

Sleep-Disordered Breathing and White Matter Disease in the Brainstem in Older Adults

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Study Objectives: To examine whether sleep-disordered breathing is associated with white matter disease in the brainstem.

Design: A population-based longitudinal study.

Setting: Allegheny County, PA; Sacramento County, CA; and Washington County, MD

Patients or Participants: A total of 789 individuals, aged 68 years or older, drawn from the Sleep Heart Health Study.

Interventions: N/A.

Measurements and Results: The participants underwent home polysomnography in 1995-1998 and cerebral magnetic resonance imaging in both 1992-1993 and 1997-1998. The apnea-hypopnea index was not associated with white matter disease in the brainstem, with or without adjusting for age, sex, race, community, body mass index, smoking status, alcohol use, systolic blood pressure, and the use of antihypertensive medication. In contrast, the arousal index (number of arousals per hour of sleep) was inversely associated with brainstem white matter disease

(odds ratio = 0.75 for a SD increase in the arousal index, 95% confidence interval: 0.62, 0.92).

Conclusions: The frequency of apneas and hypopneas was not associated with brainstem white matter disease in these older adults. A unique relationship with arousal frequency suggests that ischemic changes in the brainstem may be associated with arousals during sleep.

Key Words: Arousal, cerebrovascular disorders, polysomnography, magnetic resonance imaging

Abbreviations: WMD, white matter disease; MRI, magnetic resonance imaging; SHHS, Sleep Heart Health Study; CHS, Cardiovascular Health Study; REM, rapid eye movement; NREM, non-rapid eye movement; SDB, sleep-disordered breathing; ICC, intraclass correlation coefficients; OR, odds ratio; CI, confidence interval

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INTRODUCTION

WHITE MATTER DISEASE (WMD), DEFINED AS HYPERINTENSIVE LESIONS ON MAGNETIC RESONANCE IMAGING (MRI), IS A MARKER OF SUBCLINICAL CEREBROVASCULAR DISEASE.¹ Physiologic and pathologic studies suggest that WMD is primarily ischemic in origin,²⁻⁵ and epidemiologic studies demonstrate that WMD is associated with decline in cognitive function and stroke.⁶⁻⁸

There is growing evidence that sleep-disordered breathing (SDB) is associated with hypertension,^{9,10} ischemic heart disease,^{11,12} and stroke.¹³⁻¹⁵ The putative association of SDB with vascular disease raises the possibility that WMD in the brainstem may be increased in individuals with frequent respiratory events during sleep. Such lesions could be

postulated as the markers of secondary damage from apnea-associated hypertension. Alternatively, WMD in the brainstem, the location related to central respiratory control,¹⁶ may identify individuals with an increased propensity for underlying SDB due to the instability of respiratory control. However, epidemiologic studies have not yet addressed the association of SDB with WMD in the brainstem.

The present study used standardized polysomnography and MRI of the brainstem to examine the associations of various measures of SDB with WMD in the brainstem in a large community-based sample of older adults. We hypothesized that the frequencies of apneas, hypopneas, or arousals during sleep are positively associated with WMD in the brainstem.

METHODS

Study Population

The Sleep Heart Health Study (SHHS), designed to investigate the association of sleep apnea with the development of cardiovascular disease, recruited 6,841 participants from 6 ongoing cohort studies in 1995.¹⁷ The exclusion criteria were treatment for sleep apnea with continuous positive airway pressure, oxygen therapy at home, or having a tracheostomy. An unattended overnight polysomnogram was conducted in each SHHS participant's home in 1995-1998.¹⁸ One of the parent cohorts of the SHHS is the Cardiovascular Health Study (CHS).¹⁹ Three of the 4 CHS communities (Allegheny County, PA; Sacramento County, CA; and Washington County, MD) served as a part of the sampling frame for the SHHS. As a part of the CHS, participants underwent the first MRI study of the brain in 1992-1993 and the second MRI study of the brain from 1997 to 1998.²⁰ The average time interval was 3.6 years from the first MRI study to the polysomnography study and 1.4 years from the polysomnography study to the second MRI study. WMD in the brainstem in 1997-1998, instead of WMD in the brainstem in 1992-

Disclosure Statement

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1993, was chosen as the main outcome for the present analysis because it was assessed after polysomnography. A total of 1,250 people participated in both the CHS and the SHHS. Among them, 917 had an MRI scan in 1997-1998. For technical reasons (unreadable MRI scans or inability of MRI scans to be transferred to a reading station), only 801 MRI scans in 1997-1998 were read for WMD in the brainstem for the present study. The characteristics of the individuals who were excluded due to technical reasons were similar to those who had a readable MRI scan. Because there were only 12 participants with infarction in the brainstem in 1997-1998, those participants with infarction in the brainstem were excluded from all analyses. Therefore, a total of 789 participants, aged 68 years or older, constituted the study population of the present analysis. Both the SHHS and the CHS were approved by the institutional review board of each participating institution.

Polysomnography

A portable Compumedics PS-2 system (Compumedics Pty Ltd, Abbotsford, Victoria, Australia) was used for the unattended overnight polysomnography. The recorded channels included central electroencephalograms (C₃/A₂ and C₄/A₁), 2 electrooculograms, a bipolar chin electromyogram, a bipolar electrocardiogram, a finger pulse oximeter, chest and abdominal excursions measured by respiratory inductance plethysmography, airflow measured by oronasal thermocouples, body position measured by mercury gauge, and ambient light. The sleep studies from each field center were sent to the Sleep Reading Center (Case Western Reserve University, Cleveland, OH) for scoring, which followed the rigorous criteria of quality assurance previously described.¹⁸ Apnea was identified if airflow was absent or nearly absent (at least 75% below the baseline value) for at least 10 seconds. Hypopnea was identified if a discernible discrete reduction in airflow or thoracoabdominal movement (at least 30% below the baseline value) occurred for at least 10 seconds. The apnea-hypopnea index was defined as the average number of apneas or hypopneas, each associated with a decrease in oxygen saturation greater than or equal to 4%, per hour of sleep.¹⁷ The obstructive and central apnea indexes also were derived by dividing the total number of apneas with or without respiratory effort, respectively, by total sleep time. Arousal was identified, according to the American Academy of Sleep Medicine criteria, as an abrupt shift of at least 3 seconds in electroencephalographic frequency.²¹ The arousal index was defined as the average number of arousals per hour of sleep. The arousal

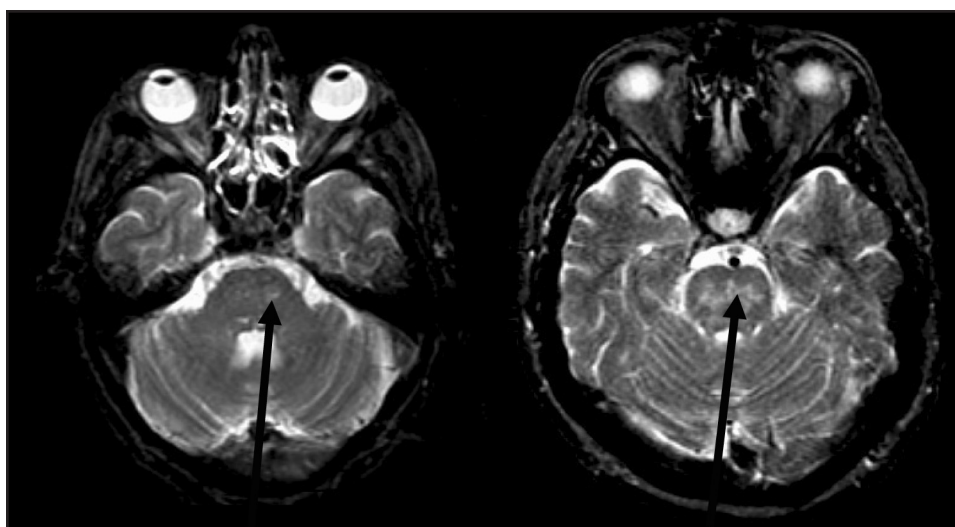
index was also obtained during both rapid eye movement (REM) and non-REM (NREM) sleep. The percentage of sleep time with oxygen saturation below 90%, the percentage of sleep time in apneas and hypopneas, the minimum oxygen saturation in each of REM and NREM sleep, the percentage of sleep time in each sleep stage, and sleep efficiency (sleep time / time in bed) were also quantified.

Compared to that of the laboratory polysomnography, the night-to-night (within 4 months) variability of the home polysomnography in the SHHS was acceptable, with the intraclass correlation coefficients (ICC) over 0.75 for both the apnea-hypopnea index and the arousal index.²² The SHHS also achieved a high degree of interscorer reliability for the apnea-hypopnea index, with the ICCs as 0.99.²³ The reliability of scoring for the arousal index was moderate. Although a study of early scoring showed that the ICC for the arousal index varied between 0.54 and 0.72, according to the experience of scorers,²³ subsequent tracking of reliability showed that, over the course of the SHHS, the ICC varied between 0.72 and 0.78. The results from 169 participants were excluded from the analysis of the arousal index because of technical problems with the electromyographic or electroencephalographic channel that limited the reliability of scoring arousals in their studies. The individuals whose data were excluded had a similar proportion of WMD in the brainstem but a higher apnea-hypopnea index (mean: 11.5 vs 9.3 per hour), compared to those who were included in the analysis.

MRI Measurement

Cerebral MRI was performed on 1.5-T imagers (GE Medical Systems, Milwaukee, Wisc; Picker, Cleveland, OH) at each field center. Three scanning sequences from the CHS were utilized in the present study: axial spin-echo T1 (repetition time millisecond per echo time millisecond, 500/15-25) weighted, axial spin-density (3000/20-35) weighted, and axial T2 (3000/70-100) weighted imaging.²⁴ All axial sections with 5-mm thickness and no gaps were parallel to the anterior commissure-posterior commissure line. Images were archived on magnetic tapes and sent to the CHS MRI Reading Center (Department of Radiology, Johns Hopkins Hospital, Baltimore, MD) for interpretation. An atlas containing the anatomic localizations of the midbrain, the pons including the parabrachial nucleus within the pons, and the medulla was developed to aid MRI reading.^{25,26} The diencephalon-midbrain junction was identified by a low-intensity dot posteriorly, which is the highest end of the aqueduct of sylvius. Axial sections through the midbrain were also recog-

nized by the presence of the cerebral peduncles anterolaterally. The junction of the midbrain and the pons was identified by the junction of the aqueduct and the upper fourth ventricle. The junction of the pons and medulla was identified by the presence of the inferior cerebellar peduncles posterolaterally. The caudal medulla was characterized by the ventral sulcus anteriorly and the preolivary and postolivary sulci laterally. The criteria for WMD in the brainstem were hypointense or isointense but less hypointense than cerebrospinal fluid on T1 and hyperintense (relative to normal white matter) on proton density and T2 weighted MRI (Figure 1). The criteria for infarction in the brainstem were hypointense as cerebrospinal fluid on T1 and hyperintense (relative to normal gray matter) on proton density and T2 weighted MRI. WMD volume in the brainstem was defined as the sum of WMD volumes (areas of WMD × 5 mm) for contiguous axial sections from midbrain, pons, and medulla. WMD in the brainstem was defined as WMD volume in the brainstem greater than 100 mm³. Using 0, instead of 100 mm³, as the cutoff point, the results were virtually identical to those presented here. In addi-



Mild white matter disease in the brainstem on T2

Moderate/severe white matter disease in the brainstem on T2

Figure 1—Examples of mild and moderate/severe white matter disease in the brainstem on T2 weighted magnetic resonance imaging

tion, MRI stroke was defined as the presence of at least 1 lesion (equal to or larger than 3 mm), hypointense as cerebrospinal fluid on T1, and hyperintense (relative to normal gray matter) on proton density and T2 weighted MRI in the periventricular and subcortical areas of the brain.²⁷

The trained reader (a medical doctor), masked to the identities and characteristics of the participants, read all MRIs. A 10% random sample of the MRIs for the study population was also selected for rereading. An experienced radiologist reviewed 32 participants (8 participants each month) randomly over the period of data collection. The κ statistic, describing the intrareader reliability for identifying WMD in the brainstem, was 0.79 for the 1997 to 1998 studies; and the corresponding κ statistic for the interreader reliability was 0.86. For WMD volume in the brainstem, the ICC for the intrareader reliability was 0.93 for the 1997-1998 studies.

Other Covariates

Blood pressure and weight were measured at the time of polysomnography. A mercury sphygmomanometer was used to measure seated blood pressure, recorded as the average of the second and third readings.⁹ Hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg, or diastolic blood pressure greater than or equal to 90 mm Hg, or a self-reported use of antihypertensive medication. Weight was measured on a portable calibrated digital scale. Smoking history was obtained from a questionnaire administered at the time of polysomnography.

Other information such as age, height, alcohol use, prevalent coronary heart disease, and prevalent diabetes was obtained from the CHS database at the time of the first MRI study. Body mass index was calculated as weight in kilograms divided by square of height in meters. Alcohol use was defined as the self-reported number of alcoholic drinks per week. Prevalent coronary heart disease and diabetes were defined as whether a participant reported a diagnosis by physician.

Statistical Analysis

The distribution of participants' characteristics was examined according to the presence of WMD in the brainstem. To examine the independent associations of the measures of SDB with WMD in the brainstem, logistic regression analysis was utilized, adjusting for age, sex, race, community, body mass index, smoking status, alcohol use, systolic blood pressure, and use of antihypertensive medication. Because body mass index is a strong risk factor for SDB²⁸ and hypertension could be a causal pathway lying between SDB and vascular disease,⁹ the adjustment of body mass index, systolic blood pressure, and use of antihypertensive medication in the present analysis may be over adjusting. However, the results without adjusting for those factors were similar. To assess the consistency of the findings, multivariable logistic regression analysis was performed for each sex and race subgroup. Because the prevalence of SDB is higher in older adults¹⁴ and WMD in the brainstem is associated with MRI stroke, multivariable logistic regression analysis was also stratified by age (with approximately equal numbers of participants in each subgroup) and MRI stroke to examine the possible interactions. To further examine the effects of the measures of SDB on the development of WMD in the brainstem, multivariable logistic regression analysis was conducted after excluding those participants with WMD in the brainstem in 1992-1993. In addition, multivariable linear regression analysis was used to explore the associations of the measures of SDB with WMD volume in the brainstem. The associations of the measures of SDB with the change in WMD volume in the brainstem from 1992-1993 to 1997-1998 was also investigated after adjusting for WMD volume in the brainstem in 1992-1993, using multivariable linear regression analysis.

RESULTS

The proportion of participants with WMD in the brainstem was 26.9%. WMD in the brainstem was predominantly distributed in the pons (99% for pons, 8% for midbrain, and 1% for medulla). The proportion of participants with WMD in the brainstem that involved the parabrachial nucleus was 18.6%. Compared to those without WMD in the brainstem, the participants with WMD in the brainstem were older and more likely to be women, current smokers, and have evidence of MRI stroke (Table 1). There were no apparent differences between participants with and without WMD in the brainstem relative to the apnea-hypopnea index, the central or obstructive apnea indexes, the percentage of sleep time with less than 90% oxygen saturation, the percentage sleep time in apneas and hypopneas, the minimum oxygen saturation in REM or NREM sleep, the percentage of sleep time in stages 3 and 4 or in REM sleep, or sleep efficiency. However, participants with WMD in the brainstem had fewer arousals per hour of sleep (mean, [SD]: 18.1 [10.3] vs 21.0 [11.5]). Similarly, the number of arousals per hour of REM sleep (13.1 [9.8] vs 15.1 [11.3]) or of NREM sleep (19.3 [11.1] vs 22.3 [12.4]) was lower in participants with WMD in the brainstem.

In crude logistic regression analyses, the apnea-hypopnea index and the percentage of sleep time with less than 90% oxygen saturation were not associated with WMD in the brainstem (Table 2). Moreover, neither the central nor obstructive apnea index, nor the percentage of sleep time in apneas and hypopneas, nor the minimum oxygen saturation in each of REM and NREM sleep were associated with WMD in the brainstem. In contrast, the arousal index was inversely and significantly associated with WMD in the brainstem (odds ratio [OR] = 0.75 for a SD increase in the arousal index, 95% confidence interval [CI]: 0.62, 0.92). In addition, the ORs of WMD in the brainstem for a SD increase in the arousal index were 0.81 (95% CI: 0.67, 0.99) and 0.78 (95% CI: 0.65, 0.93) during REM sleep and NREM sleep, respectively. After adjusting for age, sex, race, community, body mass index, smoking status, alcohol use, systolic blood pressure, and use of antihypertensive medication, the arousal index was still significantly associated with WMD in the brainstem. Further adjustment for either the apnea-hypopnea index, the percentage of sleep time in stage 3 and 4, the percentage of sleep time in

Table 1—Distribution of baseline (1995-1998) characteristics according to white matter disease in the brainstem in 1997-1998

	No WMD (n = 577)	WMD (n = 212)
Age, y*	77.5 ± 4.0	78.8 ± 4.8
Women, %	56.2	67.0
Caucasian, %	81.8	80.2
Diastolic blood pressure, mm Hg*†	68.4 ± 11.2	68.3 ± 13.0
Systolic blood pressure, mm Hg*†	134.1 ± 18.2	135.3 ± 18.2
Hypertension, %	72.2	72.2
Smoker, %		
Never	54.6	46.2
Former	40.5	44.8
Current	4.9	9.0
Body mass index, kg/m ² *	27.22 ± 4.3	27.16 ± 5.1
Alcohol use, drinks/week*	1.88 ± 4.6	1.71 ± 5.9
Coronary heart disease, %	15.1	19.5
Diabetes, %	24.0	20.1
MRI stroke, %	22.5	44.2
Apnea-hypopnea index, per hour*	10.0 ± 12.4	9.1 ± 11.9
Central apnea index, per hour*	0.6 ± 2.7	0.6 ± 3.5
Obstructive apnea index, per hour*	3.6 ± 6.8	3.4 ± 5.8
Sleep time < 90% oxygen saturation, %*	4.2 ± 11.7	3.6 ± 9.7
Sleep time in apneas and hypopneas, %*	13.5 ± 19.7	12.0 ± 17.2
Minimum oxygen saturation in REM sleep, %*	83.1 ± 17.7	81.4 ± 21.0
Minimum oxygen saturation in NREM sleep, %*	86.5 ± 6.3	86.6 ± 5.1
Arousal index, per hour *	21.0 ± 11.5	18.1 ± 10.3
Arousal index in REM, per hour*	15.1 ± 11.3	13.1 ± 9.8
Arousal index in NREM, per hour *	22.3 ± 12.4	19.3 ± 11.1
Sleep time in REM, %*	18.1 ± 13.2	19.7 ± 12.7
Sleep time in NREM, %*	18.6 ± 6.4	18.1 ± 6.4
Sleep efficiency, %*	79.0 ± 11.2	79.6 ± 9.6

*Data are presented as mean ± SD

†Only participants not using antihypertensive medication

WMD refers to white matter disease; REM, rapid eye movement sleep; NREM, non-REM sleep.

REM sleep, or sleep efficiency did not change the results. With WMD in the brainstem that involved the parabrachial nucleus within the pons as the outcome, the results were similar.

Stratifying by age, sex, race, and MRI stroke, respectively, the apnea-hypopnea index and the percentage of sleep time with less than 90% oxygen saturation were not associated with WMD in the brainstem in

Table 2—Logistic regression analyses of the associations of the measures of sleep-disordered breathing in 1995-1998 with white matter disease in the brainstem in 1997-1998

	No.	Odds Ratio (95% Confidence Interval)		
		Crude	Adjusted*	Further adjusted†
Apnea-hypopnea index‡	781	0.93 (0.78, 1.10)	0.97 (0.81, 1.17)	0.96 (0.79, 1.17)
Sleep time < 90% oxygen saturation‡	781	0.94 (0.78, 1.13)	0.98 (0.81, 1.18)	0.93 (0.75, 1.15)
Arousal index‡	620	0.75 (0.62, 0.92)	0.78 (0.63, 0.95)	0.76 (0.61, 0.93)

*Adjusting for age, sex, race, and community

†Adjusting for age, sex, race, community, body mass index, smoking status, alcohol use, systolic blood pressure, and use of antihypertensive medication.

‡A SD of the measures of sleep-disordered breathing as the unit: 13 per hour for the apnea-hypopnea index, 12% for the sleep time < 90% oxygen saturation, and 11 per hour for the arousal index

Table 3—Stratified logistic regression analyses of the associations of the arousal index in 1995-1998 with white matter disease in the brainstem in 1997-1998 by age, sex, race, and MRI stroke

	Arousal Index* N	Odds Ratio (95% Confidence Interval)
Overall	620	0.76 (0.61, 0.93)
Age		
< 78 years	332	0.72 (0.52, 1.01)
≥ 78 years	278	0.79 (0.60, 1.05)
Sex		
Women	356	0.74 (0.55, 0.99)
Men	254	0.79 (0.58, 1.08)
Race		
Caucasian	505	0.78 (0.62, 0.98)
African American	105	0.69 (0.39, 1.23)
MRI stroke		
No	419	0.74 (0.55, 0.99)
Yes	145	0.78 (0.54, 1.12)

*A SD of the arousal index as the unit (11 per hour); adjusting for age, sex, race, community, body mass index, smoking status, alcohol use, systolic blood pressure, and use of antihypertensive medication. MRI refers to magnetic resonance imaging.

each of all subgroups. In contrast, the associations of the arousal index with WMD in the brainstem showed consistent patterns across all subgroups, although, probably because of smaller numbers, some of these associations were not statistically significant (Table 3). To further explore the dose-response relationship between the arousal index and WMD in the brainstem, the arousal index was grouped into 5 categories with approximately even numbers of participants in each category: less than 12, between 12 and 16, between 17 and 22, between 23 and 29, and greater than 29 arousals per hour during sleep (Figure 2). Logistic regression analysis was used to compare each of the higher categories with the category of less than 12 arousals per hour, after adjusting for age, sex, race, and community. With each increased category of the arousal index, odds of WMD in the brainstem reduced gradually at first, then reached a relative plateau in the category of between 23 and 29 arousals per hour (trend test: $P < .01$).

After excluding those participants with WMD in the brainstem in 1992-1993, the association of the apnea-hypopnea index with the newly acquired WMD in the brainstem (WMD developed between 1992-1993 and 1997-1998) was only marginally significant (OR = 1.34 for a SD increase in the apnea-hypopnea index, 95% CI: 0.98, 1.84) (Table 4). However, consistent with the previous analyses, a significant inverse association for arousal index (OR = 0.62 for a SD increase in the arousal index, 95% CI: 0.40, 0.98) was observed.

In multivariable linear regression analyses, using WMD volume (WMD severity) in the brainstem as the outcome, there were no significant associations of the measures of SDB with WMD severity in the brainstem. However, after adjusting for WMD volume in the brainstem in 1992-1993, the arousal index was inversely and significantly associated with the change in WMD volume in the brainstem from 1992-1993 to 1997-1998 (Table 5).

DISCUSSION

The current analysis provides no support for a positive association between the frequency of apneas and hypopneas and WMD in the brainstem. Contrary to our hypothesis, the subgroup with a lower frequency of arousals was identified as having a higher prevalence of WMD in the brainstem.

None of the measures of apneas and hypopneas, including the apnea-hypopnea index (the most widely used measure of SDB), indexes based on exclusively central or obstructive events, or time in apneas and hypopneas were associated with WMD in the brainstem in the present analysis. The lack of an association between direct measures of SDB severity and WMD in the brainstem is supported by a case-control study with 90 participants in which moderate and severe obstructive sleep apnea was not associated with MRI-detected subclinical cerebrovascular disease.²⁹ In a prospective MRI study with 14 participants, sleep apnea syndrome was not associated with ischemic cerebral lesions either.³⁰ Participants in the present study were drawn from population-based cohorts of older adults who generally had lower levels of sleep apnea than is found in samples derived from clinic referrals. Additionally, some individuals who were treated for sleep apnea and, therefore, might have higher levels of sleep apnea were excluded from the present study. Thus, the relative low levels of sleep apnea in the present study may have reduced the ability to detect any association of more-severe levels of sleep apnea with WMD in the brainstem. Alternatively, negative findings may be due to competitive risk factors for vascular disease operating in older adults or survival biases. Regarding the latter, if individuals with

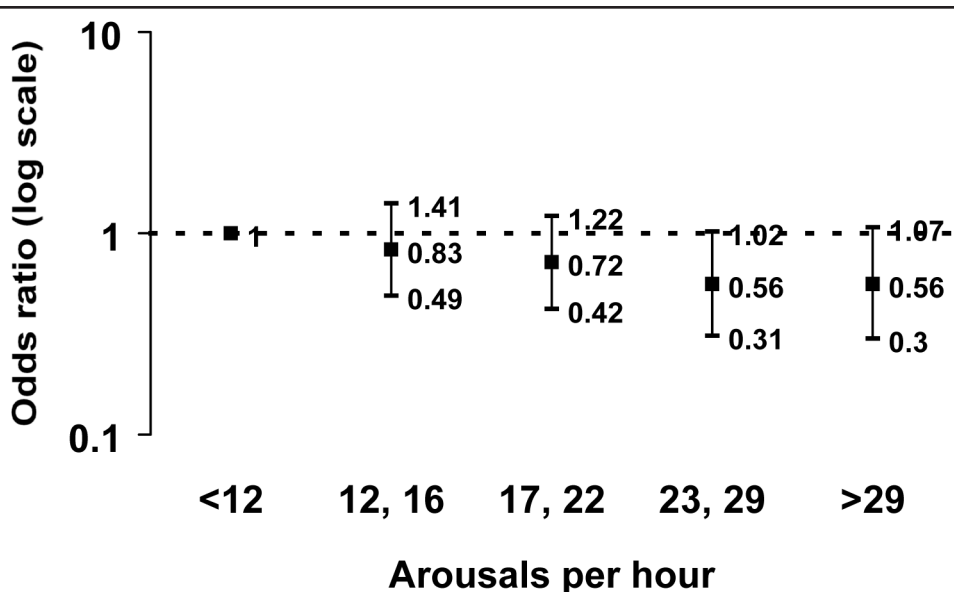


Figure 2—Odds ratios (95% confidence interval) of white matter disease in the brainstem in 1997-1998 comparing each of higher categories of the arousal index in 1995-1998 with the category of < 12 arousals per hour, adjusting for age, sex, race, and community (trend test: $P < .01$).

both WMD in the brainstem and a higher apnea-hypopnea index have a shorter survival, the association of the apnea-hypopnea index with WMD in the brainstem may be masked in this survival cohort. Additional studies, possibly in younger adults, are needed to examine this association further.

In contrast, the frequency of arousals was inversely associated with WMD in the brainstem. The frequency of arousals was also associated with the development of WMD in the brainstem. However, a determination of the temporality of the association was limited because polysomnography was conducted after the first MRI study. The underlying mechanism for this association cannot be determined from the observational data available. Nonetheless, the data suggest that the arousal response may be a protective mechanism against WMD in the brainstem. In fact, the arousal response has been considered as a protective mechanism against sudden infant death syndrome.³¹ Because the arousal response is associated with termination of apneas,³² failure to generate such response may prolong apneas, with consequent hypoxemia, ischemia, or both. Although we did not find any association of WMD in the brainstem with mean duration of apneas, more-precise characterization of the distribution of the duration of each apnea and hypopnea may have improved our ability to address this issue. Alternatively, it is plausible that the inverse association of the arousal response with WMD in the brainstem represents a reverse causality, ie, that WMD in the brainstem may indicate pathologic changes in the brain regions involved with the arousal response. Physiologic studies³³ and animal studies^{34,35} suggest that the brainstem is responsible for the rhythm of spontaneous arousals. The present study provides the first population-based epidemiologic data on this postulation.

Nevertheless, because these latter findings were unexpected, the association between the arousal index and WMD in the brainstem should be

interpreted with caution. Although these associations were observed among multiple population strata, they still could represent a chance finding. Additionally, although the association of the arousal index with WMD in the brainstem is statistically significant, the clinical significance of small differences remains unclear. Finally, various stimuli, including respiratory, acoustic, and periodic limb movements, can induce arousals from sleep.³⁶ Because we cannot distinguish arousals resulting from various stimuli, the specificity of changes in the arousal index in relationship to SDB cannot be determined.

Although the population of the present study is not entirely representative of the general population of older adults, it is more representative than those of studies that rely on data from patients referred to sleep laboratories. Furthermore, the consistency of the results across all subgroups of the study population supports the internal validity of this study. The exclusions due to technical issues with polysomnography resulted in a population with few events of apnea and hypopnea for the analysis of arousal index. However, the proportion of WMD in the brainstem in the excluded individuals was similar to that in those who were included in the analysis. The reliability of scoring the arousal index was only moderate. Nevertheless, because the readers were masked to the participants' characteristics, the possible misclassification may be non-differential and would be anticipated to attenuate the association of the arousal index with WMD in the brainstem.

In summary, the findings in this large community-based sample of older adults do not suggest a clear association of the frequency of apneas and hypopneas with WMD in the brainstem. A posthoc inverse association of the arousal response with WMD in the brainstem needs to be confirmed by future studies.

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Table 4—Logistic regression analyses of the associations of the measures of sleep-disordered breathing in 1995-1998 with white matter disease in the brainstem in 1997-1998, excluding those with white matter disease in the brainstem in 1992-1993

	WMD, no.	Total, no.	Odds ratio (95% confidence interval)*
Apnea-hypopnea index†	45	417	1.34 (0.98, 1.84)
Sleep time < 90%			
oxygen saturation†	45	417	0.94 (0.60, 1.50)
Arousal index†	37	342	0.62 (0.40, 0.98)

*Adjusting for age, sex, race, community, body mass index, smoking status, alcohol use, systolic blood pressure, and use of antihypertensive medication

†A SD of the measures of sleep-disordered breathing as the unit: 13 per hour for the apnea-hypopnea index, 12% for the sleep time < 90% oxygen saturation, and 11 per hour for the arousal index

Table 5—Linear regression analyses of the associations of the measures of sleep-disordered breathing in 1995-1998 with white matter disease volume (mm³) in the brainstem in 1992-1993 and 1997-1998

	No.	WMD volume in the brainstem in 1997-1998*		Change in WMD volume in the brainstem from 1992-1993 to 1997-1998†	
		β‡	P	β‡	P
Apnea-hypopnea index§	582	-4.22 ± 12.29	.73	-4.33 ± 7.12	.54
Sleep time < 90%					
oxygen saturation§	582	-6.17 ± 12.22	.61	6.62 ± 7.50	.38
Arousal index§	469	-17.94 ± 11.13	.11	-15.15 ± 7.02	.03

*Adjusting for age, sex, race, community, body mass index, smoking status, alcohol use, systolic blood pressure, and use of antihypertensive medication.

†Adjusting for age, sex, race, community, body mass index, smoking status, alcohol use, systolic blood pressure, use of antihypertensive medication, and white matter disease (WMD) volume in the brainstem in 1992-1993.

‡Indicates the increase in mean ± SEM WMD volume for each unit increase in the measures of sleep-disordered breathing.

§A SD of the measures of sleep-disordered breathing as the unit: 13 per hour for the apnea-hypopnea index, 12% for the sleep time < 90% oxygen saturation, and 11 per hour for the arousal index

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