ARIC Manuscript Proposal #3390 (Amended)

PC Reviewed: 12/14/21 **Status: _____**
Priority: 2
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Interaction between Heart Rate Variability and Physical Activity in Relation to Cognitive Function and Dementia: the ARIC Neurocognitive Study

b. Abbreviated Title (Length 26 characters): HRV, PA, Cognition and Dementia

2. Writing Group:

Writing group members: Francesca Marino, Hervaldo Sampaio Carvalho, Jennifer Schrack, Jennifer Deal, Amal Wanigatunga, Hau-Tieng Wu, Jacek Urbanek, Elizabeth Selvin, Mary Rooney, Faye L. Norby, Alvaro Alonso, Elsayed Z. Soliman, B. Gwen Windham, Joe Coresh, Lin Y. Chen, others welcome.

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

First author: Francesca Marino, BS
Address: 2024 E. Monument Street, Suite 2-700, Baltimore, MD 21287
Phone: 508-847-5930
E-mail: fmarino1@jh.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: Lin Y. Chen, MD**,** MS
Address: Cardiac Arrhythmia Center, Cardiovascular Division,
Department of Medicine,
University of Minnesota Medical School,
420 Delaware Street SE, MMC 508,
Minneapolis, MN 55455.

Phone: 612-625-4401 Fax: 612-624-4937
E-mail: chenx484@umn.edu

3. Timeline: Statistical Analysis: 3 months
Manuscript Preparation: 4 months

4. Rationale:

The heart rate variability (HRV) is an expression of different regulating factors over the cardiac function and measures the variation in the RR intervals along time during sinus rhythm. It has been used for a long time as a measurement of the autonomic nervous system (ANS) influence over the heart rate, but other regulating systems have also been implicated in the HRV (1). HRV analysis includes a great number of features derived from the time, frequency and non-linear domains (2). The ANS is related to cognitive capacity in healthy subjects. HRV has been associated with language skills such as higher vagal tonus higher ability (3), learning process (4), metacognitive judgments (5), and task-switching (6). Low HRV has been related to lower cognitive function (7,8,9,10,11,12).

The relationship between ANS and physical activity (PA) has been studied extensively, but the correlation of objective accelerometer-based PA measurements in daily life has been used only recently. There is evidence that regular PA improves cognitive function, but there is controversy regarding whether PA interventions can reduce cognitive decline (13,14). The association between physical activity and dementia has been evaluated, mainly using self-reported PA data or coarsely defined metrics of objectively measures PA (15). Thus, the true magnitude and intensity of daily activity patterns and trends (captured in free living wearable device monitoring) and their relationship to cognitive impairment and dementia remain undefined. Further, prior studies have shown that higher moderate-to-vigorous PA and higher routine activity are associated with higher HRV (16, 17). That said, there is a paucity of data on the interaction / effect modification between HRV and PA (measured by raw accelerometer data) in relation to cognitive function.

Figure 1 represents our causal model. It shows low HRV and low PA as causal factors for MCI/dementia. Importantly, as represented by the red arrow, higher PA may modify the relationship between low HRV and MCI/dementia.

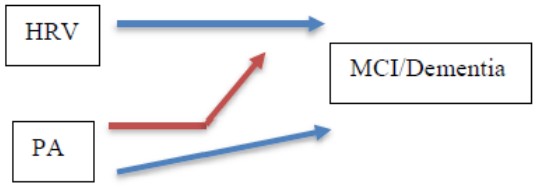

Figure 1: The causal model

5. Main Hypothesis/Study Questions:

Aim 1: To evaluate whether HRV and PA are cross-sectionally associated with cognitive function and mild cognitive impairment / dementia in ARIC participants based on Zio XT Patch data at Visit 6 and to investigate whether HRV and PA are longitudinally associated with cognitive decline from Visit 6 to Visit 7 and mild cognitive impairment / dementia at Visit 7 in ARIC participants based on Zio XT Patch data at Visit 6.

Hypothesis 1: Low HRV and low physical activity are cross-sectionally associated with lower cognitive test scores and higher odds of dementia and longitudinally associated with greater cognitive decline and higher odds of dementia.

Aim 2: To evaluate the interaction between HRV and PA in relation to cognitive function and mild cognitive impairment / dementia in ARIC participants cross-sectionally, based on Zio XT Patch data at Visit 6, and longitudinally, based on cognitive decline from Visit 6 to Visit 7, mild cognitive impairment / dementia status at Visit 7, and Zio XT Patch data at Visit 6.

Hypothesis 2: Physical activity modifies the association of low HRV with lower cognitive test scores, greater cognitive decline, and higher odds of dementia, such that individuals with low HRV but high PA have higher cognitive test scores, lesser cognitive decline, and lower odds of dementia as compared to those with low HRV and low PA.

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 Population: We will include all participants who attended the Visits 6 and 7 and wore Zio XT Patch. We will exclude those with missing Zio XT Patch data, atrial fibrillation, missing cognitive test data, and missing covariates. We will also exclude those using beta blockers, calcium channel blockers, and antiarrhythmic drugs.

Exposure

HRV measures: We will use HRV measures derived by the Zio XT Working Group from the raw ECG data recorded by the Zio XT Patch. We will evaluate metrics in the time (i.e. average NN, SDNN, SDANN, pNN50 and related percent NN intervals, rMSSD) and frequency (i.e. total power, ultra low frequency power, very low frequency power, low frequency power, high frequency power, low frequency-to-high frequency ratio, normalized low frequency power) domains and also consider non-linear HRV parameters to help differentiate among those with normal vs. low HRV. Model fit parameters (Adjusted R2, AIC, BIC, etc.) will be compared to determine which metrics have the strongest association. We will consider HRV measurements during short periods of time (256 RR intervals) and long periods of time (awake and sleep times).

PA measures: PA measures will be derived from the raw accelerometry data recorded by the Zio XT patch. We will evaluate total daily physical activity counts to help differentiate among those with normal vs. reduced physical activity. Differences in physical activity patterns including fragmentation, intensity, time-of-day, and variability will also be evaluated. Model fit parameters (Adjusted R2, AIC, BIC, etc.) will be compared to determine which PA metrics have the strongest association.

We will analyze PA in 1-minute epoch levels but also explore raw data at sub-second levels and other epoch lengths (i.e. 10-minute intervals). We will also analyze PA during 2 time periods: (1) 0600 to 2359 hours (awake time) and (2) 0000 to 0559 hours (sleep time). We will measure:

X axis: acceleration (g) Median, Mean, and SD
Y Axis: acceleration (g) Median, Mean, and SD
Z Axis: acceleration (g) Median, Mean, and SD
Vector Magnitude: acceleration (g) Median, Mean, and SD

Outcome

1. Cognitive function: cognitive domain scores for memory, executive function, language, and global cognition at Visits 6 and 7

2. Adjudicated normal/MCI/dementia variable at Visits 6 and 7

Covariates:

Covariates will include but are not limited to age, sex, race-center, education, APOE genotype, smoking, alcohol consumption, body mass index, systolic blood pressure, use of hypertension medications, use of antidepressants, diabetes, coronary heart disease, heart failure, and stroke. All covariates will be based on V6 data.

Statistical Analysis:

We will use multivariable linear regression to assess the associations of HRV and PA with cognitive domain and test scores. To better account for within-person change, we will also explore GEE and/or MLM models to assess the longitudinal associations of HRV and PA with cognitive decline. Separate models will be constructed for each HRV and PA measure, and multivariable main predictor models may also be explored.

Model 1: Age, sex, race-field center, education, and APOE genotype.
Model 2: Model 1 + smoking, alcohol consumption, body mass index, systolic blood pressure, use of hypertension medications, use of antidepressants, diabetes, coronary heart disease, heart failure, and stroke.

Next, to evaluate the interaction between HRV and PA, we will add an interaction term, HRV*PA

Model 3: Model 2 + HRV + PA +_ HRV*PA

Using the same models above, we will use multinomial logistic regression to assess the cross-sectional association of HRV and PA with odds of MCI and dementia. We will also explore longitudinal logistic regression models to assess the longitudinal association of HRV and PA with odds of MCI and dementia. We will also evaluate the interaction between HRV and PA in relation to odds of MCI and dementia.

We will also conduct a sensitivity analysis using the same models above and excluding individuals with a history of stroke.

Limitations: Although we hypothesize that HRV and PA will contribute to poor cognitive outcomes, we acknowledge the possibility of reverse causation, e.g., participants with dementia are likely to have lower PA. This research will provide evidence for future work to help determine directionality of this association.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes ___x_ No

7b. 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)?

#1740 –Chen
#2804 –Alonso
#1365 –Alonso
#2433 –Faye Norby

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*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.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-yearsfrom 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 fromhttp://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.htmshowsyou which journals automatically upload articles to Pubmed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu.
I will be using CMS data in my manuscript ____ Yes __x__ No.

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