ARIC Manuscript Proposal #2754

PC Reviewed: 5/10/16  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: The Combined Effect of Diabetes and Sleep Apnea on Incident Cardiovascular Disease and Mortality in a Community Cohort

b. Abbreviated Title: Diabetes, Sleep Apnea, Cardiovascular Disease and Mortality

2. Writing Group:
   Writing group members: R. Nisha Aurora, Natalie Daya; Pamela Lutsey; Naresh M. Punjabi, Elizabeth Selvin

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

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3. Timeline: Data are all currently available; analysis is to start as soon as manuscript proposal is approved.
4. Rationale:

Cardiovascular disease is the leading cause of death in the United States (1). Consequently, considerable efforts have been made in identifying and mitigating risk factors for cardiovascular morbidity and mortality. For example, type 2 diabetes mellitus is a well-established risk factor for incident cardiovascular disease (2), and substantial efforts have been made towards early detection of diabetes mellitus. Additionally, over recent years, there has been mounting evidence demonstrating an association between obstructive sleep apnea (OSA) and cardiovascular disease (3-5) as well as mortality (6). Moreover, research over the last two decades has shown that OSA is associated with both prevalent and incident diabetes mellitus (7-9). Interestingly, while obesity is a shared risk factor for both diabetes mellitus and OSA, pioneering work has demonstrated that the association between OSA and diabetes mellitus is in fact independent of obesity and likely mediated through recurrent episodes of intermittent hypoxemia and arousals during sleep, known pathophysiological consequences of OSA (10, 11). It has been previously shown that through these mechanisms, OSA can cause significant decreases in insulin sensitivity as well as insulin secretion (12).

Given that obesity is a common risk factor for both diabetes mellitus and OSA, it is not surprising that the prevalence of OSA in persons with diabetes is elevated compared to persons without diabetes (13). However, the presence of OSA in diabetes mellitus is particularly concerning given that each condition is independently associated with cardiovascular disease and mortality. Thus, the risk for incident cardiovascular disease and mortality may be compounded in individuals with both diseases. Furthermore, given the high prevalence of both diabetes mellitus and OSA, 9% (14) and 5% (15), respectively, as well as the fact that both disorders remain underdiagnosed, the potential public health impact is enormous. While several studies have prospectively investigated cardiovascular and mortality outcomes with each condition individually, there is a dearth of evidence examining the collective effect of diabetes mellitus and OSA on incident cardiovascular disease or mortality. Hence, the objective of the current analysis is to assess the additive effect of OSA and diabetes mellitus on the occurrence of cardiovascular disease and mortality in a cohort of middle-aged and older adults in the general community.

5. Main Hypothesis/Study Questions:

Primary Aim: To assess the combined effect of both diabetes mellitus and sleep apnea on incident cardiovascular disease and mortality compared to those without either disorder or those with only diabetes mellitus or sleep apnea.

Main hypothesis: Persons with both diabetes mellitus and sleep apnea will have a higher incidence of cardiovascular disease and mortality compared to persons with only one of these disorders or without either sleep apnea or diabetes mellitus, thereby suggesting an interactive effect between sleep apnea and diabetes mellitus on the outcomes of cardiovascular disease and mortality.

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).
Study design: Prospective cohort study starting at ARIC visit 4 which corresponds to Sleep Heart Health Study (SHHS) visit 1 with in-home polysomnographic data collection. The primary outcome will be incident cardiovascular disease and mortality status using the most recently follow-up data available (currently through 2011). There are approximately 1890 participants at baseline whose data will be included in the analyses.

Inclusion/exclusion: Only participants who took part in ARIC Visit 4 and SHHS will be eligible for the analysis.

Analytical Plan: The proposed analyses will use demographic and health data from Visit 4 of ARIC along with polysomnographic data from Visit 1 of the Sleep Heart Health Study (SHHS) to examine the association between the following four groups of participants and the outcome of incident cardiovascular disease and all-cause mortality:
1) No diabetes or sleep apnea;
2) Persons with diabetes but NO sleep apnea;
3) Persons sleep apnea but NO diabetes; and
4) Persons with both diabetes and sleep apnea.

Diabetes will be defined as a self-reported diabetes diagnosis, current use of glucose-lowering medication, fasting glucose greater than or equal to 126 mg/dL, or non-fasting glucose greater than or equal to 200 mg/dL.

Sleep apnea will be defined as the following: apneas will be identified if airflow is absent or nearly absent for at least ten seconds. Hypopneas will be identified when there is at least 30% reduction in airflow or thoracoabdominal movement below baseline values for at least 10 seconds associated with a 4% decrease in oxygen saturation. The apnea-hypopnea index (AHI) will be defined as the number of apneas and hypopneas per hour of sleep.

We will employ standard survival analysis methods including Kaplan-Meier survival curves to examine the unadjusted association between each of the four groups and incident cardiovascular disease, as well as mortality. Cox proportional hazards regression models will be constructed to estimate the hazard ratios for cardiovascular disease and all-cause mortality before and after adjustment for age, sex, race, smoking status, and body mass index (BMI). Additionally, to account for potential confounding from preexisting medical conditions such as prevalent hypertension, cardiovascular disease (angina, heart failure, myocardial infarction, stroke, and coronary revascularization) will be included in the model. We will use Poisson regression to estimate adjusted and unadjusted incidence rates to compare absolute risk across the four groups. We will evaluate the risk differences on both an absolute (difference) and multiplicative (ratio) scales. We will evaluate the joint effects with tests for both additive and multiplicative interaction. We will also conduct analyses stratified by age, race and sex.

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 ICTDER 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  ____ No

8.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”? – NA - ____ 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)?

ARIC Manuscript Proposal #2199: Sleep Disordered Breathing, Sleep Duration, and Risk of Incident Self-Reported Diabetes: The Atherosclerosis in Communities Study.

ARIC Manuscript Proposal #1313: Sleep-disordered breathing (SDB) and mortality: The Results of the Sleep Heart Health Study. Manuscript published:

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

11.b. If yes, is the proposal

____ X____ A. primarily the result of an ancillary study (list number* 1995.12)

____ 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.cscce.unc.edu/aric/forms/
12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.csc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes __X__ No.
Reference List


