Manuscript Proposal #1313(SHHS099)

Title: Sleep-disordered breathing (SDB) and mortality: The Results of the Sleep Heart Health Study

Short Title: Sleep-disordered breathing and mortality

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Timeline: After completion of event adjudication, analyses relating SDB to mortality will commence. The anticipated completion date for the manuscript is June 2008.

Rationale: Sleep-disordered breathing is a prevalent condition that has been associated with an increased prevalence of coronary artery disease, heart failure, and stroke (1). SDB has also been associated with incident hypertension (2). Although cause and effect for a number of proposed complications of SDB has not been definitively established, numerous clinic-based studies have demonstrated an increase in mortality risk. However, community-based studies that have used robust methodology for assessing sleep and breathing abnormalities while controlling for confounding factors are not available. The overall objective of this proposal is to examine the mortality burden associated with SDB in a community cohort of middle-aged and older adults participating in the Sleep Heart Health Study (SHHS).

Hypotheses: For proposed analyses, several hypotheses will be tested. These include:

1. SDB (as assessed at the baseline polysomnogram) will be independently associated with all-cause mortality independent of covariates such as age, gender, race, body mass index (BMI), and measures of central obesity.
2. Overweight and obesity will augment the mortality risk associated with SDB.
3. Compared to subjects free of prevalent hypertension, cardiovascular disease, heart failure, and stroke at the baseline SHHS visit, those with these conditions will have higher overall and cause-specific mortality.
4. Compared to subjects with stable or improved SDB parameters over the follow-up period, subjects that experience an increase in SDB severity will have higher all cause mortality rates.
5. In the each of the above analyses, we will determine whether measures of sleep-related hypoxemia and/or sleep fragmentation are mediate the higher mortality risk of SDB after adjusting for relevant confounders.

Data Requested: The mortality experience of the entire SHHS will be determined up to 04/01/2006 and will constitute the primary independent variable. Cause of death (e.g., coronary artery disease, stroke, heart failure, etc) will comprise the panel of secondary independent variables. The primary predictors will include a repertoire of measures that quantify SDB severity. These include (a) apnea-hypopnea index (aggregate and stratified by NREM/REM sleep); (b) average oxygen saturation during sleep (aggregate and stratified by NREM/REM sleep); (c) average event related desaturation (aggregate and stratified by NREM/REM sleep); (d) sleep time spent below an oxygen saturation < 90%; (e) frequency of arousals; and (f) summary statistics of sleep stages. Covariates of interest will include: age, gender, race, BMI, waist circumference, neck circumference, and prevalent medical disease (hypertension, coronary artery disease, stroke, heart failure, chronic obstructive lung disease). For those with follow-up visits, data on the independent and dependent variables will be extracted to ascertain whether changes in SDB severity are associated with mortality.

Journal: Sleep, AJRCCM, JAMA, NEJM
**Analysis:** Central

**Background:** Sleep-disordered breathing (SDB) is being increasingly recognized as an important cause of medical morbidity and mortality. It is characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep. The ensuing reduction of airflow often leads to acute derangements in gas exchange and recurrent arousals from sleep. The health consequences of obstructive sleep apnea are numerous. If left untreated, it leads to excessive daytime sleepiness, cognitive dysfunction, and impaired work performance, decrements in health-related quality of life (3). Patients with SDB also experience higher rates of motor vehicle crashes as well as impairments in health-related quality of life. Observational and experimental evidence also suggests that obstructive sleep apnea may contribute to the development of diurnal hypertension, cardiovascular disease, and neurobehavioral sequelae.

At present, data on the association between SDB and mortality are limited and conflicting. In a prospective study of 1,620 patients with SDB, Lavie et al. (4) reported an independent association between the apnea index and all-cause mortality after adjusting for age, BMI, and history of hypertension. The analysis, which excluded the small number of women, showed that the increase in mortality associated with SDB was age dependent. Younger and middle-aged patients were at higher risk than older patients. Subsequent work form the same laboratory on a larger group of male patients with SDB has shown similar findings (5). Additional evidence for the link between SDB and mortality comes from a Swedish study that prospectively followed 1,300 men for a ten-year period. Using a population-based registry, Lindberg et al. (6) showed that men with habitual snoring and excessive daytime sleepiness had higher mortality rates than men without these symptoms. Interestingly, snoring without excessive daytime sleepiness was not associated with increased mortality. Unfortunately, the lack of polysomnographic data in that study is a major limitation. However, a number of more recent and relatively well-designed studies of clinical cohorts have shown that sudden death (7) or cardiovascular mortality (8;9) are in fact increased in those with polysomnographically-defined SDB.

Additional support for SDB-related risk for mortality is also found in studies that have examined the effect of treatment on long-term outcome in patients with SDB. In one of the earliest reports, He et al. (10) showed decreased survival in untreated individuals with greater than 20 apneic events per hour. Although similar findings have been reported by others (11), treatment has not necessarily been found to improve outcomes across all studies (9;12;13).

The evidence implicating SDB as risk factor for mortality is balanced by several reports that have failed to show an independent effect. In a community sample of older adults, Ancoli-Israel and coworkers (14) found that over a 8- to 10-year follow-up period, SDB was not a predictor of decreased survival after accounting for numerous covariates. Similarly, after accounting for age-related medical conditions, several others have also failed to find an independent SDB-mortality association. However, limitations are abundant in the literature on SDB and mortality including the use of clinic-based samples, inadequate control for confounding variables, lack of polysomnographic measurements, and insufficient statistical power. As longitudinal outcome and mortality data from the Sleep Heart Health Study becomes available, the question of whether SDB portends excess mortality can be thoroughly addressed by overcoming many of the above limitations. Other important, but unanswered, questions that remain are whether other indices of disease severity, such as the degree of intermittent nocturnal hypoxemia and arousal frequency, have any role in the increased mortality risk associated with SDB.

**Analytical Plan:** The primary outcome will be mortality status as of April 1, 2006. The independent variables will consist of several key measures of SDB. Because the SHHS data include repeated
assessments in a large subset of the cohort (N=3290 with PSG), the data will be initially examined as a function of baseline variables. Subsequently, data from the second visit will be incorporated to construct an analytic dataset with time-dependent data. Such structuring will allow us, for example, to test (a) the effects of baseline AHI and (b) the change in AHI over time on mortality. Other polysomnographic variables of interest will include average oxygen saturation, average desaturation, time below a saturation of 90%, and arousal frequency.

The overall plan is to model survival vs. death as a function of SDB. Measures of SDB (e.g., AHI) will be used as categorical (based on quartiles and/or clinical cut-points) and continuous variables. Time-to-event methods including the Kaplan-Meier method will be used to examine the unadjusted association between SDB and mortality. Similar analyses will also be undertaken for confounding covariates such as age, BMI, and prevalent medical disease to determine which set of variables should be considered in modeling building. The log-rank test will be used to determine the statistical significance of differences in Kaplan-Meier curves across ordered categories of each predictor variable. The proportional hazards regression model will then be employed to parameterize the association between SDB and mortality while accounting for key covariates. Hazard ratios for the primary independent variables will be determined for the variables such as AHI, arousal frequency, and average oxygen saturation during sleep. The likelihood ratio test will be used at each stage to compare multivariable proportional hazards regression models with and without the predictor variable of interest. Threshold effects and dose-response effects will be examined using methods of penalized regression splines. Effect modification will be tested between SDB and variables such as age, BMI, gender, race, and history of prevalent medical disease at the baseline visit. For those subjects with repeat polysomnography, analyses will be undertaken to model whether the change in SDB measures predicts mortality risk. Model assumptions, including the proportionality of hazards, will be assessed using standard methods such examining the log(-log \[S(t)\]) against time plots where S(t) is the survivorship function. The distribution of the scaled Schoenfeld’s residuals will also be examined used to assess model fit.

In addition to the use of time-to-event methods, techniques of logistic regression will also be used to model the outcome of mortality. Model building strategies will parallel those outlined above for time-to-event methods. Major concerns in model building for the binary outcome will be adequacy of the model fit. The Hosmer-Lemeshow goodness-of-fit test and residual diagnostics will be employed for model checking.

In all of the above analyses, we will incorporate covariates such as age, gender, race and the time-dependent history of other variables such as BMI and waist circumference. In addition, we will also consider the mediating effects of nocturnal hypoxemia and sleep disruption by including indices of oxygen desaturation and sleep architecture. Because model building will include numerous correlated predictors, significance testing will be based strictly on a priori hypotheses, rather than isolated p-values. Predictors in the final model will also be chosen by a priori hypotheses, global model fit, and parsimony.

**Summary:** The overarching aim of the analyses proposed herein is to test the hypothesis that SDB is associated with an increase in mortality burden independent of confounders in the general adult community.
Reference List


