ARIC Manuscript Proposal # 1487

PC Reviewed: 03/17/08   Status: A   Priority: 2
SC Reviewed: __________   Status: _____   Priority: ____

1.a. Full Title: Severe Sleep-Disordered Breathing and Incident Atrial Fibrillation: The Sleep Heart Health Study

b. Abbreviated Title (Length 26 characters): SDB and Incident AF

2. Writing Group:
   Writing group members (order to be determined)
   • Susan Redline (Case Western Reserve University, SHHS)
   • Stuart Quan (Harvard School of Public Health, SHHS, Tucson)
   • Emelia Benjamin (Boston University School of Medicine and FHS)
   • Naresh Punjabi (Johns Hopkins School of Public Health, ARIC)
   • Mark Unruh (University of Pittsburgh, CHS)
   • Peter Okin (Cornell, SHS)
   • Catherine Thomas (SHHS Coordinating Center analyst)
   • Alvaro Alonso (University of Minnesota, ARIC)
   • Reena Mehra (Case Western, SHHS)
   • Yamini Levitzky (Case Western, SHHS)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _YL____ [please confirm with your initials electronically or in writing]

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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3. **Timeline:**

   - **Feb-March 2009** – Data collection from parent cohorts
   - **April-June 2009** – Analyses
   - **June-August 2009** – Manuscript drafting and revision
   - **September 2009** – Target date for submission

4. **Rationale:**

   Severe sleep-disordered breathing (SDB) is becoming more widely recognized by clinicians as a potential contributor to cardiovascular disease (CVD), as they share many of the same risk factors. It is extremely difficult to study how SDB is related to CVD given the complex inter-relationship with risk factors and physical characteristics (such as BMI) which predispose patients to both diseases. It is unclear whether SDB is related to the development of incident cardiovascular events, specifically atrial fibrillation, in a community-based cohort previously untreated for SDB and without pre-existing AF. We propose here to investigate one aspect of the complex interface between pulmonary and cardiovascular medicine; specifically, how sleep-disordered breathing is related to the development of atrial fibrillation in a community-based sample.

5. **Main Hypothesis/Study Questions:**

   We hypothesize that:

   1. Patients in a community-based cohort with severe sleep disordered breathing (defined as a Respiratory Disturbance Index (RDI) >30) will have a significantly greater incidence of atrial fibrillation.
   2. SDB is associated with incident atrial fibrillation independent of body mass index, age, and known CVD.
   3. There may be a relation across strata defined by age, BMI, and presence or absence of CVD.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

   **Participants**

   The SHHS is an ongoing multi-center, prospective study of 6,441 participants drawn from other cohorts, including: Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, the Strong Heart Study, New York Hypertension Cohorts, Tucson Epidemiologic Study of Airways Obstructive Diseases, and Health and Environment Study, and was originally designed to elucidate the cardiovascular sequelae of SDB. To be included, participants had to be age 40 years or older at recruitment and have no co-morbid conditions which would preclude overnight, unattended polysomnography (PSG), such as tracheostomy, or otherwise be treated for OSA already with oxygen or positive airway pressure therapy. All 215 subjects from the New York Hypertension Cohorts were excluded due to poor data quality. In total, 6441
participants were enrolled from 1995-1998, drawn from 11,145 possible participants enrolled the parent cohorts and had overnight PSG. Participants with prevalent AF will be excluded.

**Exposure**
Overnight PSG was performed using a portable system (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia) according to a previously-described protocol.\(^{12}\) Apnea was defined as complete or near complete cessation of airflow (at least <25% of baseline) for more than 10 seconds as detected by thermocouple signal. A hypopneic event was identified by flow or volume of <70% of baseline for greater than 10 seconds, but did not meet criteria for apnea. A Respiratory Disturbance Index (RDI) was calculated as the sum of apnea and hypopnea events with at least a 4% oxyhemoglobin desaturation divided by total sleep time. The RDI has previously been shown to have excellent within-subject reproducibility as well as intra-observer reproducibility.\(^{13, 14}\) In summary, the exposure for the proposed project is SDB of severity as characterized by the RDI.

**Outcome Ascertainment** –
The outcome will be incident AF, either detected by electrocardiography at SHHS Exam 2 approximately 4 years after the initial PSG, or ascertained by the source studies' ongoing morbidity/follow-up procedures. SHHS Exam 2 ECGs were performed using GE/Marquette computerized electrocardiographs analysis program, and centrally processed at Cornell University Medical Center, with identification of atrial fibrillation using the Minnesota Coding system. Due to the small number of incident events captured solely with the 12-lead ECGs (in approximately 2.1% of participants), other mechanisms of capturing incident events are needed. Some of the parent cohorts capture interim events through review of hospital records, participant interview, or self-report which is then verified and adjudicated. Where available, these events will be included in the present analysis. Further, if it is possible to include AF events detected on the single-lead ECG tracing from the follow-up PSG, these will also be included.

**Brief Analysis Plan**
We are assuming a 3% atrial fibrillation incidence rate and a four-fold difference in outcome events between exposed (RDI\(4\%)>25\)) and unexposed groups (RDI\(4\%)<25\)) (i.e. approximately 0.6% in the unexposed group and 2.4% in the exposed group) based on previous work in the same cohort which demonstrated a four-fold increased odds of AF was noted in fully-adjusted models in a cross-sectional analysis.\(^9\) Follow-up electrocardiograms are available on approximately 3000 participants.

The primary analysis will be a time-to-event (incident AF) analysis. We assumed a p-value of 0.05, \(\beta=0.80\), and an estimated median time to AF of 70 years for participants with an RDI<25\),\(^{14}\) with accrual time of 0.5 years and 4-year follow-up using an exponential model. Given these parameters, we estimate we will be able to detect a hazard ratio of 2.11. Noting this estimate is for RDI as a dichotomous outcome, we speculate this may improve if RDI is modeled as a continuous outcome. However, this underscored the need to capture incident AF events as thoroughly as possible, since we would have reduced power to detect a robust association.
7. a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  _x___ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ____ Yes  _____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8. a. Will the DNA data be used in this manuscript?  ____ Yes  _x___ No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  ____Yes  ____No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:  http://www.cscc.unc.edu/ARIC/search.php

  ____x___ Yes  _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

(Non-functional link above.) Dr. Naresh Punjabi an established collaborator, and have already contact Dr. Alvaro Alonso to participate.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  _x__ No

b. If yes, is the proposal  ____  A. primarily the result of an ancillary study (list number* ___________)
B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*

*ancillary studies are listed by number at [http://www.cscc.unc.edu/aric/forms/](http://www.cscc.unc.edu/aric/forms/)

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.