

ARIC Manuscript Proposal #2855

PC Reviewed: 10/11/16
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Heart Rate Variability and Lifetime Risk of Cardiovascular Disease: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): HRV & lifetime risk

2. Writing Group:

Writing group members: Yasuhiko Kubota, Lin Chen, Eric Whitsel, Aaron Folsom, others welcome

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

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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: 1-2 months from manuscript approval date.

First draft of the manuscript: 2-3 months from manuscript approval date.

4. Rationale:

Heart rate variability (HRV) is a well-established marker of autonomic nervous system function—both sympathetic and parasympathetic (1). Reduced HRV, which reflects sympatho-vagal imbalance (i.e. increased sympathetic or reduced vagal activity), has been shown to be associated with not only cardiovascular risk factors such as smoking,

physical inactivity, diabetes, stress and depression (2–7), but also cardiovascular disease (CVD) itself (8–10). As more commercial devices are available, this simple and non-invasive measure has become more feasible in risk assessment. Thus, it is important to further understand the association between HRV and CVD.

One way to achieve this purpose may be to calculate the lifetime risk of CVD according to HRV. Lifetime risk estimates, that is, absolute risks from a certain age through death, can readily convey the burden of CVD in a population (11). Yet, to the best of our knowledge, there has been no study so far estimating lifetime risks of CVD according to HRV.

We aimed to evaluate the association between HRV and CVD risk by estimating the lifetime risks of CVD (coronary heart disease, heart failure, and stroke) in a large biracial cohort study in the US.

5. Main Hypothesis/Study Questions:

To estimate individual lifetime risks of incident CVD (coronary heart disease, stroke, and heart failure) by level of HRV.

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).

Design

Prospective cohort

Inclusion/exclusion criteria

Inclusion: participants who provided information on HRV at visit 1.

Exclusion: those who had prevalent CVD at visit 1.

Main exposure

HRV: Participants will be categorized into 3 groups by tertiles of HRV.

Time domain measures of HRV

1. SDNN (total power) (ms) – standard deviation of all normal RR intervals; *estimate of overall variability in measurement period.*
2. r-MSSD (ms) – root mean square successive difference, the square root of the mean of the squared differences between adjacent normal RR intervals; *estimate of short term components of variability in the measurement period.*
3. MeanNN (ms) – mean of all normal RR intervals

Frequency domain measures of HRV

1. HF (high frequency power) (ms^2) – the energy in the heart period power spectrum between 0.15 and 0.40 Hz; *linked to parasympathetic nervous system activity.*
2. LF (low frequency power) (ms^2) – the energy in the heart period power

spectrum between 0.04 and 0.15 Hz; *less known, may reflect sympathetic nervous system activity, likely reflects general autonomic nervous system activity.*

3. LF/HF ratio; *less known, may reflect balance sympathetic and parasympathetic nervous system activities.*

Statistical analysis

First, we will present the prevalences of CVD risk factors (smoking, physical activity, body mass index, hypertension, diabetes, hypercholesterolemia and education) according to HRV (Table 1). Next, we will update ARIC's prior report of the hazard ratio for the association between HRV and CVD using Cox proportional hazard modeling (Table 2). Then, we will also compute lifetime risk of CVD according to HRV categories using a macro from Dr. Donald Lloyd-Jones (11) (Table 2). It employs a Kaplan Meier analysis that incorporates competing risks, with deaths from other causes as competing events. Remaining conditional lifetime risk at age 45 years through 85 years will be calculated.

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)?**

Multiple ARIC papers on individual outcomes. For example:

- #2432: Cardiac Autonomic Function Assessed by Heart Rate Variability and Incident CHD: A Population Based Case-Cohort Study - The ARIC Study
- #2250: Heart Rate Variability and Incident Stroke: The Atherosclerosis Risk in Communities Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* 2006.16)**
- 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 No.

References:

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