ARIC Manuscript Proposal #4420

PC Reviewed: 03/12/24 **Status: _____** **Priority: 2**

1.a. Full Title: Association between circadian rest/activity rhythms and incident dementia in older adults: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): **circadian RARs & dementia**

2. Writing Group: Wendy Wang, Amal A. Wanigatunga, Jill A. Rabinowitz, Priya Palta, James R. Pike, Ryan J. Dougherty, Vadim Zipunnikov, Francesca R. Marino, Ciprian Crainiceanu, Lacey H. Etzkorn, Adam P. Spira, Jennifer A. Schrack, Lin Yee Chen, others welcome

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

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3. Timeline:
Data analysis to begin immediately; pen draft expected within 6-9 months.

4. Rationale:
Circadian rhythm alterations occur with aging,[1] and evidence suggests that circadian rhythm disturbances may be a risk factor for neurodegenerative diseases.[2,3] Rest-activity rhythms (RARs) are markers of circadian rhythm[2] and can be measured from wearable accelerometers.

As accelerometers continuously measure movement over 24 hours, we are able to derive 24-hour RARs from accelerometetry data, including rhythm strength (amplitude), fragmentation (intradaily variability), and stability (interdaily stability).[4] Intradaily variability measures the amount of alterations of activity-inactivity, interdaily stability measures the day-to-day RARs consistency, and amplitude is the difference between the activity and inactivity phases.[5,6]

Prior studies have assessed associations of RARs measures with dementia; however, conflicting results have been reported, particularly for intradaily variability. In the Rush Memory and Aging Project, participants were followed for up to 15 years and those with higher intradaily variability had a higher risk of developing Alzheimer's dementia.[7] However, in the Rotterdam Study and Study of Osteoporotic Fractures, no association between intradaily variability and incident dementia was noted.[5,8] More consistent results have been observed with interdaily stability and amplitude. Lower amplitude was associated with a higher risk of dementia or composite outcome of mild cognitive impairment and dementia,[8,9] while no association between interdaily stability and incident dementia was noted.[5,8,9]

In addition to these inconsistent results, these studies have largely been done in cohorts of women only[6,8,9] or predominately white participants.[8,9] Therefore, using data from the Atherosclerosis Risk in Communities (ARIC) study Black and white males and females, we aim to use accelerometer data from the Zio XT Patch to analyze the association between circadian RARs and incident dementia.

5. Main Hypothesis/Study Questions:

Aim: To evaluate the association between circadian RARs and incident dementia.

Hypothesis: Participants with greater intradaily variability (RAR fragmentation), lower interdaily stability (day-to-day RAR consistency), and lower relative amplitude (rhythm strength) will have a higher risk of dementia.

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:

Prospective cohort from visit 6 (2016-17) to 2020 (or most recent data available).

Inclusion/Exclusion:

We will include all participants who wore the Zio XT Patch at visit 6 for $\geq$3 days. We will exclude participants with prevalent dementia at visit 6 and those with missing covariates. Those whose race was other than Black or white will be excluded, as well as Black participants from the MN and MD centers due to low numbers.

Variables

Exposure: RAR measures were derived from the Zio XT Patch from visit 6 (2016-17) and include intradaily variability (RAR fragmentation), interdaily stability (day-to-day RAR consistency), and relative amplitude (rhythm strength). Measures will be assessed continuously in 1-SD increments.

Primary outcome: Dementia events after visit 6 (through 2020 or latest available data); level 3 dementia diagnosis will be used for all analyses.

- Level 1 includes adjudicated outcomes from visits 6 and 7 NCS evaluations, including evidence of cognitive decline based on assessments from prior visits.
- Level 2 includes cases identified in level 1, as well as participants who did not attend NCS visits, but had their cognitive status evaluated through a validated phone-based cognitive assessment interview.
- Level 3 includes level 1 and 2 cases, as well as participants identified through surveillance for hospitalization discharge codes (ICD-9) or death certificate codes related to dementia.

Other confounders/covariates (obtained from visit 6, unless otherwise noted): age, sex, race/center (visit 1), education (visit 1), APOE ε4, body mass index, systolic blood pressure, antihypertensive medication use, diabetes, smoking status, alcohol status, coronary heart disease, stroke, heart failure, short physical performance battery (SPPB)

Statistical analysis

- Baseline characteristics will be described using mean ± SD for continuous variables and proportions for categorical variables.
- Cox proportional hazards models will be used to assess the association between RAR measures and incident dementia.
- For all analyses, we will use the following models:
  - Model 1 will adjust for age, sex, race/center, education, APOE ε4
  - Model 2 will additionally adjust for body mass index, systolic blood pressure, antihypertensive medication use, diabetes, smoking status, alcohol status
  - Model 3 will further adjust for coronary heart disease, stroke, heart failure
- Interactions by sex, race, APOE ε4, and self-reported physical activity (met recommended vs. not) will be explored and stratified models will be reported when appropriate.
- In a sensitivity analysis, we will additionally adjust for SPPB (as a continuous variable).

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? __x__ 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"? __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)?

#4253: Circadian RARs & MRI (Spira)

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, 2021.01_____)

___ 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 https://www2.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.

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.

References:

1. Hood S, Amir S. The aging clock: circadian rhythms and later life. *Journal of Clinical Investigation*. 2017;127:437-446. doi: 10.1172/jci90328
2. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol*. 2019;18:307-318. doi: 10.1016/s1474-4422(18)30461-7
3. Musiek ES, Holtzman DM. Mechanisms linking circadian clocks, sleep, and neurodegeneration. *Science*. 2016;354:1004-1008. doi: 10.1126/science.aah4968
4. Witting W, Kwa IH, Eikelenboom P, Mirmiran M, Swaab DF. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. *Biological Psychiatry*. 1990;27:563-572. doi: 10.1016/0006-3223(90)90523-5
5. Lysen TS, Luik AI, Ikram MK, Tiemeier H, Ikram MA. Actigraphy-estimated sleep and 24-hour activity rhythms and the risk of dementia. *Alzheimer's & Dementia*. 2020;16:1259-1267. doi: 10.1002/alz.12122
6. Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, Cauley JA, Redline S, Hillier TA, Cummings SR, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Annals of Neurology*. 2011;70:722-732. doi: 10.1002/ana.22468
7. Li P, Gao L, Gaba A, Yu L, Cui L, Fan W, Lim ASP, Bennett DA, Buchman AS, Hu K. Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults. *Lancet Healthy Longev*. 2020;1:e96-e105. doi: 10.1016/s2666-7568(20)30015-5
8. Posner AB, Tranah GJ, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Leng Y, Zeitzer JM, Chen DM, Webber KR, et al. Predicting incident dementia and mild cognitive impairment in older women with nonparametric analysis of circadian activity rhythms in the Study of Osteoporotic Fractures. *Sleep*. 2021;44. doi: 10.1093/sleep/zsab119
9. Xiao Q, Shadyab AH, Rapp SR, Stone KL, Yaffe K, Sampson JN, Chen JC, Hayden KM, Henderson VW, Lacroix AZ. Rest-activity rhythms and cognitive impairment and dementia in older women: Results from the Women's Health Initiative. *Journal of the American Geriatrics Society*. 2022;70:2925-2937. doi: 10.1111/jgs.17926