1.a. Full Title: Heart Rate Variability and its Association with Cognitive Decline over 20 years: The ARIC Neurocognitive Study (ARIC-NCS)

b. Abbreviated Title (Length 26 characters): Heart rate variability and cognitive function

2. Writing Group:

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

First author: Faye Lopez
Address: Division of Epidemiology & Community Health
         School of Public Health, University of Minnesota
         1300 S 2nd St, Suite 300
         Minneapolis, MN 55454
         Phone: 612-626-9096       Fax: 612-624-0315
         E-mail: flopez@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: Alvaro Alonso, MD, PhD
Address: Division of Epidemiology and Community Health
         School of Public Health, University Of Minnesota
         1300 S. 2nd Street, Suite 300
         Minneapolis, MN 55454
         Phone: 612-626-8597       Fax: 612-624-0315
         E-mail: alonso@umn.edu

3. Timeline: Statistical analysis: 3 month
   Manuscript preparation: 6 months
   We expect to submit an abstract with preliminary results to the AHA Epi conference (submission deadline Oct 2014)
4. **Rationale:**

Heart rate variability (HRV) is a non-invasive marker of autonomic nervous system (ANS) function, and it involves the interaction of activity from the sympathetic and parasympathetic nervous systems. In the general population, low HRV is associated with an increased risk of coronary heart disease (CHD) and total mortality. Factors known to be associated with lower HRV include higher heart rate, older age, use of beta-blockers, history of myocardial infarction, heart failure, diuretic use, diabetes mellitus, and smoking. Modifiable factors such as body habitus and physical activity or fitness may be associated with HRV.

Many of the risk factors associated with lower HRV are also risk factors for cognitive impairment, such as age, lifestyle (lower physical activity, smoking and high alcohol consumption), metabolic dysregulation (obesity, impaired glucose tolerance, diabetes), cardiovascular disease (hypertension, atherosclerosis, stroke) and inflammatory markers, many of which are modifiable. Recent studies indicate reduced HRV could be associated with cognitive decline independent of those traditional risk factors. However, previous studies have been cross-sectional and limited, not encompassing community-based populations over time.

Current literature suggests several potential mechanisms by which the ANS may influence brain structure and cognitive function. The association may reflect shared anatomical or mechanistic pathways, for example, via CHD, vascular disease, hypertension, immune dysfunction/inflammation and type 2 diabetes mellitus. Another explanation is through the interaction of HRV and blood pressure variability in the baroflex mechanism, which regulates blood flow and perfusion to vital organs, including the brain. HRV and blood pressure variability are inversely related in response to stress; therefore, individuals with cardiac autonomic dysfunction, as indicated by reduced HRV, are more prone to increased blood pressure variation. Studies show fluctuations in blood pressure (and thus most likely low HRV) have been associated with cognitive dysfunction and brain structure damage. Consequently, reduced HRV, as a marker of poor modulation of cardiac autonomic function through vascular diseases, could be associated with cognitive decline via a reduction in blood flow to the brain, through structural brain changes, including strokes and subclinical cerebral infarcts.
In this study, we would look at the association of HRV and cognitive decline over time (approximately 20 years) in a bi-racial community sample. We will evaluate whether this association is independent of risk factors, which could help better understand the role of the ANS in cognitive decline. We would be using data from the cognitive tests from the ARIC Neurocognitive Study (ARIC-NCS, 2011-2013), along with data from previous ARIC visits.

5. Main Hypothesis/Study Questions:
Aim: Evaluate the association of HRV with cognitive change in ARIC participants
Hypothesis: Participants with lower HRV will experience greater decline in cognitive function over time.

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
- Inclusion criteria: Individuals with HRV data at visit 1, and with cognitive data at least at visit 2.
- Exclusion criteria: Missing or indeterminate HRV data at visit 1, prevalent stroke at visit 1, race/ethnicity other than white or black and those missing covariates.

Exposure
HRV data will be obtained from 2-minute beat-to-beat heart rate recordings (visit 1)

Time domain measures of HRV
1. SDNN (ms) – standard deviation of all normal RR intervals
2. r-MSSD (ms) – root mean square successive difference, the square root of the mean of the squared differences between adjacent normal RR intervals

Frequency domain measures of HRV
1. LF (low frequency power) (ms²) – the energy in the heart period power spectrum between 0.04 and 0.15 Hz
2. HF (high frequency power) (ms^2) – the energy in the heart period power spectrum between 0.15 and 0.40 Hz
3. LF/HF ratio

Outcomes
Cognitive function (visit 2, visit 4, and visit 5)
z-scores of 3 neuropsychological tests: Delayed Word Recall (DWR) Test, Digit Symbol Substitution (DSS) Test, and Word Fluency (WF) Test; and a global cognitive score will be used to assess cognitive function and determine cognitive decline.

Covariates
Baseline variables: Age, sex, race, study center, educational level, occupation, APOE genotype, smoking (never, former, current), alcohol drinking, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, LDL cholesterol, HDL cholesterol, diabetes, coronary heart disease, myocardial infarction, and heart failure.

Statistical analysis
We will use restricted cubic splines to examine the possibility that the association is non-linear, and use natural log transformation for HRV variables as needed.
To test the association between HRV measurements and cognitive decline rate, we will follow recommendations from the ARIC-NCS Analysis Committee. Specifically, we will use linear regression models fit with generalized estimating equations (PROC GENMOD, SAS Software 9.3; SAS Institute, Cary, NC) to evaluate associations with cognitive performance trajectories using robust variance and an unstructured correlation matrix. Models will include a term for time since baseline, and interactions between follow-up time and covariates will be explored as appropriate. Separate models will be run for each cognitive test (DWR, DSS, and WF) and a global cognitive score.

The models will adjust for the following covariates (and if necessary, interaction of these covariates with time):

• Model 1 is adjusted for age, race, and sex
Model 2 is adjusted for adjusted for model 1, center, education, smoking (never, former, current), alcohol drinking, body mass index, systolic and diastolic blood pressure, LDL cholesterol, HDL cholesterol, use of antihypertensive medication, diabetes, coronary heart disease, myocardial infarction, and heart failure

In addition, we will conduct sensitivity analysis using inverse probability of attrition weighting to adjust for selection bias due to censoring.

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.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)?
There are no similar manuscripts exploring the association of HRV with cognitive decline. Similar manuscripts include:
#1459: Cardiac autonomic imbalance and AF – Agarwal
#2175: Hypertension and cognitive change – Gottesman
#2250: Heart Rate Variability and stroke – Fyfe-Johnson
#2273A: ULF HRV on 14-day ECG and cognitive function – Tereshchenko: This is a cross-sectional analysis restricted to participants in the ZioPatch ancillary study. It will not explore cognitive decline.
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* __________)

___x__  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 1999.01 – ARIC MRI Study, 1996.03—HRV ancillary study)

*ancillary studies are listed by number at http://www.cscce.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.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:


