

Online Supplemental Material

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

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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 $\geq 3\%$. A 3% oxygen desaturation index (ODI) was constructed based on increments of $\geq 3\%$ 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 $\geq 6.5\%$ 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.

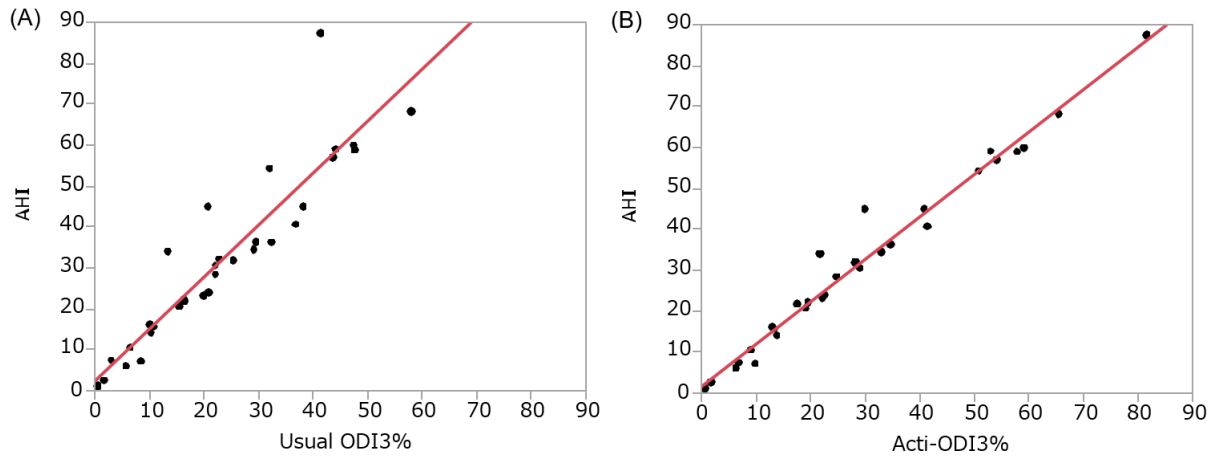
Assessment of sleep quality

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

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

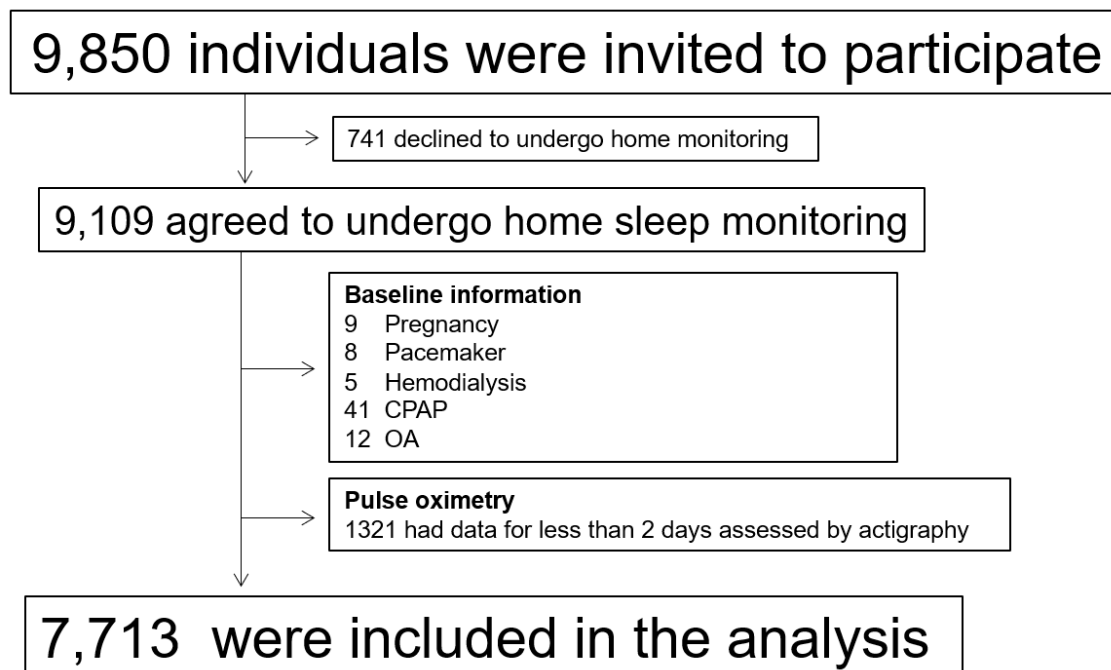


(A) Comparison between AHI and usual ODI3%. (B) Comparison between AHI and Acti-ODI3%.

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

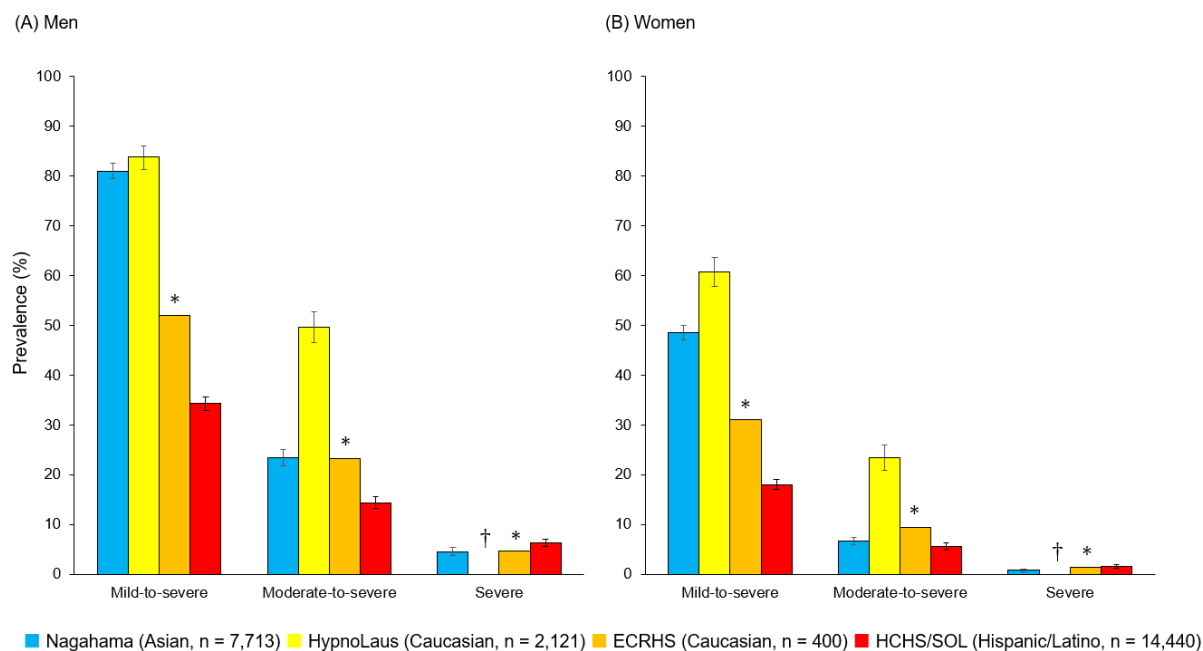
AHI, apnea-hypopnea index; oxygen desaturation index, ODI.

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.

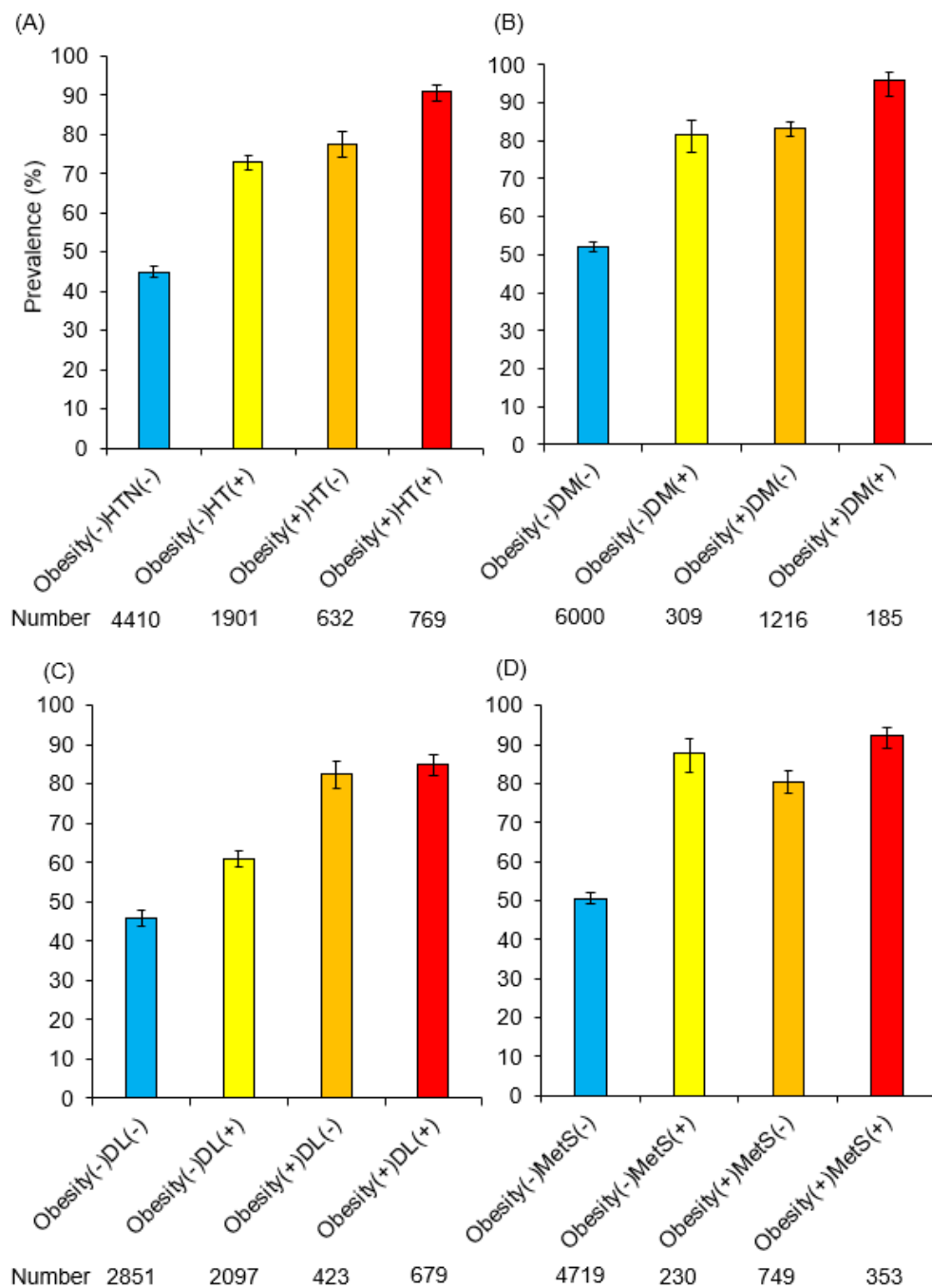
Nagahama study is shown as the representative of East Asians (age 59.9 ± 12.5 y, BMI 23.3 ± 3.1 kg/m² in men; age 56.9 ± 11.8 y, mean BMI 21.8 ± 3.3 kg/m² in women), HypnoLaus study is shown as the representative of Caucasians (age 56 [49-67] y, BMI 26.2 ± 3.7 kg/m² in men; age 58 [50-69] y, mean BMI 25.1 ± 4.6 kg/m² in women)[9], ECRHS is shown as another representative of Caucasians (age 54.8 ± 6.9 y, BMI 28.6 ± 4.4 kg/m² in men; age 54.6 ± 6.8 y, mean BMI 27.8 ± 5.4 kg/m² 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/m² 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.

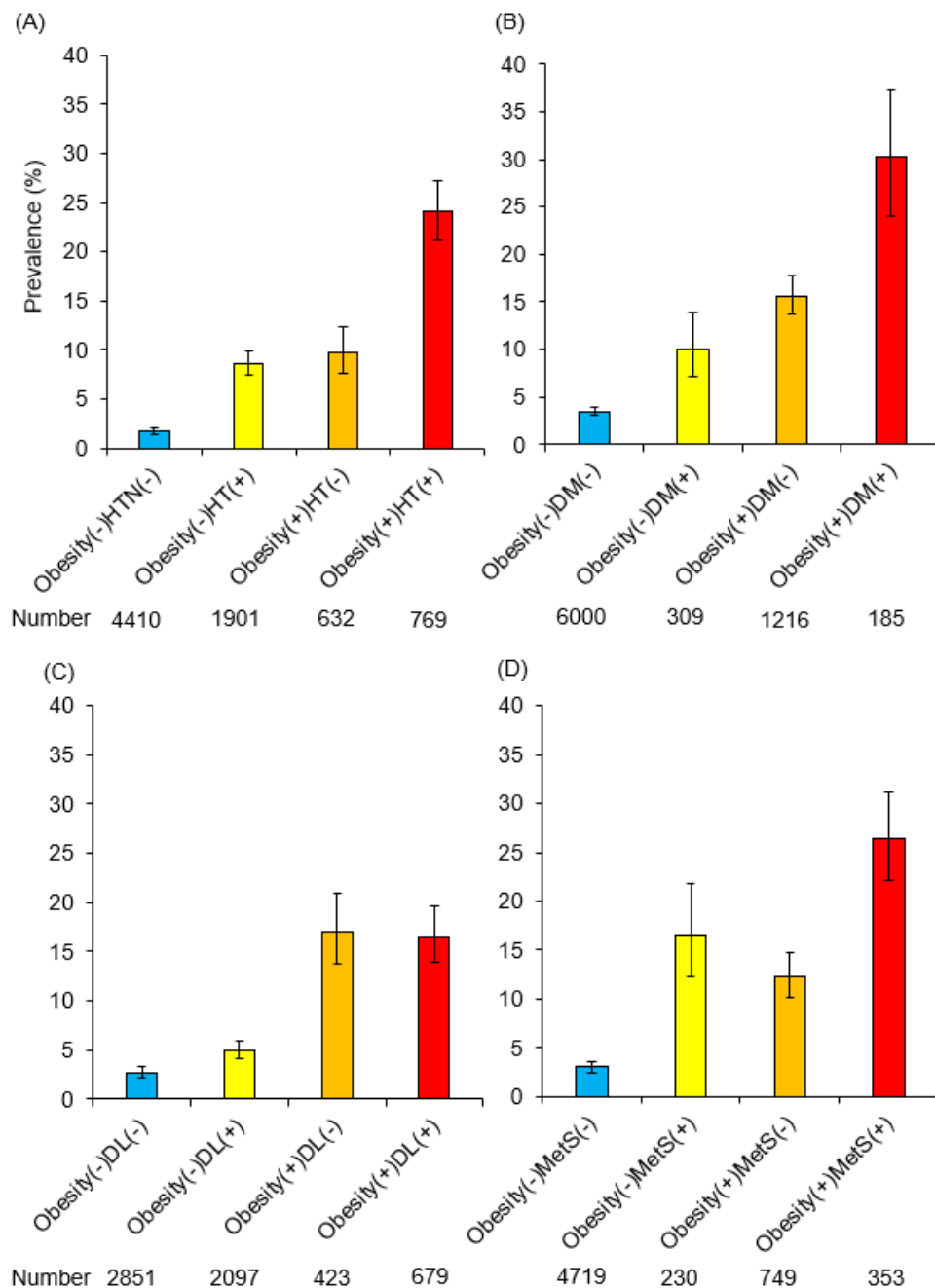


(A) Presence or absence of hypertension and/or obesity, (B) Presence or absence of diabetes and/or obesity, (C) Presence or absence of dyslipidemia and/or obesity, (D) Presence or absence of metabolic syndrome and/or obesity.

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% \geq 20 according to comorbidity and/or obesity.

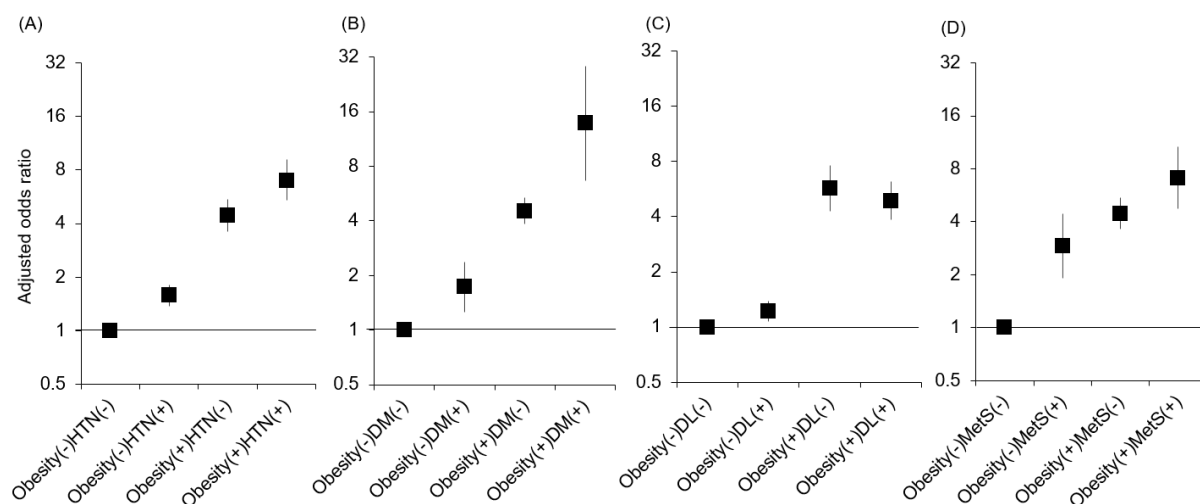


(A) Presence or absence of hypertension and/or obesity, (B) Presence or absence of diabetes and/or obesity, (C) Presence or absence of dyslipidemia and/or obesity, (D) Presence or absence of metabolic syndrome and/or obesity.

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.

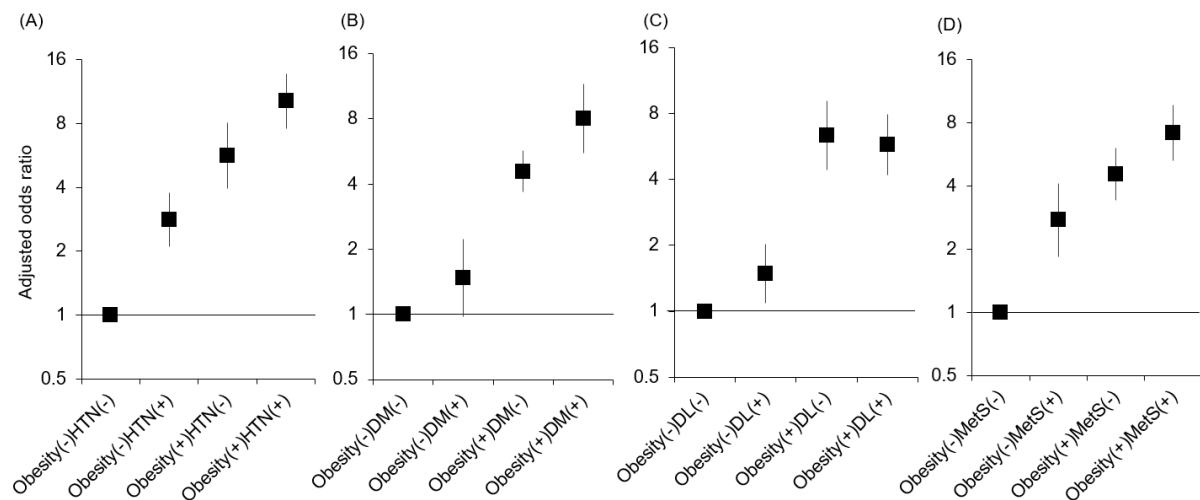
Point estimates value and 95% confidence interval are shown in the Figure. Vertical lines are shown as the log-transformed scale.

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% \geq 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.

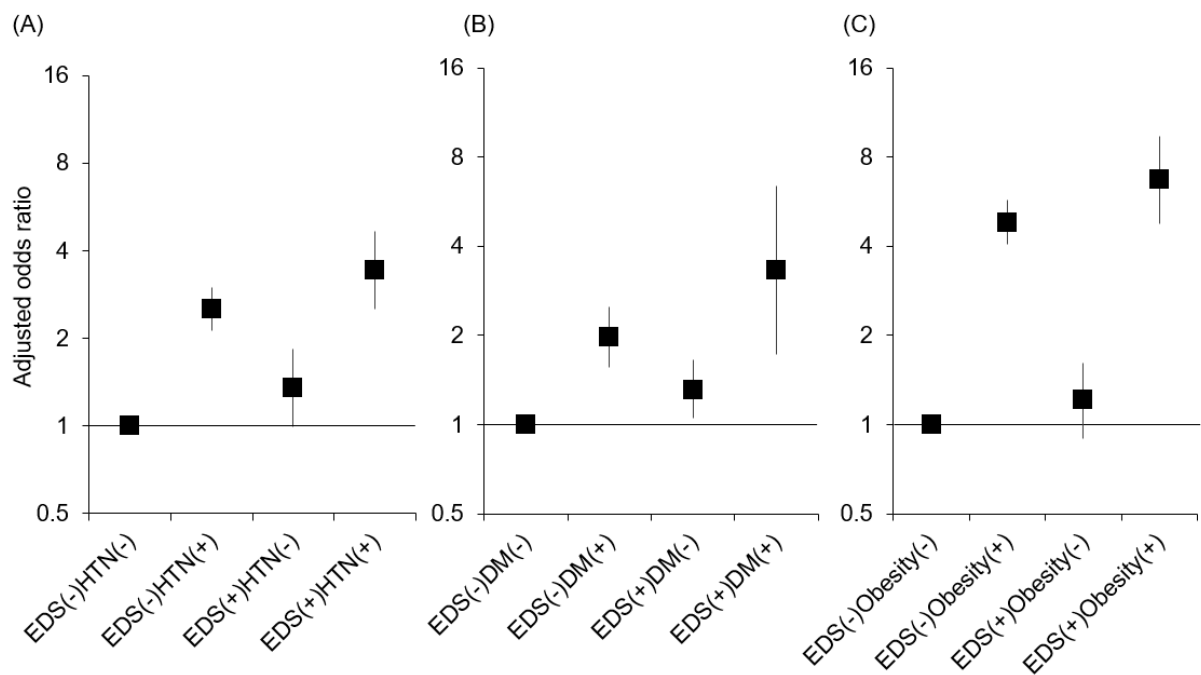
Point estimates value and 95% confidence interval are shown in the Figure. Vertical lines are shown as the log-transformed scale.

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.



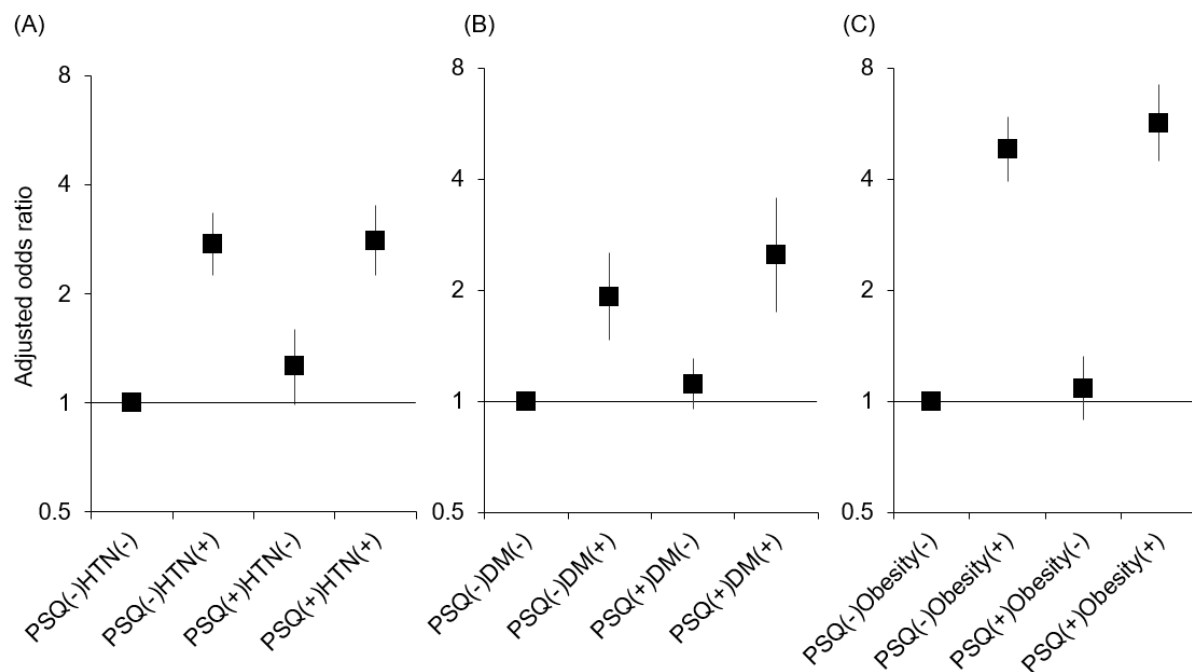
(A) Presence or absence of hypertension and/or EDS, (B) Presence or absence of diabetes and/or EDS, (C) Presence or absence of obesity and/or EDS.

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.

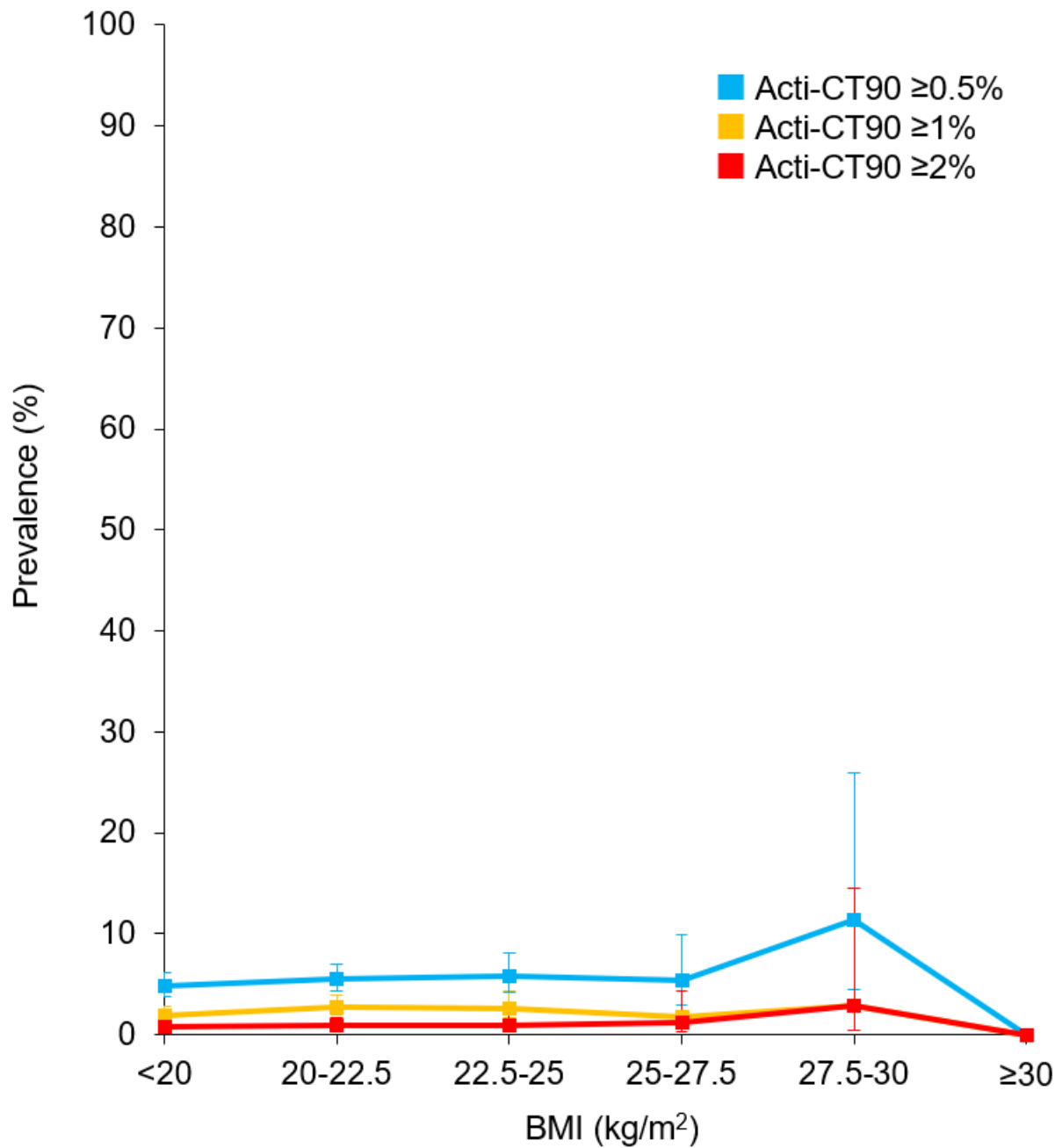


(A) Presence or absence of hypertension and/or poor sleep quality, (B) Presence or absence of diabetes and/or poor sleep quality, (C) Presence or absence of obesity and/or poor sleep quality. Point estimates value and 95% confidence interval are shown in the Figure. Vertical lines are shown as the log-transformed scale.

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

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

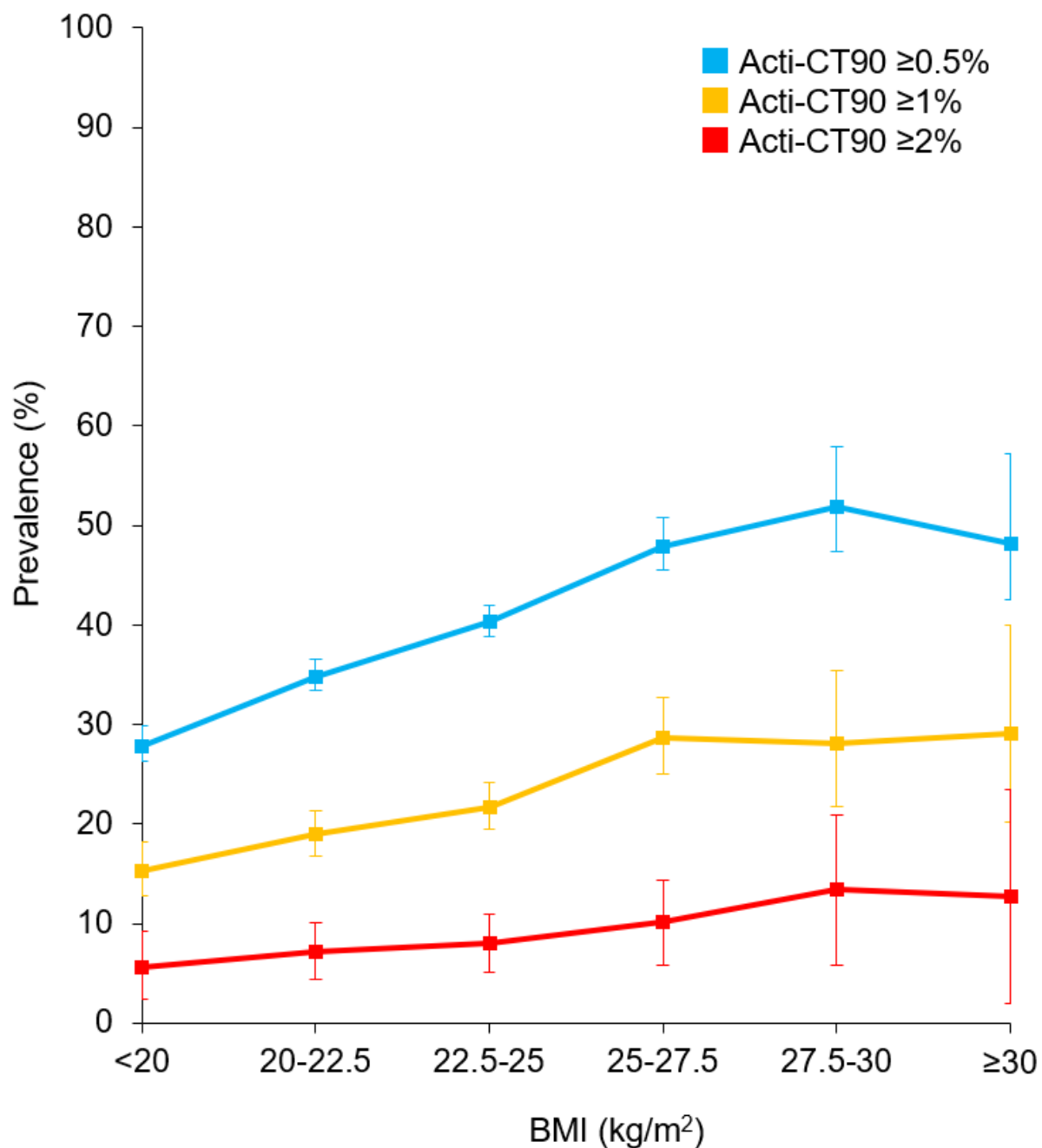
Figure S10. Percentages of high Acti-CT90 among those without SDB according to severity of obesity



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

Acti-CT90, actigraphy-modified cumulative percentage of sleep time with SpO₂ <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 SpO₂ <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	<i>P</i>	r	<i>P</i>	R	<i>P</i>
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)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
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.