

ARIC Manuscript Proposal #3300

PC Reviewed: 12/11/18 **Status:** _____ **Priority:** 2
SC Reviewed: _____ **Status:** _____ **Priority:** _____

1.a. Full Title: Cognitive decline and subsequent sleep quality and quantity

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

From ARIC: Nancy West, Tom Mosley, Pamela Lutsey, others welcome

From Jackson Heart Study: Susan Redline, Jim Wilson, Dayna Johnson

Note: This manuscript proposal was approved by the Jackson Heart Study (#P1024) in February 2018 and the objectively-measured sleep variables for this proposal were obtained in May 2018.

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

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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: All data is currently available. We plan to submit for publication within 9 months of manuscript proposal approval.

4. Rationale:

Recent epidemiological evidence has suggested that abnormal sleep quality and quantity may be modifiable risk factors for cognitive decline and dementia; however, the directionality of these associations remain unclear¹⁻³. Cognitive impairment and sleep disturbances are common among older adults. Changes in sleep patterns, including a decrease in sleep quantity and quality, could be a function of normal aging; however, some changes in sleep might result from underlying neurodegenerative processes. Sleep cycles are regulated by complex interactions between brain regions and neurotransmitter systems, many of which are also involved in memory and cognitive function^{4,5}. Sleep disorders are prevalent in Alzheimer disease and sleep abnormalities can also appear years before cognitive decline. Age-related disorders of both cognition and sleep are posited to have a long preclinical phase with some evidence that the etiologically important stage of life may be middle age for both of these pathophysiological processes.

African Americans are disproportionately burdened by short sleep duration and poor sleep quality as well as age-related cognitive impairment⁶⁻⁸, but few studies of sleep and cognitive function have included many African American participants. To investigate whether cognitive decline is associated with increased risk of objectively measured subsequent sleep disturbances in a cohort of community-dwelling African Americans, we will evaluate data from a cohort of ~200 men and women, who had repeated measures of cognitive function assessed at 2 time points during a 20-year period across the mid- to late-life transition, in relation to measures of sleep duration and quality measured at the end of the study period.

Summary of gaps in literature

Cross-sectional studies have suggested an association between poor sleep quantity and quality and cognitive impairment⁹⁻¹¹; however, results from longitudinal studies that have examined poor sleep as a precursor to cognitive decline have been mixed^{2,12}, limiting the ability to draw conclusions about the directionality of the association. Further, most studies exploring this association have used non-objective measures of sleep, have focused on older individuals in whom pathophysiological processes through which both poor sleep and cognitive decline develop may be well underway, have had limited follow-up, or have been done in predominately white populations. Thus, the interplay between cognitive decline and poor sleep, especially among non-white populations, remains unclear.

5. Main Hypothesis/Study Questions:

We aim to characterize the relationship between rate of cognitive decline and subsequent poor sleep quantity and quality in an African American population across the mid- to late-life transition. Based on results from a previous study of preclinical cognitive decline and subsequent sleep disturbances in older, mostly white women³ we hypothesize that a higher rate of cognitive decline will be associated with:

- i) greater number of apnea/hypopnea events;
- ii) reduced sleep efficiency;
- iii) greater sleep fragmentation;
- iv) longer wake duration after sleep onset; but

v) will not be associated sleep time (duration)

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

Retrospective cohort study among the overlap of African American participants of the Jackson Heart Sleep Study conducted between 2012-15 and ARIC study visits 2 and 5.

Inclusions

A total of 196 participants have both the objectively measured sleep data (from the Jackson Heart Study) and cognitive decline data (from ARIC).

Exclusions

Participants with RES_OTH = "CVD Research"

Exposure

Rate of cognitive decline based on a summary measure (global-Z) of 3 cognitive tests given at ARIC visits 2 and 5:

- Delayed word recall test (DWRT)
- Digit symbol substitution test (DSST)
- Word Fluency Test (WFT)

For each test, a Z-score will be calculated by subtracting the test mean and dividing by the standard deviation. To create the "global-Z", the Z-score from each test will be averaged.

Rate of cognitive decline will be estimated as follows:

$(\text{Visit 2 global-z score} - \text{Visit 5 global-z score}) / \text{time between V2 and V5}$.

Outcomes

Apnea-Hypopnea Index = number of all apneas and hypopneas with $\geq 3\%$ oxygen desaturations per hour of sleep, measured by in-home sleep assessment.

Sleep fragmentation = percentage of restlessness during the sleep period, measured by 7-day wrist actigraphy.

Wake after sleep onset = average wake duration after sleep onset, measured by 7-day wrist actigraphy

Sleep efficiency = percentage of time spent asleep during the in bed period, measured by 7-day wrist actigraphy.

Sleep time = Average time (minutes) spent asleep per main sleep (all days), measured by 7-day wrist actigraphy.

Statistical analysis

Graphical inspection of the relationships between rate of cognitive decline and each of the five sleep outcomes show a linear relationship, so associations will be estimated using multiple linear regression. Analyses will be adjusted for age, sex, BMI, education, diabetes status, hypertension status, and history of stroke.

Model 1: Age-adjusted

Model 2: Age + BMI + sex + education + baseline diabetes status + baseline hypertension status + stroke history

Challenges/Limitations

A limitation is that the in-home sleep assessment and actigraphy were performed only at follow-up, so it is not possible to objectively determine whether sleep disturbances were present in some participants at study baseline (ARIC visit 2). However, participant self-report of a history of physician-diagnosed sleep apnea at the sleep study visit will be used to mitigate this limitation. The moderate sample size will also limit the statistical power.

Preliminary results

Of a total of 196 study participants, 71% are female, mean age at first cognitive visit was 53 years (range = 47-65), and the median follow-up period between cognitive tests was 21 years (range = 19-23). The mean decline on the composite global Z-score over the study period was 0.48 SDs.

Table 1. Age-adjusted means for continuous measures of sleep quality and quantity in association with rate of annual cognitive decline over the 20-year time period.

Sleep outcome	Lowest tertile of decline	Middle tertile of decline	Highest tertile of decline	P
Apnea-hypopnea index	7.3	8.2	14.4	0.03
Fragmentation (percentage)	26.5	29.8	31.6	0.0003
Efficiency (percentage)	88.7	87.2	87.4	0.05
Wake after sleep onset (minutes)	47	52	55	0.03
Sleep time	422	406	421	0.69

Further analysis will be done to adjust for other covariates. Exploratory analysis will also be done to evaluate the associations with specific cognitive domains captured by rate of decline in the Delayed Word Recall test, the Digit Symbol Substitution test, and the Word Fluency test.

**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. Will the DNA data be used in this manuscript? 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.csc.unc.edu/ARIC/search.php>

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)?

Three publications by lead author Pamela L Lutsey:

1. Obstructive Sleep Apnea and 15-Year Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Study. **Lutsey PL**, Bengtson LG, Punjabi NM, Shahar E, Mosley TH, Gottesman RF, Wruck LM, MacLehose RF, Alonso A. Sleep. 2016 Feb 1;39(2):309-16. doi: 10.5665/sleep.5434.
2. Sleep characteristics and risk of dementia and Alzheimer's disease: The Atherosclerosis Risk in Communities Study. **Lutsey PL**, Misialek JR, Mosley TH, Gottesman RF, Punjabi NM, Shahar E, MacLehose R, Ogilvie RP, Knopman D, Alonso A. Alzheimers Dement. 2018 Feb;14(2):157-166. doi:10.1016/j.jalz.2017.06.2269.
3. Sleep Apnea, Sleep Duration and Brain MRI Markers of Cerebral Vascular Disease and Alzheimer's Disease: The Atherosclerosis Risk in Communities Study (ARIC). **Lutsey PL**, Norby FL, Gottesman RF, Mosley T, MacLehose RF, Punjabi NM, Shahar E, Jack CR Jr, Alonso A.

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

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* _ARIC-NCS)
 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.csc.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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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.

References

1. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of Sleep-Disordered Breathing With Cognitive Function and Risk of Cognitive Impairment: A Systematic Review and Meta-analysis. *JAMA Neurol.* 2017;74(10):1237-1245.
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7. Hale L, Do DP. Racial differences in self-reports of sleep duration in a population-based study. *Sleep.* 2007;30(9):1096-1103.
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12. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA*. 2011;306(6):613-619.