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:

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

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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). Park & Thayer described the modulation between the heart and the mind related to perception and attention to emotional stimuli (7). Low HRV has been related to lower cognitive function (8,9,10,11,12,13).

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 (14,15). The association between physical activity and dementia has been evaluated, mainly using self-reported PA data or coarsely defined metrics of objectively measures PA (16). 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, 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.

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

Aim 1: Evaluate the cross-sectional association of HRV and PA with cognitive function and mild cognitive impairment / dementia in ARIC participants based on Zio XT Patch data at Visit 6.

Hypothesis 1: Low HRV and low physical activity will be associated with lower cognitive test scores and higher odds of dementia.
**Aim 2:** Evaluate the interaction between HRV and PA in relation to cognitive function and mild cognitive impairment / dementia in ARIC participants based on Zio XT Patch data at Visit 6.

Hypothesis 2: Physical activity will modify the association of low HRV with lower cognitive test scores and higher odds 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 Population:** We will include all participants who attended the Visit 6 examination. 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:** HRV measures will be derived from the raw ECG data recorded by the Zio XT Patch. We will evaluate the metrics listed below to help differentiate among those with normal vs. low HRV. Model fit parameters (Adjusted $R^2$, 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).

**Time domain HRV**

- Average NN in milliseconds (and/or heart rate in beats per minute).
- SDNN in milliseconds – Standard deviation of NN (normal to normal RR)
- SDANN in milliseconds – Standard deviation of the average NN intervals for all of the five-minute intervals in a 24-hour continuous ECG recording.
- pNN50 and related – Percent NN intervals >50 ms different from the prior interval
- rMSSD in milliseconds – Root mean square of differences between successive NN intervals;

**Frequency domain HRV**

- Total power (TP) in ms$^2$ – TP captures the total variance in HRV.
- Ultra-low frequency power (ULF) in ms$^2$ – ULF captures the magnitude of underlying rhythms in heart rate at frequencies of every five minutes to once in 24 hours.
• Very low frequency power (VLF) in ms² – VLF captures the magnitude of underlying oscillations in the heart rate pattern at frequencies between every 25 seconds and every five minutes (0.003 to 0.04 Hz).
• Low-frequency power (LF) in ms² – LF captures the magnitude of heart rate oscillations in the range of three to nine cycles per minute (0.04 to 0.15 Hz).
• High-frequency power (HF) in ms² – HF captures heart rate oscillations in the range of 9 to 24 cycles per minute, which is the range of typical adult respiratory frequencies (0.15 to 0.40 Hz).
• LF/HF ratio – "sympathovagal" balance.
• Normalized LF power (NLF) in percent – NLF captures the proportion of HRV accounted for by low frequency power

PA measures: We will evaluate the metrics listed below to help differentiate among those with normal vs. reduced and fragmented physical activity. Model fit parameters (Adjusted R², AIC, BIC, etc.) will be compared to determine which PA metrics have the strongest association. These PA measures are derived from the raw accelerometry data from the Zio XT patch.

We will analyze PA in intervals of 1 minute, 5 minutes, 10 minutes, and 60 minutes. We will analyze PA during 2 time periods: (1) 0600 to 2359 hours (awake time) and (2) 0000 to 0559 hours (sleep time). In each interval or time period, 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

2) Adjudicated normal/MCI/dementia variable at Visit 6

Covariates:

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. Separate models will be constructed for each HRV and PA measure.

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 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.

Limitations: We acknowledge that the cross-sectional nature of this study impedes our ability to infer direction of relationships, e.g., participants with dementia are likely to have lower PA.

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)?

#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.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.

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.
References:


