

ORIGINAL ARTICLE

Obstructive Sleep Apnea as a Risk Factor for Stroke and Death

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ABSTRACT

BACKGROUND

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METHODS

In this observational cohort study, consecutive patients underwent polysomnography, and subsequent events (strokes and deaths) were verified. The diagnosis of the obstructive sleep apnea syndrome was based on an apnea-hypopnea index of 5 or higher (five or more events per hour); patients with an apnea-hypopnea index of less than 5 served as the comparison group. Proportional-hazards analysis was used to determine the independent effect of the obstructive sleep apnea syndrome on the composite outcome of stroke or death from any cause.

RESULTS

Among 1022 enrolled patients, 697 (68 percent) had the obstructive sleep apnea syndrome. At baseline, the mean apnea-hypopnea index in the patients with the syndrome was 35, as compared with a mean apnea-hypopnea index of 2 in the comparison group. In an unadjusted analysis, the obstructive sleep apnea syndrome was associated with stroke or death from any cause (hazard ratio, 2.24; 95 percent confidence interval, 1.30 to 3.86; $P=0.004$). After adjustment for age, sex, race, smoking status, alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension, the obstructive sleep apnea syndrome retained a statistically significant association with stroke or death (hazard ratio, 1.97; 95 percent confidence interval, 1.12 to 3.48; $P=0.01$). In a trend analysis, increased severity of sleep apnea at baseline was associated with an increased risk of the development of the composite end point ($P=0.005$).

CONCLUSIONS

The obstructive sleep apnea syndrome significantly increases the risk of stroke or death from any cause, and the increase is independent of other risk factors, including hypertension.

STROKE IS THE SECOND LEADING CAUSE of death worldwide and the leading cause of long-term disability.^{1,2} Strategies for stroke prevention, including the control of hypertension, treatment of atrial fibrillation, and smoking cessation, have reduced the disease burden, but stroke still remains an important public health challenge. A better understanding of the risk factors for stroke is needed to develop additional preventive strategies.

The obstructive sleep apnea syndrome is a treatable form of disordered breathing in which the upper airway closes repeatedly during sleep. The syndrome is associated with vascular risk factors and with substantial cardiovascular morbidity and mortality.³ Several studies have shown a prevalence of the syndrome among patients with stroke that exceeds 60 percent,⁴⁻⁷ as compared with 4 percent in the middle-aged adult population.⁸

Whether the relation between the syndrome and stroke is independent of confounding risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, and smoking, is not clear. Several cross-sectional analyses^{6,9-14} have shown an increase in the risk of stroke with sleep-disordered breathing that is similar in magnitude to the effect of other cardiovascular risk factors. A study of patients with acute stroke⁷ demonstrated that obstructive apnea persisted despite neurologic recovery, suggesting that the obstructive sleep apnea syndrome may have predated the development of stroke. We therefore hypothesized that patients with the syndrome have an increased risk of stroke or death from any cause that is independent of other cerebrovascular risk factors.

METHODS

STUDY POPULATION

We conducted an observational cohort study. The cohort consisted of patients who were referred to the Yale Center for Sleep Medicine specifically for the evaluation of sleep-disordered breathing, underwent at least two hours of attended sleep monitoring, completed a 10-page questionnaire on their sleep and medical history, and were 50 or more years old. The exposure group was defined a priori as having an apnea-hypopnea index of 5 or higher (five or more events per hour of sleep); patients with an apnea-hypopnea index of less than 5 constituted the comparison group.

Patients were excluded if they had been referred

for reasons other than the evaluation of suspected sleep-disordered breathing (e.g., narcolepsy or movement disorder); if they had a history of stroke, myocardial infarction, or tracheostomy; or if the entire polysomnographic study was performed with airway pressurization (e.g., continuous positive airway pressure for therapeutic purposes).

Participants or their family members gave either written or oral informed consent at the time of follow-up ascertainment. The study was approved by the Human Investigation Committee at Yale University School of Medicine.

BASELINE ASSESSMENT

Data on demographic characteristics, sleep and medical history, medication use, and habits were obtained with the use of a standardized questionnaire administered by a trained technologist before the initiation of overnight polysomnography; the questionnaires were reviewed by a physician. Each patient's height and weight were recorded at the time of polysomnography and used to calculate the body-mass index.

Sleep-history data included a validated measure of daytime sleepiness (the Epworth Sleepiness Scale)¹⁵ and self-reported habitual snoring, which was defined as loud snoring occurring "frequently" or "constantly." Data regarding medications included the daily use of beta-blockers, angiotensin-converting-enzyme inhibitors, other antihypertensive medications, antiplatelet therapy, anticoagulants, oral medications for the treatment of diabetes, insulin, and lipid-lowering medications. Risk-factor data included a history of hypertension, atrial fibrillation, diabetes mellitus, or hyperlipidemia, either reported by the patient on the baseline medical questionnaire or noted by the referring physician. In addition, atrial fibrillation on electrocardiography during polysomnography was considered sufficient evidence to establish that diagnosis.

Patients were classified according to whether they were current or former smokers or had never smoked; data were elicited, if applicable, on the number of pack-years of smoking. The history of alcohol consumption was based on the average number of drinks per day and the number of years of drinking.

POLYSOMNOGRAPHY

Participants underwent attended overnight polysomnography with the use of Grass data-acquisition

systems (Astro-Med) on the basis of a protocol described previously.⁴ A single, attended polysomnographic study that was conducted during an entire night was used to establish the presence of sleep apnea.¹⁶ Sleep stages were scored in 30-second epochs according to standard criteria.¹⁷ Total cessation of airflow at the nose and mouth for at least 10 seconds was classified as apnea (as obstructive apnea if respiratory efforts were present and as central apnea if respiratory efforts were absent). Partial airway closure, resulting in a diminution of airflow by more than 30 percent for at least 10 seconds and associated with oxygen desaturation of 4 percent or more, was termed hypopnea.¹⁸ Calculated polysomnographic variables included the apnea–hypopnea index and the arousal index (the number of arousals per hour of sleep).

OUTCOMES

Each patient was sent a follow-up questionnaire, which included questions regarding current state of health, occurrence of stroke, hospitalizations, and treatment of sleep disorders since the baseline assessment. Strokes and transient ischemic attacks (TIA) were ascertained with the use of a validated questionnaire designed to be a practical and reliable means of ascertaining stroke status.¹⁹ Attempts were made to telephone patients who had not responded to the initial mailed questionnaire. Family members were asked to provide information about patients who were not able to participate owing to death, illness, or dementia.

A physician investigator who was unaware of the patient's status with regard to the obstructive sleep apnea syndrome validated reported strokes and TIAs by reviewing medical records. Diagnoses were determined according to criteria of the National Institute of Neurological Disorders and Stroke²⁰ for the classification of cerebrovascular events. The exact date of the stroke or TIA was recorded. Vital records from the Connecticut Department of Public Health (regarding in-state deaths) and the Social Security Administration Death Master File^{21,22} (regarding out-of-state deaths) were used to determine or confirm death. The exact date of death was recorded.

STATISTICAL ANALYSIS

The primary outcome was the composite end point of incident stroke (including TIA, which hereafter will be reported as stroke) or death from any cause. With the assumption of a prevalence of 60 percent

for sleep apnea in our cohort and an incidence of stroke per year of 1.5 percent²³ during a four-year follow-up period, a sample of 840 patients was required in order to achieve 80 percent power to detect a relative risk of 2.0 at the 5 percent (two-tailed) significance level.

A series of prespecified time-to-event analyses were performed to examine the effect of the obstructive sleep apnea syndrome on the outcome. The time until the composite end point was taken to be the time until stroke, if the patient was contacted and found to have had a stroke, and the time until death, if the patient was not reached but was found to have died. Data were censored at the time of the contact if the patient was reached and was found not to have had a stroke and were censored at day 1 if the patient was not reached (or unwilling to be contacted) and was not found to have died.

The Kaplan–Meier method and the log-rank test were used to compare event-free survival among patients with and those without the obstructive sleep apnea syndrome. With the use of proportional-hazards analysis, hazard ratios and 95 percent confidence intervals were generated for the unadjusted association between sleep-apnea status or other baseline characteristics and the end point of stroke or death from any cause. Hazard ratios were then adjusted for the confounding effects of other baseline characteristics, including age, sex, race, smoking status, alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension. Because of the possibility that controlling for hypertension could constitute “overadjustment” (i.e., accounting for a variable on the causal pathway),²⁴ models were created both with and without the inclusion of hypertension. Finally, a trend analysis, with the use of the chi-square test for linear trend, was performed to analyze whether an increased severity of the obstructive sleep apnea syndrome (on the basis of quartiles of the apnea–hypopnea index) was associated with an increased risk of stroke or death from any cause.

Student's t-test was used to compare mean values at baseline among patients who had the obstructive sleep apnea syndrome with those in the comparison group. Categorical data were compared with the use of the chi-square test. All statistical tests were performed with the use of SAS software (SAS Institute). All reported P values are two-sided, and no interim analyses were conducted. S-Plus soft-

ware was used to generate the Kaplan-Meier survival curves (Mathsoft Engineering and Education).

RESULTS

Between January 1, 1997, and December 31, 2000, 3635 consecutive patients were referred to the sleep center, of whom 1022 were eligible to participate in the study. A total of 2402 patients were ineligible because they were less than 50 years of age, and 159 patients were ineligible because they had clinical evidence of previous myocardial infarction or stroke at entry. Another 52 patients were excluded because of unavailability of baseline data, having undergone a tracheostomy, or having been referred for conditions other than sleep-disordered breathing.

A total of 697 of the 1022 study participants (68 percent) were classified as having the obstructive sleep apnea syndrome (Table 1). The mean (\pm SD) apnea-hypopnea index among the patients with the syndrome was 35 ± 29 , as compared with 2.0 ± 1.5 in the comparison group. As expected, the prevalence of hypertension and diabetes mellitus was higher in the group with the syndrome than in the comparison group (Table 1). Patients with the syndrome also were more obese, as reflected by the higher body-mass index, and had lower nadir oxygen saturations and a higher arousal index. Obstructive apnea was the predominant apneic event; central apnea was rare.

Many patients with the obstructive sleep apnea syndrome received some type of treatment for sleep apnea after the initial evaluation. Thirty-one percent achieved a weight reduction of 10 percent or more; 58 percent were using airway pressurization for at least four hours per night for five nights or more per week; 15 percent underwent upper-airway surgery.

Follow-up after the single sleep study took place between June 1, 2002, and December 31, 2003. Patients with the syndrome had a median duration of follow-up of 3.4 years (interquartile range, 2.6 to 3.9), and the comparison group had a median duration of follow-up of 3.3 years (interquartile range, 2.8 to 4.2). Among the 1022 study patients, data on stroke events and death from any cause were obtained for 842 patients (82 percent). Investigators were unable to contact the remaining 180 patients (18 percent), and the vital-records search did not indicate that they had died. This group included 124 patients with the syndrome and 56 patients in

the comparison group. The baseline characteristics of these patients were similar to the characteristics of the group with complete follow-up (data not shown).

Incident stroke or death from any cause occurred in 88 patients (9 percent). The 88 confirmed events among these patients included 22 strokes and 50 deaths in the group with the obstructive sleep apnea syndrome (3.48 events per 100 person-years), as compared with 2 strokes and 14 deaths in the comparison group (1.60 events per 100 person-years). Figure 1 shows the Kaplan-Meier estimates of the time to the composite event of stroke or death. The probability of event-free survival was significantly lower for patients with the syndrome than for the comparison group ($P=0.003$ by the log-rank test). A time-to-event analysis for death only showed a similar result ($P=0.02$ by the log-rank test) (Fig. 2).

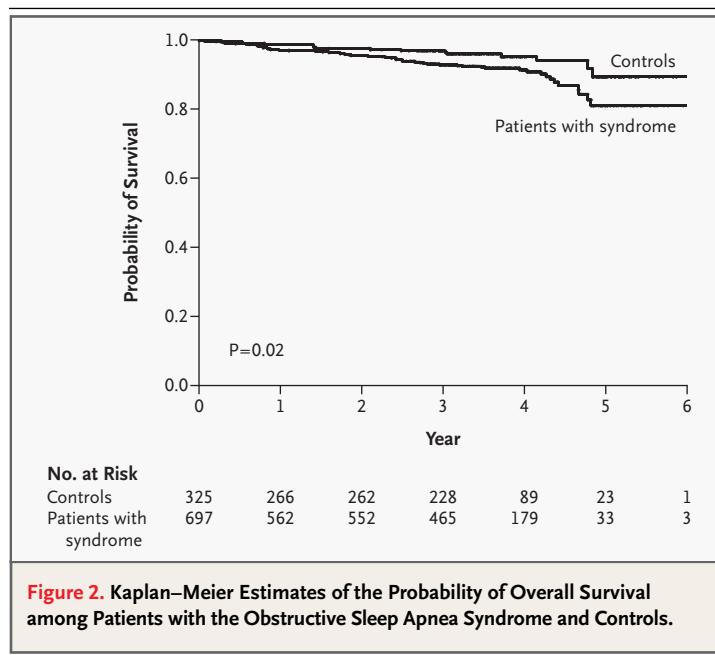
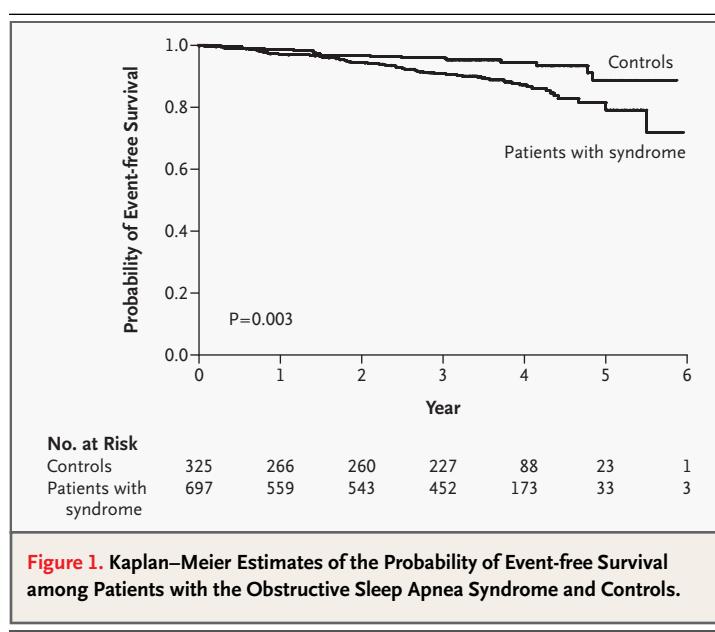
In an unadjusted analysis (Table 2), a significant

Table 1. Baseline Characteristics of Patients with the Obstructive Sleep Apnea Syndrome and Controls.

| Characteristic | Patients with the Syndrome (N=697) | Controls (N=325) | P Value |
|---|------------------------------------|------------------|---------|
| Mean age (yr) | 60.9 | 58.7 | 0.005 |
| Male sex (%) | 77 | 59 | <0.001 |
| White race (%)* | 84 | 89 | 0.02 |
| Mean body-mass index† | 33.8 | 30.5 | <0.001 |
| Current smoker (%) | 10 | 11 | 0.61 |
| Current consumption of alcohol (%) | 24 | 20 | 0.04 |
| Hypertension (%) | 60 | 43 | <0.001 |
| Diabetes mellitus (%) | 16 | 10 | 0.03 |
| Atrial fibrillation (%) | 7 | 4 | 0.07 |
| Hyperlipidemia (%) | 25 | 21 | 0.20 |
| Lipid-lowering therapy (%) | 25 | 21 | 0.20 |
| Antiplatelet therapy (%) | 34 | 32 | 0.62 |
| Mean score on Epworth Sleepiness Scale | 11 | 10 | 0.004 |
| Habitual snoring (%) | 83 | 64 | <0.001 |
| Mean apnea-hypopnea index | 35 | 2 | <0.001 |
| Lowest level of arterial oxygen saturation during sleep (%) | 80.5 | 87.2 | <0.001 |
| Mean arousal index | 53 | 26 | <0.001 |

* Race was determined by the investigators.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.



association was found between the obstructive sleep apnea syndrome and stroke or death from any cause (hazard ratio, 2.24; 95 percent confidence interval, 1.30 to 3.86; $P=0.004$). The associations of age and diabetes with the composite outcome were also statistically significant. The unadjusted hazard ratios for smoking, hypertension, and atrial fibrillation were in the expected direction, although not

statistically significant. After adjustment for age, sex, race, smoking status, alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and even hypertension, the obstructive sleep apnea syndrome retained a statistically significant association with stroke or death (hazard ratio, 1.97; 95 percent confidence interval, 1.12 to 3.48; $P=0.01$). The association of age with the outcomes also persisted after adjustment, but no statistically significant association was detected for other covariates. The inclusion of antiplatelet therapy in the model also did not influence the adjusted hazard ratio for the syndrome (data not shown).

A significant unadjusted association was found between the syndrome and death as a single end point (hazard ratio, 2.0; 95 percent confidence interval, 1.11 to 3.60; $P=0.02$). Adjusting for age, sex, race, smoking status, alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension resulted in an attenuation of the hazard ratio for sleep apnea (1.70; 95 percent confidence interval, 0.92 to 3.16; $P=0.09$).

A trend analysis (Table 3) revealed a stepwise increase in the risk of stroke or death from any cause as a function of increased severity of sleep apnea ($P=0.005$). The risk of stroke or death in patients in the most severe quartile of sleep apnea was three times that in the controls.

DISCUSSION

We conducted a large observational cohort study examining the role of the obstructive sleep apnea syndrome in the development of a first stroke or death from any cause. Our results demonstrate that the syndrome is associated with an increased incidence of stroke or death from any cause and that the association is independent of other cardiovascular and cerebrovascular risk factors, including hypertension.

Our findings are consistent with recent data showing that severe obstructive sleep apnea syndrome increases the risk of fatal and nonfatal cardiovascular events.²⁵ The broad range of severity of the syndrome in our study population allowed us to demonstrate an association between increased severity of the syndrome and increased risk of stroke or death from any cause. This correlation confirms the results of previous cross-sectional data show-

Table 2. Unadjusted and Adjusted Hazard Ratios for the Risk of Stroke or Death from Any Cause.*

| Covariate | Unadjusted Hazard Ratio (95% CI) | Adjusted Hazard Ratio (95% CI) |
|----------------------------------|----------------------------------|--------------------------------|
| Age (yr) | 1.09 (1.06–1.11) | 1.08 (1.06–1.11) |
| Male sex | 0.99 (0.62–1.60) | 0.78 (0.48–1.28) |
| Race | | |
| White (reference group) | 1.00 | 1.00 |
| Black | 0.96 (0.39–2.38) | 0.98 (0.39–2.46) |
| Other | 0.91 (0.42–1.98) | 0.94 (0.43–2.05) |
| Body-mass index | 0.99 (0.97–1.02) | 0.99 (0.96–1.02) |
| Current smoker | 1.21 (0.90–1.64) | 1.46 (0.78–2.98) |
| Current consumption of alcohol | 1.03 (0.86–1.22) | 0.94 (0.75–1.18) |
| Diabetes mellitus | 1.56 (1.02–2.59) | 1.31 (0.76–2.26) |
| Atrial fibrillation | 1.56 (0.79–3.12) | 0.91 (0.45–1.86) |
| Hyperlipidemia | 1.04 (0.64–1.68) | 1.01 (0.61–1.66) |
| Hypertension | 1.48 (0.95–2.28) | 1.19 (0.75–1.90) |
| Obstructive sleep apnea syndrome | 2.24 (1.30–3.86) | 1.97 (1.12–3.48) |

* Hazard ratios were adjusted for all other covariates in the model. CI denotes confidence interval.

ing that the risk of stroke appears to increase progressively with increased severity of the syndrome.¹⁴

In contrast to cross-sectional studies¹⁴ and studies that do not exclude preexisting cerebrovascular disease²⁵ (which might reflect reverse causal pathways with the obstructive sleep apnea syndrome as the consequence, rather than the cause, of stroke), our study addressed the temporal relationship between the syndrome and stroke by including only first-time cerebrovascular events that occurred after initially abnormal results of a sleep study. The study also provides an assessment of the independent effect of sleep apnea. After an adjustment was made for cardiovascular risk factors in the multivariable model, the hazard ratio for stroke or death from any cause among patients with the obstructive sleep apnea syndrome remained significant. Although the association of the syndrome and death as a single end point was not statistically significant, the lower number of deaths as compared with the composite outcome probably reduced the ability to detect an independent effect. Overall, our results regarding the increased risk of death among patients with the obstructive sleep apnea syndrome are consistent with previous reports.^{26,27}

The addition of hypertension to the model did not significantly attenuate the hazard ratio, suggesting that additional pathogenetic mechanisms (other than increased blood pressure) contribute to the

increased risk of stroke and death. Possible mechanisms include acute hemodynamic changes during episodes of apnea,^{28,29} decreased cerebral blood flow,^{30–32} paradoxical embolization,³³ hypercoagulability,^{34,35} hypoxia-related cerebral ischemia,³⁶ and atherosclerosis.³⁷

Several studies have demonstrated that airway pressurization (the main medical therapy for the syndrome) can reverse hypercoagulability^{34,35} and hemodynamic changes^{38–42} and even reduce the risk of cardiovascular events.²⁵ The present study was not designed or powered to address adherence with treatment or the effect of treatment on outcomes. Nonetheless, our study demonstrated an increased risk of stroke or death from any cause among patients with the obstructive sleep apnea syndrome despite the administration of various therapies. Several explanations may account for this finding. First, it is likely that many of our patients had had untreated obstructive sleep apnea for years before seeking treatment, resulting in a prolonged exposure to cardiovascular risk. The median 3.4 years of follow-up may not have been a sufficient length of time to derive the potential cardiovascular therapeutic benefits. Second, reduced compliance with continuous positive airway pressure and limited efficacy of other treatments may have played a role in the failure of therapy to reduce the risk to baseline levels. Third, in contrast to the patients

Table 3. Trend Analysis for the Relationship between Increased Severity of the Obstructive Sleep Apnea Syndrome and the Composite Outcome of Stroke or Death from Any Cause (N=1022).*

| Severity of Syndrome | Stroke or Death | | Mean Follow-up Period yr | Hazard Ratio (95% CI) |
|--------------------------------|-----------------|-----------------|-----------------------------|-----------------------|
| | No. of Events | No. of Patients | | |
| AHI ≤ 3 (reference score) | 13 | 271 | 3.08 | 1.00 |
| AHI 4–12 | 21 | 258 | 3.06 | 1.75 (0.88–3.49) |
| AHI 13–36 | 20 | 243 | 3.09 | 1.74 (0.87–3.51) |
| AHI > 36 | 34 | 250 | 2.78 | 3.30 (1.74–6.26) |

* P=0.005 by the chi-square test for linear trend. AHI denotes apnea-hypopnea index, and CI confidence interval.

in a recent study that suggested a beneficial effect of treatment on outcomes,²⁵ our population was older and had a higher prevalence of cardiovascular risk factors.

Several methodologic issues should be considered in the interpretation of our results. First, the ascertainment of stroke outcome was not possible in all patients. Some patients for whom death was reported as the outcome event may have had earlier, unreported strokes. The consequences of this methodologic limitation are reduced by an analysis that focuses on the combined end point of stroke or death, but it is nonetheless possible that strokes occurring much earlier in patients who died would alter the time-dependent character of the findings. A related issue involves possible nonfatal strokes among patients who were alive but were not contacted. However, the distribution of the obstructive sleep apnea syndrome between patients with and those without confirmed follow-up was nearly identical, suggesting that the results in patients who were lost to follow-up would be similar to those for the study population as a whole.

Second, it is possible that residual confounding factors affected our adjusted hazard ratios, despite our attempts to control for major cardiovascular risk factors. All the major known risk factors for stroke were considered in our analysis, so we think it is unlikely that an important confounder was overlooked.

Finally, some of the hazard ratios for known cardiovascular risk factors did not achieve statistical significance in our modeling. There are several possible reasons. First, patients with previous cardiovascular and cerebrovascular events were excluded from our cohort and the median 3.4 years of follow-up may not have been long enough for new events related to these traditional risk factors to develop in this cohort. Second, the concurrent treatment of these conditions probably reduced their effect on the composite outcome. Third, deaths from noncardiovascular causes (which were included in our composite outcome) may have reduced the measurable effect of traditional cardiovascular risk factors.

In conclusion, the obstructive sleep apnea syndrome is significantly associated with the risk of stroke or death from any cause, and this association is independent of other risk factors, including hypertension. Increased severity of the syndrome is associated with an incremental increase in the risk of this composite outcome.

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