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SCIENTIFIC INVESTIGATIONS

Markers of cardiovascular disease risk in sleep-disordered breathing with or without comorbidities: the Nagahama study

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Study Objectives: Whether the association between sleep-disordered breathing (SDB) and cardiovascular disease is independent of comorbid risk factors for cardiovascular disease is controversial. The objective of this study was to elucidate whether the association between SDB severity and the surrogate markers of cardiovascular disease events differs in relation to the number of comorbidities.

Methods: This cross-sectional study included 7,731 participants. Severity of SDB was determined by the oxygen desaturation index adjusted by actigraph-measured objective sleep time. Participants were stratified according to SDB severity and the number of comorbidities (hypertension, diabetes, dyslipidemia, and obesity), and the associations between the maximum value of intima-media thickness of the common carotid artery (CCA-IMT-max), brachial-ankle pulse wave velocity, and cardio-ankle vascular index were evaluated.

Results: Among participants with no risk factors, CCA-IMT-max increased according to SDB severity (n = 1022, $P < .0001$). Even after matching the background, the median CCA-IMT-max value was 14% higher in moderate-severe SDB patients than those without SDB (n = 45 in each group, $P = .020$). The difference was not significant for brachial-ankle pulse wave velocity and cardio-ankle vascular index. On the other hand, a significant difference in CCA-IMT-max was not found in those with multiple comorbidities. Consistently, multiple regression analysis revealed an independent association between CCA-IMT-max and moderate-severe SDB for all study participants (β: 0.0222, 95% confidence interval: 0.0039–0.0405, $P = .017$), but the association was not significant for stratified participants with multiple comorbidities.

Conclusions: SDB severity is associated with the CCA-IMT-max level, but the independent association becomes weaker for those with multiple comorbidities.

Keywords: sleep apnea, cardiovascular diseases, clinical epidemiology

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous studies suggest that sleep-disordered breathing, most commonly obstructive sleep apnea, is associated with the increased risk of cardiovascular diseases. However, it is controversial whether this association is independent of other risk factors.

Study Impact: Our study suggests that while the association between the severity of sleep-disordered breathing and the maximum value of intima-media thickness of the common carotid artery, a surrogate marker of cardiovascular disease events, is clear for those without cardiovascular risk factors, the association becomes weaker when the number of comorbid risk factors increases. These results will help identify those who would receive a benefit from treatment for obstructive sleep apnea against cardiovascular disease and to build an optimal strategy for future clinical studies.

INTRODUCTION

Cardiovascular disease (CVD) is one of the major complications of sleep-disordered sleeping (SDB), most frequently obstructive sleep apnea (OSA).[1] CVD includes ischemic heart diseases or cerebrovascular diseases, and patients with moderate to severe OSA were reported to have more than 3 times the risk of fatal events of CVD as individuals without OSA.[2–4] This contributes to the significant increase in mortality in patients with OSA.[5] Recent population-based studies revealed that the prevalence of moderate to severe SDB is 20%–40% irrespective of the ethnic groups.[6–8] In addition, a large number of patients with CVD also have SDB.[9,10] Based on these data, the impact of SDB on CVD has been regarded as an important health issue.

Currently there are several noninvasive methods to evaluate the risk of CVD. Measurement of the maximum value of

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intima-media thickness of the common carotid artery (CCA-IMT-max) with echography is a well-validated predictor of CVD events, and is capable of representing systemic atherosclerosis.[11–14] In addition, brachial-ankle pulse wave velocity (baPWV) and the cardio-ankle vascular index (CAVI) are indicators of arterial stiffness, with higher values suggesting high risk of CVD.[15,16]

Despite the solid associations between OSA and CVD, it is still controversial whether OSA has a direct effect on CVD events. It was reported that patients with OSA had higher IMT values than study participants without OSA[17,18] and that continuous positive airway pressure (CPAP) treatment could decrease such values.[19] In addition, a recent large-scale cohort study revealed independent associations between CCA-IMT and all degrees of OSA.[20] In contrast, recent studies suggested that the severity of OSA was not independently related to the intensity of atherosclerosis or arterial stiffness.[21,22] The major obstacle in estimating the contribution of OSA to CVD events is that most OSA is often complicated by obesity. Because obesity commonly is responsible for other risk factors for CVD such as hypertension, dyslipidemia, and diabetes mellitus, it is difficult to dissect the sole effect of OSA and to clarify whether the increased CVD events in patients with OSA is not just due to the comorbid risk factors.

In the present study, we hypothesized that, while SDB has an independent association with CVD, in the event that the number of comorbidities increases, the association would disappear. We employed CCA-IMT-max, baPWV, and CAVI as surrogate markers of CVD events. Results of this study provide evidence for identifying those who are most strongly affected by SDB and will help in the construction of an optimal strategy for future clinical studies.

METHODS

Study participants

The Nagahama study included residents in Nagahama City, a rural city with approximately 125,000 inhabitants in Japan, and 9,850 participants from 34 to 80 years old were recruited. The study was conducted from 2013 to 2016, and residents without apparent physical impairments or dysfunction were recruited. Written informed consent was obtained from all participants. The ethics committee of Kyoto University Graduate School of Medicine approved the study (G0278). Participants were excluded if their sleep data, information required for the assessment of comorbidity, or the surrogate markers for CVD events (CCA-IMT-max, baPWV, and CAVI) were not available. Participants receiving treatment for SDB were also excluded.

Evaluation of SDB

The evaluation of SDB was performed as previously reported.[8] Briefly, a pulse oximeter (PULSOX-Me300; Konica Minolta, Inc., Tokyo, Japan) was used for the continuous measurement of SpO_2 oxygen saturation during sleep at night. The Actiwatch 2 or the Actiwatch Spectrum Plus wrist actigraph (Philips Respironics, Murrysville, PA) was used for the analysis of the objective sleep period. Experienced staff members reviewed the results. Oxygen desaturation index (ODI) was calculated as the number of events for 3% oxygen desaturation/h. Objective sleep period was applied to set the start and end points of analysis, and the oxygen desaturation index adjusted by the objective sleep period evaluated with actigraph (ODI-Acti3%) was used for further analyses. Participants with a minimum of 2 nights of data were included in the study. Averaged values of ODI-Acti3% were used for further analyses. ODI-Acti3% was more comparable to the apnea-hypopnea index derived from attended polysomnography ($r = .99, P < .001$; apnea-hypopnea index = ODI-Acti3% × 1.04 + 1.45) than simply measuring ODI3% without actigraphy modification ($r = .92, P < .001$; apnea-hypopnea index = usual ODI3% × 1.27 + 2.06).[23] Participants were grouped according to the severity of SDB based on the ODI-Acti3% values (no SDB, < 5/events/h; mild SDB, 5 to < 15 events/h; and moderate-severe SDB, ≥ 15 events/h.

Study design

To evaluate the sole association between SDB severity and the surrogate markers of CVD events, we excluded individuals with a smoking history, hypertension, diabetes mellitus, dyslipidemia, and body mass index (BMI) ≥ 25 kg/m^2. Premenopausal females were also excluded as having a factor with a preferable effect on atherosclerosis. Then we compared the values of CCA-IMT-max, baPWV, and CAVI between these curated participants grouped according to SDB severity (analysis 1). Next, to further equalize the confounding factors, we performed propensity-score matching between "no-SDB" group and "moderate-severe" group participants with generating "matched–no SDB" group. Similarly, we performed propensity-score matching between no-SDB group and mild-SDB group (matched–no-SDB-2 group and matched–mild-SDB group, respectively). The following factors were matched: age, BMI, sex, and systolic and diastolic blood pressures. The values of surrogate markers of CVD events were compared between the matched groups (analysis 2).

We next stratified all participants included in this study according to the number of the following comorbidities: BMI ≥ 25, dyslipidemia, diabetes, and hypertension. Then the association between SDB severity and the CCA-IMT-max values were analyzed. Further details of methods are available in the supplemental material.

Statistical analysis

For comparisons between groups, Fisher's test was used for categorical variables, and Kruskal-Wallis test or Mann-Whitney *U* test was used for continuous variables. Holm's post-hoc test was performed for comparisons of 2 out of 3 groups. To calculate propensity scores between the no-SDB group and moderate-severe group, after excluding no-SDB group from the dataset of analysis 1, we used multivariate logistic regression test with the presence of SDB set as the objective variable and the following factors as explanatory variables: age, BMI, sex, and systolic and diastolic blood pressures. Similarly, the propensity scores between no-SDB group and mild-SDB group were calculated by logistic regression test performed on the dataset excluding moderate-severe group from analysis 1. Matching was done with case-control ratio of 1:1, and unmatched participants were

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Table 1—Participants' characteristics.

	No SDB	Mild	Moderate-Severe	*P*
n	3167	3625	937	
Male sex	476 (15.0)	1435 (39.6)	586 (62.5)	< .001
Age (years)	52.00 [43.00, 62.00]	63.00 [52.00, 69.00]	67.00 [59.00, 73.00]	< .001
Body mass index (kg/m^2)	20.60 [19.10, 22.40]	22.50 [20.50, 24.50]	24.70 [22.50, 26.90]	< .001
Past history of stroke	51 (1.6)	133 (3.7)	68 (7.3)	< .001
Past history of ischemic heart disease	26 (0.8)	39 (1.1)	44 (4.7)	< .001
Brinkman index	0.00 [0.00, 2376.00]	0.00 [0.00, 2750.00]	0.00 [0.00, 2580.00]	< .001
Systolic blood pressure (mm Hg)	118.00 [109.00, 128.00]	126.00 [116.00, 137.00]	132.00 [123.00, 143.00]	< .001
Diastolic blood pressure (mm Hg)	76.00 [69.00, 84.00]	82.00 [74.00, 88.00]	86.00 [79.00, 92.00]	< .001
Pulse rate (bpm)	60.00 [55.00, 66.00]	60.00 [55.00, 67.00]	61.00 [55.00, 68.00]	.107
LDL-chol (mg/dL)	115.00 [96.00, 136.00]	118.00 [100.00, 137.00]	117.00 [100.00, 137.00]	< .001
HDL-chol (mg/dL)	71.00 [60.75, 83.00]	64.00 [53.00, 75.00]	58.00 [49.00, 70.00]	< .001
Triglycerides (mg/dL)	67.00 [50.00, 93.00]	84.00 [62.00, 118.00]	98.00 [69.00, 139.00]	< .001
Cholinesterase (IU/L)	312.00 [271.00, 361.00]	335.00 [291.00, 382.00]	344.00 [296.00, 395.00]	< .001
Total protein (g/dL)	7.20 [6.90, 7.50]	7.20 [7.00, 7.50]	7.30 [7.00, 7.60]	< .001
Albumin (g/dL)	4.30 [4.20, 4.40]	4.30 [4.10, 4.40]	4.30 [4.10, 4.40]	< .001
Blood glucose (mg/dL)	83.00 [79.00, 88.00]	86.00 [81.00, 93.00]	90.00 [84.00, 98.00]	< .001
Serum creatinine (mg/dL)	0.63 [0.57, 0.71]	0.69 [0.59, 0.81]	0.77 [0.65, 0.88]	< .001
Platelets ($\times 10^4/\mu L$)	23.40 [20.10, 26.80]	22.60 [19.30, 26.10]	21.70 [18.60, 25.60]	< .001
CCA-IMT-max (mm)	0.70 [0.60, 0.80]	0.80 [0.70, 0.98]	0.90 [0.80, 1.00]	< .001
baPWV (m/s)	1.17 [1.07, 1.31]	1.31 [1.16, 1.49]	1.42 [1.27, 1.59]	< .001
CAVI	7.33 [6.73, 8.09]	8.00 [7.21, 8.92]	8.50 [7.63, 9.26]	< .001

Data are summarized as number (%) or median [interquartile range]. Fisher's test and Kruskal-Wallis test were used. baPWV = brachial-ankle pulse wave velocity, CAVI = cardio-ankle vascular index, CCA-IMT-max = maximum value of intima-media thickness of common carotid artery, HDL-chol = high density lipoprotein cholesterol, LDL-chol = low density lipoprotein cholesterol, SDB = sleep-disordered breathing.

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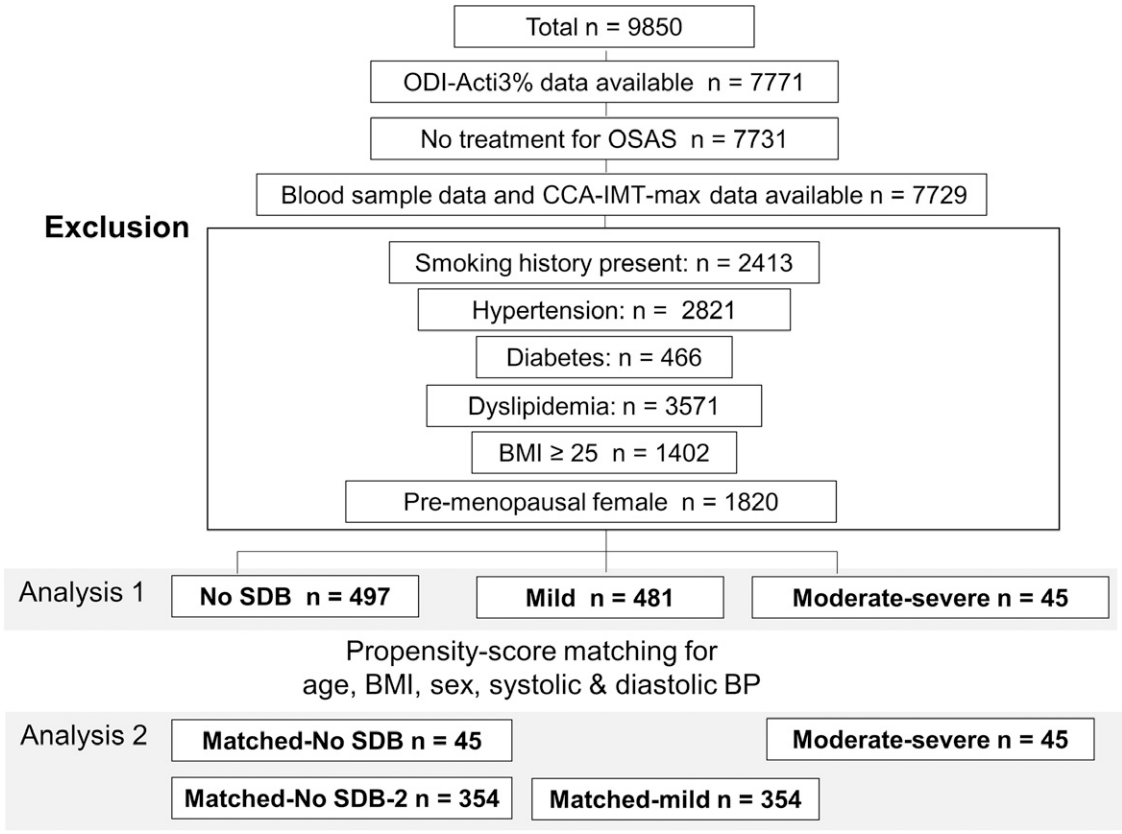
excluded. For the multiple regression test, we set log-transformed CCA-IMT-max values as the dependent variable, and the associations between log-transformed CCA-IMT-max and SDB severity were assessed with the model that included the following variables; age, BMI, glycated hemoglobin, plasma levels of high-density lipoprotein, plasma levels of low-density lipoprotein, plasma levels of systolic blood pressure, plasma levels of triglyceride, diastolic blood pressure, sex (with pre- and postmenopausal females treated as independent groups), Brinkman index, and SDB severity. Statistical analyses were performed by using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[24] A *P* value < .05 was considered significant.

RESULTS

Participants' backgrounds

ODI-Acti3% data were available for 7771 participants, and 40 participants who were receiving treatment for OSA (CPAP and/or oral appliance treatment) were excluded. Another 2 participants were excluded due to the lack of CCA-IMT or blood test data. The background of all 7729 participants included in this study is summarized in **Table 1**. After excluding participants with major risk factors for CVD or a premenopausal status (**Table S1** in the supplemental material), 1022 participants remained for analysis (analysis 1). Among those, 497 participants did not exhibit SDB, while 480 and 45 participants were classified into the "mild" and "moderate-severe" SDB groups, respectively. Differences between groups in most background items were generally small; however, there were significant differences in rates of male sex, age, BMI, and diastolic blood pressure. We then selected 45 participants from the "no-SDB" group ("matched–no-SDB" group) by matching age, BMI, sex, and systolic and diastolic blood pressures with those in the "moderate-severe" group. There were no statistically significant differences between the backgrounds of the "matched–no-SDB" group and moderate-severe group (analysis 2, **Table S2** in the supplemental material). We further performed propensity-score matching to the no-SDB group and mild-SDB group (matched–no-SDB-2 group and matched–mild-SDB group, respectively) (**Table S3** in the supplemental material). **Figure 1** is a flowchart summarizing the selection of participants.

Figure 1—Flowchart of study participants.



BMI = body mass index, BP = blood pressure, ODI-Acti3% = 3% oxygen desaturation indexadjusted by the objective sleep period evaluated with actigraphy, OSAS = obstructive sleep apnea syndrome, SDB = sleep-disordered breathing, TG = triglycerides.

Severity of SDB was associated with CCA-IMT-max value among participants without major risk factors for CVD

Next, we analyzed whether the CCA-IMT-max value was associated with the severity of SDB within each of the analyses. In both the analysis involving all included participants and the analysis of participants included in "analysis 1", the CCA-IMT-max values were significantly increased in association with the severity of SDB (**Figure 2A**, **Figure 2B**, **Table 1**, and **Table S1**). In addition, even in the comparison between the matched–no-SDB group and moderate-severe group (analysis 2), significantly higher values for CCA-IMT-max were observed for those with SDB ($P = .020$, median value [lower, higher interquartile range]: 0.70 [0.70, 0.80] mm for matched–no-SDB group, 0.80 [0.80, 1.00] mm for moderate-severe group) (**Figure 2C** and **Table S2**).

In contrast, baPWV or CAVI did not show significant differences between the matched–no-SDB group and moderate-severe SDB group in analysis 2 (**Figure S1** in the supplemental material). We further compared the matched–no-SDB-2 group and matched–mild-SDB group and found that the CCA-IMT-max values in the matched–mild-SDB group were significantly higher (**Figure S2**).

Effect of SDB on CCA-IMT-max was difficult to distinguish in those with multiple comorbidities

Next, we stratified all of the included participants according to the number of comorbidities (BMI ≥ 25 kg/m^2, dyslipidemia, diabetes, and hypertension). With regard to 2743 participants, none of these 4 comorbidities were found. Only 1 morbidity was present in 2546 participants and 2 comorbidities were present in 1707 participants, while 3 or more comorbidities were observed in 733 participants. The between-group comparison of CCA-IMT-max values revealed that the severity of SDB was associated with an increase in CCA-IMT-max values for those without or with only 1 risk factor (**Figure 3A** and **Figure 3B**). On the other hand, the difference was less significant for those with 2 risk factors (**Figure 3C**) and not significant for those with 3 or more risk factors (**Figure 3D**).

Finally, we performed multiple regression analysis to adjust the effect of comorbidities on CCA-IMT-max. The analysis of the remaining 7730 participants showed that moderate-severe SDB was an independent factor for increases in the log-transformed CCA-IMT-max values ($P = .017$, β [lower to higher 95% confidence interval]: 0.0222 [0.0039–0.0405]. In the analysis of participants with no or only 1 risk factor for CVD, we found that

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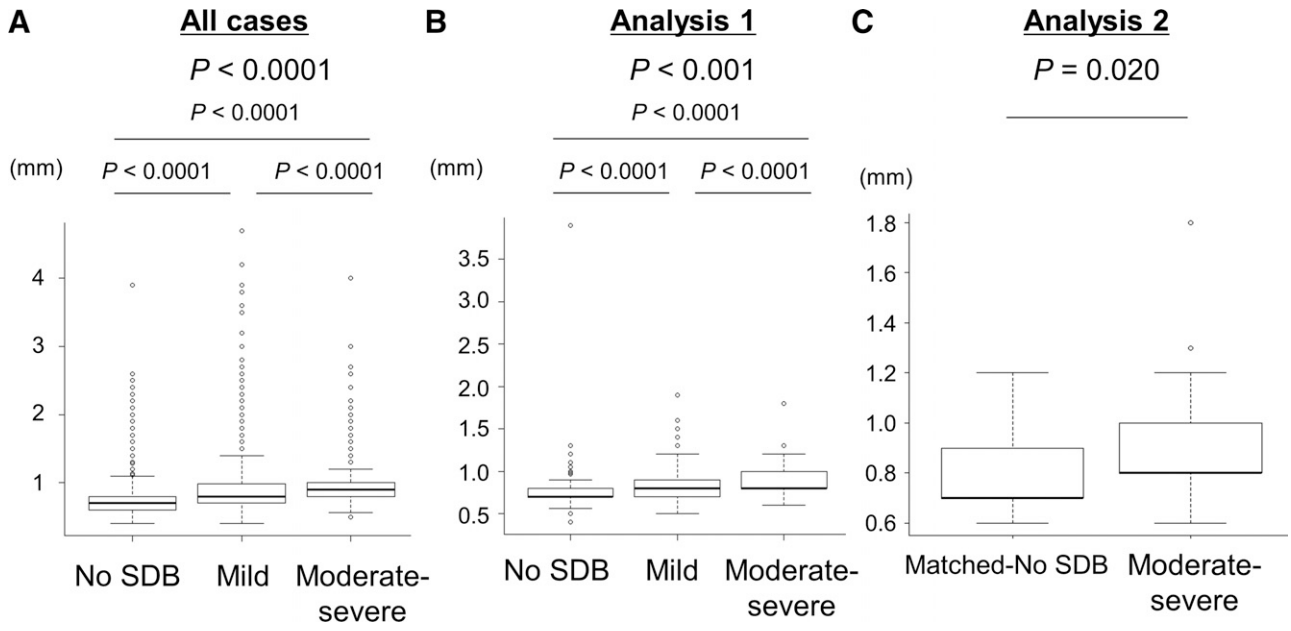
Figure 2—Comparison of CCA-IMT-max values among participants grouped according to the severity of SDB.



(A, B) Comparisons of CCA-IMT-max values among all included patients **(A)** and those without major risk factors for CVD (analysis 1; **B**). Participants were grouped according to the severity of SDB (no-SDB, mild-SDB, and moderate-severe groups) and compared. **(C)** Comparisons of CCA-IMT-max values between the "matched–no-SDB" group and "moderate-severe" group (analysis 2; **C**). Kruskal-Wallis test and post-hoc analysis between 2 groups with adjustment for multiple comparisons by Holm's method were used for **(A)** and **(B)**. Mann-Whitney *U* test was used for **(C)**. CCA-IMT-max = maximum value of intima-media thickness of common carotid artery, SDB = sleep-disordered breathing.

mild SDB was a significant factor (P = .0344, β: 0.0131 [0.0010–0.0252]). In contrast, among participants with 2 or more risk factors, SDB severity was not a significant factor (**Table 2**).

DISCUSSION

In the present study, we showed that the severity of SDB was associated with higher values of CCA-IMT-max in the absence of major risk factors for CVD. We also found that this association was not present in those with more than 2 risk factors. These results added the novel insight to the literature that the statistically significant associations between SDB and CCA-IMT-max were most evident for those who had none or 1 risk factor for cardiovascular diseases.

Among surrogate markers for CVD events, CCA-IMT-max is one of the most established parameters and can visually evaluate the degree of atherosclerosis.[25] On the other hand, markers for arterial stiffness such as baPWV and CAVI are calculated by using blood pressure values, and it has been shown that these were strongly affected by blood pressure at the time of evaluation.[26,27] That might be 1 reason why associations between SDB severity and baPWV or CAVI were not observed after the matching of blood pressure.

This study is consistent with the previous reports by Drager et al[17] and Souza et al[20] with regard to the point that SDB may directly contribute to the CCA-IMT-max independently of comorbidities, while we reached a different conclusion from other previous reports suggesting that the association between CCA-IMT and SDB largely depends on comorbid risk factors.[21,22] A major difference between the previous studies aforementioned and the present study is that previous studies included quite a few participants with risks of CVD such as obesity and dyslipidemia.[17,20–22] The present study included analyses after careful exclusion of such participants, which successfully revealed that SDB was significantly associated with the increased levels of CCA-IMT-max; therefore, our study offers the new insight that SDB could contribute to increased risk of CVD even in the absence of other risk factors. Clinically, this novel finding may highlight the importance of treating SDB patients, even those without risk factors or only 1 risk factor, for cardiovascular diseases, although a prospective interventional study is needed to verify the degree of benefit.

Another novel finding of the present study is that in the multiple regression test the independent association between SDB and CCA-IMT-max disappeared when multiple risk factors were present. This result has 2 possible interpretations: first, the contribution of SDB is scant in patients with multiple comorbidities, and, second, even though SDB has an effect on CCA-IMT-max, the comorbidities may lie in the causal pathway between SDB and CCA-IMT-max, and the effect becomes difficult to distinguish when comorbidities are adjusted for. In addition to the direct effect, SDB can increase the risk of CVD through the augmentation of other comorbidities.[28] For example, there is a solid association between the severity of SDB and the increase in blood pressure.[29] Also, intermittent hypoxia due to SDB may

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Table 2—Multiple regression analysis for the association between SDB severity and CCA-IMT-max.

	All Patients (n = 7,730)		Number of Risk Factors ≤ 1 (n = 5,289)		Number of Risk Factors ≥ 2 (n = 2,441)	
	β (Lower to Higher 95% CI)	*P*	β (Lower to Higher 95% CI)	*P*	β (Lower to Higher 95% CI)	*P*
Age	0.0101 (0.0095 to 0.0107)	< .0001	0.0101 (0.0094 to 0.0107)	< .0001	0.0098 (0.0086 to 0.0110)	< .0001
BMI	0.0045 (0.0028 to 0.0063)	< .0001	0.0033 (0.0010 to 0.0057)	.0059	0.0026 (–0.0007 to 0.0058)	.1212
HbA1c	0.0152 (0.0044 to 0.0260)	.0056	–0.0122 (–0.0290 to 0.0046)	.1557	0.0199 (0.0040 to 0.0358)	.0141
HDL-chol	–0.0008 (–0.0011 to –0.0005)	< .0001	–0.0007 (–0.0010 to –0.0003)	.0004	–0.0011 (–0.0018 to –0.0004)	.0026
LDL-chol	0.0006 (0.0005 to 0.0008	< .0001	0.0006 (0.0004 to 0.0008)	< .0001	0.0007 (0.0003 to 0.0010)	< .0001
Triglyceride	–0.0001 (–0.0002 to –0.00001)	.0325	–0.0001 (–0.0003 to 0.000003)	.0559	–0.0002 (–0.0003 to –0.00002)	.0289
Systolic blood pressure	0.0031 (0.0026 to 0.0037)	< .0001	0.0029 (0.0023 to 0.0036)	< .0001	0.0032 (0.0022 to 0.0041)	< .0001
Diastolic blood pressure	–0.0017 (–0.0025 to –0.0010)	< .0001	–0.0013 (–0.0022 to –0.0004)	.0054	–0.0030 (–0.0045 to –0.0016)	< .0001
Brinkman index	0.0001 (0.0001 to 0.0001)	< .0001	0.0001 (0.0000 to 0.0001)	.0000	0.0001 (0.0001 to 0.0001)	< .0001
Sex						
Premenopausal female	Reference		Reference		Reference	
Postmenopausal female	–0.0118 (–0.0283 to 0.0048)	.1632	–0.0068 (–0.0243 to 0.0106)	.4430	–0.0233 (–0.0673 to 0.0206)	.2975
Male	0.0242 (0.0067 to 0.0418)	.0069	0.0196 (0.0007 to 0.0385)	.0418	0.0341 (–0.0108 to 0.0790)	.1362
SDB severity						
No-SDB group	Reference		Reference		Reference	
Mild-SDB group	0.0065 (–0.0049 to 0.0179)	.2650	0.0131 (0.0010 to 0.0252)	.0344	–0.0065 (–0.0331 to 0.0201)	.6326
Moderate-severe group	0.0222 (0.0039 to 0.0405)	.0170	0.0101 (–0.0142 to 0.0344)	.4137	0.0161 (–0.0168 to 0.0490)	.3375

Risk factors counted: BMI > 25, complication of dyslipidemia, diabetes, and hypertension. BMI = body mass index, CCA-IMT-max = maximum value of intima-media thickness of common carotid artery, CI = confidence interval, HbA1c = glycated hemoglobin, HDL-chol = high-density lipoprotein cholesterol, LDL-chol = low density lipoprotein cholesterol, SDB = sleep-disordered breathing.

cause peroxidation of lipids,[30] which could exacerbate the progression of atherosclerosis in patients with dyslipidemia.[31] The adjustment of comorbidities might have canceled these secondary effects of SDB on CCA-IMT-max or made them obscure. In patients with multiple risk factors, risk factors may form a network of biological effects and affect atherosclerosis in a complicated manner, and not in an independent manner. Further investigation is required to elucidate this process.

This study may provide a clue to explaining the conflicting conclusions of previous studies concerning the contribution of SDB to surrogate markers of CVD events. Looking at the background of participants in a major study that denied the association between the severity of SDB and markers of CVD events, the number of risk factors for CVD was quite high, suggesting that the majority of participants would have been complicated with multiple comorbidities.[21] Therefore, it should have been difficult to distinguish the effect of SDB on markers of CVD in those participants.

We expect that the results of the present study will help to optimize strategies of future prospective studies, such as clinical trials to evaluate the efficacy of CPAP treatment to lower the risk of CVD events. In spite of the well-recognized efficacy of CPAP treatment for OSA, a recent prospective study failed to show a clear benefit for the prevention of CVD.[32] Since that study included a large number of participants complicated with hypertension, obesity, and dyslipidemia, the presence of these conditions might have masked the apparent benefit of CPAP treatment.[32] The present study indicated that the direct effect of

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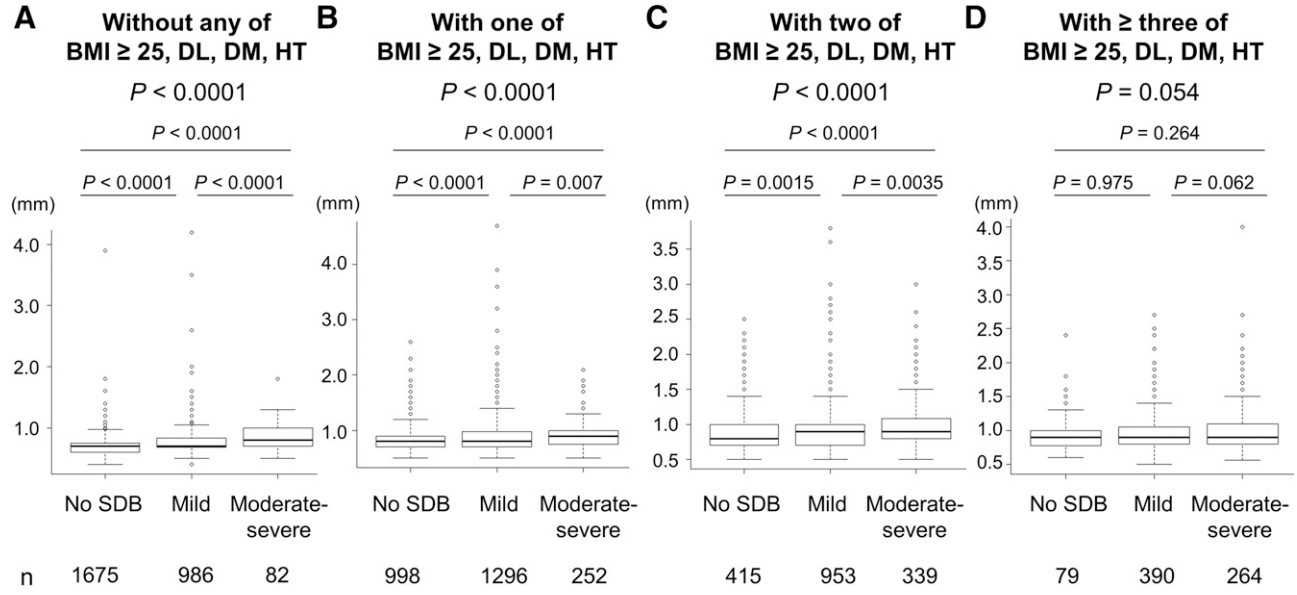
Figure 3—Comparison of CCA-IMT-max values between the participants' group stratified according to the number of comorbid risk factors.



Comparisons of CCA-IMT-max values among stratified participants according to the number of CVD risk factors (BMI ≥ 25 kg/m^2, DL, DM, HT). Participants were grouped according to the severity of SDB (no SDB, mild, and moderate-severe groups). Comparisons among the participants without any **(A)**, with 1 **(B)**, 2 **(C)**, and 3 or more **(D)** risk factors for CVD are shown. Kruskal-Wallis test and post-hoc analysis with Mann-Whitney *U* test between 2 groups with the adjustment for multiple comparisons by Holm's method. BMI = body mass index, CCA-IMT-max = maximum value of intima-media thickness of common carotid artery, CVD = cardiovascular disease, DL = dyslipidemia, DM = diabetes mellitus, HT = hypertension, SDB = sleep-disordered breathing.

SDB on CCA-IMT-max was most clearly observed in participants with no or only 1 complication. Therefore, targeting these patients in future trials could be an advantageous strategy.

Limitations

First, this was a cross-sectional study, and causal relationships between SDB and increased values of CCA-IMT-max were not analyzed. The second potential limitation is that the evaluation of SDB was based on ODI values and not based on polysomnography-measured apnea-hypopnea index. On this point, we would like to emphasize that the ODI values used for the analyses were adjusted by objective sleep duration by actigraphy, which largely resolved the underestimation of respiratory events.[23]

Future directions

A prospective study to validate the results of this study and to analyze the causal relationship between SDB and cardiovascular events is desirable. In future studies that evaluate the efficacy of CPAP for the prevention of cardiovascular disease, it could be beneficial to focus on those without major risk factors.

In conclusion, in the present study we clarified that the severity of SDB was associated with CCA-IMT-max even among those without risk factors, indicating that SDB is associated with CCA-IMT-max independently from other cardiovascular risk factors. In addition, we revealed that the independent association between SDB and CCA-IMT-max became weaker when multiple risk factors were present. Our results will help to identify those who receive the clearest benefit from treatment of OSA for the prevention of cardiovascular events and to build an optimal strategy for future clinical studies.

ABBREVIATIONS

baPWV, brachial-ankle pulse wave velocity
BMI, body mass index
CAVI, cardio-ankle vascular index
CCA-IMT-max, maximum value of intima-media thickness of common carotid artery
CPAP, continuous positive airway pressure
CVD, cardiovascular disease
ODI, oxygen desaturation index
ODI-Acti3%, oxygen desaturation index adjusted by the objective sleep period evaluated with actigraph
OSA, obstructive sleep apnea
SDB, sleep-disordered breathing

REFERENCES

1. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet.* 2014; 383(9918):736–747.
2. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005; 365(9464):1046–1053.
3. Chami HA, Resnick HE, Quan SF, Gottlieb DJ. Association of incident cardiovascular disease with progression of sleep-disordered breathing. *Circulation.* 2011;123(12): 1280–1286.

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4. Mandal S, Kent BD. Obstructive sleep apnoea and coronary artery disease. *J Thorac Dis.* 201810(Suppl 34):S4212–S4220.
5. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med.* 2005;353(19): 2034–2041.
6. Yamagishi K, Ohira T, Nakano H, et al. Cross-cultural comparison of the sleep-disordered breathing prevalence among Americans and Japanese. *Eur Respir J.* 2010;36(2):379–384.
7. Chen X, Wang R, Zee P, et al. Racial/ethnic differences in sleep disturbances: the Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep.* 2015;38(6):877–888.
8. Matsumoto T, Murase K, Tabara Y, et al. Impact of sleep characteristics and obesity on diabetes and hypertension across genders and menopausal status: the Nagahama study. *Sleep.* 2018;41(7):zsy071.
9. Schäfer H, Koehler U, Ewig S, Hasper E, Tasci S, Lüderitz B. Obstructive sleep apnea as a risk marker in coronary artery disease. *Cardiology.* 1999;92(2):79–84.
10. Yumino D, Tsurumi Y, Takagi A, Suzuki K, Kasanuki H. Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. *Am J Cardiol.* 2007; 99(1):26–30.
11. Allan PL, Mowbray PI, Lee AJ, Fowkes FG. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease. The Edinburgh Artery Study. *Stroke.* 1997;28(2):348–353.
12. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med.* 1999;340(1):14–22.
13. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke.* 2006;37(1):87–92.
14. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Nakamura F, Miyamoto Y. Impact of intima-media thickness progression in the common carotid arteries on the risk of incident cardiovascular disease in the Suita study. *J Am Heart Assoc.* 2018; 7(11):e007720.
15. Sato Y, Nagayama D, Saiki A, et al. Cardio-ankle vascular index is independently associated with future cardiovascular events in outpatients with metabolic disorders. *J Atheroscler Thromb.* 2016;23(5):596–605.
16. Ohkuma T, Ninomiya T, Tomiyama H, et al; Collaborative Group for J-BAVEL (Japan Brachial-Ankle Pulse Wave Velocity Individual Participant Data Meta-Analysis of Prospective Studies). Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: an individual participant data meta-analysis. *Hypertension.* 2017;69(6):1045–1052.
17. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2005;172(5):613–618.
18. Ciccone MM, Scicchitano P, Mitacchione G, et al. Is there a correlation between OSAS duration/severity and carotid intima-media thickness? *Respir Med.* 2012; 106(5):740–746.
19. Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2007;176(7):706–712.
20. Souza SP, Santos RB, Santos IS, et al. Obstructive sleep apnea, sleep duration, and associated mediators with carotid intima-media thickness: the ELSA-Brasil study. *Arterioscler Thromb Vasc Biol.* 2021;41(4):1549–1557.
21. Kim J, Mohler ER III, Keenan BT, et al. Carotid artery wall thickness in obese and nonobese adults with obstructive sleep apnea before and following positive airway pressure treatment. *Sleep.* 2017;40(9):zsx126.
22. Joyeux-Faure M, Tamisier R, Borel JC, et al. Contribution of obstructive sleep apnoea to arterial stiffness: a meta-analysis using individual patient data. *Thorax.* 2018;73(12):1146–1151.
23. Matsumoto T, Murase K, Tabara Y, et al. Sleep disordered breathing and metabolic comorbidities across sex and menopausal status in East Asians: the Nagahama Study. *Eur Respir J.* 2020;56(2):1902251.
24. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant.* 2013;48(3):452–458.
25. Tran LT, Park HJ, Kim HD. Is the carotid intima-media thickness really a good surrogate marker of atherosclerosis? *J Atheroscler Thromb.* 2012;19(7): 680–690.
26. Ueyama K, Miyata M, Kubozono T, et al. Noninvasive indices of arterial stiffness in hemodialysis patients. *Hypertens Res.* 2009;32(8):716–720.
27. Tabara Y, Setoh K, Kawaguchi T, et al; Nagahama Study Group. Factors affecting longitudinal changes in cardio-ankle vascular index in a large general population: the Nagahama study. *J Hypertens.* 2018;36(5):1147–1153.
28. Bonsignore MR, Baiamonte P, Mazzuca E, Castrogiovanni A, Marrone O. Obstructive sleep apnea and comorbidities: a dangerous liaison. *Multidiscip Respir Med.* 2019; 14(1):8.
29. Pépin JL, Tamisier R, Barone-Rochette G, Launois SH, Lévy P, Baguet JP. Comparison of continuous positive airway pressure and valsartan in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med.* 2010;182(7):954–960.
30. Li J, Savransky V, Nanayakkara A, Smith PL, O'Donnell CP, Polotsky VY. Hyperlipidemia and lipid peroxidation are dependent on the severity of chronic intermittent hypoxia. *J Appl Physiol (1985).* 2007;102(2):557–563.
31. Barros D, García-Río F. Obstructive sleep apnea and dyslipidemia: from animal models to clinical evidence. *Sleep.* 2019;42(3):zsy236.
32. McEvoy RD, Antic NA, Heeley E, et al; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med.* 2016;375(10):919–931.

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