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Original Article

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Nocturnal Intermittent Hypoxia and the Risk of Cardiovascular Disease among Japanese Populations: The Circulatory Risk in Communities Study (CIRCS)

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Aims: Information is limited about the influence of obstructive sleep apnea (OSA) on developing cardiovascular disease (CVD) among Asian community-dwelling populations. We examined the association between nocturnal intermittent hypoxia as a surrogate marker of OSA and the risk of CVD in a Japanese community-based cohort study.

Methods: We used baseline surveys from 2000 to 2008 to study the cohort data of 5,313 residents from three Japanese communities who were between the ages of 40 and 74 years and initially free from ischemic heart disease and stroke. We assessed the number of 3% oxygen desaturation index (ODI) as the indicator of nocturnal intermittent hypoxia. We divided individuals into two groups depending on 3% ODI (3% ODI ≥ 5 or 3% ODI <5). Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD according to 3% ODI. Age, sex, body mass index, alcohol, and smoking were adjusted in the multivariable models.

Results: During 12.8 years of the median follow-up with 66,796 person-years, 185 cases with CVD (115 stroke and 70 coronary heart disease [CHD]) were recorded. The multivariable HRs (95% CIs) were 1.49 (1.09–2.03), 2.13 (1.08–4.22), and 1.93 (1.16–3.19) for the 3% ODI ≥ 5 group versus the 3% ODI <5 group of developing CVD, lacunar infarction, and CHD, respectively.

Conclusions: Nocturnal intermittent hypoxia may increase the risk of developing lacunar infarction and CHD among community-dwelling Japanese populations. However, we could not find a significant risk of developing total stroke or stroke subtypes such as intraparenchymal hemorrhage, subarachnoid hemorrhage, and total ischemic stroke.

Key words: Asian, Cardiovascular disease, Coronary heart disease, Stroke, Nocturnal intermittent hypoxia

Introduction

Obstructive sleep apnea (OSA) is defined as having repeated episodes of a decrease or complete cessation of airflow while trying to breathe[1]. Studies conducted in Western countries have examined the

association between OSA and the risk of cardiovascular disease (CVD), contributing to that OSA has been recognized as a risk factor for CVD, which includes stroke and coronary heart disease (CHD)[2]. However, the result of this study was inconclusive. The Sleep Heart Health Study (SHHS) reported a nonsignificant association between OSA and stroke in men and women over 40 years old, except in men with apnea-hypopnea index (AHI) ≥ 19.13 [3]. The Vitoria Sleep Project documented that participants aged 70–100 years with an AHI ≥ 30, severe OSA, had a 2.5-fold higher risk of developing ischemic stroke than those with an AHI <30 according to a 6-year follow-up. However, this association was not statistically significant after adjusting for age, sex, and body mass index (BMI)[4]. Additionally, the Wisconsin Sleep Cohort Study recorded that participants aged 30–60 years old with an AHI ≥ 30 had a 2-fold higher risk of CHD incidence than those with an AHI=0 from longitudinal data[5]. The Wisconsin Sleep Cohort Study also reported that untreated female patients with 5< AHI ≤ 15 were four fold as likely to develop CHD (p=0.035 for interaction)[5]. Based on those studies, the significant risk of CVD was found among persons with moderate or severe OSA, but not for those with mild OSA[2].

Additionally, previous studies used AHI as an OSA indicator to estimate the risk of CVD. AHI assessed using laboratory-based polysomnography (PSG) has been considered as the gold standard metric of OSA severity[6]. However, owing to the complexity of using it, there is a need for simple alternative metrics for OSA screening[7]. In clinical practice, oxygen desaturation index (ODI), measured via pulse oximetry, is also commonly used to assess OSA, but the clinical significance and possible association of ODI with CVD remain unclear. An epidemiologic community-based cohort study in Cyprus found an association of 3% ODI with hypertension, but not with stroke or ischemic heart disease[8].

Aim

These studies did not find significant risks of stroke or CHD in persons with mild OSA[2]. Limited information is known about the association between ODI and CVD in the Asian population. Therefore, we examined the effect of nocturnal intermittent hypoxia, as a surrogate marker of OSA, on the risk of developing CVD in a Japanese community-based cohort study.

Methods

Study Population

The Circulatory Risk in Communities Study (CIRCS) is an ongoing community-based dynamic cohort study from five communities in Japan[9]. Participants aged 40–74 years old in the annual cardiovascular surveys during 2000 and 2008 were included in the present investigation. Overall, 516 men and 696 women from Ikawa (northeastern rural community in Akita Prefecture), 650 men and 921 women from Minami-Takayasu (mid-western suburban community in Osaka Prefecture), and 1,166 men and 1,804 women from Kyowa (mid-eastern rural community in Ibaraki Prefecture) were eligible for this study. Participants underwent a sleep test at their annual cardiovascular checkup[9]. Participants with a prior history of stroke or heart disease (n=98) and missing values for any of the covariates used in model 3 (described below) (n=342) were excluded from the analyses. Overall, this study was composed of 5,313 residents (2,006 men and 3,307 women). In a participant with two sleep tests, the first result was used for analysis in this study (n=1,051).

The study protocol was approved by the Institutional Review Boards of the Osaka Center for Cancer and Cardiovascular Disease Prevention and Juntendo University. We obtained informed consent for the use of existing data from community representatives. Because the analysis for this study was done as a secondary use of data obtained for public health practice on CVD prevention in local communities, individual consent was not required. However, participants were given the option to withdraw their data from analysis. For the purposes of this study, consent was considered granted if participants did not decline properly.

Follow-up and Ascertainment of Cases with CVD

We defined CVD as the incidence of stroke and CHD, as described below. In the present study, follow-up continued until the end of 2015 for Kyowa, 2018 for Minami-Takayasu, and 2019 for Ikawa. Follow-up was terminated at the first incidence of stroke, CHD, death, or emigration. Persons who emigrated and died during the follow-up were censored

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at the date of moving out or the date of death.

Details of cardiovascular surveillance have been described in a previous CIRCS report[9]. To ascertain diagnoses, all living patients were telephoned, visited, or invited to participate in risk factor surveys, and their medical history was obtained from their families. Trained physicians reviewed medical records from local clinics and hospitals. In the event of death, clinical history was obtained from family members or attending physicians and medical records.

Stroke was defined as rapidly developing focal neurological signs lasting at least 24 h or leading to death. Stroke subtypes were classified by computed tomography or magnetic resonance imaging as intraparenchymal hemorrhage, subarachnoid hemorrhage (SAH), ischemic stroke (lacunar infarction, large-artery occlusive infarction, embolic infarction, or thrombotic infarction of undetermined type), or stroke of undetermined type. Patients without radiologic evidence were classified based on clinical criteria.

Acute myocardial infarction, angina pectoris, and sudden cardiac death within an hour of onset were included as CHD. Briefly, acute myocardial infarction was confirmed in the medical records, which required the findings of electrocardiogram, or cardiac enzymes. If a diagnostic workup was not performed but typical chest pain of 20 min or more was reported, patients were included in cases with acute myocardial infarction. Angina pectoris was defined as repeated episodes of chest pain triggered by exertion, especially when walking, that subsided rapidly with rest or the use of sublingual nitroglycerin. Sudden cardiac death was defined as death from a witnessed cardiac arrest or sudden collapse occurring within 1 h of symptom onset without any overt underlying cause.

The final diagnosis of CHD and stroke was made by a panel of three to four physicians blinded to the data from the risk factor survey.

Baseline Examination

During a one-night sleep at a participant's home, the severity of nocturnal intermittent hypoxia was measured with a pulse oximeter (PULSOX-3Si; Minolta, Osaka, Japan)[10]. A desaturation event started with a 3% or more decrease of saturation during 8 and 120 s and terminated when the saturation increased within 20 s by the appropriate level. Because the measurement time of pulse oximetry was often longer than the actual total sleep time, we used a sleep log to exclude waking time from the analysis and minimize the potential for overestimation. In addition, cases for which it was determined from the waveforms that the equipment had been disconnected while the patient was sleeping or the measurement was otherwise deficient were excluded from the data[11]. The number of events with oxygen desaturation levels of 3% or higher per hour of the adjusted measurement time (3% ODI) was used as a nocturnal intermittent hypoxia indicator. Because this study had a small number of participants with 3% ODI ≥ 15, we classified the participants into two groups using a clinical cut-point of 5: 3% ODI <5 and 3% ODI ≥ 5 [12]. We performed further analyses using log-transformed 3% ODI (3% ODI + 1) and 3% ODI divided into three categories based on clinical cut-points of 5 and 15 (<5, 5–<15, ≥ 15)[12].

Other Covariates

Details of the risk factor survey have been described previously[9]. Briefly, participants' height in stocking feet and weight with light clothing were measured. BMI was calculated as weight (kg) divided by height squared (m^2). Participants were asked the number of cigarettes smoked per day and the usual daily intake of alcohol, measured in units of *go* (a traditional Japanese unit of volume corresponding to 23 g of ethanol). Blood pressure was measured by physicians or nurses using a standard mercury sphygmomanometer on the right arm of a subject while quietly seated and after at least 5 min of rest.

At the annual cardiovascular checkup, venous blood was obtained from seated participants into a plain, silicon-coated glass tube, and serum was separated for 30 min. Serum samples were stored at −80℃ until analysis. Serum glucose and serum total cholesterol were measured by an automatic analyzer (AU2700; Olympus, Tokyo, Japan). Total cholesterol was analyzed by the enzymatic method and glucose by the hexokinase method. An overnight fast was recommended before sample procurement but was not mandated. Time since the last meal was recorded, with fasting defined as more than 8 h since the last meal. Because both high and low total cholesterol values have been reported to increase the risk of CVD[9], we used cholesterol as a covariate and divided it into four categories: <200, 200–<220, 220–<240, and ≥ 240 mg/dL. Diabetes mellitus was defined as a fasting glucose of 7.0 mmol/L or more, a nonfasting glucose of 11.1 mmol/L or more, the use of medication, or a glycated hemoglobin (HbA1c; Japan Diabetes Society) of 6.5% or more.

Statistical Analyses

All statistical analyses were performed with the SAS software for Windows (version 9.4; SAS Inc., Cary, NC, USA). The mean values and prevalence of baseline characteristics with respect to 3% ODI were

Table 1. Demographics of this study

	3%ODI < 5	3%ODI ≥ 5	*p* value[a]
No. at risk	3846	1467	
3%ODI, mean (SD)	1.9 (1.3)	11.3 (8.6)	
3%ODI, median [IQR1-3]	1.6 [0.8, 2.8]	8.3 [6.4, 12.8]	
Male, %	30.5	56.7	<0.0001
Age, mean (SD)	57.3 (8.9)	60.5 (7.9)	<0.0001
Body mass index (kg/m^2), mean (SD)	23.0 (3.0)	25.4 (3.4)	<0.0001
Alcohol consumption			<0.0001
Never or past drunk, %	66.1	51.4	
Ethanol intake <23g/day, %	32.5	46.0	
Ethanol intake ≥ 23g/day, %	1.5	2.6	
Smoker			<0.0001
Never, %	68.5	49.8	
Past smoker, %	13.9	27.3	
Current smoker, %	17.6	23.0	
Systolic blood pressure (mmHg), mean (SD)	129.1 (18.4)	135.2 (17.3)	<0.0001
Diastolic blood pressure (mmHg), mean (SD)[b]	78.1 (10.5)	81.7 (10.9)	<0.0001
Use of antihypertensive medication, %	16.3	28.6	<.0001
Serum glucose, mean (SD)[b]	100.1 (19.4)	103.2 (20.2)	<0.0001
HbA1c, mean (SD)[b]	5.1 (0.6)	5.2 (0.8)	<0.0001
Use of anti-diabetec medication, %	0.6	1.0	0.183
Total cholesterol (mg/dL), mean (SD)	213.3 (35.9)	213.3 (35.3)	1.00
Use of dyslipidemia medication, %	0.6	1.0	0.18

a: *p*-values are based on Student's *t*-test and χ^2 test, as appropriate.
b: Mean (SD) was calculated by excluding missing values.

compared with Student's *t*-test and χ^2 test, respectively. Person-years were calculated as a duration from baseline survey to the occurrence of CHD, stroke, death, or emigration or the end of follow-up. We used the Cox proportional hazards regression models to calculate the age- and sex-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CVD according to 3% ODI for model 1. Multivariable-adjusted analyses were further adjusted for BMI (quartiles), smoking status (never smoked, past smoker, or current smoker), and alcohol consumption (never consumed, past consumption, ethanol intake less than 23 g/day, or intake of 23 g/day or more) in model 2 and further adjusted for systolic blood pressure, diabetes mellitus (yes and no), total cholesterol levels (<200, 200–<220, 220–<240, and ≥ 240 mg/dL), and use of antihypertensive and dyslipidemia medication (yes and no) in model 3. The interaction of 3% ODI with sex was tested using a cross-product term for these variables in the models.

We calculated the population attributable fraction (PAF) to estimate the contribution of nocturnal intermittent hypoxia to the risk of each CVD event with a standard formula: PAF = prop × (HR − 1)/HR, where prop is the proportion of cases in the group with 3% ODI ≥ 5, and HR is the multivariable HR (model 2) that was statistically significant in the analysis using two categories of 3% ODI. The PAF 95% CIs were calculated using the Bonferroni inequality[13].

We performed a sensitivity analysis by using only data for which the ODI had been measured for more than 4 h[11].

All *p* values for statistical tests were two-tailed, and *p* values less than 0.05 were considered as statistically significant.

Results

Table 1 shows the baseline characteristics according to 3% ODI. One-fourth (38.1%) of the participants had 3% ODI ≥ 5. The mean 3% ODI in participants with 3% ODI <5 and 3% ODI ≥ 5 was 1.9 and 11.3, respectively. Participants with 3% ODI ≥ 5 tended to have a higher age; higher BMI; higher systolic blood pressure, diastolic blood pressure, serum glucose, and serum HbA1c; and were more likely to be male, to be current smokers, to consume alcohol, and to use antihypertensive medication.

The median follow-up was 12.8 years, with a

Table 2. Hazard ratio of stroke, CHD, and CVD according to 3%ODI at baseline

	3%ODI	Person-year	No of events	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	PAF, % (95%CI)
Stroke	< 5	48124	64	1.00	1.00	1.00	
	≥ 5	18293	51	1.37 (0.94 to 2.00)	1.28 (0.86 to 1.90)	1.23 (0.83 to 1.84)	
	Log-transformed	66417	115	1.02 (0.81 to 1.29)	0.92 (0.71 to 1.19)	0.90 (0.69 to 1.16)	
Intraparenchymal hemorrhagic stroke	< 5	47777	16	1.00	1.00	1.00	
	≥ 5	17981	8	0.89 (0.38 to 2.12)	0.86 (0.34 to 2.15)	0.82 (0.33 to 2.08)	
	Log-transformed	65758	24	1.16 (0.70 to 1.92)	1.09 (0.62 to 1.92)	1.06 (0.60 to 1.88)	
SAH	< 5	47691	8	1.00	1.00	1.00	
	≥ 5	17958	4	1.30 (0.38 to 4.46)	1.25 (0.34 to 4.60)	1.21 (0.33 to 4.49)	
	Log-transformed	65648	12	1.03 (0.48 to 2.23)	0.99 (0.43 to 2.28)	0.93 (0.41 to 2.13)	
Ischemic stroke	< 5	47973	39	1.00	1.00	1.00	
	≥ 5	18204	39	1.60 (1.02 to 2.51)	1.50 (0.93 to 2.42)	1.45 (0.90 to 2.35)	
	Log-transformed	66177	78	0.99 (0.74 to 1.31)	0.89 (0.65 to 1.21)	0.85 (0.62 to 1.17)	
Lacunar infarction	< 5	47792	17	1.00	1.00	1.00	
	≥ 5	18061	22	1.99 (1.05 to 3.79)	2.13 (1.08 to 4.22)	2.07 (1.04 to 4.11)	30.0 (-1.0 to 58.3)
	Log-transformed	65853	39	1.23 (0.84 to 1.80)	1.25 (0.81 to 1.92)	1.21 (0.78 to 1.87)	
Large-artery occlusive infarction	< 5	47735	7	1.00	1.00	1.00	
	≥ 5	17946	2	0.47 (0.10 to 2.32)	0.33 (0.06 to 1.75)	0.31 (0.06 to 1.48)	
	Log-transformed	65681	9	0.52 (0.20 to 1.35)	0.37 (0.13 to 1.04)	0.32 (0.12 to 0.83)	
Embolic infarction	< 5	47735	10	1.00	1.00	1.00	
	≥ 5	18016	10	1.57 (0.64 to 3.82)	1.40 (0.56 to 3.53)	1.44 (0.56 to 3.67)	
	Log-transformed	65751	20	0.76 (0.43 to 1.36)	0.65 (0.35 to 1.22)	0.63 (0.33 to 1.20)	
CHD	< 5	47851	32	1.00	1.00	1.00	
	≥ 5	18115	38	2.02 (1.25 to 3.27)	1.93 (1.16 to 3.19)	1.86 (1.12 to 3.08)	26.1 (3.0 to 47.9)
	Log-transformed	65966	70	1.48 (1.11 to 1.96)	1.46 (1.07 to 1.99)	1.42 (1.03 to 1.94)	
CVD	< 5	48313	96	1.00	1.00	1.00	
	≥ 5	18483	89	1.58 (1.17 to 2.12)	1.49 (1.09 to 2.03)	1.45 (1.06 to 1.99)	15.8 (1.6 to 29.8)
	Log-transformed	66796	185	1.17 (0.98 to 1.41)	1.11 (0.91 to 1.35)	1.08 (0.88 to 1.32)	

CVD indicates cardiovascular disease; CHD, coronary heart disease; SAH, subarachnoid hemorrhage; ODI, oxygen desaturation index; HR, hazard ratio; CI, confidence interval; and PAF, population attributable fraction.
Model 1 was adjusted for age, sex; Model 2 was adjusted for factors in Model 1 plus BMI, smoking status, alcohol consumption; Model 3 was adjusted for factors in Model 2 plus systolic blood pressure, antihypertensive medication use, diabetes mellitus, total cholesterol levels, and dyslipidemia medication use.
PAF and *p* for interaction were calculated with model 2.

total of 66,796 person-years. This study documented 115 cases with stroke (24 intraparenchymal hemorrhagic strokes; 12 SAHs; 78 ischemic strokes, which included 39 lacunar infarctions, 9 large-artery occlusive infarctions, 20 embolic infarctions, and 10 thrombotic infarctions of undetermined type; and 1 stroke of undetermined type) and 70 cases with CHD.

Table 2 shows the age- and sex-adjusted multivariable HRs and PAFs of CVD according to 3% ODI. Participants with 3% ODI ≥ 5 had a higher risk of CVD, CHD, and lacunar infarction, but not other stroke subtypes. The multivariable HRs from model 2 were 1.49 (95% CI: 1.09–2.03) for CVD, 2.13 (1.08–4.22) for lacunar infarction, and 1.93 (1.16–3.19) for CHD. The PAFs of the 3% ODI ≥ 5 group for CVD, CHD, and lacunar infarction were 15.8% (1.6–29.8), 26.1% (3.0–47.9), and 30.0% (–1.0–58.3), respectively. In addition, we adjusted model 3 for hypertension, diabetes, and total serum cholesterol levels, but they did not affect the associations; the HRs were 1.45 (1.06–1.99) for CVD, 2.07 (1.04–4.11) for lacunar infarction, and 1.86 (1.12–3.08) for CHD. We also found a linear association between log-transformed 3% ODI and CHD (model 2 HR=1.46, 95% CI=1.07–1.99; model 3 HR=1.42, 95% CI=1.03–1.94), but not for CVD, stroke, or stroke subtypes. The HRs from model 2 for men and women separately, according to the analyses using two categories of 3% ODI or log-transformed 3% ODI, are shown in **Supplemental Table 1**. The HR for CHD according to log-transformed 3% ODI for women was higher than that for men;

they were 2.03 (1.13–3.67) and 1.32 (0.92–1.91), respectively. However, the interaction of sex with the association between log-transformed 3% ODI and CHD was only borderline significant (p=0.05).

The HRs in the other analysis, using three categories of 3% ODI based on the clinical cut-points of 5 and 15, are shown in **Supplemental Table 2**. The HR for ischemic stroke, lacunar infarction, CHD, and CVD in participants with 5 ≤ 3% ODI <15 was significantly higher than that in those with 3% ODI <5, but not in those with 3% ODI ≥ 15.

Our sensitivity analysis, in which we used only data where the ODI had been measured for more than 4 h (n=4,624), provided similar results to the above analysis **(Supplemental Table 3)**.

Discussion

In this large prospective cohort of community-dwelling middle-aged and older Japanese men and women, we found that nocturnal intermittent hypoxia was positively associated with an increased risk of developing CHD and lacunar infarction, independent of other risk factors such as age, sex, BMI, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, diabetes, total cholesterol, and use of dyslipidemia medication. Additionally, the PAFs of 3% ODI ≥ 5 were 15.8% for CVD, 30.0% for lacunar infarction, and 26.1% for CHD. The CIRCS reported that the PAFs due to hypertension were 46% for stroke and 29% for CHD. In addition, the PAFs due to hyperglycemia were 7.0% and 7.0%, respectively[14]. Our findings suggest that treatment for OSA may prevent lacunar infarction or CHD, similar to treatments for hypertension or diabetes. Furthermore, ODI may be a useful metric for assessing the risk of CVD in general practice.

The association between mild OSA and stroke has not been conclusive, and there is limited evidence to support it. The SHHS, with 5,422 participants from the general population aged 40 or older with an 8.7-year follow-up period, reported an increased risk of ischemic stroke in men with severe OSA (AHI ≥ 19.13) compared to those with AHI <4.05, and there was no increased risk of ischemic stroke in men with mild and moderate OSA (AHI 4.05–<9.50 and 9.50–<19.13, respectively)[3]. In our study, nocturnal intermittent hypoxia was associated with an increased risk of developing ischemic stroke, especially lacunar infarction. In general, there is a higher incidence of intracranial arteriolosclerosis in the Asian population than in other ethnicities, leading to a higher prevalence of lacunar infarction[15]. Therefore, our study adds to the literature on the association of nocturnal intermittent hypoxia with lacunar infarction.

Previous studies have not analyzed the association of OSA and stroke subtypes, and in this study, the HRs for other stroke subtypes were not significant. We could not show a linear increasing risk for the development of each stroke subtype with increasing 3% ODI. However, 78 (68%) cases with stroke in this study were ischemic strokes, half of which had lacunar infarction, and among these, the number of patients with 3% ODI ≥ 15 was only 6. The number of cases for other stroke subtypes, certainly among subjects with more severe 3% ODI, is likely too small to estimate individual HRs with sufficient statistical power. For intraparenchymal hemorrhagic stroke and SAH, hypertension is a known major risk factor[16]. Even if OSA increases blood pressure, the risk of these hemorrhagic strokes in Japan may have decreased because of the decreasing trends in mean systolic blood pressure in this country[17]. Large-artery occlusive infarction and lacunar infarction occur as a result of atherosclerosis of the intracranial artery. Atherosclerosis at the branching site of the intracranial cerebral arteries, especially the basilar artery, is likely to cause a perforating branch occlusion, which was sometimes classified as lacunar infarction in the present study and may thus have contributed to underestimating the HR of large-artery occlusive infarction. The HR for embolic infarction in subjects with 5 ≤ 3% ODI <15 or 3% ODI ≥ 15 was not significant in this study. However, considering that OSA is clearly linked to atrial fibrillation[18], there may be an association between 3% ODI and the risk of embolic infarction incidents.

Regarding CHD, the combined data from the Atherosclerosis Risk in Communities Study and the SHHS also showed increased levels of high-sensitivity troponin T in each participant with mild, moderate, and severe OSA compared to those without OSA, whose relationships were dose-responsive[19]. Similar to those US community-based studies, our results likely confirm the higher CHD risk among patients with OSA among Asian populations. The HR for CHD in the Wisconsin Sleep Cohort study showed gender difference; the HR for CHD in women with 5< AHI ≤ 15 was higher than that in men with the same AHI[5]. In the current study, we found that the graded risk of CHD development increased significantly with 3% ODI severity in the analysis using log-transformed 3% ODI **(Table 2)**. We also found a potential difference between the sexes in the association between the risk of CHD incidence and log-transformed 3% ODI (p=0.05); the HR for CHD was higher in women than in men **(Supplemental Table 1)**. Kulkas *et al.* revealed the existence of sex-related differences in

the severity of desaturation events following hypopnea and obstructive apnea; these events were more severe in females than in males with the same AHI[20]. This difference may have contributed to the sex differences in the effects of OSA (whether diagnosed as apnea or hypopnea) on the risk of CHD development in both the present study and the Wisconsin Sleep Cohort Study.

AHI as measured by the gold standard of PSG is also often criticized for its limitations, particularly its complexity of usage; alternative metrics are thus needed to provide diagnostic and prognostic information to make the diagnosis of OSA more accessible[7]. Although AHI is the defined as the number of apnea and hypopnea events, the severity of OSA with an equal AHI could be different as the longer the obstructive apnea event[20]. The SHHS has shown that a hypoxic burden increases CVD mortality risk[21]. An epidemiologic community-based cohort study in Cyprus found an association between 3% ODI >15 and hypertension (p=0.002) in 282 participants without known OSA (n=282). However, there was no significant association between 3% ODI and stroke or ischemic heart disease, probably because of low statistical power[8]. Our results suggested ODI as measured by pulse oximetry to be a possible metric for predicting the incidence of CVD, which is more practical than AHI in clinical contexts.

We suggest the following underlying mechanisms involved in the association between nocturnal intermittent hypoxia and CVD. First, nocturnal intermittent hypoxia activates the sympathetic nervous system, causing an increase in blood pressure and inflammation and leading to the development of hypertension and type 2 diabetes[22]. These changes exacerbate endothelial inflammation and contribute to the development of arteriolosclerosis. In the present study, since the adjustment for hypertension and diabetes did not change the associations, the underlying pathway other than hypertension and diabetes may also be important. Inflammation due to OSA may lead to the development of intracranial arteriolosclerosis[23, 24]. Additionally, OSA causes hemodynamic and arteriosclerotic changes in the coronary arteries. The negative pressure in the thoracic cavity due to obstruction of the upper airway increases the pressure gradient of the atriums, ventricles, and aorta, which may lead to hemodynamic and heart structural changes[25]. The negative pressure in the thoracic cavity increases venous return and contributes to right ventricular volume overload[26]. Hypertension due to activation of the sympathetic nervous system can cause left ventricular pressure overload, contributing to left ventricular dysfunction and hypertrophy[27]. These hemodynamic changes cause an increase in the demand for myocardial oxygen and a decrease in the supply due to hypoxia and cardiac dysfunction[28], which in turn may increase the risk of presenting CHD. Furthermore, both the hemodynamic change[18] and inflammation[29] that result from OSA are clearly related to incidents of atrial fibrillation, contributing to increasing the risk of embolic infarction.

Strengths

One of the main strengths of our study is the prospective cohort design and large-scale, long-term follow-up. Moreover, we could examine mild or more severe nocturnal intermittent hypoxia (3% ODI ≥ 5) in the Asian population. To the best of our knowledge, this is the first study to examine the associations between nocturnal intermittent hypoxia and stroke subtypes with longitudinal observation.

Limitations

Our study has several limitations. First, we only measured oxygen desaturation during sleep using pulse oximetry as a way to estimate nocturnal intermittent hypoxia. Pulse oximetry is not comparable to the gold standard of PSG because the information about sleep stage or body position was not available, and the degree of OSA may be underestimated because of low sensitivity to identify AHI ≥ 5 among individuals with low BMI (BMI ≤ 27)[30]. However, pulse oximetry conducted during sleep at home has the advantage of reflecting the individuals' usual sleep positions. Sleep time in a supine position is 1.5 fold longer during PSG[31]. Considering that the sleep environment for the study was comparatively similar to the individuals' usual situation, the results appear to reflect their actual state. Second, the low distribution of 3% ODI in this study, explained by a lower BMI compared to other populations (e.g., Hispanic or White populations)[32], made it necessary to categorize nocturnal intermittent hypoxia into two groups (3% ODI <5 and 3% ODI ≥ 5). Therefore, we are unable to provide information about the effects of OSA severity on the risk of developing CVD except for CHD. Third, we did not explore whether participants suspected to have OSA had been treated before and after enrollment. However, even if all participants had been treated with continuous positive airway pressure (CPAP), our results would not be hindered. In the real practice, the insurance system in Japan requires patients to meet an AHI ≥ 20 to qualify for CPAP use. Additionally, CPAP and OSA were not common for Japanese

clinicians in the period of baseline sleep tests, and CPAP does not have harmful effects on the cardiovascular system. Fourth, participants were not specially interviewed about pre-existing lung disease, underlying chronic obstructive pulmonary diseases, or asthma. Because the electroencephalogram and thoracic movement were not measured during the sleep test, we cannot distinguish nocturnal intermittent hypoxia due to OSA from that due to central sleep apnea and hypoventilation that is more likely to be caused by lung disease[6]. The results may have been affected. However, the effect of contamination appears to be small since only 0.1% of persons aged 40–69 years reported the presence of lung disease in the 2005 Japan National Patient Survey[33]. Finally, it is possible that the participants of this study were more health conscious and took better care of themselves to prevent CVDs than the general public, because many of them underwent annual cardiovascular health checks after their baseline examination. Therefore, we speculate that the actual prevalence of people with each of the risk factors explored here, or a high risk for CHD incidence, is likely higher than our data indicate.

Conclusion

Nocturnal intermittent hypoxia was associated with the development of lacunar infarction and CHD in community-dwelling Japanese adults. The associations remained after adjustment for hypertension, diabetes mellitus, and serum total cholesterol levels, suggesting other biological pathways than arteriolosclerosis to CVD development caused by nocturnal intermittent hypoxia. Patients with nocturnal intermittent hypoxia, even if mild, should be identified as a high CVD risk population by general practitioners and on treatment to prevent CVD.

Author Contributions

Keisuke Onuki, Ai Ikeda, and Takeshi Tanigawa contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. Keisuke Onuki and Ai Ikeda drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agreement to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflict of Interest

None.

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Supplemental Table 1. Hazard ratio of stroke, CHD, and CVD according to 3%ODI at baseline among male and female

		Men			Women			
	3%ODI	Person-year	No of events	Model 2 HR (95%CI)	Person-year	No of events	Model 2 HR (95%CI)	*p* for interaction
Stroke	<5	14541	31	1.00	33584	33	1.00	
	≥ 5	10229	40	1.59 (0.96 to 2.62)	8064	11	0.85 (0.42 to 1.73)	0.16
	Log-transformed	24769	71	1.03 (0.75 to 1.42)	41648	44	0.74 (0.46 to 1.17)	0.23
Intraparenchymal hemorrhagic stroke	<5	14341	8	1.00	33436	8	1.00	
	≥ 5	9966	6	0.73 (0.23 to 2.27)	8014	2	0.89 (0.18 to 4.44)	0.62
	Log-transformed	24307	14	0.72 (0.34 to 1.51)	41451	10	1.77 (0.74 to 4.25)	0.62
SAH	<5	14284	1	1.00	33407	7	1.00	
	≥ 5	9948	2	4.22 (0.38 to 46.77)	8009	2	0.76 (0.14 to 3.98)	0.46
	Log-transformed	24232	3	2.66 (0.63 to 11.26)	41416	9	0.65 (0.23 to 1.83)	0.34
Ischemic stroke	<5	14476	22	1.00	33498	17	1.00	
	≥ 5	10180	32	1.86 (1.05 to 3.32)	8024	7	0.94 (0.38 to 2.32)	0.33
	Log-transformed	24655	54	1.07 (0.75 to 1.54)	41522	24	0.54 (0.28 to 1.02)	0.15
Lacunar infarction	<5	14394	12	1.00	33397	5	1.00	
	≥ 5	10051	18	2.27 (1.04 to 4.98)	8010	4	1.88 (0.48 to 7.38)	0.93
	Log-transformed	24445	30	1.28 (0.79 to 2.09)	41407	9	1.30 (0.51 to 3.35)	0.65
Large-artery occlusive infarction	<5	14313	3	1.00	33421	4	1.00	
	≥ 5	9954	2	0.72 (0.10 to 5.02)	7992	0	-	0.20
	Log-transformed	24268	5	0.72 (0.22 to 2.39)	41413	4	0.13 (0.02 to 0.94)	0.17
Embolic infarction	<5	14311	5	1.00	33424	5	1.00	
	≥ 5	10018	9	1.99 (0.64 to 6.25)	7998	1	0.50 (0.06 to 4.42)	0.14
	Log-transformed	24329	14	0.97 (0.49 to 1.95)	41422	6	0.11 (0.02 to 0.57)	0.01
CHD	<5	14419	23	1.00	33432	9	1.00	
	≥ 5	10062	27	1.63 (0.90 to 2.94)	8053	11	3.02 (1.19 to 7.69)	0.10
	Log-transformed	24481	50	1.32 (0.92 to 1.91)	41485	20	2.03 (1.13 to 3.67)	0.05
CVD	<5	14680	54	1.00	33634	42	1.00	
	≥ 5	10357	67	1.60 (1.09 to 2.34)	8125	22	1.31 (0.76 to 2.26)	0.85
	Log-transformed	25037	121	1.14 (0.90 to 1.45)	41759	64	1.06 (0.74 to 1.51)	0.91

CVD indicates cardiovascular disease; CHD, coronary heart disease; SAH, subarachnoid hemorrhage; ODI, oxygen desaturation index; HR, hazard ratio; and CI, confidence interval.
Model 1 was adjusted for age, sex; Model 2 was adjusted for factors in Model 1 plus BMI, smoking status, alcohol consumption; Model 3 was adjusted for factors in Model 2 plus systolic blood pressure, anti-hypertensive medication use, diabetes mellitus, total cholesterol levels, and dyslipidemia medication use.
p for interaction was calculated with model 2.

Supplemental Table 2. Hazard ratio of stroke, CHD, and CVD according to 3%ODI accorded by clinical cut points of 5 and 15 at baseline

	3%ODI	Person-year	No of events	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	PAF, % (95%CI)
Stroke	<5	48124	64	1.00	1.00	1.00	
	≥ 5, <15	14802	42	1.46 (0.98 to 2.16)	1.37 (0.91 to 2.06)	1.33 (0.88 to 2.01)	
	≥ 15	3491	9	1.06 (0.52 to 2.15)	0.91 (0.43 to 1.90)	0.87 (0.41 to 1.82)	
Intraparenchymal hemorrhagic stroke	<5	47777	16	1.00	1.00	1.00	
	≥ 5, <15	14550	6	0.87 (0.34 to 2.24)	0.89 (0.33 to 2.38)	0.85 (0.32 to 2.30)	
	≥ 15	3430	2	0.99 (0.22 to 4.39)	0.77 (0.16 to 3.66)	0.73 (0.15 to 3.51)	
SAH	<5	47691	8	1.00	1.00	1.00	
	≥ 5, <15	14535	3	1.20 (0.31 to 4.60)	1.17 (0.29 to 4.73)	1.17 (0.29 to 4.76)	
	≥ 15	3423	1	1.80 (0.21 to 15.21)	1.70 (0.18 to 16.12)	1.39 (0.15 to 13.26)	
Ischemic stroke	<5	47973	39	1.00	1.00	1.00	
	≥ 5, <15	14732	33	1.76 (1.10 to 2.82)	1.66 (1.02 to 2.69)	1.60 (0.98 to 2.61)	16.8 (-1.6 to 35.8)
	≥ 15	3471	6	1.04 (0.44 to 2.48)	0.91 (0.37 to 2.25)	0.88 (0.35 to 2.18)	
Lacunar infarction	<5	47792	17	1.00	1.00	1.00	
	≥ 5, <15	14602	17	2.04 (1.04 to 4.02)	2.18 (1.08 to 4.41)	2.12 (1.04 to 4.31)	23.6 (-0.7 to 48.8)
	≥ 15	3459	5	1.85 (0.67 to 5.07)	1.93 (0.65 to 5.74)	1.84 (0.62 to 5.53)	
Large-artery occlusive infarction	<5	47735	7	1.00	1.00	1.00	
	≥ 5, <15	14529	2	0.61 (0.12 to 2.97)	0.45 (0.09 to 2.30)	0.43 (0.09 to 2.06)	
	≥ 15	3417	0	-	-	-	
Embolic infarction	<5	47735	10	1.00	1.00	1.00	
	≥ 5, <15	14587	9	1.85 (0.74 to 4.59)	1.62 (0.64 to 4.11)	1.63 (0.63 to 4.20)	
	≥ 15	3429	1	0.65 (0.08 to 5.15)	0.58 (0.07 to 4.81)	0.63 (0.08 to 5.24)	
CHD	<5	47851	32	1.00	1.00	1.00	
	≥ 5, <15	14642	28	1.94 (1.16 to 3.25)	1.86 (1.09 to 3.16)	1.81 (1.06 to 3.09)	18.4 (0.3 to 37.5)
	≥ 15	3472	10	2.29 (1.11 to 4.73)	2.23 (1.03 to 4.80)	2.04 (0.94 to 4.44)	7.9 (-0.4 to 19.2)
CVD	<5	48313	96	1.00	1.00	1.00	
	≥ 5, <15	14937	70	1.61 (1.18 to 2.20)	1.53 (1.11 to 2.11)	1.51 (1.09 to 2.09)	13.1 (1.6 to 25.1)
	≥ 15	3546	19	1.46 (0.89 to 2.42)	1.32 (0.78 to 2.24)	1.25 (0.74 to 2.12)	

CVD indicates cardiovascular disease; CHD, coronary heart disease; SAH, subarachnoid hemorrhage; ODI, oxygen desaturation index; HR, hazard ratio; CI, confidence interval; and PAF, population attributable fraction.
Model 1 was adjusted for age, sex; Model 2 was adjusted for factors in Model 1 plus BMI, smoking status, alcohol consumption; Model 3 was adjusted for factors in Model 2 plus systolic blood pressure, anti-hypertensive medication use, diabetes mellitus, total cholesterol levels, and dyslipidemia medication use.
PAF was calculated with model 2.

Supplemental Table 3. Hazard ratio of stroke, CHD, and CVD according to 3%ODI at baseline among participants with 4 or more 3%ODI measurement hours

	3%ODI	Person-year	No of events	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	PAF, % (95%CI)
Stroke	<5	43113	62	1.00	1.00	1.00	
	≥ 5	15844	47	1.33 (0.90 to 1.96)	1.25 (0.83 to 1.88)	1.21 (0.80 to 1.83)	
	Log-transformed	58957	109	1.03 (0.81 to 1.30)	0.94 (0.72 to 1.22)	0.92 (0.70 to 1.20)	
Intraparenchymal hemorrhagic stroke	<5	42782	16	1.00	1.00	1.00	
	≥ 5	15556	8	0.92 (0.39 to 2.17)	0.89 (0.35 to 2.22)	0.85 (0.34 to 2.14)	
	Log-transformed	58337	24	1.17 (0.71 to 1.94)	1.11 (0.63 to 1.99)	1.09 (0.61 to 1.94)	
SAH	<5	42689	7	1.00	1.00	1.00	
	≥ 5	15532	4	1.52 (0.43 to 5.39)	1.40 (0.37 to 5.31)	1.34 (0.35 to 5.10)	
	Log-transformed	58222	11	1.09 (0.49 to 2.42)	0.99 (0.42 to 2.38)	0.95 (0.40 to 2.25)	
Ischemic stroke	<5	42968	38	1.00	1.00	1.00	
	≥ 5	15755	35	1.51 (0.94 to 2.4)	1.44 (0.88 to 2.37)	1.40 (0.85 to 2.31)	
	Log-transformed	58723	73	0.98 (0.74 to 1.32)	0.90 (0.65 to 1.25)	0.87 (0.63 to 1.21)	
Lacunar infarction	<5	42797	17	1.00	1.00	1.00	
	≥ 5	15619	19	1.73 (0.89 to 3.36)	1.92 (0.95 to 3.90)	1.87 (0.92 to 3.81)	25.1 (-5.9 to 54.7)
	Log-transformed	58415	36	1.19 (0.80 to 1.77)	1.26 (0.80 to 1.97)	1.23 (0.78 to 1.93)	
Large-artery occlusive infarction	<5	42740	7	1.00	1.00	1.00	
	≥ 5	15521	2	0.48 (0.10 to 2.38)	0.34 (0.06 to 1.80)	0.32 (0.07 to 1.54)	
	Log-transformed	58260	9	0.53 (0.21 to 1.36)	0.37 (0.13 to 1.05)	0.32 (0.12 to 0.85)	
Embolic infarction	<5	42730	9	1.00	1.00	1.00	
	≥ 5	15585	9	1.66 (0.65 to 4.25)	1.45 (0.55 to 3.85)	1.54 (0.57 to 4.13)	
	Log-transformed	58314	18	0.83 (0.45 to 1.51)	0.68 (0.35 to 1.32)	0.68 (0.34 to 1.35)	
CHD	<5	42816	27	1.00	1.00	1.00	
	≥ 5	15663	34	2.13 (1.27 to 3.57)	2.14 (1.24 to 3.69)	2.03 (1.18 to 3.51)	29.6 (5.2 to 52.4)
	Log-transformed	58478	61	1.47 (1.09 to 1.99)	1.49 (1.06 to 2.08)	1.45 (1.03 to 2.04)	
CVD	<5	43262	89	1.00	1.00	1.00	
	≥ 5	16007	81	1.57 (1.15 to 2.13)	1.51 (1.09 to 2.10)	1.48 (1.07 to 2.05)	16.1 (1.5 to 30.6)
	Log-transformed	59269	170	1.17 (0.97 to 1.41)	1.12 (0.91 to 1.37)	1.09 (0.89 to 1.35)	

CVD indicates cardiovascular disease; CHD, coronary heart disease; SAH, subarachnoid hemorrhage; ODI, oxygen desaturation index; HR, hazard ratio; CI, confidence interval; and PAF, population attributable fraction.
Model 1 was adjusted for age, sex; Model 2 was adjusted for factors in Model 1 plus BMI, smoking status, alcohol consumption; Model 3 was adjusted for factors in Model 2 plus systolic blood pressure, anti-hypertensive medication use, diabetes mellitus, total cholesterol levels, and dyslipidemia medication use.
PAF was calculated with model 2.