Association of Sleep-disordered Breathing and the Occurrence of Stroke

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Rationale: **Sleep-disordered breathing has been linked to stroke in previous studies. However, these studies either used surrogate markers of sleep-disordered breathing or could not, due to cross-sectional design, address the temporal relationship between sleep-disordered breathing and stroke.**

Objectives: **To determine whether sleep-disordered breathing increases the risk for stroke.**

Methods: **We performed cross-sectional and longitudinal analyses on 1,475 and 1,189 subjects, respectively, from the general population. Sleep-disordered breathing was defined by the apnea–hypopnea index (frequency of apneas and hypopneas per hour of sleep) obtained by attended polysomnography. The protocol, including polysomnography, risk factors for stroke, and a history of physician-diagnosed stroke, was repeated at 4-yr intervals.**

Measurements and Main Results: **In the cross-sectional analysis, subjects with an apnea–hypopnea index of 20 or greater had increased odds for stroke (odds ratio, 4.33; 95% confidence interval, 1.32–14.24; $p = 0.02$) compared with those without sleep-disordered breathing (apnea–hypopnea index, <5) after adjustment for known confounding factors. In the prospective analysis, sleep-disordered breathing with an apnea–hypopnea index of 20 or greater was associated with an increased risk of suffering a first-ever stroke over the next 4 yr (unadjusted odds ratio, 4.31; 95% confidence interval, 1.31–14.15; $p = 0.02$). However, after adjustment for age, sex, and body mass index, the odds ratio was still elevated, but was no longer significant (3.08; 95% confidence interval, 0.74–12.81; $p = 0.12$).**

Conclusions: **These data demonstrate a strong association between moderate to severe sleep-disordered breathing and prevalent stroke, independent of confounding factors. They also provide the first prospective evidence that sleep-disordered breathing precedes stroke and may contribute to the development of stroke.**

Keywords: cerebrovascular disease; risk factors; sleep apnea; sleep-disordered breathing; stroke

Sleep-disordered breathing (SDB) is a condition characterized by repetitive apneas and hypopneas during sleep (1). These respiratory events are accompanied by hypoxia, arousals from sleep, and bursts of sympathetic nervous system activity that trigger surges in blood pressure and heart rate (2–5). Large epidemiologic studies have established SDB as an independent risk factor for development of hypertension (6–8). SDB is also associated with increased platelet adhesiveness (9, 10), vascular endothelial dysfunction (11–13), and early signs of atherosclerosis (14)—conditions that put patients at increased risk for cardiovascular events, including stroke.

There is increasing evidence that SDB is a risk factor for stroke. For example, in two large prospective epidemiologic studies, a history of self-reported snoring was associated with an increased risk for a self-reported stroke (15, 16). Moreover, Marin and colleagues (17) found, in an observational study of a sleep-clinic population, that those with untreated SDB had a higher rate of fatal and nonfatal cardiovascular events, including ischemic heart disease and stroke, than healthy subjects. However, none of these studies established a direct link between SDB and stroke because self-reported snoring was used as a surrogate for SDB and/or the outcome was the combined rate of stroke and coronary artery disease rather than stroke alone. In a cross-sectional analysis of the Sleep Heart Health Study cohort, a modest association between SDB, identified by unattended home polysomnography, and prevalent stroke, was reported (18). However, subjects in that cohort were recruited from middle-aged to older individuals, with high prevalences of known risk factors for stroke (18, 19) that could have weakened the ability to detect an independent relationship between SDB and stroke. The authors of recent reviews of this subject came to the conclusion that, whereas there is evidence favoring SDB as a modifiable risk factor for stroke, this evidence has not established a relationship of SDB with stroke that is independent of known risk factors, and that prospective studies are needed to determine whether a cause-and-effect relationship between SDB and stroke might exist (20, 21).

Our objectives, therefore, were to test the hypotheses that SDB is associated with an increased prevalence of stroke and also with an increased incidence of stroke. To test the first hypothesis, we performed a cross-sectional analysis of the Wisconsin Sleep Cohort Study. To test the second hypothesis, we performed a longitudinal analysis of the same cohort. Some of these data have been previously published in abstract form (22).

METHODS

Details on the sample construction, measurements and statistical analysis of the Wisconsin Sleep Cohort Study have been reported previously (7, 8, 23).

Participants and Collection of Data

The Wisconsin Sleep Cohort Study is based on a stratified random sample, assembled in 1988, of state employees in Wisconsin aged between 30 and 60 yr. Exclusion criteria were pregnancy, unstable cardiopulmonary disease, airway cancers, and recent surgery involving the upper airway. Individuals were also excluded if they had sleep studies with unusable physiologic measurements, an inadequate period of sleep (< 4 h), or no episodes of REM sleep. For the prospective analysis, individuals who had a history of stroke before entry into the study were excluded.

The 1,475 participants accepted were studied at the University of Wisconsin General Clinical Research Center with overnight protocols,

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first as a baseline and then, as follow-up, after 4, 8, and 12 yr. The protocol at all visits included assessment of SDB by polysomnography, measurement of blood pressure (8, 24) and serum cholesterol, history of physician-diagnosed stroke, and history of known risk factors for stroke, such as age, sex, body mass index, physician-diagnosed diabetes, cigarette smoking, and alcohol intake. All participants gave written, informed consent to undergo the protocol for the Wisconsin Sleep Cohort Study, which was approved by the institutional review board of the University of Wisconsin Medical School.

SDB and Occurrence of Stroke

SDB was defined by the apnea–hypopnea index (AHI; frequency of apneas and hypopneas per hour of sleep) assessed by attended polysomnography using previously described standard methodology and scoring criteria (8, 23, 25). The AHI measured by these criteria has been previously validated as a clinically important metric within the same cohort by demonstrating a graded relationship between AHI and the prevalence and severity of important clinical outcomes including hypertension (7, 8). Categories of SDB were defined according to the AHI: less than 5, no SDB; 5 or greater to less than 20, mild SDB; and 20 or greater, moderate to severe SDB. Participants and their physicians were given a summary of their overnight study that includes the AHI. In addition, a recommendation to consult their physician was given to participants with an AHI of more than 15 or to those with excessive sleepiness.

In this analysis, stroke was defined as self-reported, physician-diagnosed stroke. Participants were asked if they had had a stroke diagnosed by a doctor. To avoid overreporting of the diagnosis of stroke, details on when the stroke occurred and what treatment was received were required. Furthermore, consistency of details of the reported stroke was checked with data collected at follow-up visits subsequent to the stroke. Incident stroke was defined as a stroke that occurred in persons with no history of stroke after completing at least one overnight polysomnographic study.

Statistical Analysis

To assess the association of SDB with stroke, we performed a cross-sectional analysis of the Wisconsin Sleep Cohort, including 1,475 participants. Data were analyzed with SAS statistical software (SAS Institute, Cary, NC) (26) for descriptive statistics, contingency tables, and logistic regression. Logistic regression was used to calculate the odds ratios of prevalent stroke according to the severity of SDB while adjusting for possible confounders.

The following baseline variables were examined as covariates: age, sex, body mass index, hypertension, serum cholesterol, history of physician-diagnosed diabetes, and weekly cigarette and alcohol use. Serum cholesterol did not substantially alter the regression coefficient for the AHI and was not entered into the final model. As there is growing evidence that diabetes and hypertension may be in the causative pathway between SDB and cardiovascular diseases (6–8, 27–31), we examined models with and without these variables.

Furthermore, we investigated the association of SDB in those with no history of stroke and the incidence of stroke during each 4-yr follow-up interval. For this analysis, 1,189 participants contributed 2,340 data points: 1,166 with baseline data from Visit 1 and follow-up data from Visit 2, 803 with baseline data from Visit 2 and follow-up data from Visit 3, and 371 with baseline data from Visit 3 and follow-up data from Visit 4. An individual may contribute several 4-yr follow-up data points in this analysis. For example, an individual with a baseline study and two 4-yr follow-up studies with no incident stroke would contribute two data points in this analysis. The first data point will relate SDB and covariables at baseline to stroke incidence at the first follow-up visit and the second data point will relate SDB and covariables at the first follow-up visit to stroke incidence at the second follow-up visit. Once an individual had an incident stroke, they were excluded from further analyses.

For this prospective analysis, the odds ratios for developing a stroke during follow-up at 4-yr intervals relative to the SDB category from the previous 4 yr were calculated using the SAS Genmod procedure as described previously (26). We used the generalized estimating equations approach (32) designed for repeated measures to account for intrasubject correlation and the number of repeated visits per individual. This method produces robust standard errors for testing hypotheses and computing confidence intervals. Due to the small number of incident strokes in our cohort, we limited the number of covariates in the prospective analysis. Similar to previous epidemiologic studies (33–36), we found the association of body mass index and stroke to be weak (β coefficient = 0.0494; $p = 0.063$). Therefore, we examined models with and without body mass index in the prospective analysis.

RESULTS

Characteristics of the Subjects

Baseline characteristics of participants of the cross-sectional analysis, grouped by the AHI, are shown in Table 1. Of the 1,475 participants, 76% did not have SDB, 17% had mild SDB, and 7% had moderate to severe SDB. Subjects with moderate to severe SDB were predominantly male and had a significantly increased body mass index compared with subjects with mild or no SDB (Table 1). Furthermore, participants with SDB had higher prevalences of hypertension and diabetes than the group with no SDB (Table 1).

SDB and Prevalent Stroke

Of the 1,475 participants included in the cross-sectional analysis, 22 suffered a first-ever stroke. One subject who reported a stroke did not meet the other criteria for this diagnosis and was not counted as having suffered a stroke. All strokes occurred in adulthood at a mean age of 53 ± 9 yr. The number (prevalence in %) of strokes in the AHI less-than-5, 5-or-greater to less-than-20, and 20-or-greater groups were 14 (1.2), 2 (0.8), and 6 (6.1), respectively. None of the participants with prevalent stroke and SDB had atrial fibrillation.

Odds ratios for the prevalence of stroke in the AHI groups are given in Table 2. Results from three models are presented. The first parsimonious model (model 1A) adjusted for the variables of age, sex, body mass index, and weekly alcohol and cigarette use. The odds ratio for prevalent stroke in subjects with an AHI of 20/h or greater was increased significantly at 4.33 (95% confidence interval [CI], 1.32–14.24) compared with the reference category (AHI $<$ 5/h). In model 2A, in which hypertension was added as a potential confounder or explanatory variable, the odds ratio for stroke associated with moderate to severe SDB compared with the reference group remained significantly higher at 3.87 (95% CI, 1.19–12.63), but was reduced compared with model 1A. In model 3A, in which diabetes was added as a potential confounder or explanatory variable, the odds ratio for stroke associated with moderate to severe SDB remained significantly higher at 3.83 (95% CI, 1.17–12.56), and was unchanged compared with model 2A. Therefore, adding diabetes into the model did not alter the relationship between moderate to severe SDB and prevalent stroke. In the group with mild SDB (AHI $\geq$ 5 to $<$ 20/h), odds ratios for the prevalence of stroke were not significantly different from the reference group in any of the three models (Table 2). We also investigated a variable to reflect SDB with symptoms of sleepiness and found that the addition of excessive daytime sleepiness did not change the association of SDB (AHI $>$ 20) and stroke.

SDB and Incident Stroke

In our 4-yr prospective analysis, 14 participants suffered a first-ever stroke at a mean age of 56 ± 8 yr. The number of strokes in the AHI less-than-5, 5-or-greater to less-than-20, and 20-or-greater groups were 9, 1, and 4, respectively. The overall incidence of stroke was 1.33 per 1,000 person-yr. In the subgroups of participants with an AHI less than 5, 5 to less than 20, and 20 or greater, the incidences of strokes were 1.33, 0.54, and 5.75 per 1,000 person-yr, respectively. Table 3 displays odds ratios

TABLE 1. CHARACTERISTICS OF PARTICIPANTS INCLUDED IN THE CROSS-SECTIONAL ANALYSIS GROUPED BY THE APNEA–HYPOPNEA INDEX

	Baseline AHI			
Characteristics	< 5 (*n = 1,121; 76%*)	⩾ 5 to < 20 (*n = 255; 17%*)	⩾ 20 (*n = 99; 7%*)	Entire Group (*n = 1,475*)
Age, yr ± SD	47 ± 8	50 ± 8	50 ± 9	47 ± 8
Male sex, no. (%)	568 (51)	166 (65)	75 (76)	809 (55)
Body mass index, kg/m^2 ± SD	29 ± 6	33 ± 7	37 ± 8	30 ± 7
Hypertension, no. (%)	302 (27)	107 (42)	67 (68)	476 (32)
History of diabetes, no. (%)	25 (2)	12 (5)	10 (10)	47 (3)
Alcoholic drinks/wk, no. ± SD	4 ± 6	4 ± 6	4 ± 7	4 ± 6
Current cigarette smoker, no. (%)	209 (19)	38 (15)	18 (18)	265 (18)

Definition of abbreviation: AHI = apnea–hypopnea index.

for incident stroke after 4 yr of follow-up in the AHI groups, after correction for repeated measurements. In the unadjusted model (model 1B) and in the model controlled for age and sex (model 2B), we found participants with a baseline AHI of 20/h or greater had significantly higher odds ratios for the incidence of stroke (odds ratio, 4.31; 95% CI, 1.31–14.15; and odds ratio, 4.48; 95% CI, 1.31–15.33; respectively). After additional adjustment for body mass index (model 3B), the odds ratio for moderate to severe SDB was still higher at 3.08 (95% CI, 0.74–12.81), but was no longer statistically significant (Table 3). In all three models, the odds for incident stroke in the group with mild SDB (AHI of ⩾ 5 to < 20/h) were not significantly different compared with the reference group.

DISCUSSION

Two novel and important observations have arisen from this analysis of the Wisconsin Sleep Cohort Study. First, in the cross-sectional analysis, we provide the first evidence of a significant relationship between SDB (indicated by an AHI of at least 20), assessed objectively by attended in-laboratory polysomnography, and prevalent stroke in a sample of the general population, after adjustment for known confounding factors. Second, in the longitudinal analysis, we provide the first prospective epidemiologic evidence on the temporal relationship between SDB and stroke by demonstrating that an AHI of at least 20 is associated with a highly increased probability of suffering a stroke within the next 4 yr.

The only other epidemiologic study assessing the relationship between SDB, diagnosed by the AHI on polysomnography, and stroke was cross-sectional in design (18). In that study, Shahar and colleagues (18) analyzed data from more than 6,000 subjects from the Sleep Heart Health Study. They found a modest, but significantly higher, linear trend for the odds of prevalent stroke (1.58) among subjects with SDB who had an AHI of 11/h or greater, when using a parsimonious model that did not adjust for body mass index and hypertension. Compared with our cohort, theirs was 13 yr older, and had more coexisting cardiovascular risk factors and diseases, such as hypertension (40 vs. 32%) and diabetes (10 vs. 3%) (18). Therefore, the influence of comorbidities in the assessment of the potential association between SDB and stroke would have been greater in that study than in ours. As a result, the strength of the relationship between SDB and stroke may have been underestimated in that study even though there were more cerebrovascular events (18).

The present findings support and complement those of Shahar and colleagues (18) in three novel ways. First, in our cohort, we confirmed that there is a significant association between SDB and prevalent stroke. In addition, we demonstrated that this relationship was also independent of potential confounding by obesity, was not fully explained by hypertension, and was not explained by atrial fibrillation. Second, we found an adjusted odds ratio of prevalent stroke associated with an AHI of 20 or greater that was more than double that reported for an AHI of more than 19/h in the Sleep Heart Health Study (3.83 vs. 1.80) (18). Third, in our prospective analysis, we established that moderate to severe SDB was associated with a highly increased probability of suffering a stroke within the next 4 yr (unadjusted odds ratio, 4.31). This novel finding sheds light on the temporal relationship between SDB and stroke by demonstrating that SDB preceded and was strongly associated with the incidence of stroke. Although no other studies have directly examined the temporal relationship between SDB and stroke, several previous studies suggested that SDB precedes stroke in many cases. For example, it was reported that the frequency and severity of SDB in patients with strokes and transient ischemic attacks was similar, that there was no significant relationship between the location or

TABLE 2. ADJUSTED ODDS RATIOS FOR THE PREVALENCE OF STROKE FOR SUBJECTS GROUPED BY THE APNEA–HYPOPNEA INDEX

	Model 1A		Model 2A		Model **3A**	
AHI (*events/h*)	OR (*95% CI*), adjusted for age, sex, BMI, alcohol, and smoking	p Value	OR (*95% CI*), adjusted for age, sex, BMI, alcohol, smoking, and hypertension	p Value	OR (*95% CI*), adjusted for age, sex, BMI, alcohol, smoking, diabetes, and hypertension	p Value
< 5*	1.0		1.0		1.0	
⩾ 5 to < 20	0.50 (0.11–2.33)	0.38	0.48 (0.10–2.27)	0.36	0.49 (0.10–2.81)	0.36
⩾ 20	4.33 (1.32–14.24)	0.02	3.87 (1.19–12.63)	0.02	3.83 (1.17–12.56)	0.03

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; OR = odds ratio.
* This category served as the reference group.

TABLE 3. ADJUSTED ODDS RATIOS FOR THE INCIDENCE OF STROKE FOR SUBJECTS GROUPED BY THE APNEA–HYPOPNEA INDEX

	Model 1B		Model 2B		Model 3B	
AHI (*events/h*)	OR (*95% CI*), unadjusted	p Value	OR (*95% CI*), adjusted for age, sex	p Value	OR (*95% CI*), adjusted for age, sex, and BMI	p Value
< 5*	1.0		1.0		1.0	
≥ 5 to < 20	0.40 (0.05–3.18)	0.39	0.35 (0.05–2.69)	0.31	0.29 (0.04–2.36)	0.25
≥ 20	4.31 (1.31–14.15)	0.02	4.48 (1.31–15.33)	0.02	3.08 (0.74–12.81)	0.12

For definition of abbreviations, *see* Table 2.

* This category served as the reference group.

severity of stroke and the presence of SDB (37, 38), and that there was no significant decline in the frequency of obstructive apneas several months after the acute phase of stroke (38).

Two prospective population-based studies (15, 16) reported higher odds ratios of 2.08 and 1.33, respectively, for developing self-reported ischemic heart disease or stroke in subjects with self-reported habitual snoring compared with those not reporting habitual snoring. Assuming that the relationship between snoring and stroke is through SDB, the relatively low odds ratio for new-onset ischemic heart disease and stroke associated with snoring almost certainly underestimates the odds of having these disorders in relationship to SDB because SDB is only present in approximately 50% of snorers (23). In general, our results also lend support to those of Marin and colleagues (17), who found that patients in a sleep-clinic population with untreated SDB had a higher rate of fatal and nonfatal cardiovascular events, including ischemic heart disease and stroke, than healthy subjects from the general population.

A very high prevalence of SDB (69–77%) has also been reported in patients who have had a stroke (39–41). Because sleep studies were not performed before the strokes, it was not possible to determine which came first, the SDB or the stroke. In any case, the literature to date suggests that the presence of SDB after stroke has adverse prognostic implications: it is associated with worse functional capacity, a longer period of post-stroke rehabilitation (41–44), and a higher death rate (40, 43, 45). Therefore, not only does SDB appear to predispose to stroke but once a stroke has occurred, the presence of SDB may have a negative effect on outcome.

As in previous large-scale epidemiologic studies (16, 18, 33) in this field, in our analysis, stroke was defined as self-reported, physician-diagnosed stroke. Okura and colleagues (46) compared self-reported stroke from a questionnaire similar to ours with information from medical records and found, in participants aged between 45 and 64 yr, that there was 99% agreement between them. These data indicate that self-reported stroke is a reliable indicator that a stroke actually occurred.

It is possible that cases of stroke, particularly fatal strokes, were lost to follow-up. There could be bias if these cases were differentially related to SDB status. However, we were able to investigate mortality records for the entire cohort and we did not find any case of death attributed to stroke in any participants who had not had a prior stroke.

The incidence of stroke in the Wisconsin Sleep cohort was 1.33/1,000 person-yr, comparable to the rate reported in the Atherosclerosis Risk in Communities cohort, in subjects aged 45 to 64 yr (2.44/1,000 person-yr) (47). This low incidence of stroke, reflecting the young age of our cohort, compromises study power for explanatory analyses including, for example, the role of hypertension as a mediator on the pathway between SDB and the development of stroke. In view of the weak association of body mass index and incidence of stroke in our cohort, the drop in statistical significance for the association between an AHI of 20 or greater and incidence of stroke once body mass index is taken into account (Table 3) is likely to reflect the lack of study power rather than a lack of association.

In conclusion, we found, in a cross-sectional analysis of the Wisconsin Sleep Cohort Study, a strong association between SDB and the prevalence of stroke. This association was independent of known confounding factors. Furthermore, our longitudinal analysis provides the first prospective evidence that SDB after adjustment for age and sex is related to significantly increased odds of suffering a stroke over the next 4 yr. Although our analysis cannot shed light on the pathway by which SDB affects stroke risk, these novel findings add justification for considering SDB as a condition that precedes and may contribute to the development of stroke.

Our results raise the question of the potential role that treatment of SDB might play in primary and secondary prevention of stroke. In addition to the evidence presented herein that SDB contributes to the development of stroke, the presence of SDB after stroke may have adverse prognostic implications (40–45). This is a very important public health issue, because stroke is the commonest cause of long-term disability in the United States, where more than 1,100,000 individuals are affected, and where direct and indirect costs of stroke are estimated to be $56.8 billion in 2005 (48). Randomized clinical trials will be required to determine whether treatment of SDB prevents strokes or improves stroke outcome.

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject matter of this manuscript.

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