Obstructive sleep apnea as a risk factor for silent cerebral infarction

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Keywords
basal ganglia, lacunar infarction, obstructive sleep apnea, risk factors, silent cerebral infarction, stroke

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Accepted in revised form 22 December 2012; received 8 August 2012

DOI: 10.1111/jsr.12034

SUMMARY

Previous studies have suggested that obstructive sleep apnea (OSA) may be a risk factor for stroke. In this study, we assessed that OSA is an independent risk factor of silent cerebral infarction (SCI) in the general population, and in a non-obese population. This study recruited a total of 746 participants (252 men and 494 women) aged 50–79 years as part of the Korean Genome and Epidemiology Study (KoGES); they underwent polysomnography, brain magnetic resonance imaging and health screening examinations. SCI was assessed by subtypes and brain regions, and lacunar infarction represented lesions <15 mm in size in the penetrating arteries. Moderate–severe OSA was determined by apnea–hypopnea index $\geq$15. The results indicated that 12.06% had moderate–severe OSA, 7.64% of participants had SCI and 4.96% had lacunar infarction. Moderate–severe OSA was associated positively with SCI [odds ratio (OR): 2.44, 95% confidence interval (CI): 1.03–5.80] and lacunar infarction (OR: 3.48, 95% CI: 1.31–9.23) in the age $\geq$65-year group compared with those with non-OSA. Additionally, in the basal ganglia, OSA was associated with an increase in the odds for SCI and lacunar infarction in all age groups, and especially in the $\geq$65-year age group. In the non-obese participants, OSA was also associated positively with SCI in the $\geq$65-year age group, lacunar infarction in all age groups, and especially in the $\geq$65-year age group. There was also a positive association with the basal ganglia. Moderate–severe OSA was associated positively with SCI and lacunar infarction in elderly participants. Treatment of OSA may reduce new first-time cerebrovascular events and recurrences.

INTRODUCTION

Stroke is an important cause of mortality and a major cause of disability among adults, leading to considerable economic and social problems (Lloyd-Jones *et al.*, 2009). Worldwide, stroke accounts for 5.7 million deaths and 16 million first-time events each year, and these numbers may reach 7.8 and 23 million by 2030, respectively (WHO, 2008). According to the Korean National Health and Nutrition Examination Survey (KNHANES) in 2010, the prevalence of stroke was 2.9% in patients $\geq$50 years of age and 4.5% in patients $\geq$65 years of age (KCDCP, 2010). Although the incidence of stroke has been decreasing in recent years, stroke is still the leading cause of death and disability in Korea; thus, recognizing and treating modifiable risk factors for stroke are of particular importance.

Obstructive sleep apnea (OSA) is characterized by intermittent episodes of hypoxia, which often results in systemic inflammation, blood pressure surges and increased risk for cerebrovascular and cardiovascular diseases (Arzt *et al.*, 2005; Elwood *et al.*, 2006; Yaggi *et al.*, 2005). A study by Arzt *et al.* (2005) reported an odds ratio (OR) for stroke of 4.33 in patients affected by sleep-disordered breathing (SDB). Additionally, cross-sectional data from the Sleep Heart Health Study demonstrated greater odds for stroke in the highest apnea–hypopnea index (AHI) quartile com-

pared to the lowest quartile [OR: 1.58, 95% confidence interval (CI): 1.02–2.46] (Shahar *et al.*, 2001). Given the strong relationship between stroke and sleep apnea, it becomes increasingly plausible that there exists a high correlation between subclinical stroke and OSA.

As a result of the advancement of brain imaging techniques in recent years, asymptomatic brain lesions can be recognized. Previous studies have reported that silent cerebral infarct (SCI) increases the annual incidence of clinical strokes, suggesting the possibility of using silent stroke as a surrogate endpoint for subclinical brain damage (Kobayashi *et al.*, 1997). Therefore, early detection of SCI and its risk factors is critical for preventing symptomatic stroke.

The aim of our study was to investigate OSA as an independent risk factor for the onset and progression of SCI based on stroke subtypes and brain regions in both the general population and in a non-obese population. Several previous studies have attempted to examine the relationship between these two conditions, but there is a lack of epidemiological data that could determine the relationship between OSA and silent stroke in a low-risk, population-based sample (Davies *et al.*, 2001; Eguchi *et al.*, 2005; Minoguchi *et al.*, 2007; Nishibayashi *et al.*, 2008).

Moreover, very few studies have investigated the relationship between OSA and stroke subtypes, such as lacunar infarction and particularly cerebral regions (Alchanatis *et al.*, 2004; Bassetti *et al.*, 2006; Bonnin-Vilaplana *et al.*, 2009; Jackson and Sudlow, 2005). This is an important consideration, given that analysis of the subtype of stroke and related brain regions may help to lay the groundwork for establishing the relationship between these infarct areas and the presence of OSA.

MATERIALS AND METHODS

Study participants

The Korean Genome and Epidemiology Study (KoGES) is an ongoing, population-based cohort study which began in 2001, and has undergone periodic examinations for more than 10 years to identify environmental or genomic risk factors for chronic disease. The original 5020 cohort members were followed with biennial examinations that included a range of demographic characteristics, medical history and health status (Kim *et al.*, 2004). Current protocol for polysomnography (PSG) and magnetic resonance imaging (MRI) were added to the study in 2009 (fifth evaluation) and 2011 (sixth evaluation), respectively, thus participants from the sixth evaluation were targeted for analysis. A total of 1528 cohort members attended the core examination in 2011, and we selected 784 individuals randomly to participate in the two additional studies. However, participants with recording errors in the PSG (n = 1), or missing information on smoking status and habitual snoring (n = 6), or who had cardiovascular disease (n = 9) were excluded from the analysis. We also excluded those with a history of symptomatic cerebrovascular disease (n = 14) based on the record of previous diagnosis, hospitalization or current medication. After these exclusions, 746 participants aged 50–79 years remained for the final analyses. Written informed consent was obtained from all participants, and all procedures were approved by the Institutional Review Board of Korea University Ansan Hospital.

Data collection

All participants completed interviewer-administered questionnaires about their demographic characteristics, such as age, gender, smoking status, medical history, medication use and habitual snoring. Smoking status was assessed using three categories (non-smoker, ex-smoker and current smoker). Presence or past history of hypertension, diabetes mellitus and habitual snoring were assessed as dichotomous variables (yes/no). At the time of screening, each participant's height and weight were measured and calculated to obtain body mass index [BMI; weight (kg) divided by the height squared (m^2)], and an overnight fasting blood sample was taken to determine glucose and lipid levels. Systolic and diastolic blood pressures were measured three times with a sphygmomanometer, and the average was obtained. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, use of antihypertensive medication or a diagnosis history of hypertension. Diabetes mellitus was defined as a fasting glucose level of $\geq$126 mg dL^{-1} or use of any diabetes medication or a diagnosis history of diabetes.

Diagnosis of SCI

The presence of cerebrovascular lesions was evaluated by MRI of the whole brain. Each participant underwent MRI scan within an average of 2.30 days [standard deviation (SD) 3.96 days] from PSG monitoring. All scans were performed on a GE Signal HDxt 1.5T MR imaging scanner (GE Medical Systems, Waukesha, WI, USA) with an 8-channel head coil. High-intensity T2-weighted fluid-attenuated inversion recovery (FLAIR) images were used to evaluate the SCI, and lacunar infarction represented lesions <15 mm in size in the region of the penetrating arteries (NINDS, 1990). The FLAIR parameters were FOV = 220 $\times$ 220 mm^2, matrix = 256 $\times$ 224, 5-mm section thickness with a 2-mm interval gap, TR = 8802 ms, TE = 129 ms, TI = 2200 ms and number of acquisition = 1. A trained radiologist who was blinded to the history and diagnosis of the participants evaluated the existence, location and size of SCI on MRI.

Stroke subtypes were also categorized using the National Institute of Neurological Disorders and Stroke classification (NINDS, 1990). The following subtypes were considered: ischaemic stroke (lacunar infarction, large vessel stroke) and haemorrhagic stroke (intracerebral haemorrhage, subarachnoid haemorrhage). SCI was evaluated in eight different regions (basal ganglia, frontal, thalamus, temporal, parietal, occipital, brainstem and cerebellum).

Polysomnography

Each participant underwent standard PSG using a comprehensive portable device (Embletta® X-100; Embla Systems, Broomfield, CO, USA) at home or at the sleep laboratory on site. All PSG results were scored manually by an experienced sleep technologist according to standard criteria (Iber *et al.*, 2007). Apnea was defined as absence of the airflow for 10 s, and hypopnea was defined as a discernible reduction of the airflow associated with a reduction of oxygen saturation by 4% from the baseline. The AHI was defined as the average number of apnea and hypopnea events per sleep hour and was used to classify OSA as mild (AHI 5–15 h^{-1}), moderate (AHI 15–30 h^{-1}) and severe (AHI $\geq$ 30 h^{-1}). In this study, the presence of moderate–severe OSA was defined as AHI $\geq$ 15.

Statistical analysis

The descriptive analysis comprised means, standard deviations and percentage of cases observed. The *P*-value was calculated from *t*-tests for continuous variables and chi-square tests for categorical variables. To assess the association of moderate–severe OSA with SCI and lacunar infarction, multiple logistic regression models were used to calculate the ORs and 95% CIs. Factors that were associated significantly with the presence of SCI in univariate analyses (age, history of hypertension and diabetes mellitus) were included as covariates in all models. We conducted a stratified analysis using age group (<65 and $\geq$65 years) to examine the possibility of the effect modification by age. In addition, we repeated the subgroup analysis in the non-obese population (BMI < 27.5, n = 635) to investigate whether the associations of OSA was independent of risk factors for SCI without the effects of obesity. The cutoff point for obesity using BMI was determined in the basis of recent WHO recommendations for Asian populations (WHO, 2004). To determine the sample size necessary to detect a significant difference between the proportions of OSA and SCI, we conducted a power analysis (PROC POWER procedure in SAS) and obtained the required sample size (n = 410) with significance level (α) of 0.05, a false negative rate (β) of 0.05 and the desired power of 0.95. All analyses were conducted using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA), and a two-sided *P*-value <0.05 was considered to be statistically significant.

RESULTS

Table 1 shows the demographic characteristics and prevalence of SCI by OSA. Among the 746 participants, 252 were men (33.78%), mean age 59.25 years (range 50–79 years). The mean AHI was 6.59 (SD 8.26) and 12.06% had moderate–severe OSA (AHI $\geq$ 15). Overall, 57 (7.64%)

Table 1 Participants characteristics and prevalence of silent cerebral infarction by OSA, *n* (%)

Characteristics	*Total* (n = *746*)	*Non-OSA* (n = *656*)	*OSA* (n = *90*)
Age (years), mean (SD)	59.3 (7.2)	58.7 (6.9)	63.2 (8.1)*
BMI (kg m^{-2}), mean (SD)	24.7 (3.0)	24.5 (2.8)	26.4 (3.6)*
History of hypertension	273 (36.6)	217 (33.1)	56 (62.2)*
History of diabetes mellitus	158 (21.2)	126 (19.2)	32 (35.6)*
Smoking (ever/current)	210 (28.2)	175 (26.7)	35 (38.9)*
Habitual snoring	142 (19.0)	103 (15.7)	39 (43.3)*
AHI, mean (SD)	6.6 (8.3)	4.2 (3.9)	24.1 (10.5)*
AHI $\geq$ 15	90 (12.1)	0 (0.0)	90 (100.0)
Silent cerebral infarction†	57 (7.6)	43 (6.6)	14 (15.6)*
Lacunar infarction (small vessel stroke)†	37 (5.0)	25 (3.8)	12 (13.3)*
Basal ganglia	24 (3.2)	14 (2.1)	10 (11.1)*
Frontal	10 (1.3)	7 (1.1)	3 (3.3)
Thalamus	3 (0.4)	3 (0.5)	0 (0.0)
Temporal	3 (0.4)	2 (0.3)	1 (1.1)
Parietal	2 (0.3)	2 (0.3)	0 (0.0)
Occipital	1 (0.1)	0 (0.0)	1 (1.1)
Brainstem	1 (0.1)	1 (0.2)	0 (0.0)
Cerebellum	1 (0.1)	1 (0.2)	0 (0.0)
Large vessel stroke	6 (0.8)	5 (0.8)	1 (1.1)
Intracerebral haemorrhage	2 (0.3)	1 (0.2)	1 (1.1)
Basal ganglia	1 (0.1)	1 (0.2)	0 (0.0)
Subarachnoid haemorrhage	21 (2.8)	15 (2.3)	6 (6.7)
Basal ganglia	8 (1.1)	5 (0.8)	3 (3.3)

BMI, body mass index; AHI, apnea–hypopnea index; SD, standard deviation; OSA, obstructive sleep apnea.
**P*-value < 0.01.
†Some participants had multiple numbers of silent cerebral infarction and lacunar infarction, which allowed them to be classified into more than one category.

had SCI, and the prevalence of lacunar infarction was determined by the highest rate of SCI from 4.96% of participants. Among the brain regions, the basal ganglia displayed the highest prevalence of lacunar infarction (3.22%) or haemorrhagic stroke (1.20%). Subjects with OSA were found to have higher AHI (mean 24.05; SD 10.53) and prevalence of SCI (15.56%) and lacunar infarction (13.33%) than subjects without OSA ($P < 0.001$).

Table 2 shows the prevalence of demographic variables and known cerebrovascular risk factors in SCI and lacunar infarction. Elderly age group ($P < 0.001$), hypertension ($P < 0.001$) and diabetes mellitus ($P = 0.056$) were present more frequently in SCI and lacunar infarction. However, gender, smoking status, habitual snoring and mean BMI showed no significant group differences. The overall prevalence of moderate–severe OSA was 24.56% in SCI and 32.43% in lacunar infarction; the differences were significant ($P = 0.006$ and 0.001, respectively).

Table 3 presents the results for multivariate logistic regression analyses of the associations of moderate–severe OSA with SCI and lacunar infarction in all participants, also divided by age groups (<65 and ≥65 years). For SCI, moderate–severe OSA was associated positively with SCI in the ≥65-year age group only (OR: 2.44, 95% CI: 1.03–5.80) compared to the non-OSA group after adjustment for covariates. In the regions of basal ganglia, OSA was associated with SCI (OR: 2.35, 95% CI: 1.02–5.44) in the total, and this effect was also more pronounced in the ≥65-year age group (OR: 4.68, 95% CI: 1.60–13.73). Moderate–severe OSA was associated positively with lacunar infarction in the ≥65-year age group (OR: 3.48, 95% CI: 1.31–9.23) compared to the non-OSA group. In the basal ganglia, OSA was associated with lacunar infarction in total (OR: 2.86, 95% CI: 1.15–7.11), and this effect was also more pronounced in the ≥65-year age group (OR: 4.94, 95% CI: 1.58–15.44).

To evaluate the association between OSA and SCI after removing the effect of obesity, we excluded subjects whose BMI ≥ 27.5, which resulted in a total of 635 participants (Table 4). Moderate–severe OSA was associated positively with SCI in the ≥65-year age group (OR: 2.75, 95% CI: 1.07–7.10) only, but not in all non-obese subjects. Additionally, in the basal ganglia, OSA was associated with SCI (OR: 3.46, 95% CI: 1.38–8.69) in total and in the ≥65-year age group (OR: 7.86, 95% CI: 2.15–28.82). Moderate–severe OSA was also associated positively with lacunar infarction (OR: 2.47, 95% CI: 1.06–5.76), and this effect was more pronounced in the ≥65-year age group (OR: 3.87, 95% CI: 1.32–11.37). In the basal ganglia, OSA was associated with lacunar infarction (OR: 4.05, 95% CI: 1.49–11.02) and in the ≥65-year age group (OR: 6.78, 95% CI: 1.80–25.56).

DISCUSSION

In this study, the presence of moderate–severe OSA was associated with increased risk of SCI and lacunar infarction in the elderly general population (age 65 years and over),

Table 2 Cerebrovascular risk factors for silent cerebral infarction and lacunar infarction

	Silent cerebral infarction			*Lacunar infarction*		
	No (n = *689*) N *(%)*	*Yes* (n = *57*) N *(%)*	P	*No* (n = *709*) N *(%)*	*Yes* (n = *37*) N *(%)*	P
Age (years)						
50–64	553 (80.3)	27 (47.4)	<0.001	564 (79.6)	16 (43.2)	<0.001
65–79	136 (19.7)	30 (52.6)		145 (20.5)	21 (56.8)	
Gender						
Women	460 (66.8)	34 (59.7)	0.281	470 (66.3)	24 (64.9)	0.859
Men	229 (33.2)	23 (40.4)		239 (33.7)	13 (35.1)	
Hypertension						
No	454 (66.0)	18 (31.6)	<0.001	462 (65.3)	10 (27.0)	<0.001
Yes	235 (34.0)	39 (68.4)		247 (34.7)	27 (73.0)	
Diabetes mellitus						
No	549 (79.7)	39 (68.4)	0.056	564 (79.6)	24 (64.9)	0.033
Yes	140 (20.3)	18 (31.6)		145 (20.5)	13 (35.1)	
Smoking status						
No	499 (72.4)	37 (64.9)	0.235	512 (72.2)	24 (64.9)	0.343
Ever/current	190 (27.6)	20 (35.1)		197 (27.8)	13 (35.1)	
Habitual snoring						
No	555 (80.6)	49 (86.0)	0.300	573 (80.8)	31 (83.8)	0.648
Yes	134 (19.5)	8 (14.0)		136 (19.2)	6 (16.2)	
BMI (mean, SD)	24.7 (3.0)	24.3 (2.6)	0.295	24.7 (3.0)	24.8 (2.7)	0.902
AHI						
<15	613 (89.0)	43 (75.4)	0.006	631 (89.0)	25 (67.6)	0.001
≥15	76 (11.0)	14 (24.6)		78 (11.0)	12 (32.4)	

BMI, body mass index; AHI, apnea-hypopnea index; SD, standard deviation.

Table 3 Adjusted odds ratios (OR) for association of obstructive sleep apnea with silent cerebral infarction and lacunar infarction by age group

		Total		*Age 50–64 years*		*Age ≥ 65 years*	
	AHI	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Silent cerebral infarction		(*n* = 57/746)		(*n* = 27/580)		(*n* = 30/166)	
	<15	1		1		1	
	≥15	1.36	0.68–2.77	0.31	0.04–2.38	2.44	1.03–5.80
Basal ganglia		(*n* = 30/746)		(*n* = 13/580)		(*n* = 17/166)	
	<15	1		1		1	
	≥15	2.35	1.02–5.44	0.62	0.08–4.95	4.68	1.60–13.73
Lacunar infarction		(*n* = 37/746)		(*n* = 16/580)		(*n* = 21/166)	
	<15	1		1		1	
	≥15	2.00	0.91–4.39	0.53	0.07–4.20	3.48	1.31–9.23
Basal ganglia		(*n* = 24/746)		(*n* = 9/580)		(*n* = 15/166)	
	<15	1		1		1	
	≥15	2.86	1.15–7.11	0.97	0.12–8.11	4.94	1.58–15.44

OR, odds ratio; CI, confidence intervals; AHI, apnea-hypopnea index.
Analysis adjusted for age, hypertension and diabetes mellitus.

Table 4 Adjusted odds ratios (OR) for association of obstructive sleep apnea with silent cerebral infarction and lacunar infarction by age group in non-obese subjects (BMI < 27.5)

		Total		*Age 50–64 years*		*Age ≥ 65 years*	
	AHI	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Silent cerebral infarction		(*n* = 52/635)		(*n* = 26/500)		(*n* = 26/135)	
	<15	1		1		1	
	≥15	1.67	0.78–3.55	0.44	0.06–3.42	2.75	1.07–7.10
Basal ganglia		(*n* = 25/635)		(*n* = 8/500)		(*n* = 13/135)	
	<15	1		1		1	
	≥15	3.46	1.38–8.69	0.93	0.11–7.70	7.86	2.15–28.82
Lacunar infarction		(*n* = 33/635)		(*n* = 15/500)		(*n* = 18/135)	
	<15	1		1		1	
	≥15	2.47	1.06–5.76	0.80	0.10–6.41	3.87	1.32–11.37
Basal ganglia		(*n* = 20/635)		(*n* = 8/500)		(*n* = 12/135)	
	<15	1		1		1	
	≥15	4.05	1.49–11.02	1.58	0.18–13.90	6.78	1.80–25.56

OR, odds ratio; CI, confidence intervals; AHI, apnea–hypopnea index.
Analysis adjusted for age, hypertension and diabetes mellitus.

independent of gender, hypertension, diabetes mellitus, BMI and smoking status. More specifically, among the brain regions, the association was significant in the basal ganglia. These findings remained consistent when conducting the same analyses in non-obese participants, highlighting the importance of OSA as a risk factor for SCI and lacunar infarction independent of obesity.

Stroke is a serious and common disorder and a major cause of death worldwide. Several well-known risk factors for stroke, such as age, hypertension, diabetes mellitus, smoking and obesity have been well established in the literature (Lloyd-Jones *et al.*, 2009). However, these traditional risk factors do not fully explain the occurrence of stroke, and this study emphasizes the importance of considering OSA as a risk factor independent of existing risk factors. Since the first study published on the association of stroke with OSA in 1999 (Bassetti and Aldrich, 1999), several studies have examined the relationship between OSA and stroke and SCI using AHI as the risk factor.

Davies *et al.* (2001) assessed the relationship between SCI and OSA in 45 sleep clinic patients but did not find any sign of subclinical brain damage in this group compared to controls, who were matched for age, BMI, alcohol, smoking, hypertension, heart disease and diabetes. In this study, only the level of blood pressure was different in the OSA group, and the authors concluded that OSA may associate with

increased cerebrovascular risks rather than damages *per se*. None the less, Eguchi *et al.* (2005) conducted PSG and MRI in 170 community-dwelling individuals at high cardiovascular risk and found that elevated level of hypoxia was related to higher prevalence of SCI. Results from Minoguchi *et al.*'s study (2007) and Nishibayashi *et al.*'s study (2008) also found a positive correlation between moderate–severe OSA, which added to the plausibility of OSA's contribution to silent brain damage.

A number of pathological mechanisms are involved in the association between OSA and stroke. Possible mechanisms include acute haemodynamic changes during episodes of apnea, paradoxical embolization, hypercoagulability, hypoxia-related cerebral ischaemia and atherosclerosis (Yaggi *et al.*, 2005). In addition, a significant decline in the blood flow of the middle cerebral artery occurring during obstructive hypopneas could result in vascular damage (Netzer *et al.*, 1998).

Lacunar infarctions are small subcortical infarcts in the region of the penetrating arteries, namely in the basal ganglia, thalamus, internal capsule, corona radiate and the brainstem (NINDS, 1990). In the present study, lacunar infarction consisted of the highest proportion of prevalence of stroke subtypes, and moderate–severe OSA was associated positively with lacunar infarction in the $\geq$65-year age group. Previous studies have shown that lacunar infarcts accompanied SDB with similar incidence to larger brain infarctions (Parra *et al.*, 2000). In a study of 87 lacunar stroke patients, lacunar infarctions was associated independently with AHI $\geq$ 10 (OR: 3.17, 95% CI: 1.02–9.79). More specifically, they found that lacunar infarction, the internal capsule and pons were associated with OSA (Bonnin-Vilaplana *et al.*, 2009). Results from an Asian study conducted in Japan were consistent with our findings in that moderate–severe OSA was associated with a higher prevalence of silent lacunar infarctions ($P < 0.001$) (Nishibayashi *et al.*, 2008).

Additionally, among the various brain regions, SCI and lacunar infarcts were most prevalent in the basal ganglia. Classic anatomists have described the 'deep large grey masses' collectively as the basal ganglia of the telencephalon, which are embedded in the white matter of each cerebral hemisphere. The basal ganglia are involved in many neuronal pathways, including emotional, motivational and cognitive functions (Herrero *et al.*, 2002). To our knowledge, no previous study has evaluated prospectively the risk of stroke based on specific brain regions. Additionally, little information has been published on the risk factors for different subtypes of stroke, and this approach would provide the basis for a better definition of potential high-risk subgroups and lead to more focused prevention measures for stroke subtypes, especially based on specific brain regions.

In this study, moderate–severe OSA represents a risk factor for SCI in the elderly. This is consistent with previous findings by Munoz *et al.* (2006), which showed that elderly subjects with severe OSA (AHI > 30) had an increased risk for ischaemic stroke when adjusted for sex (hazard ratio 2.52, 95% CI: 1.04–6.01) after a 6-year follow-up. Our study did not find a significant association between SCI and OSA in the total sample, but this negative finding may be due to a limited number of events rather than a lack of effect. Further study with increased sample size and increased incidence of SCI may reveal a stronger association between the two conditions.

Our results also indicate that OSA is a risk factor for SCI, independent of obesity. Although we found that mean BMI was not significantly different between case and controls of SCI and lacunar infarction in the present study, BMI is known to be one of the strongest risk factors for OSA. Tishler *et al.* (2003) showed that AHI was associated significantly with BMI (OR per 1-unit increase: 1.14, 95% CI: 1.10–1.19), and in a longitudinal analysis of the Wisconsin cohort with a 4-year follow-up a 10% increase in weight was associated with a sixfold greater risk of developing OSA among individuals initially free of OSA (Peppard *et al.*, 2000). In our data, subjects with OSA were also found to have higher mean BMI than subjects without OSA (26.42 versus 24.46, $P < 0.001$). In this regard, we wanted to emphasize the independent role of OSA in contributing to the prevalence of brain damages, without the contribution from obesity. The existing literature has also shown that obesity indicated by BMI is a major risk factor of both OSA and stroke followed by age, male gender and ethnicity (Kripke *et al.*, 1997). In our results (Table 4), a statistically significant association between OSA and SCI or lacunar infarction in the elderly persisted when analysing non-obese participants. These findings indicate that even non-obese populations can be at risk when they have pre-existing OSA; that is, obesity not only has a direct influence on the development of OSA but also has an indirect causative role in SCI. Thus, we suggest that early detection of OSA in non-obese individuals could decrease the risk of stroke in this population.

The strengths of the present study include the large number of participants who underwent both PSG and MRI, which allows standard and objective diagnoses of OSA and stroke, respectively. It is also noteworthy that our study is representative of the community-based general population. Most past studies investigating sleep and stroke include stroke patients admitted to hospitals, which may have created heterogeneity among study samples. We also performed subgroup analyses using a group of non-obese participants, and made it possible to investigate the independent impact of OSA on stroke without obesity as a confounder. Furthermore, the availability of stroke subtype segmentation enabled us to investigate not only the subtype of SCI, but also the differentiation between brain regions.

As a limitation, this study was cross-sectional, so we cannot establish the causal nature between OSA and SCI, which would require the analysis of incident events in prospective cohort studies. Secondly, in the basal ganglia, there was a small sample size for SCI and lacunar infarction which might have led to a slightly wider range of confidence intervals. Lastly, gender asymmetry favouring women may misrepresent the relationship between smoking status and SCI or lacunar infarction.

In summary, moderate–severe OSA was associated with an increase in SCI and lacunar infarction in the elderly population, and especially in the basal ganglia. These findings were also observed in a non-obese population. Therefore, OSA should be considered a risk factor for SCI independent of obesity, and we suggest that the diagnosis and treatment of OSA may provide an effective way to prevent stroke.

ACKNOWLEDGEMENTS

This study was supported by grants from the Korean Center for Disease Control and Prevention and the Korean Ministry for Health and Welfare (grant no. 2011-E71004-0) and Korea University grant.

DISCLOSURE STATEMENT

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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