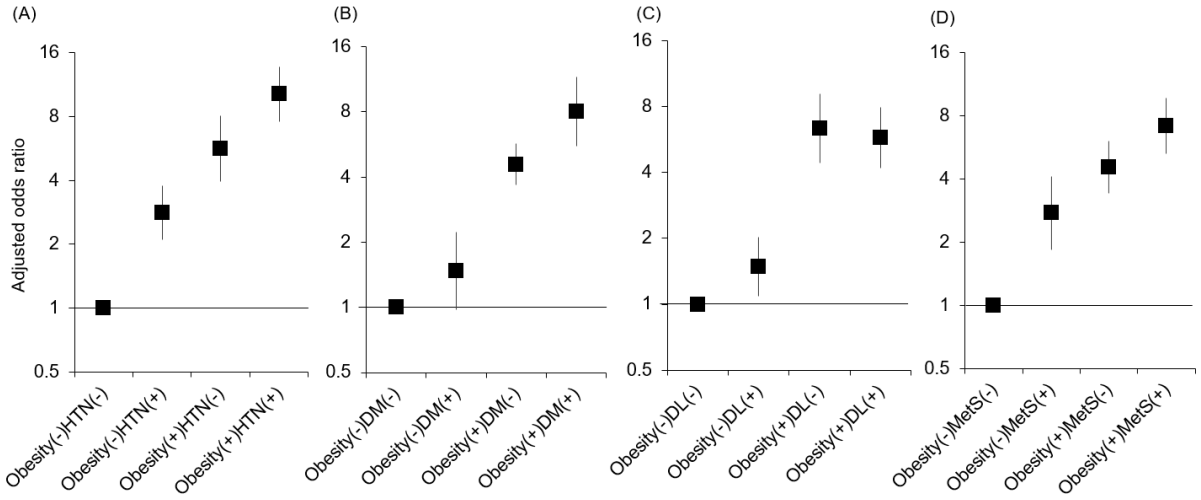
Point estimates value and 95% confidence interval are shown in the Figure. Vertical lines are shown as the log-transformed scale.

Results were adjusted for age, sex, smoking, and alcohol status.

Data on dyslipidemia and metabolic syndrome were limited to participants in a fasting state.

HTN, hypertension; DM, diabetes; DL, dyslipidemia, MetS, metabolic syndrome; SDB, sleep disordered breathing.

Figure S7. Odds ratios for SDB with Acti-ODI3%≥20 according to comorbidity and/or obesity.



(A) Presence or absence of hypertension and/or obesity, (B) Presence or absence of diabetes and/or obesity, (C) Presence or absence of dyslipidemia and/or obesity, (D) Presence or absence of metabolic syndrome and/or obesity.

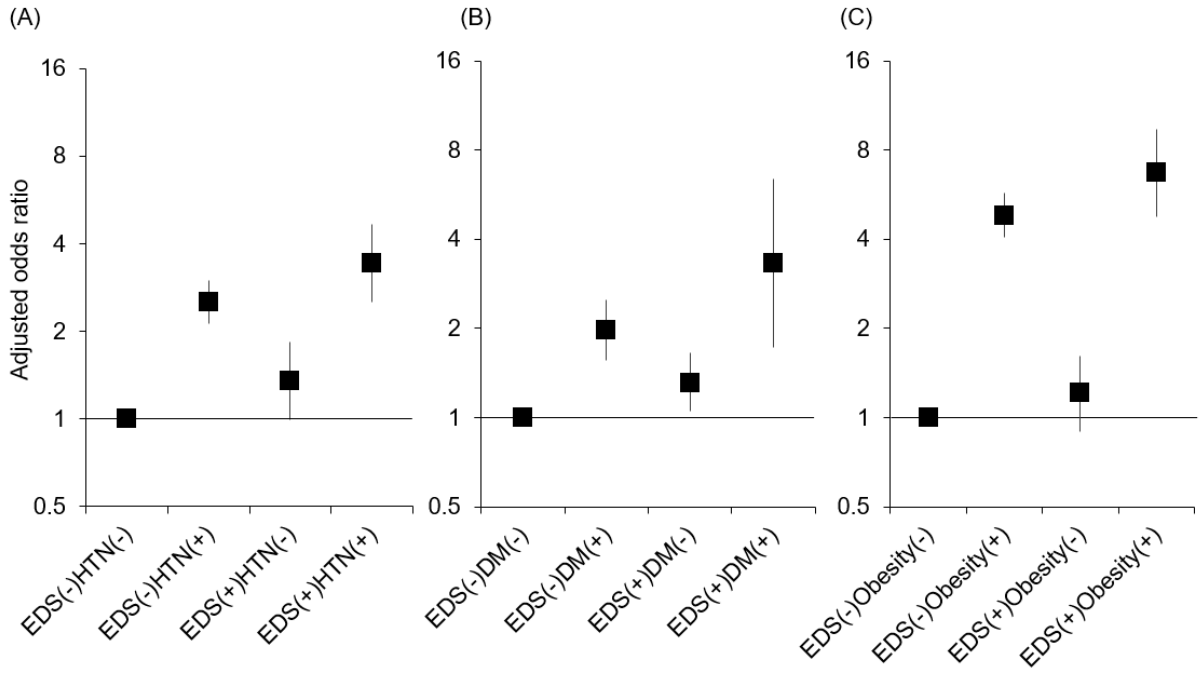
Point estimates value and 95% confidence interval are shown in the Figure. Vertical lines are shown as the log-transformed scale.

Results were adjusted for age, sex, smoking, and alcohol status.

Data on dyslipidemia and metabolic syndrome were limited to participants in a fasting state.

HTN, hypertension; DM, diabetes; DL, dyslipidemia, MetS, metabolic syndrome; SDB, sleep disordered breathing.

Figure S8. Odds ratios for moderate-to-severe SDB according to comorbidity and/or EDS.



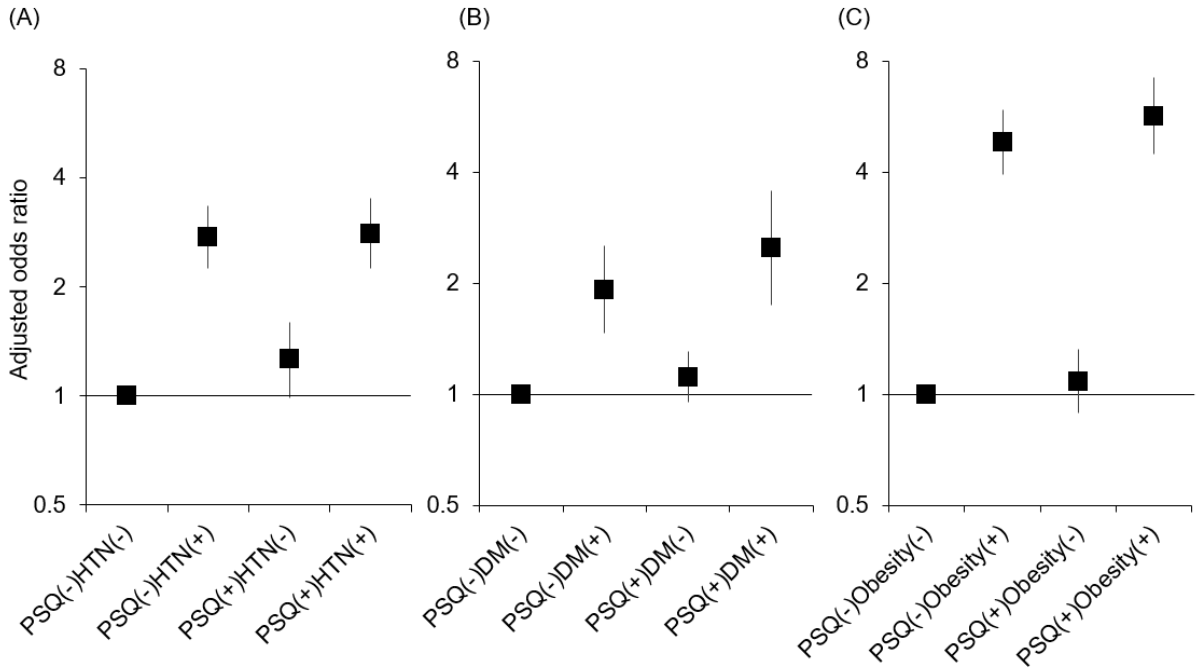
(A) Presence or absence of hypertension and/or EDS, (B) Presence or absence of diabetes and/or EDS, (C) Presence or absence of obesity and/or EDS.

Point estimates value and 95% confidence interval are shown in the Figure. Vertical lines are shown as the log-transformed scale.

Results were adjusted for age, sex, smoking, and alcohol status.

HTN, hypertension; DM, diabetes; EDS, excessive daytime sleepiness; SDB, sleep disordered breathing.

Figure S9. Odds ratios for moderate-to-severe SDB according to comorbidity and/or poor sleep quality.



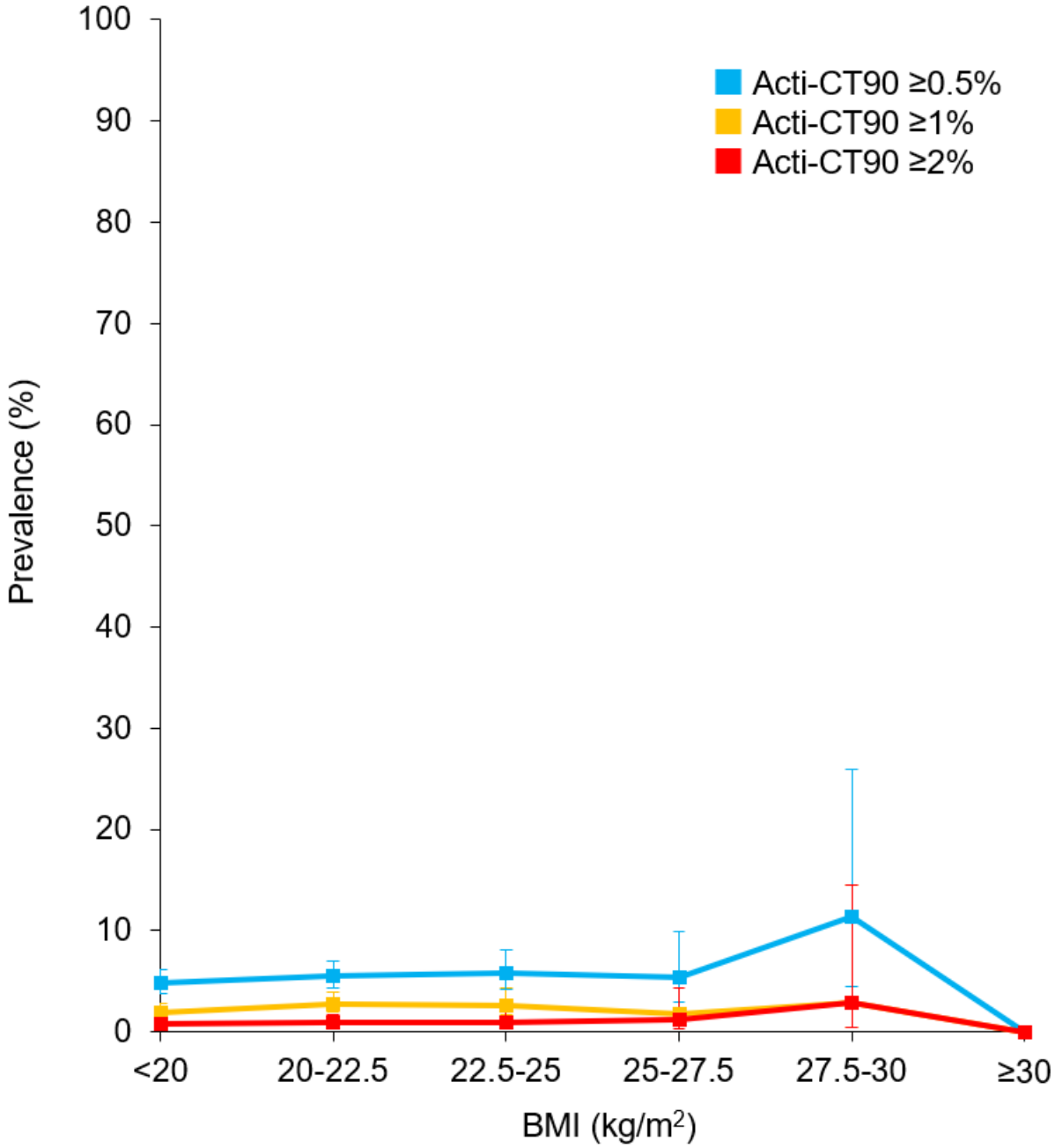
(A) Presence or absence of hypertension and/or poor sleep quality, (B) Presence or absence of diabetes and/or poor sleep quality, (C) Presence or absence of obesity and/or poor sleep quality.

Point estimates value and 95% confidence interval are shown in the Figure. Vertical lines are shown as the log-transformed scale.

Results were adjusted for age, sex, smoking, and alcohol status.

HTN, hypertension; DM, diabetes; PSQ, poor sleep quality; SDB, sleep disordered breathing.

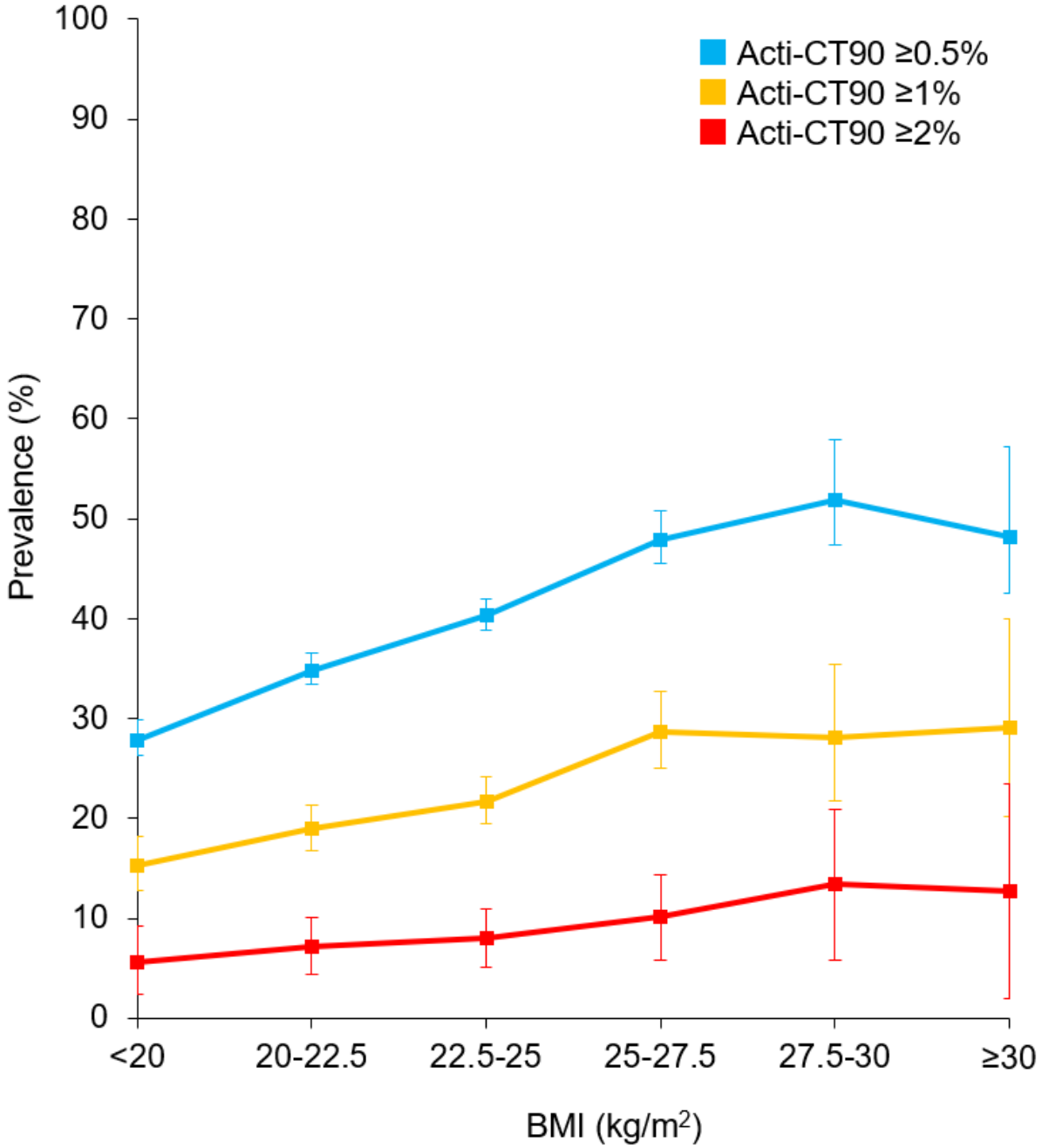
Figure S10. Percentages of high Acti-CT90 among those without SDB according to severity of obesity



Point estimates value and 95% confidence interval are shown in the Figure.

Acti-CT90, actigraphy-modified cumulative percentage of sleep time with SpO_2 <90%; SDB, sleep disordered breathing; BMI, body mass index.

Figure S11. Percentages of high Acti-CT90 among participants with mild SDB according to severity of obesity



Point estimates value and 95% confidence interval are shown in the Figure.

Acti-CT90, actigraphy-modified cumulative percentage of sleep time with SpO_2 <90%; SDB, sleep disordered breathing; BMI, body mass index.

Table S1. Association among obesity parameters in men, pre-menopausal women, and post-menopausal women.

	Men		Pre-menopausal women		Post-menopausal women	
	r	*P*	r	*P*	R	*P*
Body mass index and waist circumference	0.86	<0.001	0.86	<0.001	0.82	<0.001
Body mass index and body fat percentage	0.76	<0.001	0.85	<0.001	0.84	<0.001
Waist circumference and body fat percentage	0.76	<0.001	0.78	<0.001	0.75	<0.001

Table S2. Odds ratio for moderate-to-severe SDB for each obesity parameter in men, pre-menopausal women, and post-menopausal women.

	Men		Pre-menopausal women		Post-menopausal women	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Body mass index (per 1 kg/m^2)	1.32 (1.27-1.37)	<0.001	1.38 (1.28-1.50)	<0.001	1.28 (1.24-1.33)	<0.001
Waist circumference (per 2 cm)	1.20 (1.17-1.24)	<0.001	1.33 (1.24-1.42)	<0.001	1.20 (1.16-1.23)	<0.001
Fat mass (per 2%)	1.26 (1.21-1.30)	<0.001	1.55 (1.37-1.75)	<0.001	1.23 (1.19-1.28)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval.

Data are adjusted for age, smoking, and alcohol status.