Sleep Disordered Breathing and White Matter Hyperintensities in Community-Dwelling Elders

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Study Objectives: To examine the association between markers of sleep-disordered breathing (SDB) and white matter hyperintensity (WMH) volume in an elderly, multiethnic, community-dwelling cohort.

Methods: This is a cross-sectional analysis from the Washington Heights-Inwood Columbia Aging Project (WHICAP), a community-based epidemiological study of older adults. Structural magnetic resonance imaging was obtained starting in 2004; the Medical Outcomes Study-Sleep Scale (MOS-SS) was administered to participants starting in 2007. Linear regression models were used to assess the relationship between the two MOS-SS questions that measure respiratory dysfunction during sleep and quantified WMH volume among WHICAP participants with brain imaging.

Results: A total of 483 older adults had both structural magnetic resonance imaging and sleep assessment. Self-reported SDB was associated with WMH. After adjusting for demographic and vascular risk factors, WMH volumes were larger in individuals with frequent snoring (β = 2.113, P = 0.004) and among those who reported waking short of breath or with headache (β = 1.862, P = 0.048).

Conclusions: In community-dwelling older adults, self-reported measures of SDB are associated with larger WMH volumes. The cognitive effects of SDB that are increasingly being recognized may be mediated at the small vessel level.

Keywords: cerebrovascular disease, cognition, sleep disordered breathing


Significance
White matter hyperintensities are a frequent manifestation of subclinical cerebrovascular disease and are linked to dementia. Our study confirms the association between sleep-disordered breathing and white matter hyperintensities in an elderly, community-dwelling cohort. These findings significantly enhance the generalizability of this relationship and may have implications for dementia prevention and treatment.

INTRODUCTION
Sleep disordered breathing (SDB) is a general term that refers to nocturnal apneas, hypopneas, and intermittent hypoxemia, most often due to obstructive sleep apnea (OSA). It is a condition that increases in frequency with advancing age. Estimates of the prevalence of SDB range from 2% to 4% in middle age to 7% to 44% in the elderly, although a prevalence as high as 60% has been reported in some community-dwelling elderly individuals. Although SDB has a well-established relationship with cardiovascular disease and stroke, the extent to which it is associated with subclinical cerebrovascular disease is less well understood.

Subclinical cerebrovascular disease frequently manifests as white matter hyperintensities (WMH), areas of increased signal on T2-weighted magnetic resonance imaging (MRI) scans. In addition to their association with overt cerebrovascular disease, WMH are linked to cognitive aging and dementia and are hypothesized to be in the causal pathway to Alzheimer disease. The identification of reversible risk factors for WMH therefore has important public health implications. To date, few studies have examined the relationship between WMH and SDB. Those that have shown a positive association are limited in their generalizability because data were ascertained in racially and ethnically homogeneous cohorts or were limited to a sleep clinic population. We therefore evaluated the association between self-reported measures of SDB and WMH volume in an elderly, multiethnic, community-dwelling cohort using quantified WMH volumes. Our goal was to determine whether or not participants who endorsed symptoms of SDB would have larger WMH volumes.

METHODS
Study Population
This study was a cross-sectional analysis from the ongoing Washington Heights-Inwood Columbia Aging Project (WHICAP), a community-based longitudinal study of aging in older adults of northern Manhattan. Sampling and follow-up methods of the WHICAP study have been previously described in detail. Participants received in-home visits approximately every 18 to 24 months, which included physical and neurologic examinations and a detailed neuropsychological test battery. Dementia was diagnosed using standard criteria at a consensus conference of physicians and neuropsychologists with expertise in cognitive aging and dementia as previously described. Depressive symptoms were assessed with the 10-item version of the Center for Epidemiologic Studies-Depression (CES-D) scale. The conventional cutoff score of ≥ 4 was used to indicate the presence of depressive symptoms. Recruitment, informed consent, and study procedures were approved by the institutional review board of Columbia University Medical Center.
In our study, we used the two Likert-type MOS-SS questions that measure respiratory dysfunction during sleep: “how often do you snore during your sleep” and “how often do you awake short of breath or with headache”. These self-reported factors have been shown to have a high predictive accuracy for SDB and are incorporated into many SDB screening scales. We dichotomized the responses to these two questions into high and low frequency, taking into account the distribution of responses to each question in our study population. Specifically, individuals were considered to have a high likelihood of SDB if they reported 1 through 4 to “waking short of breath or with headache” and 1 through 3 to “snoring”. These dichotomized SDB variables were then used in the regression models as described below.

To further assess the likelihood of SDB, we calculated a “four variable” score for each subject following the work of Takagami et al. and Silva et al. This score assesses risk of SDB using a combination of factors such as sex, blood pressure (BP), body mass index (BMI) and self-reported snoring frequency. Sex was assigned a value of 4 for men and 0 for women; BMI in kg/m² was assigned a value between 1 and 6 based on the following categories: < 21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, ≥ 30; BP in mmHg was assigned a value between 1 and 4 based on the following categories: systolic BP [SBP] < 140 or diastolic BP [DBP] < 90, SBP 140–159 or DBP 90–99, SBP 160–179 or DBP 100–109, SBP ≥ 180 or DBP ≥ 110; and snoring was assigned a value of 4 if high frequency and 0 if low frequency, as determined by MOS-SS response. These variables were then combined in the following equation: (sex) + (BMI category value) + (BP category value) + (snoring), where the maximum score is 18. We calculated a score for each participant and dichotomized participants into “high likelihood” (score ≥ 11) and “low likelihood” (score < 11) of SDB. A cutoff of 11 had a sensitivity of 0.93 and specificity of 0.66 for moderate to severe SDB confirmed by polysomnography in the derivation cohort.

Statistical Analysis
Baseline characteristics were compared between participants with and without MRI data. In the subsample of those with both sleep and MRI data, baseline characteristics of those with a high likelihood of SDB were compared to those without. Chi-square tests and analysis of variance were used to compare dichotomous and continuous variables, respectively, across groups.

Linear regression models were used to evaluate the relationship between WMH volume (as the outcome variable) and dichotomized responses to the two MOS-SS SDB questions and the four-variable score. A series of models was used to adjust for potential relevant variables. Model 1 adjusted only for intracranial volume (ICV); model 2 included ICV and demographic factors including race/ethnicity (white race as the reference), age (as a continuous variable), sex (male as the reference); model 3 included ICV, demographic factors, and history of hypertension (as a dichotomous variable, no hypertension as the reference) and apolipoprotein E (APOE) ε4 genotype (as a dichotomous variable, no ε4 alleles as the reference). This analysis was then repeated excluding participants who
met criteria for dementia at the time of sleep data acquisition. A stratified analysis was conducted to evaluate whether the relationship between WMH and dichotomized responses to the two MOS-SS SDB questions and the four-variable score varied by race/ethnicity. As years of education were associated with snoring in univariate testing, we did a post hoc analysis to assess whether the association between snoring and WMH would remain after adjusting for years of education. All analyses were conducted with SPSS Statistics version 21.0 (IBM, Armonk, NY). All P values were based on two-sided tests with the significance level set at 0.05.

RESULTS

Missing Data Analysis

Of the 1,306 individuals eligible for follow-up in 2007 when the MOS-SS was introduced, 1,002 completed the questionnaire (Figure 1). Compared with those without sleep data (n = 304), those with sleep information had a higher mean BMI; other characteristics did not differ (Table 1). Of the 1,002 individuals with sleep information, MRI scans were obtained from 516 (Table 2). Compared with those who did not undergo MRI (n = 486), those who did were more likely to be African American, less likely to have hypertension, and had more years of education. There were no other significant differences between the groups.

Subject Characteristics

Four hundred eighty-three of the 516 participants who underwent MRI (94%) had complete FLAIR and T1 imaging and served as the basis for our analysis. On average, sleep data were collected 3.4 y (standard deviation [SD] 1.4 y) after the time of MRI. The average age of the sample at the time of sleep data collection was 83 y (SD 5.3 y). At the time of MRI acquisition, 19 participants met diagnostic criteria for dementia; dementia developed in an additional 37 participants in the interval between MRI and sleep data collection.

Detailed baseline characteristics at the time of MRI for those with and without SDB as determined by responses to MOS-SS are presented in Table 3. Individuals with frequent snoring had larger WMH volumes. Additionally, individuals with frequent snoring were more likely to be Hispanic, had a history of hypertension, and had fewer years of education than those with infrequent snoring. Individuals with frequent waking short of breath were more likely to have dementia than those with infrequent waking short of breath. The remaining baseline characteristics did not differ between the two groups.

Association between SDB and WMH Volume

Across all three models, individuals with frequent waking short of breath and frequent snoring had larger WMH volumes than those with infrequent events. Individuals with a high likelihood of SDB by four-variable score had a larger volume of WMH compared with those with a low likelihood (Table 4).

Sensitivity Analyses

When participants with dementia at the time of sleep data acquisition (n = 56) were excluded from the analysis, the results remained similar. In the fully adjusted model, those who reported frequent snoring or a high likelihood of SDB by four-variable score had larger WMH volumes (Table 4). However, there was only a trend toward significance for those with frequent waking short of breath. We additionally adjusted for years of education in the model as years of education were

| Table 1—Demographic and clinical characteristics of sleep-eligible subjects. |
|-----------------------------------|-----------------------------------|-----------------|
|                                   | Answered Sleep Questionnaire      | Did Not Answer Sleep Questionnaire |
|                                   | (n = 1,002)                       | (n = 304)       | P value |
| Age in y, mean (SD)               | 79.7 (5.9)                        | 80.1 (6.7)      | 0.32    |
| Female, n (%)                     | 729 (72.8)                        | 209 (68.8)      | 0.19    |
| Race/ethnicity, n (%)             |                                   |                 | 0.18    |
| African American                  | 277 (27.6)                        | 102 (33.6)      |         |
| Hispanic                          | 422 (42.1)                        | 210 (69.1)      |         |
| White                             | 289 (28.8)                        | 87 (28.6)       |         |
| Other                             | 14 (1.4)                          | 5 (1.6)         |         |
| Education y, mean (SD)            | 10.3 (5.1)                        | 10.0 (4.6)      | 0.40    |
| Hypertension, n (%)               | 733 (73.2)                        | 215 (70.7)      | 0.42    |
| Diabetes, n (%)                   | 183 (18.3)                        | 56 (18.4)       | 0.93    |
| Stroke                            | 78 (7.8)                          | 26 (8.6)        | 0.72    |
| Body mass index in kg/m², mean (SD)| 28.2 (5.7)                        | 27.2 (5.5)      | 0.02    |
| APOE e4, n (%)                    | 235 (23.5)                        | 79 (26.0)       | 0.19    |
| Depression, n (%)                 | 43 (4.3)                          | 20 (6.6)        | 0.12    |
| Frequent waking short of breath, n (%)| 73 (7.3)                        |                 |         |
| Frequent snoring, n (%)           | 132 (13.2)                        |                 |         |

Baseline characteristics, aside from sleep disordered breathing frequency, are from the time of magnetic resonance imaging for participants with imaging. For participants without imaging, baseline characteristics are from the follow-up visit closest to 2004, the time the imaging study began. APOE, apolipoprotein E; SD, standard deviation.
associated with snoring in univariate analyses (Table 3); the association between snoring and WMH remained ($\beta = 2.093$, $P = 0.005$) after adjustment.

In stratified analyses, the association between SDB and WMH volume varied by race/ethnicity (Table 5). The association was strongest in African Americans (frequent snoring...
We found that individuals who reported respiratory impair-
ment during sleep had larger WMH volumes. Similarly, WMH
volumes were larger in those with a higher likelihood of SDB
(frequent snoring $\beta = 0.61$, $P = 0.493$; frequent waking short of
breath $\beta = 0.01$, $P = 0.992$). In white participants, only the
association between snoring and WMH was significant (frequent
snoring $\beta = 2.48$, $P = 0.019$; frequent waking short of breath
$\beta = 1.25$, $P = 0.347$). When likelihood of SDB was approxi-
mated by the four-variable score, the association with WMH
volume also differed across race/ethnicity groups. Statistical
significance was seen among white participants ($\beta = 1.99$,
$P = 0.003$) with a trend toward significance in African Ameri-
cans ($\beta = 3.08$, $P = 0.076$). The association was not significant
among Hispanics ($\beta = 1.16$, $P = 0.279$). The association be-
tween between SDB and WMH volume did not differ between
men and women.

**DISCUSSION**

We found that individuals who reported respiratory impair-
ment during sleep had larger WMH volumes. Similarly, WMH
volumes were larger in those with a higher likelihood of SDB
determined by the four-variable score. These associations
remained significant when controlling for WMH risk factors,
including hypertension and age, and after a sensitivity analysis
excluding participants with dementia. These findings suggest
a relationship between SDB and WMH.

Our study adds to the small but emerging body of litera-
ture on SDB and WMH, which has shown mixed results. A
relationship between WMH and obstructive sleep apnea (OSA)
measured by polysomnography was previously reported in a
middle-aged Korean population. Similarly, an association was
demonstrated between polysomnography-confirmed OSA and
visually rated WMH in a middle-aged Japanese group referred
to a sleep clinic. In a subset of the Sleep Heart Health Study,
a predominantly white cohort, WMH were associated only
with central but not with obstructive apneic events. However,
some investigations have failed to show an association be-
tween WMH and SDB or are limited by small sample size.

It is important to note that prior studies of SDB and WMH
used visual rating scales to measure WMH. We use a fully
automated quantification method, which makes direct compari-
son between the WMH volumes we describe and those of
prior studies difficult. Furthermore, because our sample was
older than that of prior studies of imaging and SDB, we would
expect our WMH volumes to be larger as age is the strongest
predictor of WMH.

To our knowledge, our study is the first to examine the as-
sociation between SDB and quantified WMH volumes in an
elderly, multiethnic, community-dwelling cohort. Although
there was a suggestion of a difference in association between
SDB and WMH by race/ethnicity in our study, the overall
number of participants with SDB within each racial group is
small, raising issues of power in the stratified analysis. In
addition, those with and without sleep data were not evenly
matched in terms of the proportion of African American and
Hispanic participants; thus, there may be inherent selection
bias in this sample underlying the race/ethnic differences.
Interpretation of these stratified results requires further study.

The association between SDB and WMH that we observed
may be particularly relevant as an explanatory factor for sleep
related cognitive changes. The cognitive effects of SDB are an
active area of investigation. In two recent prospective studies
on cognition and SDB, measures of hypoxia were associ-
ated with the development of incident cognitive impairment
over the study period. Because of the known association

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**Table 4**—Association between sleep disordered breathing and white matter hyperintensity volume.

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 3 for Individuals without Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
<td>$\beta$</td>
<td>$P$</td>
</tr>
<tr>
<td>Frequent snoring</td>
<td>2.047</td>
<td>0.005</td>
<td>1.940</td>
<td>0.006</td>
</tr>
<tr>
<td>Frequent waking short of breath</td>
<td>2.024</td>
<td>0.039</td>
<td>1.909</td>
<td>0.041</td>
</tr>
<tr>
<td>Four-variable score</td>
<td>1.686</td>
<td>0.016</td>
<td>1.610</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for intracranial volume (ICV). Model 2: Adjusted for ICV, age, race, and sex. Model 3: Adjusted for ICV, age, race, sex, hypertension, and apolipoprotein E $\varepsilon$4. Excludes 56 individuals with dementia. When the four-variable score is used as a predictor, sex and hypertension are no longer included in the models as they are incorporated into the score.

**Table 5**—Association between sleep disordered breathing and white matter hyperintensity volume, stratified by race/ethnicity.

<table>
<thead>
<tr>
<th></th>
<th>Frequent Snoring</th>
<th>Frequent Waking Short of Breath</th>
<th>Four-Variable Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 3a</td>
<td>Model 3a</td>
<td>Model 3a</td>
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<tr>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
<td>$\beta$</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>5.38</td>
<td>0.008</td>
<td>5.72</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.61</td>
<td>0.493</td>
<td>0.01</td>
</tr>
<tr>
<td>White</td>
<td>2.48</td>
<td>0.019</td>
<td>1.25</td>
</tr>
</tbody>
</table>

*Adjusted for intracranial volume, age, sex, hypertension, and apolipoprotein E $\varepsilon$4. When the four-variable score is used as a predictor, sex and hypertension are no longer included in the models as they are incorporated into the score.
between WMH and cognitive impairment, we speculate that the cognitive effects of SDB may be a function of small-vessel cerebrovascular disease, with hypoxia as a potential mediator. Altered cerebral autoregulation may offer a mechanistic link. Cerebral autoregulation is the brain’s ability to maintain constant blood flow across a wide range of perfusion pressures and is essential for normal brain function. Several studies have shown that cerebral autoregulation is altered in SDB. This autoregulatory dysfunction may render the brain, particularly the white matter, vulnerable to hypoperfusion and hypoxia, which may manifest as WMH.

Alternatively, SDB may mediate small-vessel cerebrovascular disease by increasing cardiovascular risk factors including hypertension. Interestingly, the association between WMH volume and SDB remained significant after adjusting for hypertension, suggesting that blood pressure alone is not the primary mediator of the association. Because of the emerging relationship between Alzheimer disease and WMH, and specific data linking APOE ε4 carriers to larger WMH volumes, we adjusted for APOE ε4 to remove variance that could be related to biological risk factors for Alzheimer disease. In addition, as APOE ε4 has also been associated with SDB in two large sleep cohorts, we adjusted for it to account for a possible shared genetic basis for SDB and WMH. Adjusting for APOE ε4 had no effect on our results. Although the exact pathophysiological relationship remains to be clarified, the role that WMH play in the cognitive effects of SDB is an emerging area of study.

Strengths and Limitations
The major limitation of this study is the use of self-reported sleep data, which risks inaccurate approximation of SDB. Without overnight polysomnography, the gold standard for SDB diagnosis, we cannot verify the true prevalence of SDB. Our prevalence of SDB is lower than that of another community-based study of elderly individuals where SDB diagnosis was made with polysomnogram. Our prevalence of SDB may be lower because reports of snoring decrease with age due to less accurate reporting of snoring by elderly bed partners. Our prevalence of SDB is also lower compared with a racial and ethnically diverse community-based study where frequent snoring was reported. The proportion of men in our study is smaller than in this other community-based study. Given rates of SDB are two to three times higher in men compared with women, this difference in sex distribution may have contributed to the lower prevalence of SDB we observed. We also do not have information on treatment for SDB so cannot exclude the possibility that some participants may have been treated.

Additionally, the inclusion of participants with dementia may have affected the accuracy of sleep questionnaire responses. However, half of these participants had assistance from family in answering the questions and our results remained when participants with dementia were excluded. Another important limitation stems from the fact that our sample was one of convenience from the WHICAP cohort. To address this limitation we provide detailed comparisons between those with and without sleep data as well as those who had and who had not undergone MRI. However, there are differences between the groups that may have contributed to selection bias in our sample. Most importantly, we may have oversampled participants with SDB, as those with sleep data had a higher BMI than those lacking sleep data.

In terms of our imaging data, we do not have regional distributions of WMH in our cohort. However, in our data in general, we see no notable differences in clinical outcome as a function of periventricular versus deep distribution and, consistent with other investigators, view the distinction as arbitrary. In addition, our WMH processing stream excludes WMH in the basal ganglia.

Last, the cross-sectional design limits our ability to infer causality in the observed associations. We cannot rule out the possibility that existing WMH actually lead to SDB, especially because most MRI scans were obtained prior to sleep data collection.

The main strength of this study is our ability to evaluate the relationship between WMH and SDB in a large, multiethnic, elderly, community-dwelling population. As prior studies have not included a diverse, community-dwelling population, our results significantly enhance the generalizability of the association between WMH and SDB among African American and white individuals and emphasize the need for additional study in multiethnic cohorts given the suggestion of differences by race/ethnicity that we observed. Furthermore, using rigorously quantified WMH allows more accurate lesion measurements and better potential for comparison with future studies. Although we used self-reported sleep measures, our results remained when we used the four-variable score, a validated SDB screening tool.

Our results indicate that self-reported SDB is associated with larger WMH volumes among the elderly. Given emerging data on the cognitive effects of SDB, we suggest that this relationship may be mediated at the small-vessel level. We hope that our results create a useful framework for future study.

REFERENCES


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