

# Obstructive Sleep Apnea as a Risk Factor for Cerebral White Matter Change in a Middle-Aged and Older General Population

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**Study Objective:** Obstructive sleep apnea (OSA) contributes to the development of systemic hypertension, and hypertension strongly predicts the development of white matter change (WMC). Thus, it is plausible that OSA mediates WMC. The goal of the current study is to determine whether a contextual relationship exists between OSA and cerebral WMC.

**Design:** Cross-sectional analyses conducted in a population-based study.

**Setting:** Korean community-based sample from the Korean Genome and Epidemiology Study (KoGES) who attended examinations in 2011 at a medical center.

**Participants:** There were 503 individuals (mean  $\pm$  SD, age 59.63  $\pm$  7.48 y) who were free of previously diagnosed cardiovascular and neurologic diseases.

**Measurements and Results:** Participants underwent 1-night polysomnography and were classified as no OSA (obstructive apnea-hypopnea index [AHI] < 5, n = 289), mild OSA (AHI 5-15, n = 161), and moderate to severe OSA (AHI  $\geq$  15, n = 53). WMC was identified with brain magnetic resonance imaging (MRI) and was found in 199 individuals (39.56%). Multivariate logistic regression analyses adjusted for covariates revealed that moderate to severe OSA was significantly associated with the presence of WMC (odds ratio [OR] 2.08, 95% confidence interval [CI] 1.05-4.13) compared with no OSA. Additional adjustment of hypertension to the model did not alter the significance of the association (OR 2.03, 95% CI 1.02-4.05).

**Conclusions:** Moderate to severe OSA is an independent risk factor for WMC in middle-aged and older individuals. Thus, early recognition and treatment of OSA could reduce the risk of stroke and vascular dementia.

**Keywords:** General population; obstructive sleep apnea; stroke; white matter change

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## INTRODUCTION

Cerebral white matter change (WMC) has been described as the lesions in periventricular or subcortical areas, appearing as hyperintensities on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences of brain MRI.<sup>1</sup> Although the pathologic correlates are heterogeneous, the presence of focal myelinolysis, axonal loss, and gliosis associated with vessel wall hyalinosis suggests that chronic hypoperfusion contributes to the development of WMC.<sup>2,3</sup> The fact that old age, hypertension, diabetes, metabolic syndrome, and smoking are common risk factors for stroke and cerebral WMC also explains its origin in vascular pathogenesis.<sup>4,6</sup> The clinical importance of WMC posits a very important public health issue, because it

has been highlighted in previous studies that demonstrated its association with incident stroke, dementia, and mortality.<sup>6-8</sup> The burden of WMC is correlated with cognitive dysfunction<sup>9,10</sup> and thus identifying treatable or preventable causes is essential.

Obstructive sleep apnea (OSA), a disorder characterized by repeated episodes of partial or complete upper airway obstruction during sleep, is associated with sleep fragmentation, intermittent hypoxia, systemic inflammation, blood pressure surges, endothelial dysfunction, and metabolic syndrome, which are well-known factors that could induce direct brain injury.<sup>11,12</sup> Emerging epidemiologic studies have shown that OSA is an independent risk factor for hypertension and stroke.<sup>13-16</sup> A recent study also documented that OSA precedes the development of cognitive impairment or dementia in a community-based elderly cohort.<sup>17</sup>

Existing research on both OSA and WMC provide convincing evidence for a contextual relationship between the two conditions. As OSA contributes to the development of systemic hypertension<sup>13,15</sup> and hypertension strongly predicts the development of WMC,<sup>4,6</sup> it is plausible that OSA mediates WMC. Considering the high prevalence of OSA coexisting with WMC that precedes stroke and cognitive impairment,<sup>7,8,16</sup> it becomes increasingly plausible that cerebral WMC may mediate the development of stroke and dementia in individuals with OSA.

Although several studies have previously explored cerebral white matter in OSA,<sup>18-25</sup> the results remain inconsistent for the

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independent effect of OSA on WMC. Three cross-sectional case-control studies documented significant evidence of white matter abnormalities in OSA populations,<sup>19,21,22,25</sup> whereas two additional studies failed to demonstrate any association between the two conditions.<sup>18,20</sup> These studies reported small sample size and were composed of clinical populations referred for sleep studies or individuals from the community who were at high risk for OSA.<sup>18-22</sup> It is unlikely that these samples are representative of the general population. Population-based longitudinal assessments were conducted by the Sleep Health Heart Study (SHHS)<sup>23,24</sup> but only central sleep apnea was documented to be associated with WMC.<sup>23</sup> Thus, whether OSA is an independent risk for WMC in the general population is not yet known.

In the current study, we aimed to define the prevalence and severity of OSA and cerebral WMC in the adult population from an epidemiologic cohort in Korea, and examined the association between these two conditions. We hypothesized that OSA would be accompanied by cerebral WMC, and that these changes are dependent on the severity of the disease. Testing this hypothesis is a very important issue considering the significant societal burden in regard to the aging population, stroke, and dementia. If OSA is found to be associated with WMC, early detection and treatment of OSA may be able to reduce the risk of dementia and stroke.

## MATERIALS AND METHODS

### Study Design and Sample

Study participants were recruited as part of the Korean Genome and Epidemiology Study (KoGES), an ongoing prospective cohort study that started in 2001. The original 5,020 cohort members from Ansan were followed with biennial examinations that included a range of demographic characteristics, medical history, health status, and sleep related factors. The study design and aims of the KoGES have been previously reported.<sup>26,27</sup> (See supplemental material for detailed description of the study procedure). The current polysomnography (PSG) protocol was introduced to this study in 2009 (fifth evaluation), and structural brain magnetic resonance imaging (MRI) was included in 2011 (sixth evaluation) as a substudy on aging. For the purpose of this study, cohort members who performed adjunct MRI and PSG protocols in 2011 were targeted for analyses.

A total of 1,529 cohort members participated in the core examination from March to December 2011, and PSG and MRI were performed on those who attended follow-up examinations and were eligible to participate in both procedures. We used random selection to recruit our participants for the two adjunct studies, but our current study sample was generally older (age 59.63 y versus 57.74 y,  $P < 0.0001$ ) and had greater proportion of females (70.97% versus 53.27%,  $P < 0.0001$ ) compared with those who were not included in the current analysis. The prevalence of hypertension and diabetes mellitus were not significantly different between the two groups.

Nocturnal PSG was performed on 542 individuals and MRI was performed on 551 individuals, comprising a total of 525 for those who completed both examinations. However, we excluded those who had preexisting cerebrovascular diseases ( $N = 10$ ) or major cardiovascular accidents ( $N = 21$ ) from the analyses, and a total of 503 individuals remained as the final sample of

the current study. This number exceeds the targeted sample size ( $N = 145$ ) that was determined by a power analysis,<sup>28</sup> with error probability ( $\alpha$ ) of 0.05, false-negative rate ( $\beta$ ) of 0.05 (i.e., power of 0.95), and effect size ( $\omega$ ) of 0.37, which was calculated from our preliminary analysis on the distribution of WMC in different OSA groups. An informed consent form was signed by each participant, and the study procedure was approved by the institutional review board of the Korea University Ansan Hospital.

### Polysomnography

Overnight PSG was performed with a comprehensive portable device (Embletta<sup>®</sup> X-100; Embla Systems, Broomfield, CO, USA) at home or at the sleep laboratory onsite. Apneas were defined when airflow was reduced to  $\geq 90\%$  of the baseline values for at least 10 sec, and apneas were further classified as obstructive if respiratory efforts were noted on either the chest or abdominal inductance channel, or as central if no respiratory effort was noted. Additionally, hypopneas were defined by a  $\geq 30\%$  reduction of airflow for at least 10 sec accompanied by at least a 4% drop in oxygen saturation ( $\text{SaO}_2$ ).<sup>29</sup> The apnea-hypopnea index (AHI) was calculated by averaging the total number of obstructive apneas and hypopneas per h of sleep and OSA severity was defined by three AHI categories: no OSA ( $\text{AHI} < 5$ ), mild OSA ( $5 \leq \text{AHI} < 15$ ), and moderate to severe OSA ( $\text{AHI} \geq 15$ ).

Data were scored by two well-trained technicians who had  $\geq 5$  y of experience with PSG monitoring and scoring. Internal consistency for scoring AHI was high (Cronbach alpha = 0.996 and 1.00 for each rater), and interrater reliability was also very strong (Cronbach alpha = 0.998). The scorers were also blinded to each other's scoring results. (See supplemental material for more detailed information).

### Structural Neuroimaging

Each participant underwent MRI within an average of 2.30 days (standard deviation, 3.96 days) from PSG monitoring. All scans were performed on a GE Signal HDxt 1.5 T MRI scanner (GE Medical Systems, Waukesha, WI) with an eight-channel head coil. T2-weighted FLAIR images were used to evaluate the white matter in the brain. The FLAIR parameters were field of view (FOV) =  $220 \times 220 \text{ mm}^2$ , matrix =  $256 \times 224$ , 5-mm section thickness with 2-mm interval gap, repetition time (TR) = 8,802 ms, echo time (TE) = 129 ms, inversion time (TI) = 2,200 ms and number of acquisition = 1.

WMC on MRI were identified when there were hyperintensities  $\geq 5$  mm on FLAIR images. The degree of WMC was scored using a four-point age-related white matter change (ARWMC) scale designed by Wahlund et al.<sup>30</sup> WMC in each right and left hemisphere was rated as 0 (no lesion), 1 (focal lesion,  $\leq 10$  mm), 2 (beginning confluent lesions), or 3 (confluent lesions involving the entire region) in five different regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial). The WMC total score was derived from summing the individual scores in each of the five regions, with the total score ranging from 0 to 30. The total score of the WMC scale has been shown to correlate with lesion volume in previous reports.<sup>31</sup> We categorized the number of WMC into 0, 1-4, and  $\geq 5$  because scores did not follow a normal distribution. Other studies that have used the ARWMC scale have previ-

**Table 1**—Comparisons of general characteristics between WMC groups

Characteristic variable	Overall	WMC 0	WMC 1-4	WMC ≥ 5	P value
N (%)	503 (100)	304 (60.44)	160 (31.81)	39 (7.75)	
Age, mean ± SD	59.63 ± 7.48	57.30 ± 6.38	62.24 ± 7.36	67.05 ± 7.67	< 0.0001
Age ≥ 65 y, n (%)	120 (23.86)	36 (11.84)	57 (35.63)	27 (69.23)	< 0.0001
Sex (male), n (%)	146 (29.03)	88 (28.95)	48 (30.00)	10 (25.64)	0.86
BMI, mean ± SD	24.60 ± 2.92	24.49 ± 2.85	24.79 ± 2.99	24.75 ± 2.99	0.37
Current smoker, n (%)	36 (7.16)	6 (6.91)	6 (3.75)	2 (5.13)	0.94
Moderate to heavy drinking, n (%)	34 (6.76)	26 (8.55)	11 (6.88)	4 (10.26)	0.26
Hypertension, n (%)	177 (35.19)	88 (28.95)	65 (40.63)	24 (61.54)	< 0.0001
Diabetes mellitus, n (%)	136 (27.04)	60 (19.74)	60 (37.50)	16 (41.03)	< 0.0001
C-reactive protein (mg/dL), n ± SD	1.18 ± 2.27	1.23 ± 2.67	1.10 ± 1.54	1.10 ± 1.04	0.19
Total cholesterol (mg/dL), n ± SD	197.27 ± 36.15	200.39 ± 35.09	192.15 ± 35.44	194.00 ± 44.60	0.05
Triglyceride (mg/dL), n ± SD	139.06 ± 103.55	138.49 ± 88.83	143.14 ± 134.44	126.72 ± 53.61	0.04
HDL (mg/dL), n ± SD	56.50 ± 14.19	56.94 ± 14.68	55.31 ± 12.90	57.97 ± 15.34	0.4
LDL (mg/dL), n ± SD	194.76 ± 36.03	197.90 ± 34.99	189.51 ± 35.19	191.78 ± 44.75	0.05
Hyperlipidemia, n (%)	102 (20.28)	59 (19.41)	34 (21.25)	9 (23.08)	0.81
CAI, mean ± SD	0.16 ± 0.70	0.11 ± 0.56	0.22 ± 0.81	0.31 ± 1.05	0.72
AHI, mean ± SD	6.24 ± 7.43	5.18 ± 6.12	7.82 ± 8.99	8.05 ± 8.42	0.0004
Severity of OSA, n (%)					
No OSA (AHI < 5)	289 (57.46)	192 (66.43)	77 (48.13)	20 (51.28)	0.002
Mild OSA (5 ≤ AHI < 15)	161 (32.01)	92 (30.26)	57 (35.63)	26 (30.77)	
Moderate to severe OSA (AHI ≥ 15)	53 (10.54)	20 (6.58)	26 (16.25)	7 (17.95)	

P values were calculated from the analysis of variance and the Kruskal-Wallis test for continuous variables and the  $\chi^2$  test for categorical variables. AHI, obstructive apnea-hypopnea index; BMI, body mass index ( $\text{kg}/\text{m}^2$ ); CAI, central apnea index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SD, standard deviation; WMC, white matter change.

ously used five as a significant cutoff score to categorize the severity of WMC.<sup>20,32</sup>

All WMC were rated by a single reader (HSS) who was blinded to the study participants' OSA status. Cronbach alpha reliability was 0.96 (supplemental material).

### Other Covariates

Covariate measures were determined from a health examination and a questionnaire-based interview that were held onsite. Cardiovascular disease was determined by the presence of one of the following: myocardial infarction, congestive heart failure, coronary artery disease, or peripheral vascular disease. Diabetes mellitus was defined as taking insulin or hypoglycemic medication or fasting glucose  $\geq 125$  mg/dL. Hyperlipidemia was determined when participants were taking lipid-lowering medication and total cholesterol was  $\geq 240$  mg/dL. Hypertension was defined with self-reported antihypertensive medication or systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mmHg. Body mass index ( $\text{kg}/\text{m}^2$ ), current smoking status (yes/no), and moderate to heavy alcohol consumption ( $\geq 15$  g/day)<sup>27</sup> were also considered for analyses.

### Statistical Analysis

General characteristics of the study participants were contrasted across the three WMC groups using the analysis of variance when continuous variables followed a normal curve, and the Kruskal-Wallis test was used when continuous variables were skewed. Categorical variables were contrasted with the  $\chi^2$

test. Spearman rank correlation was performed to see the correlation between the number of WMC and severity of OSA as continuous variables. The prevalence of WMC was calculated across OSA groups, and the linear trend for the proportions of WMC prevalence across OSA severity was tested using the Cochran-Armitage test. Intrascorer and interscorer reliability assessments for AHI and WMC were analyzed by Cronbach alpha.

To determine the independent effect of OSA on the prevalence of WMC, multivariate logistic regression analyses were performed after adjusting for possible confounding factors such as age, sex, current smoking status, presence of moderate to heavy drinking, diabetes, hyperlipidemia, and hypertension. Only power analysis was performed with G\*Power Version 3.1.3 (Franz Faul, Universitat Kiel, Germany) and all other data analyses were performed using SAS Version 9.1 (SAS Institute Inc., Cary, NC). Results are given as mean  $\pm$  SD unless otherwise stated.  $P < 0.05$  was considered to be statistically significant.

### RESULTS

Demographic and clinical characteristics across different WMC groups are presented in Table 1. Among 503 participants (mean age  $59.63 \pm 7.48$  y, 23% male), 304 were free of WMC, 160 had a total WMC score ranging from 1 to 4 (mean  $2.20 \pm 1.10$ ), and 39 had a score greater than 5 (mean  $6.87 \pm 2.34$ ). Age and prevalence of hypertension and diabetes mellitus were significantly different across WMC groups ( $P < 0.0001$ ). When comparing AHI of the three groups, the group with no WMC exhibited the lowest value ( $5.18 \pm 6.12$ ), followed by



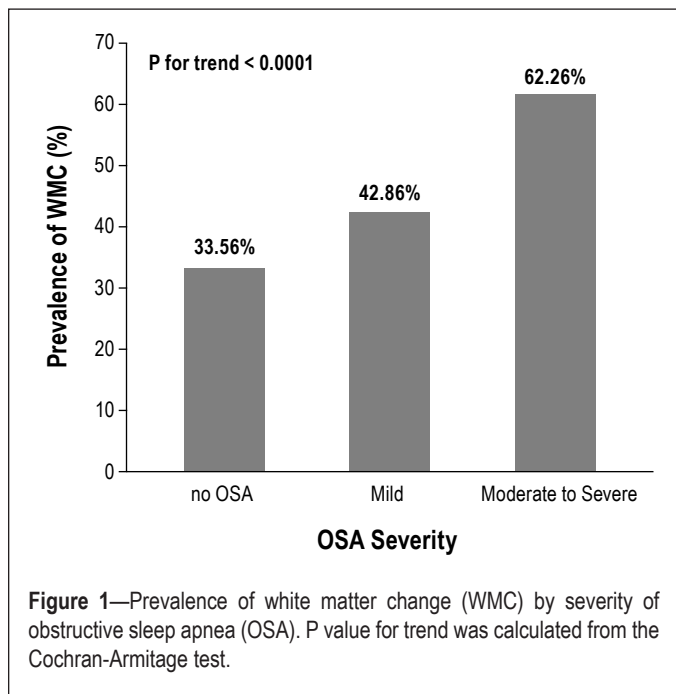
the WMC 1-4 group ( $7.82 \pm 8.99$ ) and  $WMC \geq 5$  group ( $8.05 \pm 8.42$ ) in increasing order ( $P = 0.0004$ ). Correlation analysis also confirmed that AHI and the number of WMC were positively correlated (Spearman rank correlation coefficient ( $r_s$ ) = 0.17,  $P = 0.0001$ ). (Table 2)

OSA groups were divided based on AHI severity. Overall, 57.46% ( $n = 289$ ) of the study sample was free of OSA, 32.01% ( $n = 161$ ) had mild OSA, and 10.54% ( $n = 53$ ) had moderate to severe OSA. Figure 1 presents the prevalence of WMC in different OSA groups, which showed a significant increasing trend for WMC with increasing severity of OSA ( $P < 0.0001$ ). There were 62.26% of the individuals ( $n = 33$ ) with moder-

**Table 2—Correlation between AHI and the number of WMC**

	<b>WMC</b>	<b>AHI</b>
<b>WMC</b>	1.00	
<b>AHI</b>	0.17**	1.00

P values were calculated using the Spearman correlation analyses. \*\* $P < 0.0001$ . AHI, apnea hypopnea index; WMC, white matter change.



**Table 3—Estimated odds ratios for presence of white matter change in obstructive sleep apnea groups**

Severity of OSA	N (%)	Odds ratios (95% confidence intervals)		
		Adjusted for age, sex, and BMI	Adjusted for age, sex, BMI, and other characteristics <sup>a</sup>	All covariates + Hypertension additionally adjusted
No OSA (AHI < 5)	289 (57.46)	REF	REF	REF
Mild OSA ( $5 \leq$ AHI < 15)	161 (32.01)	1.00 (0.64-1.56)	0.90 (0.57-1.42)	0.89 (0.56-1.40)
Moderate-to-severe OSA (AHI $\geq$ 15)	53 (10.54)	2.39 (1.22-4.68)	2.08 (1.05-4.13)	2.03 (1.02-4.05)

Odds ratios and 95% confidence intervals were calculated from multivariate logistic regression analyses. <sup>a</sup>Moderate to heavy drinking, current smoking, diabetes, and hyperlipidemia. AHI, apnea-hypopnea index; BMI, body mass index; OSA, obstructive sleep apnea.

ate to severe OSA who exhibited WMC, followed by 42.86% ( $n = 69$ ) with mild OSA and 33.56% ( $n = 97$ ) with no OSA. WMC were predominantly seen in the frontal lobe (89.45% of all WMCs and 35.39% of all participants), and similar increasing trend was also noted for the frontal WMC across OSA severity groups ( $P < 0.0001$ ) (data not shown).

We also examined the distribution of OSA severity in different WMC groups and found that no WMC was related to the highest rate of no OSA, in comparison with the other WMC groups (66.43% versus 48.13% and 51.28%, respectively), whereas presence of  $WMC \geq 5$  displayed the highest rate of moderate to severe OSA (17.95% compared with 6.58% in no WMC and 16.25% in 1-4 WMC). The distribution of OSA severity was significantly different across WMC groups ( $P = 0.002$ ) (Table 1).

To investigate an independent association between the severity of OSA and the prevalence of WMC, possible confounding factors were adjusted into a multivariate logistic regression model (Table 3). With age, sex, body mass index, moderate to heavy drinking, current smoking, and history of diabetes and hyperlipidemia adjusted, moderate-severe OSA was significantly associated with presence of WMC (OR 2.08, 95% CI 1.05-4.13) compared with the no OSA group. Additional adjustment of hypertension to the model did not attenuate the significant association (OR 2.03, 95% CI 1.02-4.05). The rate of WMC prevalence in the mild OSA group did not differ significantly from that of the control group.

## DISCUSSION

The main finding of our study provides evidence for the relationship between OSA and WMC. Mean AHI and the prevalence of OSA were higher in the groups with WMC, and particularly individuals with moderate to severe OSA had a twofold increased risk of exhibiting WMC even after adjusting for covariates. Additional adjustment of hypertension to our multivariate logistics model did not significantly attenuate the OR, suggesting that an additional mechanism may contribute to the pathogenesis of WMC in OSA. Considering that moderate OSA—but not mild severity—was associated with WMC, we could infer that the severity of disease may mediate the pathogenesis of WMC, rather than the presence of OSA.

## Comparison With Previous Studies

Previous investigations of cerebral WMC in OSA have reported conflicting results. Eguchi et al.<sup>19</sup> observed that patients

with hypoxia had a significantly higher prevalence of silent cerebrovascular disease compared with the nonhypoxia group, suggesting sleep disordered breathing as a contributor to a preconditioning phase of symptomatic stroke. Additional studies by Minoguchi et al.<sup>21</sup> and Nishibayashi et al.<sup>22</sup> reported a significant correlation between subclinical cerebrovascular diseases and moderate to severe OSA. Based on their findings, some authors concluded that OSA may have a detrimental effect in target organ damage and suggested that the brain could be affected in the form of a subclinical stroke.<sup>19,21,22</sup>

OSA is associated with abnormal structural, functional, and metabolic brain imaging, with features compatible with neuronal injury,<sup>25</sup> but most previous studies have focused on patients with severe OSA who were selected from a sleep clinic, and their results were contradicted by several studies that failed to demonstrate any relationship between OSA and WMC. Davies et al.<sup>18</sup> qualitatively observed white matter grade and ambulatory blood pressure in patients with OSA and reported that only blood pressure, and not white matter grades, was different between individuals with OSA and their matched control group. They concluded that OSA may be related to an excess of cerebrovascular risks rather than cerebrovascular damages. A recent study conducted by Kiernan and colleagues<sup>20</sup> also did not find a relationship between OSA and WMC. In their study with hypertensive patients, the severity of OSA was not associated with white matter disease, as defined by WMC  $\geq 5$  in the visual ARWMC scale.

Such divergent findings from these earlier cross-sectional studies could be due to differences in participant selection, which is a common limitation in clinical studies. WMC in OSA has also been investigated in a population study at the SHHS, where sleep disordered breathing with white matter abnormalities in older community-dwelling adults was examined. Ding et al.<sup>24</sup> obtained PSG and MRI data from 789 individuals enrolled in the SHHS and reported that the level of AHI was not significantly different between those with and without WMC in the brainstem. Subsequently, Robbins et al.<sup>23</sup> investigated 843 SHHS participants and examined a temporal relationship between WMC and sleep disordered breathing, which was defined as both OSA or central sleep apnea. The results indicated that only central but not obstructive apnea was associated with the development of WMC. It was equally possible that the white matter injury increased the risk for central apnea, as nonobstructive forms of sleep apnea seem common to a variety of central nervous system injuries.

It has been suggested that the negative findings observed from the SHHS may be explained by survival biases or high rates of other vascular risk factors that are commonly presented in the older adults.<sup>33</sup> Notably, cerebral WMC were determined in the study by Robbins et al.<sup>23</sup> as a longitudinal change in the WM between two MRI examinations, and they reported that 3.26% ( $n = 22$  of 674 who were categorized into OSA categories) of their older population exhibited these MRI-detected changes within a 5-y time frame. Considering their mean age of 77 y, it is possible that these participants already exhibited higher prevalence of WM abnormalities at their baseline examinations. Participants of the current study were younger, with a mean age of 59.63 y and the WMC prevalence of 39.56%, a level similar to the 33.2% prevalence previously reported in a Korean population.<sup>34</sup>

To our knowledge, no prior epidemiologic study has revealed a significant association between OSA and WMC in a middle-aged to older adult population. A major strength of our finding is that our data are representative of the general population who are at a relatively low risk of developing cerebrovascular diseases. Based on our results, we could infer that the risk of WMC is greatly increased in individuals with moderate to severe OSA, and the increase is independent of other risk factors, including hypertension.

### Potential Mechanism of Injury

Converging data indicate that white matter abnormalities may be present in individuals who are at greatest risk of developing vascular diseases due to repeated apneic episodes.<sup>35,36</sup> This mechanism is based on hypoxemia and hypercapnia during apneic events, which activates an arousal and chemoreflex-mediated increase in the sympathetic vasoconstrictor traffic to the peripheral blood vessels.<sup>37</sup> During these reflex responses and resumption of breathing, a wide range of autonomic, neuroendocrine, and hemodynamic alterations occur.<sup>12,14</sup> Increased cardiac output, together with vasoconstriction, results in a striking increase of blood pressure followed by an abrupt drop in blood pressure. Altered cerebral blood flow and velocity is accompanied by large fluctuations in blood pressure, which induces episodes of cerebrovascular shearing stress. Previous studies examining blood pressure,<sup>13,36</sup> as well as the studies measuring cerebral hemodynamics<sup>38,39</sup> in sleep apnea, suggest a direct effect of each sleep-related respiratory event on blood pressure and cerebral perfusion.<sup>11</sup> There seems to be an interaction between respiratory effort and the duration of the nocturnal hypopnea in regard to their association with increased cardiac preload, lower cardiac afterload, activation of carotid body baroreceptors, and vasodilation through both increasing arterial carbon dioxide and decreasing oxygen saturation, all of which can affect reduction in cerebral circulation.<sup>39</sup>

Ischemic effects of nocturnal apnea would be potentiated by associated oxidative stress from intermittent episodes of hypoxemia and reoxygenation, which together elicit cerebrovascular endothelial dysfunction and autoregulation that preferentially damage small vessels in the brain.<sup>35</sup> White matter hyperintensities on MRI scans are ischemic tissues that result from repeated episodes of cerebrovascular shearing stress and the processes of inflammation and atherosclerosis.<sup>2,40</sup>

Increased risk for WMC may also occur through pathophysiologic mechanisms that are not specific to the cerebral blood flow; OSA may induce generalized atherosclerosis through the effect from intermittent hypoxemia, which would promote the activation of multiple oxidative and inflammatory processes.<sup>16,21,41</sup> It has been previously reported that the expression of sensitive systemic markers, such as tumor necrosis factor,<sup>42</sup> C-reactive protein (CRP),<sup>43</sup> and platelet activation,<sup>21</sup> are elevated in patients with OSA. In particular, CRP is a reliable and widely used marker for presence and severity of inflammation and it has been suggested to contribute to the development of white matter hyperintensities,<sup>44</sup> although this association has been contested in some studies.<sup>45,46</sup> We also measured CRP level in the current study and found that the highest quartile of high-sensitivity CRP yielded an almost twofold risk of presenting WMC compared with the lowest quartile (Table S1). However,

our finding on the role of CRP as a biomarker mediating the OSA-derived WMC is inconclusive, because the level of high-sensitivity CRP was not associated with the presence or severity of OSA in our sample (Table S2).

### OSA and Stroke

Because WMC can be considered a subclinical stroke,<sup>1-4</sup> the same pathogenic mechanisms as those in stroke patients can be suggested in the individuals with WMC. Additionally, the concept of OSA as a risk factor for ischemic stroke derives from the evidence associating sleep disordered breathing with hypertension and cardiovascular events, both of which are well-known risk factors for both WMC and stroke.<sup>47,48</sup> Many existing studies establish a strong association between sleep disordered breathing and cerebrovascular diseases.<sup>14,16,49-51</sup> Of interest, Harbison et al.<sup>49</sup> addressed the association of OSA with development of WMC and stroke, suggesting that the white matter integrity in OSA may predispose to changes that may lead to stroke.

We demonstrated with our epidemiologic data that having moderate to severe OSA had an approximately twofold increased risk of exhibiting WMC. In this respect, our findings are similar to those from the previous studies that defined a relationship between increased severity of the disease and an incremental increase in the risk of the outcome, such as stroke,<sup>14</sup> death after ischemic stroke,<sup>52</sup> cardiovascular mortality,<sup>53</sup> and death.<sup>14,54</sup> In contrast to patients with more severe OSA, individuals with mild OSA were not at a higher risk than healthy individuals. These findings confirm that increased severity of the disease affects the future risk of subclinical and clinical cerebrovascular diseases, in addition to diabetes, hypertension, and other cardiovascular risk factors.

Nonetheless, the association between mild OSA and simple snoring with cardiovascular risk has been shown in few epidemiologic studies,<sup>53,55</sup> and a possible risk of mild disease severity cannot be neglected.<sup>53</sup> In our data, only 35.51% of individuals with presence of OSA (AHI  $\geq$  5) reported habitual snoring or observed apneas, and 40.65% reported additional symptom of excessive daytime sleepiness (Table S3). It is also notable that these rates were even smaller (30.43% and 35.40%, respectively) in our mild OSA group. We can infer from these data that the presence of disease is accompanied by relatively small subjective symptoms in patients. Thus, early screening and treatment of OSA could prevent vascular brain injury.

### Limitations

One limitation of this study is regarding asymmetrical sex ratio of the sample population. Because sex is known to be an important determinant of the development of WMC<sup>56</sup> and OSA,<sup>57</sup> an unequal ratio of males (29.03%,  $n = 146$ ) to females (70.97%,  $n = 357$ ) may have affected the overall prevalence of both symptoms in the current sample.

### Summary

This study provides evidence for the association between OSA and WMC. Our major finding was that moderate to severe OSA, but not mild OSA, was independently associated with the prevalence of WMC. We also observed higher prevalence of moderate to severe OSA associated with increasing WMC, suggesting that the severity of disease affects the outcome of brain

structural modification. An increased risk of WMC may be via number of pathophysiologic mechanisms influenced by direct hemodynamic changes and intermittent hypoxemia, and consequent vascular changes that could lead to the development of symptomatic cerebrovascular diseases. Thus, it is suggested that early recognition and treatment of OSA could reduce the risk of stroke and vascular dementia. Utilization of advanced brain imaging techniques, such as a diffusion-tensor imaging, may examine WMC in a seemingly normal brain and further expand our understanding of WMC in OSA.

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### DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Thomas is co-inventor and patent holder of the ECG-derived sleep spectrogram, which may be used to phenotype sleep quality and central/complex sleep apnea. The technology is licensed by Beth Israel Deaconess Medical Center to MyCardio, LLC. He is also co-inventor and patent holder of the Positive Airway Pressure Gas Modulator, being developed for treatment of central/complex sleep apnea. He is a consultant in software development for DeVilbiss. The other authors have indicated no financial conflicts of interest.

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METHOD

Study Background

Participants of the current study are individuals enrolled in the Korean Genome and Epidemiology Study (KoGES) that started in 2001 under its original title, Korean Health and Genome Study (KHGS). Detailed information on the study background has been previously published.<sup>1</sup> Korean adults age 40-69 y were recruited to participate in this project that was supported by the Korea National Institute of Health to investigate the prevalence and risk factors for various chronic diseases that are present in Koreans. Participants of this current study include individuals enrolled in the Ansan cohort, which consists of residents of a suburban community of Ansan City, 32 km southwest of Seoul. The original Ansan cohort members were randomly selected from the telephone directory entries that were put together by local telephone companies. Of the total 10,975 calls made to the residents of Ansan, 5,020 (2,523 men and 2,497 women) attended the baseline examination (positive response rate = 45.7%) and were followed with biennial examinations on medical history, health status, and sleep related problems.

Study Sample

The current polysomnography (PSG) protocol was introduced to the general KoGES examinations in 2009 (fifth evaluation), and structural brain magnetic resonance imaging (MRI) was additionally included in 2011 (sixth evaluation) as a sub-study on aging. Participants who performed all MRI, PSG, and core examinations in 2011 were targeted for the current analyses.

A total of 1,529 participants visited the Korea University Ansan Hospital between March and December of 2011, and PSG

and MRI were performed on those who attended follow-up examinations and were eligible to participate in both procedures. We used random selection to recruit our participants for the two adjunct studies, but our current study sample was generally older ( $59.63 \pm 7.48$  y versus  $57.74 \pm 7.12$  y,  $P < 0.0001$ ) and had a greater proportion of females (70.97% versus 53.27%,  $P < 0.0001$ ) compared with those who were not included in the current analysis. The prevalence of hypertension and diabetes mellitus were not significantly different between the two groups.

Nocturnal PSG was performed on 542 individuals and MRI was performed on 551 individuals, for a total of 525 who completed both examinations. However, we excluded those who had preexisting cerebrovascular diseases ( $N = 10$ ) or major cardiovascular accidents ( $N = 21$ ) from the analyses, and a total of 503 individuals remained as the final sample of the current study. This number exceeds the targeted sample size ( $N = 145$ ) that was determined by a power analysis,<sup>2</sup> with error probability ( $\alpha$ ) of 0.05 and a false-negative rate ( $\beta$ ) of 0.05 (i.e., power of 0.95). An informed consent form was signed by each participant, and the study procedure was approved by the institutional review board of the Korea University Ansan Hospital.

Polysomnography

Overnight PSG was performed with a comprehensive portable device (Embletta® X-100; Embla Systems, Broomfield, CO, USA) at home or at the sleep laboratory onsite. All PSG results were manually scored using the standard criteria<sup>3</sup> and the following outcome variables were documented: single-channel electroencephalogram (EEG) (C4-A1), electrooculogram (EOG), chin electromyogram (EMG), electrocardiography (EKG), airflow at the nose and mouth (using the pressure trans-

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**Table S1**—Odds ratio of the presence of white matter changes in high-sensitivity C-reactive protein categories

	Odds ratio (95% confidence intervals)	
	Unadjusted P value	Adjusted P value <sup>a</sup>
Log(hs-CRP)		
Quartile I (< -0.42)	132 (26.24%)	REF
Quartile II (-0.42 to < -0.20)	125 (24.85%)	1.87 (1.12-3.13)
Quartile III (-0.20 to < 0.05)	123 (24.45%)	1.58 (0.94-2.66)
Quartile IV ( $\leq 0.05$ )	123 (24.45%)	1.99 (1.19-3.34)

Unadjusted P-value was calculated from a univariate logistic regression analysis and adjusted p-value was calculated from a multivariate logistic regression analyses. <sup>a</sup>Adjusted for age, sex, body mass index, heavy drinking, current smoking, diabetes, hyperlipidemia, and hypertension. hs-CRP, high-sensitivity C-reactive protein; Log(hs CRP), log transformed value of hs-CRP.

**Table S2**—Comparisons of high-sensitivity C-reactive protein values in obstructive sleep apnea groups

	AHI < 5 N = 289	5 ≤ AHI < 15 N = 161	AHI ≥ 15 N = 53	Unadjusted P value	Adjusted P value <sup>a</sup>
Log (hs CRP)	-0.21 ± 0.40	-0.13 ± 0.41	-0.12 ± 0.46	0.11	0.87

Unadjusted P value calculated from the Kruskal-Wallis test and the adjusted P value calculated from analysis of covariance. <sup>a</sup>Adjusted for age, sex, body mass index, current smoking status, moderate-heavy drinking, diabetes mellitus, and hypertension. AHI, apnea-hypopnea index; hs-CRP, high-sensitivity C-reactive protein; Log(hs CRP) = log transformed value of hs-CRP.



**Table S3**—Subjective sleep related symptoms in obstructive sleep apnea groups

Sleep variables from the questionnaire	No OSA (AHI < 5)	Presence of OSA (AHI ≥ 5)	P value <sup>a</sup>	Mild OSA (AHI 5-15)	Moderate to severe OSA (AHI ≥ 15)	P value <sup>b</sup>
N (%)	289 (57.45%)	214 (42.54%)		161 (32.01%)	53 (10.54%)	
Habitual snoring	35 (12.11%)	60 (28.04%)	< 0.0001	38 (23.60%)	22 (41.51%)	< 0.0001
Observed apneas	15 (5.19%)	42 (19.63%)	< 0.0001	24 (14.91%)	18 (33.96%)	< 0.0001
Either habitual snoring or observed apneas	43 (14.88%)	76 (35.51%)	< 0.0001	49 (30.43%)	27 (50.94%)	< 0.0001
EDS	17 (5.88%)	24 (11.21%)	0.03	17 (10.56%)	7 (13.21%)	0.03
Either habitual snoring, observed apneas, or EDS	56 (19.38%)	87 (40.65%)	< 0.0001	57 (35.40%)	30 (56.60%)	< 0.0001

P values were calculated from the  $\chi^2$  test. <sup>a</sup>P value comparing no OSA versus presence of OSA. <sup>b</sup>P value comparing no OSA versus mild OSA versus moderate to severe OSA. AHI, apnea-hypopnea index; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea.

ducer airflow (PTAF) sensor), the chest and abdominal respiratory movement (respiratory impedance), oxygen saturation (pulse oximetry), and the body position.

Respiratory events were scored according to the American Academy of Sleep Medicine guideline.<sup>4</sup> Apneas were defined when airflow was reduced to  $\geq 90\%$  of the baseline values for at least 10 sec. Additionally, hypopneas were defined by a  $\geq 30\%$  reduction of airflow for at least 10 sec accompanied by at least a 4% drop in oxygen saturation (SaO<sub>2</sub>). Apnea-hypopnea index (AHI) was calculated by averaging the total number of obstructive apneas and hypopneas per h of sleep, and obstructive sleep apnea (OSA) severity was defined by three AHI categories: no OSA (AHI < 5), mild OSA (5  $\leq$  AHI < 15), and moderate to severe OSA (15  $\geq$  AHI).

Data were manually scored by two well-trained technicians who had  $\geq 5$  y of experience with PSG monitoring and scoring. For an intrareliability assessment, the PSG data of 30 participants were rescored across a 1-mo interval by the two scorers who were blinded to their (and each other's) previous data. Internal consistency was calculated for AHI using Cronbach alpha,<sup>5</sup> and the results showed high intrarater reliability for each rater (Cronbach alpha = 0.996 and 1.00). We also conducted an interscorer reliability assessment for AHI (n = 30) and obtained a high reliability measure (Cronbach alpha = 0.998). The scorers were also blinded to each other's scoring results.

### Structural Neuroimaging

MRI was performed within an average of 2.30 days (standard deviation, 3.96 days) from the PSG monitoring. All scans were performed on a GE Signal HDxt 1.5T MR imaging scanner (GE Medical Systems, Waukesha, WI, USA) with an eight-channel head coil. T2-weighted FLAIR images were used to evaluate the white matter in the brain. The FLAIR parameters were field of view (FOV) = 220  $\times$  220 mm<sup>2</sup>, matrix = 256  $\times$  224, 5-mm section thickness with 2-mm interval gap, repetition time (TR) = 8,802 ms, echo time (TE) = 129 ms, inversion time (TI) = 2,200 ms, and number of acquisition = 1.

White matter changes (WMC) on MRI were identified when there were hyperintensities  $\geq 5$  mm on FLAIR images. The degree of WMC was scored using a four-point age-related white matter change (ARWMC) scale designed by Wahlund et al.<sup>6</sup> WMCs in each right and left hemisphere was rated as 0 (no lesion), 1 (focal lesion,  $\leq 10$  mm), 2 (beginning confluent lesions), or 3 (confluent lesions involving the entire region) in five different regions (fron-

tal, parieto-occipital, temporal, basal ganglia, and infratentorial). The WMC total score was derived from summing the individual scores in each of the five regions, with the total score ranging from 0 to 30. The total score of the WMC scale has been shown to correlate with lesion volume in previous reports.<sup>7</sup>

WMC was rated by a single scorer (HSS) who was blinded to the study participant's OSA status. An intrascorer reliability was conducted across a 1-mo interval with the data of 56 participants, and the results indicated a high repeatability (Cronbach alpha = 0.96).

### Other Covariates

Covariate measures were determined from a health examination and a questionnaire-based interview held onsite. Cardiovascular disease was determined by the presence of one of the following: myocardial infarction, congestive heart failure, coronary artery disease, or peripheral vascular disease. Diabetes mellitus was defined as taking insulin or hypoglycemic medication or fasting glucose  $\geq 125$ mg/dL. Hyperlipidemia was determined when participants were taking lipid-lowering medication and had total cholesterol  $\geq 240$  mg/dL. Hypertension was defined with self-reported antihypertensive medication or systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg. Alcohol consumption of 15 g per day was considered as moderate to heavy drinking.<sup>1</sup>

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