ARIC Manuscript Proposal #3797

PC Reviewed: 3/9/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The contribution of sleep biomarkers to development of cognitive decline and dementia

b. Abbreviated Title (Length 26 characters): Sleep and cognitive decline

2. Writing Group: Writing group members from ARIC: Pamela Lutsey Ph.D, Rebecca Gottesman M.D., Jeffrey Misialek MPH

Non-ARIC writing group members (in no particular order): Matthew Pase Ph.D, Jayandra Himali Ph.D, Alexa Beiser Ph.D, Qiong Yan Ph.D, Shaun Purcell Ph.D, Susan Redline M.D, Sudha Seshadri M.D., Oscar Lopez M.D, Kristine Yaffe M.D, Yue Leng Ph.D, Katie Stone Ph.D, Andrée-Ann Baril Ph.D, Christopher E. Kline Ph.D, Marina Cavuoto Ph.D

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

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NOTE TO THE PUBLICATIONS COMMITTEE: This is a consortia funded by R01 AG062531, *Contributions of Sleep to Preclinical and Clinical Alzheimer's Disease* (MPI: Himali, Pase), that will combine information on sleep and dementia from ARIC, FHS, CHS, SOF, MrOS. It has Ancillary Study approval as an amendment to ARIC AS #2013.02: *Sleep disordered breathing and incident cognitive decline and dementia: The ARIC Study*, of which

Dr. Lutsey was PI. Dr. Lutsey is subcontract PI of R01 AG062531. As such, she will oversee ARIC involvement, including analysis of ARIC data at UMN.

3. Timeline: Over the next year, we will finalize the analysis datasets for ARIC and the other cohorts. Sleep measures, outcomes, and covariates will be defined and harmonized. We will then complete statistical analysis. Study level results from ARIC will be pooled in a meta-analysis that includes study-level estimates from the 4 other cohorts. Results will be written for publication.

4. Rationale: An emerging body of evidence implicates the sleep-wake cycle in key mechanisms related to dementia and brain aging, including glymapthic flow, Aβ accumulation, synaptic plasticity, learning and memory, neuroinflammation, and ischemic brain injury. Sleep disturbances are underdiagnosed in the community and are potentially modifiable. With the burden of dementia increasing, there is clear need to better understand the contributions of sleep to the risk of dementia. We propose to generate the most definitive evidence yet by pooling data across cohorts that have gold-standard assessments of sleep combined with follow-up for incident AD dementia with methodologically consistent diagnostic criteria. We will examine novel sleep biomarkers that are yet to be examined with respect to dementia risk and leverage our statistical power to explore for differences by age, sex and the APOE genotype. Study level data will be pooled in meta-analysis. ARIC will contribute study level estimates together with two other Sleep Heart Health Study cohorts (FHS, CHS) and the MrOS and SOF cohorts.

5. Main Hypothesis/Study Questions:

Aim 1a: To examine the aspects of sleep (on PSG) that relate prospectively to a higher risk of incident AD dementia, cognitive function, or MRI brain volume. We expect poorer sleep quality, more fragmented sleep, and less slow wave sleep to be associated with a higher risk of dementia and evidence of poorer brain health on MRI and cognitive testing.

Aim 1b: To test for interactions by age, sex, and the presence of an APOE ε4 allele. Based on prior work, we expect associations to be stronger in APOE ε4 non-carriers and in women.

Aim 2: To examine whether changes in sleep neurophysiology over ~6 years predict incident dementia, cognition, or brain volume. We expect a deterioration in sleep quality to be associated with incident dementia, poorer cognition, and smaller brain 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).

We propose to combine study level results from ARIC with that of four other large and richly phenotyped U.S. population-based cohorts. Traditional and novel sleep metrics will be derived by quantitative EEG analysis of overnight PSGs, each performed in the participant's home and during a representative sleep period. A novel cluster analytic framework will be used to combine sleep metrics into broader domains of sleep neurophysiology. In ARIC and the other cohorts, domains of sleep will be related to incident dementia using Cox Proportional Hazard Regression

models, adjsuting for key confounders. Associations between sleep and dementia endophenotypes (including cognitive function and brain volume on MRI) will be conducted using a series of linear and logistic regressions. Study level estimates will be pooled in meta-analysis.

Exposures. Sleep data will be obtained from the Sleep Heart Health Study visits, which were completed in ARIC between 1995 and 1998 and again from 2001 to 2003. The first sleep study will be used as baseline. The second will be used to calculate annualized change in the sleep variables. Analyses, including timing of the outcomes, will follow previous publications from our group (see section 10, PMCIDs: PMC4712410; PMC5776061; PMC4944966).

Outcomes.

Risk of dementia. Risk of dementia will be examined using the dementia follow-up data available in ARIC, using the "level 3" definition. Surveillance for dementia will commence from the time of the sleep study (sleep study 1 for Aim 1 and sleep study 2 for Aim 2) to the time of incident event over a maximum of 10 years. Non-events will be censored at death, loss-to-follow-up or administratively at the end of follow-up. Sensitivity analyses will restrict follow-up to 10 years after the sleep study. Cox-proportional hazard regression models will be used to relate the sleep metrics to risk of dementia.

Cognitive function. Three cognitive tests were administered at the time of the sleep examination (1996–1998) and repeated at the follow-up neuro-cognitive examinations at visits 5, 6 and 7: the DWRT, DSST, and WFT. Cognitive tasks will be combined into a broad cognitive domain representing general cognitive function by using a Principal component analysis and forcing a single factor solution. We will use a series of linear regressions to relate the sleep metrics to cognitive performance. Inverse probability weighting (IPW) will be used to account for death and visit nonattendance.

Brain MRI volume. In 2011–2013, all surviving ARIC participants were invited to take part in the ARIC Neurocognitive Study/ARIC Visit 5. A subset of Neurocognitive Study participants without contraindications were selected for brain MRI. We will relate the sleep metrics to total and hippocampal volume, white matter hyperintensity volume, and silent brain infarcts. Brain volumes will be adjusted for intracranial volume. We will use a series of linear and logistic regressions to relate the sleep metrics to brain MRI outcomes. Inverse probability weighting (IPW) will be used to account for death, visit nonattendance and selection for brain MRI. We may also explore use of brain MRI data collected at later time-periods.

Meta-analysis: Random effects meta-analysis will be used to pool study level estimates.

Inclusion/exclusion criteria: For inclusion in the study, participants will have provided: polysomnography at baseline, and outcome data (as appropriate for each study aim/research question). Exclusion criteria are dementia at baseline or other significant neurological disease.

Challenges and limitations. Despite use of IPW the true counterfactual is unknown. Another challenge for this multi-cohort effort is data harmonization. These specific cohorts were chosen for this effort since they all have a methodologically consistent sleep study, permitting the calculation of the same sleep metrics under the same conditions. Through our engagement in other efforts, such as the CHARGE consortium, we have also combined outcome data, such as

cognitive function and dementia risk, with other population-based cohorts. As done previously for cognitive function, we will use a principal component analysis to derive a latent cognitive factor, which yields a task independent score that can be meta-analyzed across studies. Careful consideration will also be given to the harmonization of covariates.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 Yes (at present, APOE only) ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

__**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)?

Lutsey, P. L., Bengtson, L. G., Punjabi, N. M., Shahar, E., Mosley, T. H., Gottesman, R. F., Wruck, L. M., MacLehose, R. F., & Alonso, A. (2016). Obstructive Sleep Apnea and 15-Year Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Study. *Sleep*, *39*(2), 309–316.
PMCID: PMC4712410

Lutsey, P. L., Misialek, J. R., Mosley, T. H., Gottesman, R. F., Punjabi, N. M., Shahar, E., MacLehose, R., Ogilvie, R. P., Knopman, D., & Alonso, A. (2018). Sleep characteristics and risk of dementia and Alzheimer's disease: The Atherosclerosis Risk in Communities Study. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, *14*(2), 157–166.
PMCID: PMC5776061

Lutsey, P. L., Norby, F. L., Gottesman, R. F., Mosley, T., MacLehose, R. F., Punjabi, N. M., Shahar, E., Jack, C. R., Jr, & Alonso, A. (2016). Sleep Apnea, Sleep Duration and Brain MRI Markers of Cerebral Vascular Disease and Alzheimer's Disease: The Atherosclerosis Risk in Communities Study (ARIC). *PloS one*, *11*(7), e0158758.
PMCID: PMC4944966

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)

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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

Manuscript preparation and submission are expected to be complete within 3 years.

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.