AJRCCM Articles in Press. Published on March 25, 2010 as doi:10.1164/rccm.200911-1746OC
Media embargo until 2 weeks after above posting date; see thoracic.org/go/embargo

Obstructive Sleep Apnea Hypopnea and Incident Stroke: The Sleep Heart Health Study

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Running Title: Sleep Apnea and Incident Stroke;
Code: 15.7, 15.9
Key words: Sleep apnea, stroke, epidemiology
Word Count (text only): 3836

This work was supported by National Heart, Lung and Blood Institute cooperative agreements U01HL53940 (University of Washington), U01HL53941 (Boston University), U01HL53938 (University of Arizona), U01HL53916 (University of California, Davis), U01HL53934 (University of Minnesota), U01HL53931 (New York University), U01HL53937 and U01HL64360 (Johns Hopkins University), U01HL63463 (Case Western Reserve University), and U01HL63429 (Missouri Breaks Research).

This article has an online data supplement which is available from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: Although obstructive sleep apnea is associated with physiological perturbations that increase risk of hypertension and are pro-atherogenic, it is uncertain whether sleep apnea is associated with increased stroke risk in the general population.

Objective: To quantify the incidence of ischemic stroke with sleep apnea in a community-based sample of men and women across a wide range of sleep apnea.

Methods: Baseline polysomnography was performed between 1995 and 1998 in a longitudinal cohort study. The primary exposure was the obstructive apnea hypopnea index (OAHI) and outcome was incident ischemic stroke.

Measurements and Main Results. 5422 participants without a history of stroke at the baseline exam and untreated for sleep apnea were followed for a median of 8.7 years. 193 ischemic strokes were observed. In covariate-adjusted Cox proportional hazard models, a significant positive association between ischemic stroke and OAHI was observed in men (p value for linear trend: p=.016). Men in the highest OAHI quartile (>19) had an adjusted hazard ratio of 2.86 (95% C.I.: 1.1, 7.4). In the mild to moderate range (OAHI 5 to 25), each one unit increase in OAHI in men was estimated to increase stroke risk by 6% (95% C.I.: 2 to 10%). In women, stroke was not significantly associated with OAHI quartiles, but increased risk was observed at an OAHI of > 25.

Conclusion: The strong adjusted association between ischemic stroke and OAHI in community-dwelling men with mild to moderate sleep apnea suggests that this is an appropriate target for future stroke prevention trials.

Word count in abstract: 249

At A Glance

Obstructive sleep apnea is a common health problem and frequently associated with cardiovascular morbidity. This study addresses whether sleep apnea is associated with an increased risk of ischemic stroke in men and women recruited from the community. This study further assesses whether risk is associated with severity of sleep apnea. Compared to men in the lowest sleep apnea quartile, men with moderately severe sleep apnea had an almost 3-fold increased risk of ischemic stroke. The risk of stroke increased 6% with every unit increase in baseline obstructive apnea hypopnea index (OAHI) from 5 to 25. In women, increased risk of stroke was not observed until a threshold OAHI of 25 was reached. Thus, this study provides compelling evidence based on eight-years of prospective data from a large, geographically diverse community-based cohort of middle-aged and older adults that modest to severe levels of sleep apnea increase risk of ischemic stroke in men, suggesting the need to evaluate the role of sleep apnea treatment in ameliorating stroke risk.

INTRODUCTION

Approximately 15.3 million strokes occur annually world-wide, and about one-third of these are fatal. [1] Stroke is not only the second leading cause of death globally, but it also accounts for significant disability, institutionalization, and health care costs[2]. Since stroke rates increase exponentially with advancing age, the public health importance of strokes is likely to increase as the population ages. The risk of stroke is particularly high in Blacks, American Indians, and elderly women.[2] Numerous studies have identified risk factors for stroke, including hypertension, atrial fibrillation, diabetes and smoking[2-5]. Even after considering these well-recognized risk factors, there is substantial variation in stroke rates and stroke-related outcomes.

Emerging data implicate obstructive sleep apnea (OSA) in the pathogenesis of risk factors associated with ischemic stroke; i.e., hypertension, coronary heart disease, diabetes, and atrial fibrillation[6]. These associations are believed to be mediated by adverse physiological responses to recurrent periods of pharyngeal occlusion and consequent oxyhemoglobin desaturation-resaturation. These responses result in free radical generation, release of pro-inflammatory and pro-thrombotic mediators, as well as surges in sympathetic nervous system activity and blood pressure. Thus, OSA may increase risk factors for stroke as well as directly contribute to pathophysiological stresses implicated in stroke. Variability in OSA, which includes a relatively high prevalence in young African Americans[7] and in older women[8], roughly parallels disparities in stroke prevalence in the population. This observation supports the plausibility that unrecognized OSAH may explain a portion of the population variability in stroke.

A causal association between OSA and stroke is suggested by a community study of 394 older individuals that reported an approximately 2.5-fold increased risk of ischemic stroke in association with severe OSA.[9] However, that study did not address confounders other than age and gender. In the Wisconsin Sleep Cohort, moderate to severe OSA was associated with an approximately 4-fold increased risk of having had a stroke in a cross-sectional analysis.[10] However, in prospective follow-up of the same cohort, only 14 strokes occurred, limiting that study's statistical power to detect a significant association between OSA and incident stroke. Two recent prospective studies of patients referred for evaluation of sleep disorders also reported an almost 2-fold increased risk of a composite endpoint (stroke or death; or stroke, death or coronary heart disease) in association with OSA[11, 12] . However, because of the use of a composite endpoint, the overall risk of stroke in relationship to OSA is unclear from these studies. In addition, these studies reported on patients referred for sleep studies, who are unlikely to be representative of individuals in the general population, limiting generalizability to other groups, including women and minorities. Thus, whether OSA is an independent risk factor for incident stroke in the general population is not yet known.

This report addresses the incidence of stroke in a geographically diverse, community-based sample of male and female participants in the Sleep Heart Health Study (SHHS). The SHHS is a multi-center, prospective cohort study of the cardiovascular consequences of OSA. SHHS aimed to quantify the risk of a number of outcomes, including stroke, in relationship to the physiological disturbances characteristic of OSA, including frequency of apneas and hypopneas, degree of nocturnal desaturation, and frequency of arousals.

METHODS (See On-Line Supplement for detailed Methods)

Study Design and Sample

The SHHS is a community-based, prospective cohort study of the cardiovascular consequences of OSA. Briefly, 6441 men and women ≥ age 40 years were recruited from among participants in seven large cohorts (the "parent cohorts")[13]. At the baseline SHHS examination (1995-1998), research technicians administered questionnaires for sleep habits, general health, and medication use; and performed anthropometry, blood pressure measurement, and obtained overnight unattended polysomnography.[13] Additional covariate data were provided by the parent cohorts, including prevalent stroke events adjudicated by each parent cohort. At intervals of approximately 3 and 5 years following the baseline polysomnogram, a survey regarding diagnosis of and treatment for OSA was performed. Participants also had ongoing surveillance for cardiovascular events by parent cohorts through April 2006. The protocol was approved by the Institutional Review Board of each participating institution and signed informed consent was provided by all subjects.

Incident Stroke

Incident stroke was defined as the first occurrence of stroke (non-fatal or fatal) between the date of the baseline polysomnogram and the end of follow-up. Ongoing surveillance for incident stroke was performed by parent cohorts according to cohort-specific protocols[3-5, 14]. These included a combination of direct participant contact at intervals of one to four years, surveying death certificates and discharge information from local hospitals, and by mailings to study participants. All potential events were further investigated and adjudicated using defined protocols, which were similar across cohorts and included physician review of abstracted data. Trained abstractors extracted information from hospital discharge records, including available CT and MRI examinations and physician office records, using pre-specified criteria for identifying and categorizing stroke subtypes. The current analyses considered all first episodes of events adjudicated to be definite ischemic cerebrovascular events (193 events), including 15 fatal strokes.

Other Covariates

Blood pressure were obtained using a standardized protocol at the SHHS baseline exam[13]. Medication use was classified using methods developed for epidemiologic research[15].

Diabetes was ascertained based on report of physician diagnosis or reported use of insulin or oral hypoglycemic medication. Atrial fibrillation was defined on the basis of ECG findings from the baseline examination. OAH was quantified using overnight unattended polysomnography, scored at a central reading center using published quality control methods[16]. The Obstructive Apnea Hypopnea Index (OAHI) was defined as the average number of obstructive apneas plus hypopneas per hour of sleep. Cortical arousals were scored using standard criteria.[16] The arousal index was the total number of arousals per hour of sleep, which over the course of the study, had a within scorer intraclass correlation coefficient (ICC) of 0.70 to 0.75 and between scorer ICC of 0.69 to 0.75. Hemoglobin oxygen desaturation was characterized as the percentage of sleep time at an oxygen desaturation of <90%.

Statistical analysis

Participants were followed until a first stroke occurred between the date of the polysomnogram and the final censoring date. Individuals who did not develop a stroke were censored at the date of death or last contact. The primary exposure was quartiles of baseline OAHI, with secondary exposures including the continuously measured OAHI, quartiles of the arousal index, and a 4-level ordinal variable describing categories of percentage of time in desaturation, defined as “0” (reference), with the remaining observations based on tertiles of the distribution. Participants who developed other strokes were censored at the time of the stroke occurrence.

Associations between stroke risk and OAHI were estimated using semi-parametric Cox proportional hazards model. Covariates from the baseline SHHS exam included in the primary models were: age, body mass index (BMI), smoking status, systolic blood pressure, antihypertensive medication use, diabetes status, and race. Given the marked distributional differences of OAHI and cardiovascular risk factors in men and women, analyses were stratified by gender. We also tested the linear trend for each of the predictors. Although the primary analyses did not include variables that were missing on more than 10% of the sample (e.g., cholesterol levels), secondary analyses were conducted that included alcohol use, total and HDL cholesterol and lipid lowering medications. Additional secondary analyses excluded individuals with atrial fibrillation at baseline or those using benzodiazepine medications. Non-linear associations were assessed with LOWESS smoothing methods as well as by plotting martingale residuals.[17]

RESULTS

Composition of the study sample is shown in Figure 1. Of the 6441 subjects enrolled in the SHHS, individuals excluded from analyses included 136 subjects who had a history of stroke identified by the parent cohort at baseline, 21 subjects with missing censoring times, and 102 who reported use of continuous positive airway pressure for treatment of sleep apnea. All 760 subjects recruited from one of the field sites were excluded from this analysis due to data quality problems at this site. The analytic cohort therefore consisted of 2462 men and 2960 women.

The 5422 participants without a history of stroke and untreated for OSA with pressure therapy at the baseline SHHS exam were followed for a median of 8.7 years (inter-quartile range 7.8 –9.4 years). Over this period, a total of 193 ischemic strokes were observed (85 in men and 108 in women). Assuming a constant risk of stroke over the follow-up time, the estimated incidence rates were 4.4 ischemic strokes per 1000 person-years (95% C.I.: 3.5, 5.4) in men and 4.5 (3.7, 5.4) in women.

Tables 1a and 1b show the demographic characteristics, cardiovascular risk factors, and OSA measures by stroke incidence and gender. In both men and women, incident stroke was associated with increasing age and systolic blood pressure, use of anti-hypertensive medication and atrial fibrillation. In women, stroke also was associated with race (higher among African Americans and lower among Native Americans) and marginally associated with diabetes (p=.055). Stroke was not associated with BMI, smoking status or alcohol use in men or women. At baseline, moderate or severe OSA (OAHI>15) was approximately 30% more common in men and women who subsequently had an ischemic stroke compared to those who remained stroke-free. Further, mean OAHI and categories of desaturation time were less favorable in both men and women who subsequently had a stroke compared to those who did not. In contrast, baseline arousal index did not differ by the occurrence of stroke.

Tables 1a and 1b also provide the unadjusted odds ratios for representative variables. In men, the unadjusted increased odds of incident stroke for an individual with OSA compared to someone without OSA (odds ratio: 2.26) is approximately equivalent to the increased risk associated with a 10 year increase in age (2.37). In women, a somewhat lower odds ratio for stroke was observed (1.65), roughly equivalent to the risk of stroke associated with diabetes in this cohort (1.79). In neither men nor women, was BMI significantly associated with incident stroke.

Unadjusted rates of total and ischemic strokes in men and women by quartiles of OAHI and arousal index and overnight desaturation category are shown in Table 2. In both men and women, a progressively higher crude incidence rate of stroke is observed with increasing OAHI, with similar trends seen for desaturation index but not for arousal index.

In men, a progressive increase in the unadjusted hazard ratios for ischemic stroke was observed with increasing quartiles of OAHI (Table 3a; p<.005). Attenuation of this association was observed with age-adjustment, with a further modest attenuation following additional adjustment for BMI, race, smoking, systolic blood pressure, anti-hypertensive medication, and diabetes). Following adjustment for these covariates (of which only age was significantly associated with ischemic stroke), increasing quartile of OAHI remained significantly associated with increased stroke risk. Among men with an OAHI in the top quartile (i.e., > 19 events/hr) there was an almost 3-fold increased risk of ischemic stroke relative to men with an OAHI < 4.1 events/hr. In adjusted analyses, incident stroke was not associated with the arousal index or desaturation levels.

In women, adjusted analyses showed that stroke risk was significantly associated with age (hazard ratio 2.77; 95%% C.I.: 2.12, 3.61) per 10 years), diabetes (1.98; 1.17, 3.35), hypertension medication use (1.94; 1.25, 3.05), former smoking (1.53; 1.09,2.33), and current smoking (2.46; 1.27,4.75), but was not associated with OAHI quartile or desaturation levels (Table 3b). In contrast to the findings in men, in women, a higher arousal index was associated with a reduced incidence of stroke, such that women who had an arousal index greater than 12 (i.e., the first quartile) had a 40 to 60% decreased hazard rate of ischemic stroke compared to women with a lower arousal index.

Figures 2 and 3 show the stroke-free survival curves for men and women according to OAHI quartile.

Additional analyses were conducted to explore the inverse association between arousal index and stroke incidence in women. Persistence of an inverse association between arousals and stroke in women was observed in regression models which included both arousal index and OAHI as well as in models stratified by OAHI category. These suggested that the inverse association of arousals was independent of OAHI severity. Since hypnotic medication use might reduce arousal frequency, we examined benzodiazepine use and found that those using this class of medication had a lower mean arousal index (16.4 events/hr; C.I.: 15.2, 17.5, vs.19.2; C.I.: 18.9, 19.5, in users and non-users, respectively; p<.0001). Among women, the probability of a stroke was higher among benzodiazepine users than non-users (7.4% as compared 3.4%; p=.005). However, arousal index remained a significant negative predictor of incident stroke in women even after excluding hypnotic users from the regression models, as well as in models that adjusted for benzodiazepine use. In men (3.7% reported hypnotic use), no association was observed between hypnotic use and stroke.

Secondary analyses also were conducted to further address potential confounding. Atrial fibrillation was present at the baseline exam in 37 men and 22 women. Excluding these individuals from the analyses did not materially change the findings (i.e., in men, the hazard ratio for the upper quartile of OAHI was significant at 2.70 (1.04, 7.05.) Including the additional set of extended covariates (none of which was significantly associated with stroke) modestly reduced the strength of the association between OAHI and stroke; e.g., in men the HR for the upper OAHI quartile was 2.64 (1.01, 6.88).

We explored non-linear, covariate adjusted associations with the OSA exposures and interactions with gender. In men, non-parametric modeling of OAHI identified a linear increase in hazard ratio between an OAHI of 5 and 25 events/hr, with each unit of OAHI estimated to increase hazard ratio by 6% (95%C.I.: 2 to10%). In women, a 2% increase (95% C.I. 0 to 5%) in stroke hazard ratio with each unit increment in OAHI after a threshold of 25 events/hr also was observed. In combined gender analyses, a significant interaction between gender and the highest OAHI quartile was observed (p=.0009), supporting the differences observed in gender-stratified analyses.

Discussion

Eight-years of prospective data from this large, geographically diverse community-based cohort of middle-aged and older adults provide compelling evidence that OSA increases risk of ischemic stroke in men. Compared to men in the lowest OAHI quartile, men with moderately severe OSA had an almost 3-fold increased risk of ischemic stroke. The risk of stroke increased 6% with every unit increase in baseline OAHI from 5 to 25. The relationship between OAHI and stroke risk persisted after multiple adjustments, and of the potential confounders considered in adjusted survival models, was the only significant risk factor for ischemic stroke other than age. These results are consistent with our prior cross-sectional results which identified an association between stroke and OSA, which was somewhat stronger than the association with coronary heart disease or heart failure. [18] This report: a) provides evidence that stroke risk increases across the lower to mid range of OAHI in men, b) specifically addresses stroke rather than a composite endpoint as has been reported before; c) provides data that may be applied to non-clinic populations, including women in whom no increased risk of stroke was demonstrated across the mild to moderate OAHI range; d) provides a novel observation regarding the potentially protective association between increasing arousals and stroke in women.

This epidemiologic evidence complements laboratory research that addressed mechanisms for OSA-related cerebral vascular disease. Converging data indicate that OSA-related stressors may increase stroke risk by influencing cerebral tissue oxygenation, altering cerebral blood flow and velocity, and/or altering cerebral vascular autoregulation. Two studies have demonstrated reductions in cerebral tissue hemoglobin saturation levels occur with apneas, and that the severity of tissue deoxygenation correlates with length of the respiratory disturbance and degree of related desaturation[19, 20]. Marked surges in systemic blood pressure occur with each apneic and hypopneic event, followed by abrupt drops in systemic blood pressure. Parallel large fluctuations in cerebral blood flow velocity[21, 22] suggest that patients with OSA experience repetitive episodes of cerebrovascular shearing stress, which, in addition to the known oxidative stress associated with intermittent hypoxemia and reoxygenation, likely contributes to cerebral vascular endothelial dysfunction. This is supported by a recent study which demonstrated that patients with severe OSA, compared to controls, had reduced compensatory cerebrovascular blood flow responses to experimental hypotension[23]. This response was hypothesized to reflect impaired endothelial and/or myogenic vascular responses and provide a basis for increased stroke risk.

Increased stroke risk may also occur through mechanisms that are not specific to the cerebral circulation. OSA may promote generalized atherosclerosis through effects of intermittent hypoxemia, which activates the transcription factors hypoxia-inducible factor-1 and nuclear factor kappa B, which, in turn, induce the expression of inflammatory cytokines and adhesion molecules implicated in atherosclerosis. Intermittent hypoxemia also has been shown in mice models to induce the hepatic enzyme, stearoyl co-enzyme desaturase, leading to dyslipidemia and atherosclerotic lesions[24]. The potential importance of OSA in increasing stroke risk through atherogenic pathways is consistent with the reported higher prevalence of internal carotid artery atherosclerotic lesions in stroke patients with as compared to those without OSA [25]. Carotid ultrasonography also has demonstrated that severity of OSA correlates with increased degrees of intimal medial thickness, a marker of subclinical atherosclerosis[26, 27].

Atrial fibrillation is estimated to increase the risk of stroke by 2-fold or more[28]. SHHS data have shown that moderate-severe OSA increases the risk of atrial fibrillation by 4-fold.[29] A causal role for OSA in arrhythmia genesis is supported by observational data showing that patients with treated OSA have a lower risk of recurrent atrial fibrillation than untreated patients,[30] and by data also demonstrating a temporal association between the occurrence of respiratory disturbances and paroxysms of atrial fibrillation[31]. Although the frequency of atrial fibrillation was too low to include as a covariate in the model, associations between stroke and OAHI were virtually unchanged in secondary analyses which excluded individuals with atrial fibrillation. Although this suggests that atrial fibrillation at baseline did not explain the observed associations, it is possible that paroxysmal atrial fibrillation, as may occur at night and in conjunction with breathing disturbances, was a mediating culprit. Other secondary analyses which adjusted for lipid levels and lipid medications showed only a small attenuation of the association between OSA and stroke when these additional cardiovascular risk factors were adjusted for.

In contrast to the strong findings relating OAHI level and stroke incidence in men, in women an association between stroke and OAHI was not observed across the mid-range of OAHI. There are several possible explanations. One concern relates to the statistical power to detect effects in this group of women. We investigated post-hoc power calculations in two ways. When considering a log-rank test of equality of survival curves where exposure is based on the dichotomous variable, OSA (OAHI>15), classifying 720 women as affected, and assuming a stroke-free survival rate of 98% in the unexposed group, the study had 80% power to detect a hazard ratio of ischemic stroke of 2.1 or greater. When considering the exposure, OAHI, as a continuous variable in a Cox model, assuming a standard deviation of 12.8 for OAHI, and considering a conservative correlation among covariates of 0.50, the study had approximately 80% power to detect a 3 to 4% increase in hazard of ischemic stroke per 1 OAHI event (or about 16% increase in hazard ratio per 5 OAHI events).Thus, differences between men and women in the associations observed in this study are likely to reflect that modest to moderate associations may have not been detected given the number of strokes observed. Secondly, assessment of OSA was based on a single assessment made at the baseline SHHS examination. Since the prevalence of OSA increases more steeply with advancing age in women than men[32], it is likely that the OAHI obtained from the baseline polysomnogram reflected a greater lifetime cumulative OSA burden in men than women. Conversely, more women than men may have experienced a progression in OAHI level over the 8 year follow-up period after the baseline study, causing greater misclassification of OSA status across this time period among women than men. An increase in stroke risk in women at OAHI levels greater than 25 was observed, consistent with increased stroke risk in association with severe OSA. Future work defining the specific contributions of acute and cumulative exposures as OSA risk factors, as well as further study of severely affected women, is needed. Additionally, stroke risk factors, incidence rates, and outcomes differ in men and women. First-time strokes occur at older ages in women than in men, and incidence rates are higher for older women than older men[3]. In SHHS, women with stroke were slightly older than men with stroke. Univariate risk factors for stroke in women that were not observed in men included race and diabetes, and in adjusted analyses, stroke risk in women, but not men, was significantly associated with diabetes, hypertension medication use, and smoking. A greater contribution from “competing” risk factors therefore may have diminished the impact of OSA on stroke risk in women. Propensity for vascular morbidities is known to differ by gender and is partly explained by the influence of sex hormones on vascular function. Thus, it is plausible that vascular and other cardiac responses to OSA-related stressors may differ in men and women and explain differences in stroke predilection. For example, autonomic nervous system responses to intermittent hypoxic are greater in men than women. [33]

An unexpected observation was that in women, higher arousal indices were inversely associated with stroke. In a subset of SHHS participants whom had undergone brainstem MRI examinations, we previously reported an inverse association between arousal index and incidence of brainstem white matter disease[34], a subclinical marker of cerebral ischemic injury. Apnea-related increases in cerebral blood flow velocity have been reported to be attenuated by the occurrence of arousals[22], and thus, a higher arousal response may protect the cerebral circulation from fluctuating blood pressure changes. Arousals are involved in the termination of apneas/hypopneas, and thus may play a role in reducing apnea-related stressors by shortening the duration of respiratory disturbances and reducing the degree of associated desaturation. We attempted to address this hypothesis by determining if a statistical interaction could be demonstrated between OAHI and arousal index, but our data did not provide evidence of such an interaction. We also examined risk factor distributions to determine which ones were associated with both stroke and a low arousal index, identifying hypnotic use to be associated with both. The association between low arousals and hypnotic use is consistent with the drug's known effects on sleep architecture. Secondary analyses which excluded hypnotic users from the statistical models, however, showed the persistence of an inverse association between arousal index and stroke incidence. Given that hypnotics have been associated with falls and mortality, the novel observation that hypnotic use is associated with stroke requires further investigation, and points to potential negative effects on systemic as well as cerebral blood pressure control.

A strength of these analyses was the availability of rigorously collected research polysomnograms which provided the ability to systematically assess which OAHI-related stressors-OAHI, arousal index, or oxygen desaturation time were predictive of stroke. Although intermittent hypoxemia likely contributes to the pathogenic pathways related to stroke, our data suggest that the OAHI, which reflects intermittent desaturation events, is a better stroke predictor than is time in desaturation, which does not capture the dynamic changes in oxygen saturation which may produce oxidative stress. The inverse association between arousals and strokes in women, although not clear, underscores the complexity of physiological exposures that may modulate vascular responses and tissue injury and which may not be easily measured as a frequency count of cortical arousals.

The study also had a number of other strengths, including the largest sample size and number of incident strokes reported in any cohort study to date, the inclusion of a diverse population of men and women unselected for sleep disorders, and use of standardized exposure and outcome measurements. However, the study also had several limitations including lack of standardized data on some covariates of interest and no structural cardiac measures. Having a single database of cerebral imaging studies would have provided opportunities to further assess stroke subtypes. Since follow-up sleep studies were only available on a subset of individuals, exposure was quantified using the baseline polysomnogram, which may have resulted in misclassification and did not capture cumulative lifetime burden of OSA. Additional stroke events, through additional follow-up of the cohort, would have improved the power to detect modest associations, and thus improve assessment of stroke risk in women.

The longitudinal analyses performed provide firm support for an association between incident stroke and prior exposure to OSA, and thus, address some of the short-comings of prior cross-sectional studies or case-control studies where the temporal associations between stroke and OSA could not be determined. A potential causal association between OSA and stroke is also consistent with an uncontrolled study demonstrating reduced recurrent vascular events in patients who experienced strokes and OSA who were treated with positive airway pressure therapy compared to patients with untreated OSA[35]. However, a small intervention study of OSA treatment in stroke patients did not show improved outcomes in treated compared to untreated patients[36].

In summary, these prospective data provide evidence that men with increasing OAHI levels experience an increase risk of stroke. In this data set, the effect size for stroke for OAHI levels in the upper quartile was comparable to that for a 10 year increase in age or atrial fibrillation. Increased risk may be through a number of pathogenic pathways influenced by intermittent hypoxemia and sympathetic stimulation, including those that influence the cerebral vasoregulation, atherogenesis, and atrial fibrillation. Research is needed to better define the benefits of OSA treatment and prevention in modifying stroke risk.

ACKNOWLEDGEMENTS

Sleep Heart Health Study (SHHS) acknowledges the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), the Cornell/Mt. Sinai Worksite and Hypertension Studies, the Strong Heart Study (SHS), the Tucson Epidemiologic Study of Airways Obstructive Diseases (TES) and the Tucson Health and Environment Study (H&E) for allowing their cohort members to be part of the SHHS and for permitting data acquired by them to be used in the study. SHHS is particularly grateful to the members of these cohorts who agreed to participate in SHHS as well. SHHS further recognizes all of the investigators and staff who have contributed to its success. A list of SHHS investigators, staff and their participating institutions is available on the SHHS website, www.jhucct.com/shhs.

The opinions expressed in the paper are those of the authors and do not necessarily reflect the views of the Indian Health Service.

Conflicts of Interest Statement: No conflicts were noted other than: Mark Sanders is a scientific consultant to Philips-Respironics which manufactures devices used to monitor sleep, diagnose and treat Sleep-Disordered Breathing and non-invasive ventilation. Consistent with this, he is a co-inventor of BiPAP®, manufactured by Philips-Respironics and has a financial interest in this brand and related technologies by Philips-Respironics. In the past he received research support from Respironics and has spoken at venues which received support from Respironics and Cephalon. In the past, he was on advisory panels for Sanofi-Aventis and Cephalon. Naresh Punjabi has received honoria for participating in talks and CME activities from Respironics Inc and Resmed Inc.

References

1. World Health Organization. (Accessed 2009, at http://www.who.int/cardiovascular_diseases/resources/atlas/en/.

2. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117(4):e25-146.

3. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. Stroke; a journal of cerebral circulation 2009;40(4):1032-7.

4. Zhang Y, Galloway JM, Welty TK, et al. Incidence and risk factors for stroke in American Indians: the Strong Heart Study. Circulation 2008;118(15):1577-84.

5. El-Saed A, Kuller LH, Newman AB, et al. Factors associated with geographic variations in stroke incidence among older populations in four US communities. Stroke. 2006;37(8):1980-5.

6. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008;118(10):1080-111.

7. Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr 2003;142(4):383-9.

8. Redline S, Schluchter MD, Larkin EK, Tishler PV. Predictors of longitudinal change in sleep-disordered breathing in a nonclinic population. Sleep 2003;26(6):703-9.

9. Munoz R, Duran-Cantolla J, Martinez-Vila E, et al. Severe Sleep Apnea and Risk of Ischemic Stroke in the Elderly. Stroke. 2006;37(9):2317-21.

10. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of Sleep-disordered Breathing and the Occurrence of Stroke. Am J Respir Crit Care Med 2005;172(11):1447-51.

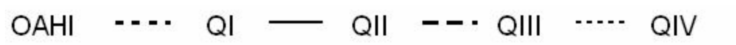
11. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365(9464):1046-53.

12. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive Sleep Apnea as a Risk Factor for Stroke and Death. N Engl J Med 2005;353(19):2034-41.
13. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. Sleep 1997;20(12):1077-85.
14. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1999;30(4):736-43.
15. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. J Clin Epidemiol 1992;45(6):683-92.
16. Redline S, Tosteson T, Boucher MA, Millman RP. Measurement of sleep-related breathing disturbances in epidemiologic studies. Assessment of the validity and reproducibility of a portable monitoring device. Chest 1991;100(5):1281-6.
17. Hosmer DW, Lemeshow S. Model Development. . In: Applied Survival Analysis New York: Wiley; 1999:158-80.
18. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163(1):19-25.
19. Hayakawa T, Terashima M, Kayukawa Y, Ohta T, Okada T. Changes in cerebral oxygenation and hemodynamics during obstructive sleep apneas. Chest 1996;109:916-21.
20. Valipour A, McGown AD, Makker H, O'Sullivan C, Spiro SG. Some factors affecting cerebral tissue saturation during obstructive sleep apnoea. Eur Respir J 2002;20(2):444-50.
21. Balfors EM, Franklin KA. Impairment of cerebral perfusion during obstructive sleep apneas. Am J Respir Crit Care Med 1994;150(6 Pt 1):1587-91.
22. Klingelhofer J, Hajak G, Sander D, Schulz-Varszegi M, Ruther E, Conrad B. Assessment of intracranial hemodynamics in sleep apnea syndrome. Stroke. 1992;23(10):1427-33.
23. Urbano F, Roux F, Schindler J, Mohsenin V. Impaired cerebral autoregulation in obstructive sleep apnea. J Appl Physiol 2008;105(6):1852-7.
24. Savransky V, Jun J, Li J, et al. Dyslipidemia and atherosclerosis induced by chronic intermittent hypoxia are attenuated by deficiency of stearoyl coenzyme A desaturase. Circulation research 2008;103(10):1173-80.
25. Dziewas R, Ritter M, Usta N, et al. Atherosclerosis and obstructive sleep apnea in patients with ischemic stroke. Cerebrovasc Dis 2007;24(1):122-6.

26. Szaboova E, Tomori Z, Donic V, Petrovicova J, Szabo P. Sleep apnoea inducing hypoxemia is associated with early signs of carotid atherosclerosis in males. Respir Physiol Neurobiol 2007;155(2):121-7.
27. Saletu M, Nosiska D, Kapfhammer G, et al. Structural and serum surrogate markers of cerebrovascular disease in obstructive sleep apnea (OSA): association of mild OSA with early atherosclerosis. J Neurol 2006;253(6):746-52.
28. Sacco RL, Boden-Albala B, Abel G, et al. Race-Ethnic Disparities in the Impact of Stroke Risk Factors: The Northern Manhattan Stroke Study. Stroke. 2001;32(8):1725-31.
29. Mehra R, Benjamin EJ, Shahar E, et al. Association of Nocturnal Arrhythmias with Sleep-Disordered Breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med 2006;173.(8):910-6.
30. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004;110(4):364-7.
31. Monahan K, Storfer-Isser A, Mehra R, et al. Triggering of Nocturnal Arrhythmias by Sleep Disordered Breathing Events. J Am Coll Cardiol 2009;(in press).
32. Redline S, Aylor J, Clark K, Graham G, Richardson S. Predictors of longitudinal change in the respiratory disturbance index. Am Resp Crit Care Med 1998;157:61.
33. Wadhwa H, Gradinaru C, Gates GJ, Badr MS, Mateika JH. Impact of intermittent hypoxia on long-term facilitation of minute ventilation and heart rate variability in men and women: do sex differences exist? J Appl Physiol 2008;104(6):1625-33.
34. Ding J, Nieto FJ, Beauchamp NJ, et al. Sleep-disordered breathing and white matter disease in the brainstem in older adults. Sleep 2004;27(3):474-9.
35. Martinez-Garcia MA, Galiano-Blancart R, Roman-Sanchez P, Soler-Cataluna JJ, Cabero-Salt L, Salcedo-Maiques E. Continuous positive airway pressure treatment in sleep apnea prevents new vascular events after ischemic stroke. Chest 2005;128(4):2123-9.
36. Hsu CY, Vennelle M, Li HY, Engleman HM, Dennis MS, Douglas NJ. Sleep-disordered breathing after stroke: a randomised controlled trial of continuous positive airway pressure. J Neurol Neurosurg Psychiatry 2006;77(10):1143-9.

Legends

Figure 1. Study schema showing derivation of the analytical sample.

Figures 2 a and b. Adjusted Kaplan-Meir stroke-free survival estimates as a function of OAHI quartile. Values are modeled in this graph for Caucasian current smoker men (a) and women (b) with no use of anti-hypertensive meds with mean values of other covariates. The first (OAHI<4.5), second (4.05-9.5), third (9.5-19.1) and fourth quartiles (>19.1) of the OAHI are shown as 

, respectively.

Table 1A: Distributions of demographic risk factors, and OSA indices in male Sleep Heart Health participants by ischemic stroke status, n= 2462

Predictors	With Ischemic Stroke	Without Ischemic Stroke	Unadjusted Odds Ratio for Stroke (95% C.I.)
N	85	2377	
Age**, median (IQR)*	72 (68 – 77)	63 (56 – 71)	Per 10 years: 2.37 (1.89, 2.98)
Race Caucasian, n (%) African American, n (%) Native American, n (%) Other, n (%)	68 (80.0) 5 (5.9) 10 (11.8) 2 (2.4)	1894 (79.7) 119 (5.0) 237 (10.0) 127 (5.3)	Caucasian vs Other: 1.01 (0.55,1.87) African American vs Other: 1.19 (0.42,3.38)
BMI (kg/m^2), median (IQR)	28.5 (25.9 – 30.4)	28.0 (25.4 –30.9)	Per 5 kg/m^2: 0.99 (0.49,1.69)
Smoking Status Current Smokers, n (%) Former Smokers, n (%) Never Smokers, n (%)	8 (9.4) 55 (64.7) 21 (24.7)	295 (12.4) 1281 (53.9) 795 (33.5)	Current: 1.05 (0.46,2.36) Former: 1.64 (0.99,2.71)
Alcohol use, n(%) None At least 1 drink	72 (84.7) 11 (12.9)	2001 (84.2) 322 (13.6)	-
Systolic BP**, median (IQR)	139 (124 – 150)	127 (117 – 140)	Per 10 mm Hg†: Above 130 mm Hg: 1.25 (1.08,1.44) Below 130 mm Hg: 1.49 (1.05,2.12)
Use of antihypertensive medications×, n (%)	45 (52.9)	863 (36.3)	2.05 (1.34,3.14)
Diabetes, n (%)	15 (17.7)	285 (12.0)	1.75 (1.00, 3.07)
Atrial Fibrillation,** n (%)	5 (5.9)	32 (1.4)	4.13 (1.65,10.37)
Sleep Apnea (OAHI>15)¥; n(%)	54 (63.5)	1041 (43.8)	2.26 (1.45,3.52)
OAHI¥, median (IQR)	19.2 (10.1 – 27.5)	13.0 (6.6 – 23.9)	
Arousal Index, median, (IQR)	20.9 (15.0 - 27.9)	19.0 (13.8 – 26.1)	
%Time < 90% Saturation ††median, (IQR)	0.9 (0.17 – 4.32)	0.4 (0.03 – 2.8)	

* IQR- interquartile range; quartile 1-3); **p<0.0001 ¥p< 0.001, × p < .01; ††p<.0.05-by Kruskal-Wallis equality-of-populations rank test or Chi-squared test; † Ratio of hazards per 10mm Hg (slope changes at a SBP of 130mm Hg).

Table 1B: Distributions of demographic, risk factors, and OSA indices in female Sleep Heart Health participants by ischemic stroke status, n=2960

Predictors	With Ischemic Stroke	Without Stroke	Unadjusted Odds Ratio for Stroke (95% C.I.)
N	108	2852	
Age**, median (IQR)*	75 (72.5 – 80.0)	62 (55 – 72)	Per 10 years: 3.33 (2.66, 4.16)
Race**			
Caucasian, n (%)	88 (81.5)	2169 (76.1)	Caucasian vs Other: 4.82 (1.77,13.15)
African American, n (%)	16 (14.8)	177 (6.2)	African American vs Other: 10.41 (3.48,31.16)
Native American, n (%)	4 (3.7)	341 (12.0)	
Other, n (%)	0 (0.0)	165 (5.8)	
BMI (kg/m^2), median (IQR)	27.1 (24.7 – 32.0)	27.6 (24.4 – 31.7)	Per 5 kg/m^2: 0.91 (0.77,1.08)
Smoking Status			
Current Smokers, n (%)	12 (11.1)	316 (11.1)	Current: 1.18 (0.63,2.21)
Former Smokers, n (%)	44 (40.7)	948 (33.2)	Former: 1.44 (0.97,2.16)
Never Smokers, n (%)	52 (48.2)	1578 (55.3)	
Alcohol use, n(%)			
None	95 (88.0)	2599 (91.1)	-
At least 1 drink	10 (9.3)	176 (6.2)	
Systolic BP**, median (IQR)	137 (126 – 155)	127 (115 – 139)	Per 10 mm Hg†: Above 130 mm Hg: 1.28 (1.14,1.44) Below 130 mm Hg: 1.59 (1.18,2.15)
Use of antihypertensive medications**, n (%)	75 (69.4)	1040 (36.5)	2.05 (1.34,3.14)
Diabetes^x^, n (%)	19 (17.8)	329 (11.5)	1.79 (1.09, 2.94)
Atrial Fibrillation**, n (%)	4 (3.7)	18 (0.6)	4.65 (1.71,12.69)
Sleep Apnea (OAHI>15)††; n(%)	37 (34.3)	683 (24.0)	1.65(1.45, 3.52)
OAHI¥, median (IQR)	10.2 (4.8 – 18.5)	6.9 (2.9 – 14.4)	
Arousal Index, median, (IQR)	14.2 (9.5 – 23.5)	15.2 (11.0 – 21.2)	
%Time < 90% Saturation¥	0.4 (0.04 – 1.9)	0.1 (0.00 – 1.1)	

* IQR- interquartile range; quartile 1-3);** p<0.0001 ¥p≤ 0.001, ††p<.0.05,ˣ p=0.055 by Kruskal-Wallis equality-of-populations rank test or Chi-squared test; †Ratio of hazards per 10mm Hg (slope changes at a SBP of 130mm Hg).

Table 2: Crude Rates of Ischemic Stroke (per 1000 person-years) by OSA Indices

	Men			Women		
Sleep Apnea Exposures	No. Observations	No. Ischemic Strokes	Rate of ischemic stroke per 1000 person/years (95% CI)*	No. Observations	No. Ischemic Strokes	Rate of ischemic stroke per 1000 person/years (95% CI)*
	2462	85	4.4 (3.5, 5.4)	2960	108	4.5 (3.7, 5.4)
OAHI						
IV quartile (19.1– 64.5)	847	43	6.6 (4.9, 9.0)	508	25	6.1 (4.1, 9.0)
III quartile (9.50 – 9.1)	690	22	4.0 (2.6, 6.1)	666	31	5.8 (4.1, 8.2)
II quartile (4.1 - <9.5)	557	15	3.3 (2.0, 5.5)	798	31	4.8 (3.4, 6.8)
I quartile (0 – <4.1)	368	5	1.7 (0.7, 4.1)	988	21	2.5 (1.7, 3.9)
P-value for linear trend	-	-	0.0004	-	-	0.002
Arousal Index						
IV quartile (23.6 –74.7)	773	32	5.3 (3.7, 7.5)	547	25	5.7 (3.8, 8.4)
III quartile (16.8 -23.6)	678	25	4.7 (3.1, 6.9)	643	15	2.8 (1.7, 4.7)
II quartile (12.0 <16.8)	531	13	3.0 (1.8, 5.3)	789	22	3.4 (2.2, 5.1)
I quartile (2.2 – <12.1)	417	14	4.3 (2.5, 7.2)	903	38	5.1 (3.7, 7.0)
P-value for linear trend	-	-	0.221	-	-	0.895
Time <90% O2 saturation						
III tertile (1.96 –100.00)	760	35	6.0 (4.3, 8.3)	587	26	5.5 (3.8, 8.1)
II tertile (0.23 - <1.96)	683	23	4.3 (2.9, 6.5)	664	40	7.4 (5.4, 10.1)
I tertile (0.003 - <0.23)	560	16	3.6 (2.2, 5.8)	787	24	3.7 (2.5, 5.6)
0 value (0)	459	11	3.0 (1.6, 5.3)	922	18	2.3 (1.5, 3.7)
P-value for linear trend	-	-	0.020	-	-	0.003

* - the rates are calculated assuming Poisson distribution for the number of ischemic stroke events

Table 3A: Results of Cox proportional hazard model regression hazard of developing incident ischemic stroke among Men, N = 2,462

Covariate	Unadjusted	Adjusted	
		Age -Adjusted	Fully Adjusted§
	Hazard Ratio (95% Confidence Interval for Ratio of Hazards)		
OAHI			
IV quartile (19.13 – 164.5)	3.91 (1.55, 9.86)	3.05 (1.21, 7.72)	2.86 (1.10, 7.39)
III quartile (9.50 – <19.13)	2.35 (0.89, 6.20)	1.97 (0.74, 5.21)	1.86 (0.70, 4.95)
II quartile (4.05 - <9.50)	1.96 (0.71, 5.40)	1.86 (0.68, 5.13)	1.86 (0.67, 5.12)
I quartile (0 – <4.05)	1.0	1.0	1.0
P-value for test of linear trend for AHI	0.0004	0.006	0.016
Arousal Index quartiles			
IV quartile (23.64 – 74.66)	1.24 (0.66, 2.32)	1.02 (0.55, 1.92)	0.98 (0.52, 1.85)
III quartile (16.83 - <23.64)	1.09 (0.57, 2.10)	1.05 (0.55, 2.02)	0.99 (0.51, 1.92)
II quartile (12.02 - <16.83)	0.71 (0.34, 1.52)	0.73 (0.34, 1.55)	0.76 (0.35, 1.62)
I quartile (2.18 – <12.07)	1.0	1.0	1.0
P-value for test of linear trend for Arousal Index	0.221	0.614	0.772
Time <90% O2 Saturation			
III tertile (1.96 – 100.00)	2.02 (1.03, 3.98)	1.66 (0.84, 3.27)	1.46 (0.71, 2.98)
II tertile (0.23 - <1.96)	1.45 (0.71, 2.98)	1.25 (0.61, 2.56)	1.17 (0.57, 2.43)
I tertile (0.003 - <0.23)	1.20 (0.56, 2.58)	1.12 (0.52, 2.42)	1.12 (0.52, 2.43)
0 value (0)	1.0	1.0	1.0
P-value for test of linear trend for Saturation Time	0.020	0.093	0.266

§ - adjusted for age, BMI, smoking status, systolic blood pressure, use of antihypertensive medications, diabetes status, and race

Table 3B: Results of Cox proportional hazard model regression hazard of developing incident ischemic stroke among women, N = 2,960

Covariate	Unadjusted	Adjusted	
		Age	Fully Adjusted[§]
	Hazard Ratio (95% Confidence Interval for Ratio of Hazards)		
OAHI			
IV quartile (19.13 – 164.5)	2.37 (1.33, 4.24)	1.24 (0.69, 2.22)	1.21 (0.65, 2.24)
III quartile (9.50 – <19.13)	2.26 (1.30, 3.94)	1.26 (0.72, 2.20)	1.20 (0.67, 2.16)
II quartile (4.05 - <9.50)	1.87 (1.08, 3.26)	1.34 (0.77, 2.34)	1.34 (0.76, 2.36)
I quartile (0 – <4.05)	1.0	1.0	1.0
P-value for test of linear trend for AHI	0.002	0.569	0.693
Arousal Index quartiles			
IV quartile (23.64 – 74.66)	1.09 (0.66, 1.81)	0.64 (0.38, 1.06)	0.64 (0.38, 1.07)
III quartile (16.83 -<23.64)	0.55 (0.30, 1.00)	0.42 (0.23, 0.76)	0.41 (0.23, 0.75)
II quartile (12.02 - <16.83)	0.66 (0.39, 1.12)	0.57 (0.34, 0.97)	0.59 (0.34, 1.01)
I quartile (2.18 – <12.07)	1.0	1.0	1.0
P-value for test of linear trend for Arousal Index	0.864	0.039	0.035
Time <90% O2 Saturation			
III tertile (1.96 – 100.00)	2.36 (1.30, 4.31)	1.22 (0.66, 2.23)	0.94 (0.50, 1.79)
II tertile (0.23 - <1.96)	3.17 (1.82, 5.53)	2.09 (1.20, 3.65)	1.78 (1.01, 3.15)
I tertile (0.003 - <0.23)	1.62 (0.88, 2.98)	1.22 (0.66, 2.26)	1.06 (0.57, 1.97)
0 value (0)	1.0	1.0	1.0
P-value for test of linear trend for Saturation Time	0.0003	0.254	0.761

[§] - adjusted for age, BMI, smoking status, systolic blood pressure, use of antihypertensive medications, diabetes status, and race

REFERENCES

Figure 1.

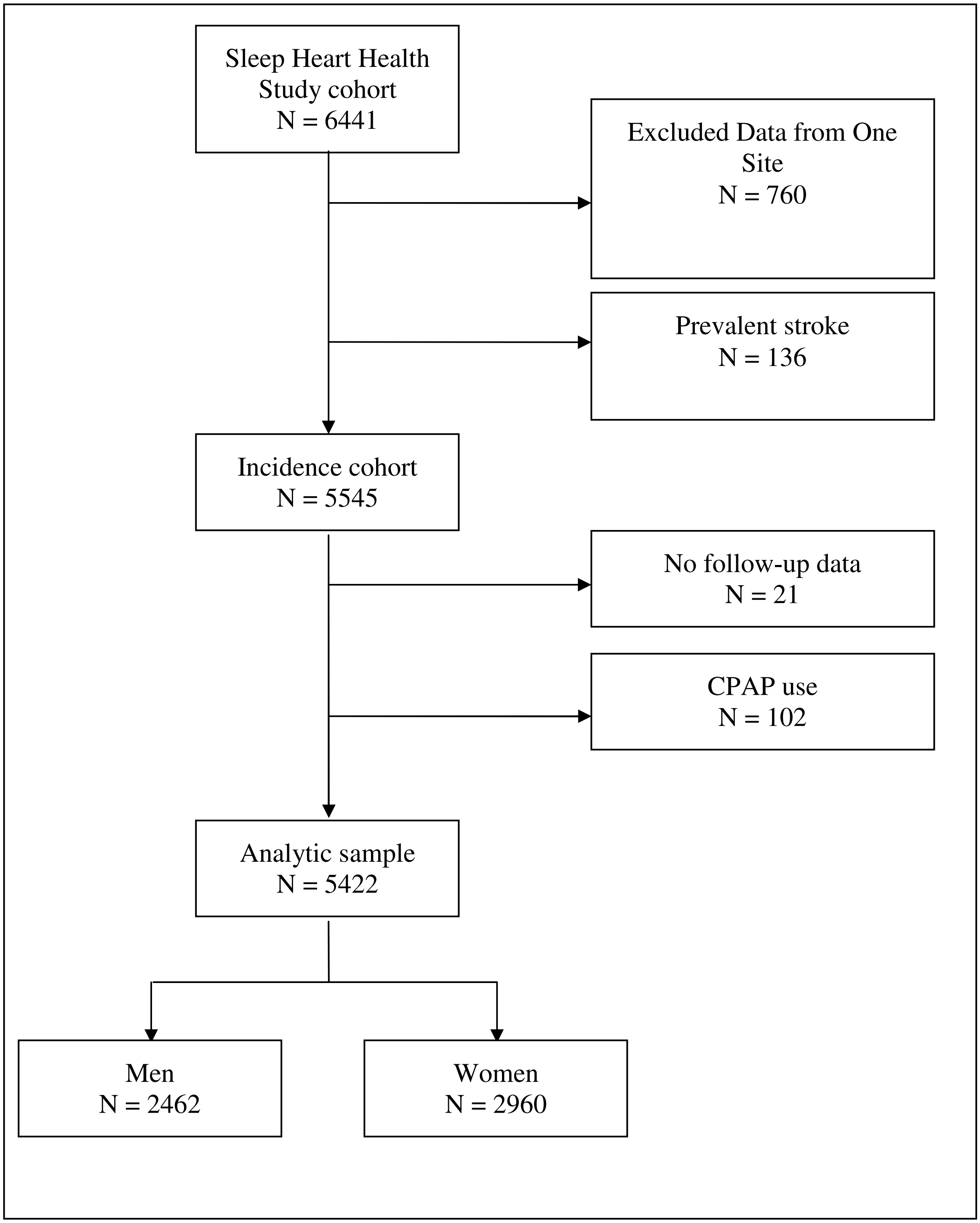


Figure 2A.

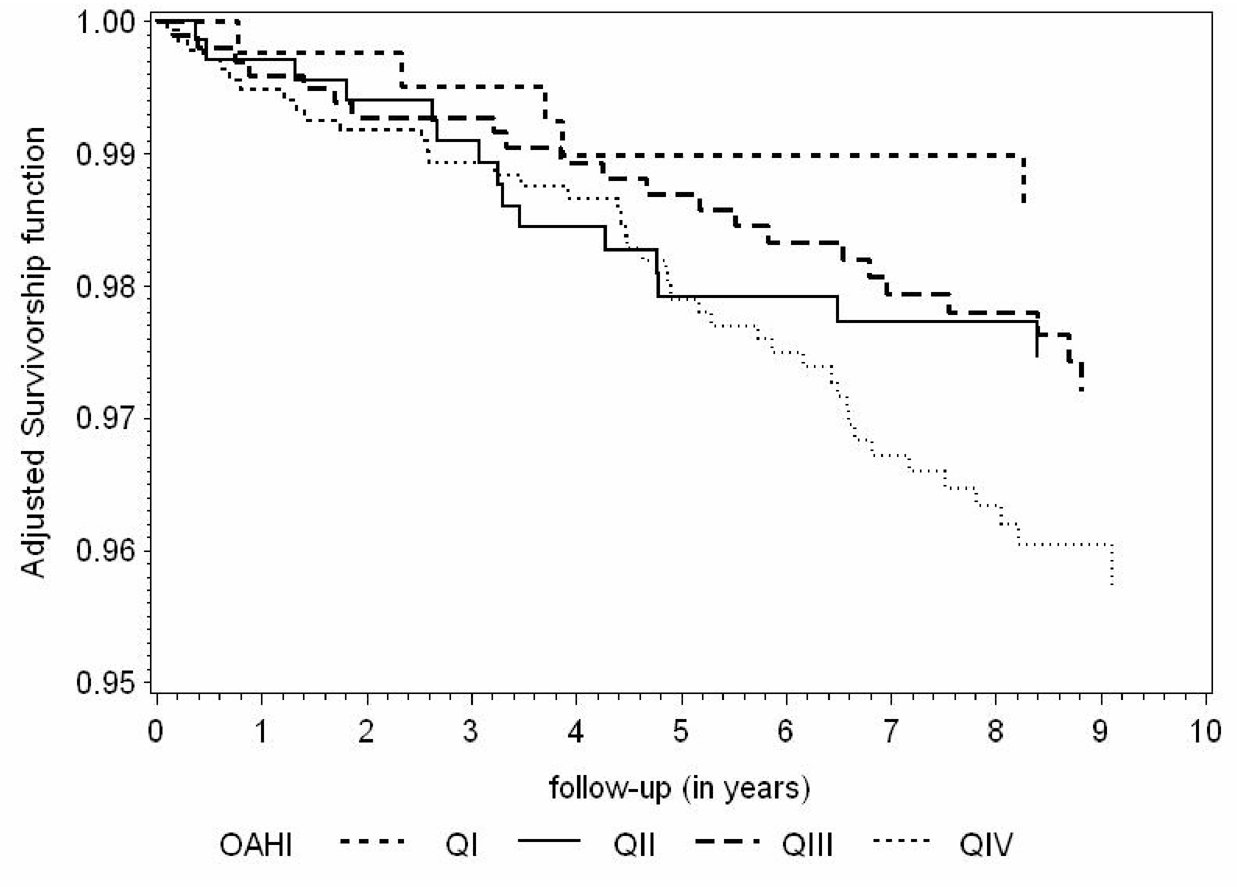

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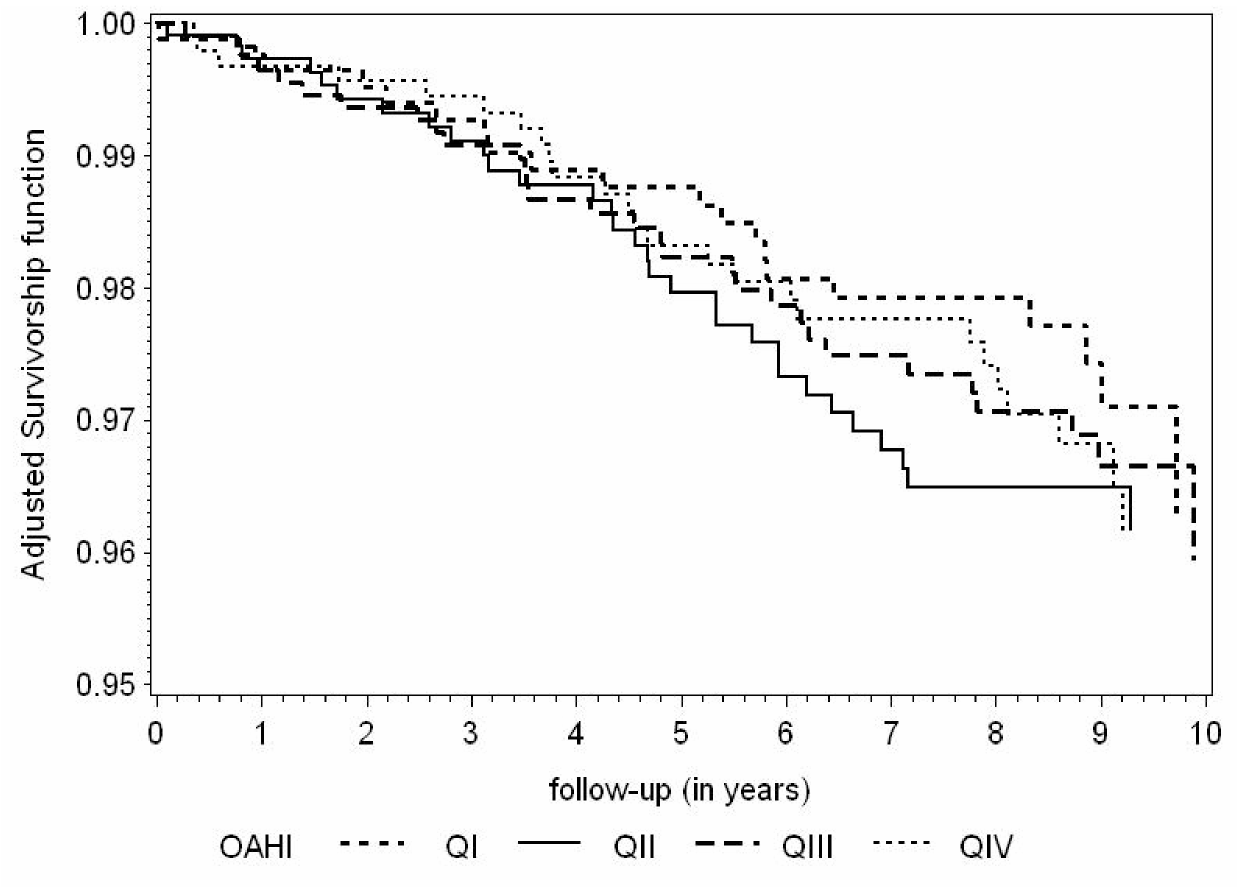
Figure 2B.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Obstructive Sleep Apnea Hypopnea and Incident Stroke: The Sleep Heart Health Study

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On-Line Supplement

METHODS

Study Design and Sample

The SHHS is a community-based, prospective cohort study of the cardiovascular consequences of OSA. Briefly, 6441 men and women age 40 years and older were recruited from among participants in seven large studies of cardiovascular and pulmonary disease (the “parent cohorts"), including the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, Strong Heart Study, Tucson Epidemiologic Study of Obstructive Lung Disease, Tucson Health and Environment Study and the New York University-Cornell Worksite and Hypertension Study. Exclusion criteria were self-reported use of pressure or oral devices for treatment of OSA, or use of nocturnal supplemental oxygen, as described elsewhere[13]. At the baseline SHHS examination (1995-1998), trained research technicians administered questionnaires for sleep habits, general health, and medication use; and performed anthropometry, blood pressure measurement, and obtained overnight unattended polysomnography. Additional covariate data were provided by the parent cohorts, including prevalent stroke events identified and adjudicated by each parent cohort. At intervals of approximately 3 and 5 years following the baseline polysomnogram, a survey regarding diagnosis of and treatment for OSA was performed. Participants also had ongoing surveillance for cardiovascular events by parent cohorts through April 2006. The protocol was approved by the Institutional Review Board of each participating institution and signed informed consent was provided by each subject.

Of the 6441 subjects enrolled in the SHHS, all 760 subjects recruited from the New York site were excluded from this analysis due to data quality problems at this site. Others excluded from analyses included 136 subjects who had a history of stroke identified by the parent cohort at baseline, 21 subjects with missing censoring times, and 102 who reported use of continuous positive airway pressure for treatment of sleep apnea. The analytic cohort therefore consisted of 2462 men and 2960 women.

Incident Stroke

Incident stroke was defined as the first occurrence of stroke between the date of the baseline polysomnogram and the end of follow-up, which was April 1, 2006. Ongoing surveillance for incident stroke was performed by parent cohorts according to cohort-specific protocols, as previously described[3-5, 14]. These included a combination of direct participant contact at intervals of one to four years, surveying death certificates and discharge information from local hospitals, and by mailings to study participants. All potential events were further investigated and adjudicated using defined protocols, which were similar across cohorts and included physician review of abstracted data. Trained abstractors extracted information from hospital discharge records, including available CT and MRI examinations and physician office records, using pre-specified criteria for identifying and categorizing stroke subtypes. The current analyses considered all first episodes of events adjudicated to be definite ischemic cerebrovascular events (193 events), including 15 fatal strokes.

Other Covariates

Blood pressure, measured in triplicate, and weight, measured using a calibrated scale, were obtained using a standardized protocol at the SHHS baseline exam[13]. Body mass index (BMI) was defined as weight (kg) divided by height (m) squared. Medication use was classified using methods developed for epidemiologic research[15]. Smoking status was classified as current versus former or never smokers. Diabetes was ascertained based on report of physician diagnosis or reported use of insulin or oral hypoglycemic medication. Atrial fibrillation was defined on the basis of ECG findings from the baseline examination. Because the most complete information on alcohol use was from a questionnaire completed at the time of the sleep study, alcohol use was defined as a sum of the reported number of drinks during the 4 hours before bed on the night of the sleep study, and used as a binary variable, indicating having consumed one drink or more vs none. Race and ethnicity were based on self-report by questionnaire and assessed given racial differences in stroke incidence. OAHI was quantified using overnight unattended polysomnography (Compumedics P-series portable monitor; Abbotsford, AU), as described previously[16]. Polysomnograms were scored at the SHHS Sleep Reading Center (Cleveland, OH) using scoring guidelines and quality control methods described previously[16]. Obstructive apneas were identified by a complete or near-complete cessation in airflow lasting for ≥ 10 seconds accompanied by respiratory effort. Hypopneas were identified by a clear decrease in airflow or chest or abdominal effort amplitude lasting for at least 10 seconds and associated with a ≥3% oxyhemoglobin desaturation. The Obstructive Apnea Hypopnea Index (OAHI) was defined as the average number of obstructive apneas plus hypopneas per hour of sleep. apnea was not considered in this calculation because of the potential bi-directional association Central between cerebrovascular disease and central apneas. Cortical arousals were scored using standard criteria and the arousal index was the total number of arousals per hour of sleep. Hemoglobin oxygen desaturation was characterized as the percentage of sleep time at an oxygen desaturation of <90%.

Statistical analysis

Participants were followed until a first stroke occurred between the date of the polysomnogram and the final censoring date. Individuals who did not develop a stroke were censored at the date of death or last contact. The primary exposure was quartiles of baseline OAHI, with secondary exposures including the continuously measured OAHI, quartiles of the arousal index, and a 4-level ordinal variable describing categories of percentage of time in desaturation, defined as "0" (reference), with the remaining observations based on tertiles of the distribution.

Associations between stroke risk and OAHI were estimated using semi-parametric Cox proportional hazards model. Covariates from the baseline SHHS exam included in the primary models were: age, BMI, smoking status, systolic blood pressure, antihypertensive medication use, diabetes status, and race. Given the marked distributional differences of OAHI and cardiovascular risk factors in men and women, analyses were stratified by gender. We also tested the linear trend for each of the predictors by entering the corresponding categorical variables into the models and treating them as linear predictors. Although the primary analyses did not include variables that were missing on more than 10% of the sample (e.g., cholesterol levels, which were only available from some of the parent cohorts, secondary analyses were conducted that included alcohol use, total and HDL cholesterol and lipid lowering medications as covariates. Since atrial fibrillation was relatively rare, its inclusion in the model caused instability of the parameter estimated. Therefore, to address potential confounding, secondary analyses were performed excluding those with atrial fibrillation from analyses. Additional secondary analyses excluded individuals using benzodiazepine medications. Non-linear associations were assessed with LOWESS smoothing methods as well as by plotting martingale residuals.[17] Heterogeneity of the effect of OAHI on hazard of ischemic stroke by gender was assessed by including an interaction term in the fully adjusted model including men and women. Adjusted survival estimates were obtained from the fully adjusted model for individuals of Caucasian race, current smokers, non-users of antihypertensive medications, with no evidence of diabetes and with mean values of age, BMI, and systolic blood pressure. The survival estimates were used to graphically depict differences by OAHI quartiles. Statistical analyses were performed using SAS versions 9.1 and 9.2.