ARIC Manuscript Proposal #2135

PC Reviewed: 5/14/11  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Abnormal sleep characteristics and cognitive change: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Sleep & cognitive change


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

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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: 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 elderly¹, 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.

In an acute setting, it is well established that poor sleep quality/duration is associated with worse cognitive function\(^2\). However, it is not known whether chronic exposure to abnormal sleep characteristics has long-lasting effects on cognitive function. There are several mechanisms through which disordered sleep may impact cognitive decline\(^2,3\): 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)\(^6,8,9\), \(\text{A} \beta\) plaque build-up\(^10\), and interaction with the APOE \(\varepsilon4\) risk allele\(^11,12\).

Several prior cross-sectional studies\(^13-24\), including an ARIC publication (Shahar second author)\(^17\), have evaluated the relation between abnormal sleep and cognition. As a whole, they generally found adverse sleep characteristics to be associated with lower cognition, with the greatest deficits occurring in the executive function and attention domains\(^13,22,25\). Consistent with pathophysiologic evidence, two reported an interaction whereby individuals with both obstructive sleep apnea (OSA) and APOE \(\varepsilon4\) had more cognitive impairment\(^14,26\). Notably, the prior cross-sectional ARIC publication reported no relation between sleep and cognitive performance\(^17\). Yet, ARIC participants were 53-74 years old at the time, and the analysis may have taken place too early in the natural history of the disease.

The relation between subjectively measured sleep characteristics and incident cognitive decline has been evaluated in four prior publications\(^27-31\). Results have been mixed, but the studies were limited by short follow-up (at most three years), and utilized varying measures of sleep disturbances and cognition.

Additionally, as reviewed recently\(^32\), several small, short, randomized trials of OSA patients have reported modest improvements in cognitive functioning after CPAP therapy, with the greatest gains observed in the executive function domain\(^22\).

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

**Study question:** Assess whether abnormal sleep characteristics (inclusive of measures of hypoxia and disordered breathing, sleep fragmentation, and sleep duration) are associated with change in cognitive functioning, as assessed by change in results on 3 cognitive tests administered at ARIC Visit 4 (1996-1998) and repeated in ARIC NCS (2011-2013): Delayed Word Recall (DWR), Word Fluency (WF), Digit Symbol Substitution (DSS).

**Hypothesis:** Participants with abnormal sleep characteristics will experience a greater decline in scores on these tests, relative to participants who do not have abnormal sleep characteristics.

**Secondary study question:** Examine the relation between sleep characteristics and 14 additional tests spanning 7 domains of cognitive functioning assessed as part of ARIC NCS. These tests were not administered previously in the entire ARIC cohort.

**Hypothesis:** Participants with abnormal sleep characteristics will perform more poorly on additional cognitive function tests administered in the ARIC NCS exam, relative to those
without abnormal sleep characteristics. This will be particularly true for tests of the executive function and attention domains.

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 1,000 participants will be included in this analysis.

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. All other participants with SHHS, visit 4, and NCS 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
Primary outcomes: Change in scores on 3 cognitive tests (DWR, DSS, WF) conducted at visit 4 and repeated in ARIC-NCS. Each cognitive test will be analyzed separately.

Secondary outcomes: Additional cognitive tests measured through ARIC-NCS.

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 association between sleep characteristics (independent variable) and the difference in test scores between ARIC visit 4 and ARIC NCS (dependent variables). 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.

In secondary analyses we will evaluate relations of sleep characteristics to cognitive tests measured only at visit 5. For these secondary analyses, we will employ methods recommended by the ARIC-NCS analysis committee.

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.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ___ Yes ___ 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”?  ____ 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.cscce.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)

11a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  

___X___ Yes _____ No

11b. 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.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.cscce.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.
References


