

## ARIC Manuscript Proposal # 3275

PC Reviewed: 11/13/18  
SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Association between excessive daytime sleepiness and burden of atrial and ventricular arrhythmias: Evidence from the Atherosclerosis Risk in Communities (ARIC) study

**b. Abbreviated Title (Length 26 characters):** Sleepiness and arrhythmia burden

**2. Writing Group:**

Kelsie M. Full, Pamela L. Lutsey, Alvaro Alonso, Elsayed Soliman, Mary R. Rooney, Faye Norby, Lin Yee Chen

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

**First author: Kelsie M. Full**

Address: 1300 S 2<sup>nd</sup> 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 2<sup>nd</sup> 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:**

The incidence and prevalence of atrial fibrillation (AF) continues to rise for the aging population in the United States.<sup>1</sup> The condition is associated with increased risk of mortality, independent of the burden attributed to the clinical cardiovascular risk factors that typically accompany AF.<sup>2</sup> To better understand the basic underlying mechanisms, researchers have started to examine AF as a dynamic condition, and explore how distinctive types and patterns of arrhythmias are uniquely associated with cardiovascular outcomes. A recent American Heart Association scientific statement recommends that, to better understand the public health concern that AF poses, we move past assessing the risk associated with the presence or absence of AF,

and examine individuals' arrhythmia burden.<sup>3</sup> Arrhythmia burden is defined as the proportion of time an individual experiences atrial arrhythmias, such as AF, or ventricular arrhythmias, over a period of time, usually the monitoring period. Randomized control trials have shown that reducing AF burden is both feasible and effective through structured lifestyle intervention programs,<sup>3-5</sup> however more research is needed on how AF burden and arrhythmia burden are defined, measured, and the lifestyle factors that may be targeted to decrease these conditions.<sup>3,5</sup>

Numerous lines of evidence suggest that abnormal or disrupted sleep may be linked to arrhythmias and AF.<sup>6-11</sup> There are multiple hypothesized mechanisms through which abnormal sleep, disrupted sleep, and sleep disordered breathing, may either stimulate or contribute to sustained arrhythmias.<sup>8,9</sup> In the epidemiologic literature, a longitudinal study by Gami et al. explored the association between obstructive sleep apnea (OSA), a highly prevalent sleep disorder<sup>12</sup>, and incident AF among individuals referred for an initial diagnostic polysomnogram. After accounting for numerous covariates including BMI, diagnosed OSA was a strong predictor of incident AF (HR:2.18) when compared to individuals without OSA.<sup>13</sup> Additionally, a cross-sectional analysis completed in the Multi-Ethnic Study of Atherosclerosis (MESA) found a lower odds of AF for individuals with better sleep quality, measured by sleep efficiency and slow wave sleep duration, than for individuals who had poorer sleep quality (slow wave sleep duration: OR:0.66 p:0.006).<sup>9</sup>

Excessive daytime sleepiness (EDS) is one the most frequent sleep complaints of older adults and a symptom many individuals present when diagnosed with a sleep disorder.<sup>14,15</sup> Clinical recommendations suggest that providers quantify EDS in order to determine whether to screen for undiagnosed sleep disorders, including OSA.<sup>16,17</sup> This recommendation is important considering it is estimated that up to 60% of OSA is undiagnosed in the older adult population.<sup>7</sup> The Epworth Sleepiness Scale<sup>18</sup>, a self-reported measure used to characterize an individual's level of daytime sleepiness, is a well-established screening measure for disordered sleep and has shown to correlate strongly with sleep disorder diagnosis and OSA severity.<sup>7,16</sup>

Despite the growing evidence on abnormal sleep and arrhythmic conditions, there is a need for a more evidence on the relationship between abnormal sleep and AF and arrhythmia burden in the older adult population. Much of the research on abnormal sleep and AF and arrhythmia burden has been conducted in populations with diagnosed sleep disorders, including OSA. Less is known about how general symptoms of abnormal sleep, including EDS, may be associated with AF and arrhythmia burden in the older adult population. Further, there is a limited number of studies examining the relationship between abnormal sleep and AF and arrhythmia burden which have comprehensive information on arrhythmia burden intensity, duration, and frequency. In the proposed study we will leverage 2-weeks of data from a continuous ECG recording device to examine the cross-sectional relationship between EDS and patterns in AF and arrhythmia burden in over 2,000 older adult ARIC participants.

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

We hypothesize that EDS, estimated by an ESS >16,<sup>18</sup> will be associated with a higher burden of AF and ventricular arrhythmias, defined by longer arrhythmia burden durations, greater number of episodes, and proportion of time in arrhythmia.

**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

The proposed study will be a cross-sectional analysis of data from visit 6. The study will include ARIC participants who wore the Zio® XT Patch and have complete ESS data from visit 6.

- *Exposure:* The primary exposure for this analysis will be Excessive Daytime Sleepiness, measured by the Epworth Sleepiness Scale (ESS). Possible ESS scores range from 0-24 with EDS defined as an ESS score greater than 16.<sup>18</sup>
- *Outcome:* The primary outcome for this analysis will be arrhythmia burden. At visit 6 ARIC participants wore the Zio® XT Patch for a 14-day period. From this wear, estimates of atrial and ventricular arrhythmias were derived including measures of AF burden.
- *Covariates:* The covariates included in this analysis will be: age, sex, race, study center, smoking status, drinking status, body mass index, physical activity, diabetes status, systolic and diastolic blood pressure, antihypertensive medication use, antiarrhythmic medication use, coronary heart disease, heart failure, sleep medication use (both prescribed and supplemental)

Data analysis

Basic descriptive statistics will be performed and presented including mean  $\pm$ SD/proportions of the included covariates for the study sample. Descriptives will also be presented stratified across categories of ESS correlated with mild, moderate, and severe OSA (<9, 9-16, >16).<sup>18</sup> Between ESS group differences in covariates will be explored using chi-square and one-way ANOVA.

Linear regression will be used for analyses involving continuous outcomes. Where appropriate, we will log-transform continuous arrhythmia burdens. Unconditional logistic regression will be used to assess the association between EDS and binary measures of arrhythmias. Multinomial logistic regression will be used for categorical outcomes (e.g. AF burden).

Proposed model progression:

- Model 1 = age, sex, race, study center
- Model 2 = Model 1 + smoking status, drinking status, physical activity
- Model 4 = Model 3 + systolic blood pressure, antihypertensive medication use, antiarrhythmic medication use, diabetes status

Additional sensitivity analyses using stratification will be performed on obesity status, type 2 diabetes status, and hypertension status to examine possible effect modification. Further, interactions by sex, age, and race/ethnicity will be evaluated.

**7.a. Will the data be used for non-CVD analysis in this manuscript? \_\_\_ Yes \_\_\_X\_\_\_ 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.csc.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)?**

MS918: “Association of Nocturnal Cardiac Arrhythmias with Sleep- Disordered Breathing”  
MS1301: “Temporal Associations Between of Respiratory Disturbances and Cardiac Arrhythmias Occurring During Sleep”

**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 (list number\* 2014.18 \_\_\_)**  
\_\_\_ **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](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

## References

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of Diagnosed Atrial Fibrillation in Adults. *JAMA*. 2001;285(18):2370. doi:10.1001/jama.285.18.2370.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of Atrial Fibrillation on the Risk of Death : The Framingham Heart Study Impact of Atrial Fibrillation on the Risk of Death The Framingham Heart Study. 2013. doi:10.1161/01.CIR.98.10.946.
3. Chen LY, Mina Chung CK, Chair Larry Allen VA, et al. Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity. *Circulation*. 2018;137:623-644. doi:10.1161/CIR.0000000000000568.
4. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: A randomized clinical trial. *JAMA - J Am Med Assoc*. 2013;310(19):2050-2060. doi:10.1001/jama.2013.280521.
5. Zakeri R, Van Wagoner DR, Calkins H, et al. The burden of proof: The current state of atrial fibrillation prevention and treatment trials. *Heart Rhythm*. 2017;14(5):763-782. doi:10.1016/j.hrthm.2017.01.032.
6. Digby GC, Baranchuk A. Sleep apnea and atrial fibrillation; 2012 update. *Curr Cardiol Rev*. 2012;8(4):265-272. doi:10.2174/157340312803760811.
7. Gami AS, Somers VK. Implications of Obstructive Sleep Apnea for Atrial Fibrillation and Sudden Cardiac Death. *J Cardiovasc Electrophysiol*. 2008;19(9):997-1003. doi:10.1111/j.1540-8167.2008.01136.x.
8. Zhang L, Hou Y, Po SS. Obstructive Sleep Apnoea and Atrial Fibrillation. *Arrhythmia Electrophysiol Rev*. 2015;4(1):14-18. doi:10.15420/aer.2015.4.1.14.
9. Kwon Y, Gharib SA, Biggs ML, et al. Association of sleep characteristics with atrial fibrillation: The multi-ethnic study of atherosclerosis. *Thorax*. 2015;70(9):873-879. doi:10.1136/thoraxjnl-2014-206655.
10. Khawaja O, Sarwar A, Albert CM, Gaziano JM, Djoussé L. Sleep duration and risk of atrial fibrillation (from the Physicians' Health Study). *Am J Cardiol*. 2013;111(4):547-551. doi:10.1016/j.amjcard.2012.10.038.
11. Cadby G, McArdle N, Briffa T, et al. Severity of OSA Is an Independent Predictor of Incident Atrial Fibrillation Hospitalization in a Large Sleep-Clinic Cohort. *Chest*. 2015;148(4):945-952. doi:10.1378/CHEST.15-0229.
12. Senaratna C V., Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev*. 2017;34:70-81. doi:10.1016/j.smrv.2016.07.002.
13. Gami AS, Hodge DO, Herges RM, et al. Obstructive Sleep Apnea, Obesity, and the Risk of Incident Atrial Fibrillation. 2007. doi:10.1016/j.jacc.2006.08.060.
14. Hays JC, Blazer DG, Foley DJ]. *Risk of Napping: Excessive Daytime Sleepiness and Mortality in an Older Community Population*. Vol 44.; 1996. doi:10.1111/j.1532-5415.1996.tb01834.x.

15. Crowley K. Sleep and sleep disorders in older adults. *Neuropsychol Rev*. 2011;21(1):41-53. doi:10.1007/s11065-010-9154-6.
16. Epstein LJ, Kristo D, Strollo PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5(3):263-276. <http://www.ncbi.nlm.nih.gov/pubmed/19960649>. Accessed September 26, 2018.
17. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.
18. Johns M. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. 1991;14(6):540-545.