

ARIC Manuscript Proposal #3979

PC Reviewed: 12/14/21
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Status: _____
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Priority: 2
Priority: _____

1a. Full Title: Sleep medications, physical functioning, and incident injurious falls risk in The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:

Kelsie M. Full, Snigdha Pusalavidyasagar, Priya Palta, Caitlin W. Hicks, Adam P. Spira, B. Gwen Windham, Stephen P. Juraschek, Matthew Pase, Jayandra J. Himali (invited), Pamela L. Lutsey, others welcome

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

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

4. Rationale:

For older adults in the United States (US), accidental falls are the leading cause of injury and often result in long hospitalization, recurrent falls, or even death.^{1,2} In 2018, accidental falls were responsible for an estimated 3 million emergency department visits, over 950,000 hospitalizations, and approximately 32,000 deaths.³ Accidental falls place a large burden on the

US health care system, with estimated health care expenditures due to falls totaling approximately \$50 billion annually.⁴ One in three US older adults, 65 years or older, experience one fall every year.³ Identifying risk factors for falls prevention is a public health priority due to the aging of the US population,⁵ the high prevalence of falls among older adults,³ and the numerous risks associated with falls.

While poor sleep is associated with falls risk,⁶⁻⁸ some researchers have hypothesized that sleep medications may be an alternate pathway through which poor sleep is connected to physical functioning decline and falls. Many sleep medications are central nervous system depressants, which can lead to sedation, vestibular dysfunction, and physical functioning impairment.

Of the many falls-prevention recommendations, the National Institute on Aging supports screening for modifiable risk factors, including appropriate medication management and withdrawal of psychoactive medications.⁹ Approximately 6-10% of US adults over the age of 60 are currently taking hypnotic drugs to treat poor sleep,¹⁰ and the estimated proportion of adults using sleep medication is believed to significantly increase with advancing age.¹⁰ Prescription sleep medications are most commonly prescribed for short-term use, however many adults continue with long-term use.¹¹ The US Food and Drug Administration (FDA) has approved several medications to treat sleep, including non-benzodiazepine receptor agonists, benzodiazepines (BZDs), orexin receptor antagonists, melatonin receptor agonists, and antidepressants. Additionally, some off-label drugs are used. Of the approved drugs, long-term hypnotic drug use (BZDs) has been consistently linked to adverse outcomes,^{12,13} including increased risk of falls.^{14,15} The use of BZDs has also been linked to physical functioning decline,

a predominant risk factor for future falls.¹⁶ This overwhelming evidence has led to recommendations against the prescription of BZDs.^{17,18}

While there is mounting evidence and recommendations warning against BZDs, less is known about the other types of medications commonly prescribed to treat poor and disordered sleep and the risk of falls. Recently, both SSRI anti-depressants and Z-drugs, generally believed to be safer than BZDs, have been connected to falls risk, however previous research has been limited by the assessment of both medications and falls outcomes.^{19–21} Overall, sleep medication use and associations with physical functioning decline and subsequent falls risk remains largely unexplored.²²

The ARIC cohort provides a rare opportunity to examine the association between sleep medication use, physical functioning decline, and incident falls over a 7-year period in a large community-based sample of older adults. This prospective analysis will explore several different medication classes commonly prescribed to treat poor and disordered sleep and associations with incident falls, as well as change in physical functioning over time. With the current prevalence of sleep medication use among older adults, and the current population burden of falls, determining if sleep medication use is associated with increased risk of incident falls has important implications for clinical practice.

5. Main Hypothesis/Study Questions:

We hypothesize that use of sleep medications (regardless of indication) will be associated with increased risk of incident injurious falls over 7 years of follow-up. Additionally, we hypothesize that sleep medication use will also be associated with decline in physical functioning over the 7-year period. We will explore if the association differs by age, sex, prior self-reported falls, type of sleep medications used, as well as number of medications used.

This analysis will have 2 parts:

- Part 1 will use Visit 5 (2011-2013) sleep medication data and follow participants to most recent ascertainment of injurious falls incidence.
- Part 2 will examine Visit 5 (2011-2013) sleep medication data and examine associations with changes in physical functioning measures (Visit 5 to Visit 6 and Visit 7).

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 5 and ending Visit 7, or at current injurious falls ascertainment.

Inclusion/Exclusion:

Inclusion: The study will include all black or white ARIC participants who participated in ARIC Visit 5.

Exclusion: We will exclude participants who (1) did not attend Visit 5 or (2) who had prevalent dementia at Visit 5 or incident dementia at Visit 6 or Visit 7 or (3) those with missing physical functioning data or falls follow-up data (separately based on the analysis).

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 (See Table 1):

- All sleep medications (any of below)
- Barbiturates
- Benzodiazepine derivatives (e.g., alprazolam, lorazepam, triazolam, estazolam, temazepam, flurazepam, and quazepam, etc.)
- Benzodiazepine-related drugs (Z-drugs)
- Anti-depressants (SSRIs, SNRIs, TCAs)
- Other hypnotics and sedatives

Outcome: The primary outcome for this analysis will be incident injurious falls. An incident injurious fall will be defined as any fall-related hospitalization or claim for hospital services captured in the ARIC hospitalization records or Medicare claims after ARIC Visit 5. This definition has been used in previous ARIC publications.²³ Falls will be captured through ARIC active surveillance for all hospitalization records or linkage to Centers for Medicare and Medicaid Services (CMS) claims data after Visit 5 using ICD-9 (until 2015) and ICD-10 (after 2015) diagnosis codes. In a previous ARIC analysis, ICD-9 codes for falls have been mapped on to ICD-10 codes and we will apply this same approach.

The secondary outcome for this analysis will be change in physical functioning, defined by changes in SPPB score (across Visits 5, 6, and 7), modeled continuously for both composite and

individual SPPB components. Trained ARIC staff conducted the 3 part SPPB²⁴ assessment at ARIC visits.

As an additional outcome, we will also explore self-reported falls data collected at the semi-annual follow-ups. In the semi-annual interview, participants self-reported falls in the past 12 months. Self-reported falls reported between Visit 5 and Visit 7 will be examined.

Covariates: The covariates included in this analysis will be derived from ARIC Visit 5 questionnaire and study visit assessments, including: demographics (age, sex, race-center, educational attainment), lifestyle characteristics (smoking status, alcohol consumption, body mass index [BMI], self-reported physical activity (Baecke questionnaire), systolic blood pressure, antihypertensive medication use, cognitive status (Mild cognitive impairment or normal), baseline SPPB physical functioning score (for falls outcome only), comorbid conditions (prevalent cardiovascular disease [CVD], heart failure, diabetes, stroke), and self-reported falls (in the past 12-months).

Data analysis

Prior to performing data analyses, we will address issues with missingness and confounding. We will use inverse probability weighting to address the fact that those experiencing decline are more likely to have missing physical functioning data at baseline and over time. To further address confounding, we will use a propensity score matching approach. Logistic regression propensity score matching will be used to match each sleep medication user with non-medication users by age, sex, race, and education level.

Basic descriptive statistics will be performed and presented including mean $\pm$ SD/proportions of the included covariates for the study sample. Descriptive statistics will be presented by sleep medication status (users vs. non-users) and by incident injurious falls status (fall vs no falls). Between-group differences in covariates will be explored using chi-square and one-way ANOVA.

Aim 1: The first analysis will use Cox proportional hazards regression to assess the associations of sleep medication use at Visit 5 with incident injurious falls (follow-up time beginning Visit 5) adjusting for relevant covariates and prevalent comorbid conditions.

Aim 2: The second analysis will use longitudinal mixed-effect regression models to assess the associations of sleep medication use with change in physical functioning (across visits 5, 6, and 7) adjusting for relevant covariates and prevalent comorbid conditions.

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)

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

Model 3: will further adjust for health characteristics (BMI, diabetes status, systolic blood pressure, antihypertensive medication use) and prevalent comorbid conditions (CVD, hypertension, diabetes, stroke) and self-reported falls.

For both Aims 1 and 2, the primary analysis will use a composite (any sleep medication) variable, and additional analyses will explore associations with individual medication classes.

Multiplicative interactions by sex and age will be assessed by including cross-product terms in the models, and stratified results reported when appropriate. We will also look at differences by self-reported prior falls and type of sleep medication.

The proportional hazards assumption will be tested in all Cox models.

Anticipated Methodologic Limitations

We acknowledge that missing data at baseline will likely be for individuals with poorer function, and overtime those with decline in physical functioning will be more likely to be missing. To address this, we will use IPW in our analyses. With the data available we are unable to assess the frequency and duration of sleep medication use and confounding by indication will also be present. Lastly, the assessment of sleep disturbances, quality, sleep architecture, and sleep disorders (including Insomnia and OSA) are limited in the overall ARIC cohort and we cannot account for these sleep characteristics as possible confounders in our models.

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.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)?

- Deal JA, Sharrett ARichey, Bandeen-Roche K, Kritchevsky SB, Pompeii LA, B Windham G. "Hearing Impairment and Physical Function and Falls in the Atherosclerosis Risk in Communities Hearing Pilot Study." *J Am Geriatr Soc.* 2016;64(4):906-8.

- Juraschek SP, Daya N, Appel LJ, et al. "Orthostatic Hypotension in Middle-Age and Risk of Falls." *Am J Hypertens.* 2017;30(2):188-195.
- Gabriel KPettee, Griswold ME, Wang W, et al. "Physical activity trajectories and subsequent fall risk: ARIC Study." *Prev Med.* 2019;121:40-46
- **Full KM**, Pusalavidyasagar S, Palta P, Sullivan K, Shin JI, Gottesman R, Spira AP, Pase MP, & Lutsey PL. Associations of late-life sleep medication use with incident dementia among aging adults in the Atherosclerosis Risk in Communities (ARIC) Study. (*in submission*).

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

2008.06 X A. primarily the result of an ancillary study (list number* 1995.12,

____ **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.

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2. Pohl P, Nordin E, Lundquist A, Bergström U, Lundin-Olsson L. Community-dwelling older people with an injurious fall are likely to sustain new injurious falls within 5 years - a prospective long-term follow-up study. *BMC Geriatr* 2014 141. 2014;14(1):1-7. doi:10.1186/1471-2318-14-120
3. Moreland B, Kakara R, Henry A. Trends in Nonfatal Falls and Fall-Related Injuries Among Adults Aged ≥ 65 Years — United States, 2012–2018. *Morb Mortal Wkly Rep*. 2020;69(27):875. doi:10.15585/MMWR.MM6927A5
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- Fatal Falls and Fall Injuries among Older Adults. *J Am Geriatr Soc.* 2018;66(4):693. doi:10.1111/JGS.15304
5. Sander M, Oxlund B, Jespersen A, et al. The challenges of human population ageing. *Age Ageing.* 2015;44(2):185-187. doi:10.1093/AGEING/AFU189
 6. Stone KL, Ancoli-Israel S, Blackwell T, et al. Actigraphy-measured sleep characteristics and risk of falls in older women. *Arch Intern Med.* 2008;168(16):1768-1775. doi:10.1001/archinte.168.16.1768
 7. Stone KL, Blackwell TL, Ancoli-Israel S, et al. Sleep Disturbances and Risk of Falls in Older Community-Dwelling Men: The Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. *J Am Geriatr Soc.* 2014;62(2):299-305. doi:10.1111/JGS.12649
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- Med Toxicol.* 2013;9(2):163-171. doi:10.1007/s13181-013-0294-y
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 23. Juraschek SP, Daya N, Appel LJ, et al. Orthostatic Hypotension in Middle-Age and Risk of Falls. *Am J Hypertens.* 2017;30(2):188-195. doi:10.1093/AJH/HPW108
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Table 1. Medication classes to be included in sleep medication use analysis

Barbiturates	Benzodiazepine Derivatives	Antidepressants	Hypnotics	Non-benzodiazepine sedatives (Z-drugs)
Xanthines <i>Aminophylline, Dyphylline, Theophylline, Theophylline in Dextrose</i>	Benzodiazepines <i>Alprazolam, Chlordiazepoxide, Clorazepate Dipotassium, Diazepam, Lorazepam, Oxazepam, Prazepam</i>	Monoamine Oxidase Inhibitors (MAOIs) <i>Isocarboxazide, Phenelzine Sulfate, Selegiline, Tranylcypromine Sulfate</i>	Non-Barbiturate Hypnotics <i>Chloral Hydrate, Paraldehyde</i>	Non-Benzodiazepine - GABA-Receptor Modulators <i>Zolpidem Tartrate, Eszopiclone, Zaleplon</i>
Xanthine-Expectorants <i>Dyphylline-Guaifenesin, Theophylline-Guaifenesin, Theophylline Sodium</i>	Benzodiazepine Hypnotics <i>Estazolam, Flurazepam, Midazolam, Quazepam, Temazepam, Triazolam</i>	Selective Serotonin Reuptake Inhibitors (SSRIs) <i>Citalopram Hydrobromide, Escitalopram Oxalate, Fluoxetine HCl, Fluvoxamine Maleate, Paroxetine HCl, Paroxetine Mesylate, Sertraline HCl</i>	Antihistamine Hypnotics <i>Doxylamine Succinate, Diphenhydramine HCl</i>	Zolpidem & Dietary Management Product
Xanthine-Sympathomimetics-Expectorant <i>Theophylline-PSE-GG</i>	Anticonvulsants - Benzodiazepines <i>Clonazepam, Diazepam (Anticonvulsant)</i>	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) <i>Desvenlafaxine Succinate, Duloxetine HCl, Venlafaxine HCl</i>	Antihistamine Hypnotic Combinations <i>Diphenhydramine – APAP, Ibuprofen Diphenhydramine Citrate, Ibuprofen-Diphenhydramine HCl</i>	
Xanthine-Nutritional Supplement Combinations	Benzodiazepine-Nutritional Supplement Combinations <i>Alprazolam-Dietary, Diazepam-Dietary, Temazepam-Dietary</i>	Tricyclic Agents <i>Amitriptyline HCl, Amoxapine, Clomipramine HCl, Desipramine HCl, Doxepin HCl, Imipramine HCl, Imipramine Pamoate, Nortriptyline HCl, Protriptyline HCl</i>	Hypnotic Tricyclic Agents Combinations <i>Doxepin HCl (sleep)</i>	
Barbiturate Hypnotics <i>Amobarbital Sodium, Butabarbital Sodium, Mephobarbital, Pentobarbital, Phenobarbital, Phenobarbital Sodium, Secobarbital Sodium</i>	Benzodiazepines & Tricyclic Agents <i>Chlordiazepoxide-Amitriptyline</i>	Tricyclic Agents-Nutritional Combination <i>Amitriptyline HCl - Dietary</i>		
		Tetracyclics & Other Misc. Antidepressants <i>Mirtazapine, Maprotiline HCl, Bupropion HCl, Bupropion, Trazodone HCl</i>		
		Antidepressant- Nutritional Combinations <i>Amitriptyline HCl - Dietary, Trazodone HCl-Dietary</i>		

