ARIC Manuscript Proposal #3567

PC Reviewed: 2/11/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Sleep medications and risk of dementia in The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Sleep medications and dementia risk

2. Writing Group:

Kelsie M. Full, Snigdha Pusalavidyasagar, Priya Palta, Kevin Sullivan, Jung-Im Shin, Rebecca Gottesman, Adam P. Spira, Pamela L. Lutsey, others welcome

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

First author: **Kelsie M. Full**
Address: 1300 S 2nd St Suite 300
Minneapolis, MN 55454
Phone: 319- 330-0964
E-mail: fullx003@umn.edu

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).

Name: Pamela L. Lutsey
Address: 1300 S 2nd St Suite 300
Minneapolis, MN 55454
Phone: 612-624-5812
E-mail: lutsey@umn.edu

3. Timeline: Data analysis will begin immediately. A manuscript draft will be prepared in less than one year.

4. Rationale:

Emerging evidence suggests an association between poor sleep and risk of dementia,[1,2] although study findings have been inconsistent.[3,4] Despite the critical role sleep plays in health, over 1/3 of adults in the United States (US) do not meet current sleep duration recommendations.[5] Poor sleep poses a unique challenge to the aging population, with evidence indicating that approximately 50% of older adults report experiencing sleep problems including poor sleep quality, frequently disrupted sleep, and sleep disordered breathing.[6–8] Additionally, sleep disorders, such as insomnia and obstructive sleep apnea, remain largely underdiagnosed in the general population.[8–10]

In the past two decades, sleep medication use has increased in the US and it is estimated that over 6% of US adults over the age of 60 are taking hypnotic drugs to treat poor sleep.[11] Both sleep quality and quantity typically decline throughout the life-course,[12] and concurrently the proportion of adults using sleep medication significantly increases in late-adulthood (>7% for adults +80 years of age).[11] Prescription sleep medications are commonly prescribed for short-term treatment, however many adults continue their use chronically. There are many different classes of medications used in the treatment of sleep disorders.[13] Medications approved by the US Food and Drug Administration (FDA) include non-benzodiazepine receptor agonists, benzodiazepines (BZDs), orexin receptor antagonists, melatonin receptor agonists, antidepressants, and additional off-label drugs. Of these, research has focused on long-term hypnotic drug use (not including antidepressants or off-label drugs) with associations with risk of several adverse outcomes reported, including cancer, incident stroke, and mortality.[14,15]

More recently, the use of sleep medications has been explored in relation to the development of dementia. In a 2018 meta-analysis, the authors reported BZDs users were at 1.38 greater odds of developing dementia (1.07-1.77) as compared to non-users. However, this pooled analysis was limited by the variation across studies in the classification of the exposure (number of studies comparing ever use of BZDs vs non-users), the classification of the outcome (DSM vs ICD classifications), and the length of study follow-up (short in most instances).[16] Other sleep medications remain largely unexplored.[13] There are multiple pathways which may link sleep medication use and dementia: 1) sleep medication use could be an indicator of sleep disturbances that are early markers of neurologic degeneration, 2) the medications themselves could be causally related to dementia risk, or 3) poor sleep treated with medications could simply be correlated with other dementia risk factors. The existing published data focuses largely on BZDs, and questions remain about alternate pharmacologic agents, the dose response association, the impacts of long-term use, and the possibility of reverse causality given the long natural history of dementia development.[16,17]

With over 30 years of follow-up, the ARIC cohort provides a unique opportunity to examine the association between sleep medication use and dementia outcomes over a 30-year period in a sample of older adults. This prospective analysis will enhance the existing literature as it will explore several different medication classes over a long follow-up (important given the long natural history of dementia), and include repeated measures of the exposure and cumulative exposure. With the current prevalence of poor sleep and sleep medication use among older adults, and the current population burden of dementia, determining if sleep medication use increases risk of dementia has important implications for clinical practice.

5. Main Hypothesis/Study Questions:

We hypothesize that sleep medication use will be associated with greater dementia risk. We will explore if the association differs by type of sleep medications used and life period of use.

- The primary analysis will use visit 1 (1987-1989) as baseline, incorporate sleep medication use as time-dependent exposure, and follow through the most recent dementia ascertainment.

- A secondary analysis will use visit 5 (2011-2013) as baseline, incorporate sleep medication use as time-dependent exposure, and follow through the most recent dementia ascertainment.

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

This will be a longitudinal analysis with follow-up time starting with ARIC visit 1 and ending at dementia incidence, death, or end of ascertainment.

Inclusion/Exclusion:

Inclusion: The study will include all ARIC participants.

Exclusion: The exclusion criteria will vary depending on the statistical analyses. For the primary analysis, we will use the usual ARIC race and center exclusions (i.e. exclude participants who are not black or white, and blacks from MN and MD. For the secondary analyses, we will further exclude participants who did not attend Visit 5 or who had prevalent dementia at Visit 5.

Variables of Interest

Exposure: The primary exposures for this analysis will be sleep medication use. At each ARIC exam participants were asked to bring all medications they are currently taking to the exam. Medications were verified and recorded by ARIC staff. The following medication types will be assessed in this analysis:

- Composite of all sleep medications (any of below)
- Barbiturates
- Benzodiazepine derivatives (triazolam, estazolam, temazepam, flurazepam, and quazepam)
- Benzodiazepine-related drugs (Z-drugs)
- Anti-depressants (doxepin and trazodone; if numbers are sufficient these will be evaluated separately given the potential for different etiological effects)
- Other hypnotics and sedatives

Outcome: The primary outcome for this analysis will be incident dementia (ARIC Level 3 dementia diagnosis). Dementia incidence will be defined according to the standard definition used in the ARIC cohort.[18] Dementia incidence will be ascertained using ARIC follow-up protocol based on the following:

- Adjudication by an expert panel for participants attending the visit 5, 6 or 7 examinations, based on full neuropsychological assessment plus a functional activities questionnaire, a clinical dementia rating interview, and a neuropsychiatric inventory interview
- Telephone instrument of cognitive status-modified (TICS-m)
- ICD-9 hospital discharge diagnostic codes

Covariates: For the primary analysis, covariates will come from ARIC visit 1, while for the secondary analysis they will come from ARIC visit 5. The covariates included in this analysis

were derived from ARIC questionnaire and study visit assessments, including: age, sex, race, study center, educational attainment, health insurance status, APOE, smoking status, drinking status, body mass index (BMI), physical activity, diabetes status, systolic blood pressure, antihypertensive medication use and estimated glomerular filtration rate (eGFR) categories.

Data analysis

Basic descriptive statistics will be performed and presented including mean ±SD/proportions of the included covariates for the study sample. Descriptive statistics will be presented by sleep medication status (users vs. non-users). Between group differences in covariates will be explored using chi-square and one-way ANOVA.

Aim 1: The primary analysis will use Cox proportional hazards regression to assess the associations of sleep medication use (modeled as a time-dependent variable) with risk of incident dementia (Visit 1 to present). Hazard ratios and 95% confidence intervals by sleep medication status (user vs non-user) will be calculated. We will also explore competing risk models, using the Fine and Gray method.

Aim 2: The secondary analysis will use Cox proportional hazards regression to assess the associations of sleep medication use at Visit 5 with incident dementia (follow-up time beginning Visit 5). Similar to Aim 1, the Fine and Gray method will also be incorporated to address competing risk of death.

The following progressive modeling approach will be used for both aims:

Model 1: will adjust for socio-demographics (age, sex, race, study center, educational attainment, health insurance status, APOE)

Model 2: will include additional adjustment for health behaviors (smoking status, drinking status, physical activity)

Model 3: will further adjust for prevalent CVD and CVD risk factors (BMI, diabetes status, systolic blood pressure, antihypertensive medication use and eGFR) and risk factors for OSA (neck circumference)

For both Aims 1 and 2, the primary analysis will use a composite (any sleep medication) variable, and secondarily associations with individual medication classes and groups of medications with known effects on sleep characteristics will be explored.

To further address confounding, we may also consider use of propensity scores.

Multiplicative interactions by race, sex, and age will be assessed by including cross-product terms in the models, and stratified results reported when appropriate.

The proportional hazards assumption will be tested in all models.

In sensitivity analysis, if there is reasonable precision, we will explore interrelationships between opioids and BZDs. Specifically, examining a) if there is an interaction whereby opioids and BZDs users are at highest risk of incident dementia, and b) whether the association between BZD's and dementia confounded by opioid use.

Anticipated Methodologic Limitations

The research team has discussed the numerous study design considerations, and therefore we have proposed two different statistical approaches. There is a limited understanding of the prevalence and patterns of sleep medication use in the ARIC cohort. This information will drive decision-making around the best analysis approach to answer the proposed research question. Further, assessment of sleep disturbances, quality, sleep architecture, and sleep disorders (including insomnia and OSA) are limited in the overall ARIC cohort and therefore we cannot account for these sleep characteristics as possible confounders in our models. Thus, we will not assume causality between the medication and dementia; if we do find significant results it may be due to sleep medications simply being a marker of early pathologic changes, or residual confounding.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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 __X__ 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.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)?

- Lutsey PL, Bengtson LGS, Punjabi NM, et al. "Obstructive Sleep Apnea and 15-Year Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Study." *Sleep*. 2016;39(2):309-16.
- Lutsey PL, Norby FL, Gottesman RF, et al. "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*. 2016;11(7):e0158758.

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

__ A. primarily the result of an ancillary study (list number* 1995.12 _____)

__X_ 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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2. Luojus MK, Lehto SM, Tolmunen T, Brem A-K, Lönnroos E, Kauhanen J. Self-reported sleep disturbance and incidence of dementia in ageing men. *J Epidemiol Community Health*. 2017;71(4):329-335. doi:10.1136/jech-2016-207764
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sleep habits in the United States. *Sleep Breath*. 2010;14(1):63-70. doi:10.1007/s11325-009-0281-3
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