SHHS Manuscript/Abstract Proposal

1. a. Full Title: Sleep-disordered breathing and risk of incident cerebrovascular disease: The Sleep Heart Health Study
   b. Abbreviated Title: Sleep-disordered breathing and Stroke

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3. Timeline: Planned start is after completion of outcomes data collection. If that occurs in August 2007, as planned, initial analyses will be conducted in the fall of 2007 with a first draft anticipated in January 2008.

4. Rationale: Prior research has identified significant cross-sectional associations between sleep disordered breathing (SDB) and stroke. Some prospective studies have confirmed an association, but these studies have been limited by lack of rigorous data on covariates, studies of selected patient groups or small sample size, or limited assessment of threshold exposure effects. A major thrust of the SHHS is to identify whether incident CV disease is associated with SDB.

5. Hypotheses:
   a. Sleep-disordered breathing is associated with increased risk of incident cerebrovascular disease, including fatal or non-fatal stroke and transient ischemic attacks (TIAs).
   b. Sleep-disordered breathing is associated with increased of recurrent cerebrovascular disease, including fatal or non-fatal stroke and transient ischemic attacks (TIAs) cerebrovascular disease at the time of the baseline SHHS examination.
   c. Incident and recurrent cerebrovascular disease increase in proportion to the severity of SDB (as described by the apnea hypopnea index, arousal index, and desaturation level), and these associations are independent of selected confounders.

6. Data: Variables included will be measures of SDB (AHI, arousal index and oxyhemoglobin saturation) at SHHS-1 and SHHS-2, cerebrovascular disease status at baseline, incident cerebrovascular disease during follow-up (with event dates), and covariates including age, sex, BMI, smoking status, total and HDL cholesterol, systolic and diastolic blood pressure and anti hypertension medications, lung function, diabetes, use of cardiovascular medications and fasting blood glucose (if available at baseline), and atrial fibrillation (from ECG).

7. Type of Study: Primary

8. Target Journal: Internal Medicine or Epidemiology journal

9. Analysis Responsibility: Central

10. Introduction: Sleep disordered breathing (SDB) is considered to pose a potentially large potential health burden to the population related to its putative causal role in increasing risk of incident and recurrent vascular diseases, including cerebrovascular diseases. Causal associations are supported by limited experimental and some observational data showing that SDB is associated with endothelial dysfunction, insulin resistance, hypertension, oxidative
stress, abnormal sympathetic traffic, augmented levels of pro-atherosclerotic inflammatory cytokines, and propensity for atrial fibrillation (1-4). Adverse physiological responses are thought to be associated with intermittent hypoxemia, sympathetic activation, and changes in intrathoracic pressures. A recent study has described abnormal cerebral vascular responses to hypoxia in patients with SDB compared to controls, with improvement in these responses after CPAP treatment (5), suggesting that SDB-related hypoxia impairs cerebral vascular reactivity. Other work also has implicated snoring-related trauma to carotid arteries as another mechanism that may explain associations with cerebrovascular disease.

There are several epidemiological studies that support an association between SDB and cerebrovascular disease. Cross sectional studies of stroke patients have shown that upwards of 50 to 75% of patients who have had a stroke have SDB, measured acutely to one month after the stroke (6,7). However, in these studies, reverse causality could not be excluded. Several larger scale observational studies have utilized composite CV endpoints and have shown that patients with untreated moderate to severe SDB have worse outcomes than less affected or treated SDB patients (8-10). However, outcomes may differ among patients who decline and accept treatment for reasons other than the treatment effect. In addition, the use of surrogate outcomes limits the ability to infer specific associations with cerebrovascular disease. Data from the Wisconsin Sleep Cohort have shown that participants with an AHI > 20 were approximately 3-fold more likely to have a stroke in cross-sectional analyses, with a similar point estimate described for incident stroke. The latter inferences were made in a subgroup of only 90 individuals, in whom 6 experienced a stroke (11). Interestingly, in the group with an AHI 5-20, the point estimate for stroke was actually less than 1, and although not statistically different than the least affected group, raises questions regarding threshold and dose-response effects. A population-based study of individuals > 70 years from Spain also has shown an approximately 2.5 fold increased risk of stroke over a 6 year period in those with an AHI >30 compared with others with lower AHI levels (12). This study did not examine dose-response associations. In prior work, the SHHS has shown a modest cross-sectional association (odds ratio about 1.4) between self reported stroke and SDB (measured as AHI in uppermost quartile) (13). One study of CPAP treatment in patients after a stroke showed that those with an AHI >20 who were treated with CPAP (n=15) had fewer vascular events (7%) than a group of 33 people who can not tolerate CPAP (n=33) (14).

The proposed study is designed to overcome several limitations of prior research as well as extend previous studies. In particular, the sample is 5 to 6 fold larger than the largest prior publication, and provides excellent representation of both men and women. Longitudinal sleep data are available for a subgroup, also allowing more detailed assessments of exposure over time to be addressed. The sleep data were rigorously collected and afford a large variety of exposure indices amenable to testing dose-response and threshold relationships. Finally, the covariates were collected using well defined protocols. Only a limited number of subjects underwent treatment for SDB.

11. Brief Analysis Plan: Subjects included in this analysis will be all subjects enrolled in the SHHS with an acceptable baseline PSG, non-missing data for cerebrovascular disease at baseline and at least one follow-up time point, and non-missing data for key risk factors included in the analysis. The primary outcome variable will be stroke and TIA, with separate models for incident and recurrent cerebrovascular disease. The primary exposure variable for this analysis will be AHI (defined as RDI4P for the main analysis), treated as a categorical exposure variable using common clinical cut-points of 1.5, 5, 15, 30, and 50 events per hour. Alternative exposure variables will include percentage time oxygen saturation <90% (categorized given extreme skewness) and the Arousal Index. Covariates that will be considered include: age, sex, race,
BMI, waist, smoking status, total and HDL cholesterol, hypertension status and systolic and diastolic blood pressure, lung function, use of anti-hypertensive or anti-diabetic medication, and fasting blood glucose (if available). (Models with vary according to whether certain covariates, such as hypertension, are included, to explore mediation.)

The distribution of covariates across these categories at baseline will be examined in bivariate analyses. Non-parametric graphing techniques (splines) will be used to explore dose-response relationships and to identify potential threshold effects. If the association appears linear or log-linear, then AHI (or ln(AHI)) will be treated as a continuous variable in the main analysis; otherwise, the above-mentioned categories will be used.

Kaplan-Meier curves will be used for an unadjusted analysis of the association of SDB with cerebrovascular disease. The main analysis will utilize proportional hazards modeling with AHI as a time-dependent variable (to incorporate AHI measured at both SHHS-1 and SHHS-2). (Covariates measured during the follow-up period, such as BMI and blood pressure, may also be included as time-dependent variables.) Exploratory models will include change in AHI level, measures of hypoxemia, sleepiness, and arousal. Exploratory analyses also will consider possible effect modification by sex, age, race, atrial fibrillation, and hypertension status.

12. Summary: This paper will describe the relation of sleep-disordered breathing to incident and recurrent cerebrovascular disease.

13. References:
1. Ip MS, Lam B, Chan LY, et al.. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Am J Respir Crit Care Med 2000; 162(6):2166-71
4. Vgontzas AN; Bixler EO; Chrousos GP; Metabolic disturbances in obesity vs sleep apnea:the importance of visceral obesity and insulin resistance; 2003, Journal of Int Med; 254, no 1 (2003 Jul): 32-44.