ARIC Manuscript Proposal #2136

PC Reviewed: 5/14/13   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a.   Full Title: Abnormal sleep characteristics and brain MRI markers of cerebral vascular disease and Alzheimer's disease: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Sleep & cerebral MRI

2.   Writing Group: Pamela L Lutsey, Alvaro Alonso, Thomas Mosley, Rebecca Gottesman, Eyal Shahar, Naresh Punjabi, Richard MacLehose, Clifford Jack. <u>Others welcome</u>.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __X__

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3.   Timeline: We anticipate data analyses to be complete within ~ 1.5 years of when final ARIC NCS data are available.

4.   Rationale:
Dementia and mild cognitive impairment (MCI) are common among U.S elderly[1], yet despite their immense and growing burden relatively little is known about characteristics which lead to cognitive decline. Recent evidence, both epidemiological and pathophysiological, has suggested a possible relation between abnormal sleep

characteristics and cognitive impairment due to both cerebral vascular etiologies and Alzheimer's disease. However, understanding of this relation is incomplete.

       There are several mechanisms through which disordered sleep may lead to mild cognitive impairment and dementia[2, 3]: Chronic nocturnal hypoxia[4 5, 6], sleep fragmentation[7], mediation through cardiovascular disease risk factors (e.g. hypertension, diabetes, inflammation), stroke (both clinical and subclinical) [6, 8, 9], Aβ plaque build-up[10], and interaction with the APOE ε4 risk allele[11, 12].

       The hypothesis that sleep disordered breathing is associated with cognitive impairment is supported by brain morphological changes. Small neuroimaging studies have reported that silent infarcts are more common among patients with obstructive sleep apnea (OSA) than among controls[13, 14], and white matter disease severity is correlated with the number of apnea/hypopnea events in patients with prevalent stroke[15]. Numerous other small studies have reported OSA patients to have smaller gray-matter volumes/densities than controls in a variety of brain regions[16-21], with the hippocampus most frequently noted. The consistency with which structural differences have been observed between those with OSA and controls is intriguing; however, existing studies are limited in that they are not prospective and likely suffer from reverse-causality, often use selected populations (e.g. from a sleep clinic), and have small sample sizes (n generally <50). In concordance with the human literature, animal models have shown that both intermittent hypoxia[22, 23] and sleep fragmentation[24, 25] can independently lead to neuronal loss in the hippocampus and prefrontal cortex.

5.   Main Hypothesis/Study Questions:

Question: Explore the relation of abnormal sleep characteristics with cerebral markers of vascular dementia (white matter hyperintensity (WMH) volume, number of lacunar infarcts, cerebral micro hemorrhages) and Alzheimer's disease (hippocampal and gray matter (GM) volume) measured via MRI as part of the ARIC NCS exam.

Hypothesis: Abnormal sleep characteristics will be associated with a greater WMH volume, a higher number of lacunar infarcts, more cerebral micro hemorrhages, and with lower hippocampal and GM volumes.

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. We will link data from 1,892 individuals who participated in both ARIC Visit 4 and had an in-home overnight polysomnography (PSG) as part of the Sleep Heart Health Study (SHHS) with outcome data presently being collected as part of the ARIC NCS exam. We anticipate that about 200 participants will have SHHS data and brain MRIs, and be included in this analysis.

       Assuming a two-tailed alpha = 0.05, 80% power, and a prevalence of moderate/severe OSA (RDI of ≥ 15 events/h) of 16% in the SHHS visit, we will have

80% power to detect differences in continuous brain MRI measures (e.g. WMH volumes) of 0.54 standard deviations or larger in those with OSA compared to those without it.

Inclusion/Exclusion

Participants who at visit 4 scored below the sex- and race-specific 5th percentile in any of the cognitive tests will be excluded, as they may have had prevalent dementia at visit 4[26]. All other participants with SHHS, visit 4, and NCS brain MRI data will be included.

Exposures

Measures of hypoxia and disordered breathing, sleep fragmentation, and sleep duration, as previously defined in SHHS.

Hypoxia and disordered breathing
- Obstructive sleep apnea (Respiratory Disturbance Index of ≥/< 15 events/h)
- Oxygen saturation <90% (≥/<1% of sleep time)
- Sleep time in apnea or hypopnea, % (continuous)
- Total apnea or hypopnea events, n events/night

Sleep fragmentation
- Arousal index, arousals/hour (continuous)
- Wake after sleep onset, min (continuous)

Sleep duration
- Time in sleep, min (categorical; will not assume linearity)

Outcomes

WMH volume, number of lacunar infarcts, cerebral micro hemorrhages, GM and hippocampal volumes.

Confounders and effect modifiers

Age, race, sex, education, physical activity, smoking status, BMI, diabetes, inflammatory markers, hypertension, APOE ε4 risk allele.

Data analysis

Our analysis will follow recommendations presently being developed by the ARIC-NCS Analysis Committee. The date of the SHHS exam will serve as baseline for the current analysis. Visit 4 participant characteristics will be described using means and proportions stratified by levels of the exposures.

For the primary analysis, linear regression will be used to estimate the mean change in brain volumes (WMH, hippocampal, GM) associated with differences in sleep characteristics. To model lacunar infarcts and cerebral micro hemorrhages, which are counts, we will use Poisson regression with sleep characteristics remaining as the independent variable.

We anticipate running a series of models, using 'baseline' covariates collected at ARIC visit 4. The first will likely adjust for demographics (age, race, sex), while further

models will additionally adjust for behaviors, psychological characteristics (e.g. depressive symptoms), and physiologic characteristics (e.g. BMI, inflammatory markers, diabetes, hypertension). We also anticipate exploring whether age, sex, and APOE ε4 modify relations between sleep and cognitive impairment by including interaction terms in the models. Selection bias is of concern in this analysis, as people who attend the ARIC-NCS exam may have better cognitive functioning than those who do not attend or died, and may also differ from the rest of the ARIC population in regard to their sleep characteristics. To help address this, inverse probability weighting will be used to model selection into the study using information in ARIC as well as TICS and hospital records[27-29].

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?
      __X (only APOE ε4)__ 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"?
      __X__ 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)?

MS#884: Measures of Cognitive Function in Persons with Varying Degrees of Sleep-Disordered Breathing: The Sleep Heart Health Study (Shahar 2nd author).

MS#1298: Sleep-disordered breathing and risk of incident cerebrovascular disease: The Sleep Heart Health Study (Shahar coauthor, Punjabi senior author)

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

1995.12   Sleep Heart Health Study (SHHS) (PI: Punjabi NM)

2008.06   Prediction of cognitive impairment from mid-life vascular risk factors and markers: The ARIC Neurocognitive Study (ARIC-NCS) (PI: Coresh J)

(Under review)
2013.02   Sleep disordered breathing and incident cognitive decline and dementia: The ARIC Study (PI: Lutsey PL)

___ **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/

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.cscc.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.

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