ARIC Manuscript Proposal # 3012

PC Reviewed: 7/11/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Resting Heart Rate and Cognitive Change Over 20-years: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Resting Heart Rate and Cognitive Function

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

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3. Timeline:
Abstract by October 2017 for submission to ACC Spring meeting
Manuscript completion by end of December 2017

4. Rationale:

Resting heart rate (RHR) is a universally measured vital sign. It is slightly higher in women than in men, seems to decrease with age, and has a circadian rhythm with the highest values during waking hours.[1, 2] RHR is also positional with lower rates in supine versus sitting.

Resting heart rate has been used as a measure of cardiorespiratory fitness. However, our prior work and that of others have shown RHR to also be a predictor of mortality, even independent of traditional cardiovascular disease risk factors and fitness measures (METS).[3, 4] High RHR has been associated with increased cardiovascular and non-cardiovascular mortality,[5, 6] and is a risk factor for hypertension,[7, 8] coronary artery disease (CAD),[9] and heart failure.[10] In addition to being an easily obtained low-tech measure of risk, RHR is an attractive marker to study because it is also a potentially modifiable target. For example, improving one's fitness level can improve resting vagal tone and in turn lower RHR. Pharmacologic modulation of heart rate might also be beneficial. For example, a study using ivabradine to slow heart rates in mice has shown to decrease rate of atherosclerosis in mice.[11] Another study showed that decreasing heart rate in monkeys also decreased coronary atherosclerosis.[12] However, in the BEAUTIFUL randomized clinical trial, a reduction in heart rate with ivabradine in patients with stable CAD did not reduce the risk of subsequent cardiovascular outcomes, although there may be a benefit in the subgroup with a RHR >70 bpm.[13] More work is needed in this area.

As cardiovascular disease mortality is declining in the U.S.,[14] there is a great interest in promoting ideal cardiovascular health and freedom from morbidity from chronic diseases. In particular for an aging population, the identification of risk factors and other modifiable factors linked to cognitive decline and dementia has gained attention as a key focus for preventive interventions. Cardiovascular diseases such as hypertension, diabetes, and hyperlipidemia are associated with cognitive decline and dementia.[15] Furthermore, mid-life vascular risk factors are also associated with late-life amyloid deposition, a marker of Alzheimer's risk.[16] Taken together, this literature suggests many of the risk factors for cardiovascular diseases also contribute to neurodegeneration. Given that RHR can be used as a marker for cardiovascular health, it is equally important to examine associations between RHR and brain health (i.e. cognition).

One prior study found that lower RHR was associated with less cognitive decline in patients who have experienced ischemic strokes.[17] However, little is currently known about the relationship of RHR and cognitive decline in the general population. Resting heart rate can be a marker of subclinical disease such as autonomic dysfunction, as RHR reflects a combination of sympathetic and parasympathetic influences, and in patients with mild cognitive impairment (MCI), autonomic dysfunction is common.[18, 19] Both parasympathetic and sympathetic pathways appear to be affected, with MCI patients having increased odds of orthostasis and decreased heart rate variability.[19] A decreased parasympathetic and increased sympathetic state appears to be present in dementia,[20] suggesting that decreased cholinergic activity is significant in cognitive decline. Additionally, cognitive decline may also be mediated by dysregulation in cerebral perfusion, arterial stiffness, and pulse pressures.[21, 22] Medication use that influence heart rate and blood pressure (i.e. beta-blockers) may also confound these associations.[23]

Resting heart rate may also be a marker of subclinical inflammation. We have previously shown RHR to be associated with several inflammatory markers,[24] and inflammation has also been linked to cognitive decline; for example, elevated C-reactive protein (CRP) levels are found in MCI patients.[25] There is a possible vagal modulation of inflammation that modulate cognitive decline. Efferent vagal stimulation has been shown to decrease TNF in inflammatory states,[26] and it could be conjectured that an anti-inflammatory effect could also extend to neurodegeneration.

In summary, there are several potential mechanisms by which RHR may influence cognitive function or be a marker of cognitive risk. RHR is a low-tech easily measured marker of cardiovascular risk in the general population, a vital sign already measured at almost every patient clinic visit encounter and potentially modifiable, but its relationship to cognitive function is not well established. Using prospective data from the population-based Atherosclerosis Risk in Communities (ARIC) study, we wish to investigate the associations of RHR with cognitive decline over 20-years, and determine whether any associations are independent of potential confounding factors such as age, sex, race, lifestyle factors (such as physical activity), SES factors, etc, and whether associations remained significant after further considering potential mediators such as blood pressure and inflammation.

5. Main Hypothesis/Study Questions:

1. To determine whether increased RHR at ARIC visit 2 is independently associated with *cross-sectional* cognitive performance assessed by the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), the Word Fluency Test (WFT), and a composite (global z-score) at ARIC Visit 2.

   Hypothesis: Increased RHR will be associated with lower global cognitive function, lower cognitive function on DSST and WFT (reflective primarily of vascular disease pathology) and on DWRT (test of memory, more reflective of Alzheimer's disease pathology) in the *cross-sectional* analysis of the participant cohort at ARIC Visit 2. This will be independent of demographic, lifestyle, SES, and vascular risk factors.

2. To determine whether elevated RHR is independently associated with *prospective* cognitive change assessed by DWRT, the DSST, the WFT, and a composite global z-score) over 20 years of follow-up (ARIC visit 2 through 5).

   Hypothesis: Elevated RHR will be associated with cognitive decline as assessed by the individual and the global test scores in *prospective* analysis over 20 years of follow-up. This will be independent of demographic, lifestyle, SES, and vascular risk factors.

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: ARIC visit 2, the time of first cognitive testing, will be the baseline for these analyses. Study design will be both cross-sectional (ARIC Visit 2: 1990-1992) and prospective (ARIC Visit 2: 1990-1992 through ARIC visit 5: 2011-2013).

Participants:
All participants with measured RHR in sinus rhythm and cognitive testing from ARIC Visit 2 will be included. We will exclude participants who have self-reported a prior stroke at visit 1 or had an incident stroke before ARIC visit 2. We will exclude participants who are missing key covariates in our primary model 2. Participants will also be excluded if their RHR (determined by ECG) was measured while in a heart rhythm abnormality such as atrial fibrillation/flutter, paced rhythm, or supraventricular tachycardia. In sensitivity analyses, we will exclude participants taking any AV-nodal blocking medications.

Exposure Ascertainment:

Resting heart rate was obtained from a standard supine 12-lead resting electrocardiogram (ECG) that was recorded at baseline. We will only consider RHR measurements for participants that were in sinus rhythm at the time of their ECG.

Heart rate, measured at visits 2, 4, and 5, will be examined in several ways including (1) quartiles based on overall distribution (2) clinical categories of <60, 60-80, 80-99, ≥100 bpm, and (2) as a continuous variable (per 10 bpm increase). We will also explore potential non-linear relationships using restricted cubic spline models. For cross-sectional analysis, we will consider RHR at visit 2. For prospective analyses, we will use a time-varying approach, and RHR will be updated at each subsequent visit (visit 2, 4, and 5).

Covariates: (measured at ARIC visit 2, unless otherwise noted):

Demographic factors: age (continuous, centered), age^2 (continuous, centered), sex (male; female), and race/center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks).

Socioeconomic and lifestyle factors: education (measured at visit 1, <high school; high school, GED, vocational school; college, graduate or professional school), smoking (never; former; current), alcohol consumption (current, former, never), physical activity by Baecke score[27] (measured at visit 1, scored 1 to 5): body mass index (<25 kg/m^2; 25-<30 kg/m^2, ≥30 kg/m^2).

Cardiovascular disease related factors: systolic blood pressure (continuous), use of antihypertensive medications, pulse pressure, diabetes (yes; no; defined as fasting glucose ≥126 mg/dl or non-fasting glucose ≥200 mg/dl or self-reported physician diagnosis or diabetes medication use); total cholesterol and HDL-cholesterol (continuous); use of lipid lowering medications, prevalent coronary heart disease (yes; no; defined by standardized criteria and physician adjudication).

Use of AV-nodal blocker medications

Use of beta-blockers, calcium channel blockers, amiodarone, and/or digitalis will be assessed from medication questionnaires. In primary analyses, we will adjust for use of AV-nodal blocking medications. In sensitivity analyses, we will repeat results only in participants who are not taking these medications.

Genetic factors: We will evaluate if results differ by APOE4 genotype, although this genotype linked to cognition is not known to also be linked to heart rate.

Outcome Ascertainments:

Cognitive function was assessed using the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), the Word Fluency Test (WFT), and a composite global z-score at ARIC Visits 2, 4, and 5.

The DWRT[28] is a test of verbal learning and recent memory. Participants were given 10 common nouns that they were asked to learn by using each word in one or two sentences. After a five-minute delay, participants were given 60 seconds to recall the 10 words. The score is the number of words correctly recalled.

The DSST[29] is a test of executive function and processing speed. Participants were asked to translate numbers to symbols using a key. The score (range 0-93) is the total number of numbers correctly translated to symbols within 90-seconds.

The WFT[30] is a test of executive function and language, and tests the ability to spontaneously generate words beginning with a particular letter, excluding proper names or places. Participants were given 60 seconds for each of the letters "F", "A", and "S". The score is the total number of words generated across the three trials.

Our primary outcome measure will be a global z-score, which is calculated by the average of the z-scores from each of the 3 individual cognitive tests within each study visit (at visits 2, 4, and 5) and standardized using the visit 2 global z-mean and standard deviation. We will also evaluate the association of RHR with each of the 3 individual cognitive tests.

Additionally, participants of the ARIC Neurocognitive Study underwent comprehensive neuropsychological testing at visit 5,[31] and the diagnosis of prevalent clinical dementia was adjudicated by one physician and one neuropsychologist based on the longitudinal cognitive testing performed at visits 2,4, and 5 and the complete neurocognitive battery of tests performed at visit 5.[31] In exploratory analysis, we will also consider the association of RHR (updated at each ARIC visit) with *prevalent adjudicated dementia or MCI* at ARIC visit 5. We will also consider RHR at visit 2 with *incident dementia* over follow-up (defined by adjudicated dementia present at Exam 5, informant interviews, and/or dementia ICD codes during hospitalizations).

Statistical analysis:

All analyses will be performed in accordance with the ARIC-NCS analysis working group recommendations (details can be found in the ARIC-NCS analysis plan).

Multivariable-adjusted mixed effect regression models with random intercepts and slopes will be used to assess the cross-sectional and longitudinal associations of RHR with cognitive function (global and individual z-scores).

In supplemental analyses, using relative risk regression, we will assess the association of RHR (time-varying, updated at each visit) with prevalent adjudicated dementia/MCI at visit 5. We will also consider RHR with incident dementia over follow-up.

We will examine the effects of attrition on our sample. Elevated RHR are correlated with increased cardiovascular risk factors, so we anticipate that participants with higher RHR at visit 2 will be more likely to withdraw or die before ARIC Visit 5. Also those with cognitive decline are also more likely not to return. Thus, for the prospective analysis, we plan to account for this attrition by using multiple imputation by chained equations (MICE) methods.[32]

For all analyses, we will use progressively adjusted models as follows:

Model 1 will adjust for demographic variables: age, sex, race/center, and education level

Model 2 will also adjust for behavioral variables including education, body mass index, smoking status, alcohol, and physical activity

Model 3 will adjust for Model 2 and cardiovascular factors including systolic blood pressure, pulse pressure, use of hypertension medication, diabetes, HDL cholesterol, total cholesterol, cholesterol lowering medications, and history of prevalent CAD.

Model 4 will additionally adjust for use of AV-nodal blocking medications

Model 5 will additionally adjust for APOE4 genotype

Modifiers:

We will assess for age (above below 60), sex, race, physical activity status (high vs low), and APOE4 genotype (yes/no) as potential effect modifiers using Walds Tests. We will performed stratified analyses if significant interactions are found.

Sensitivity analysis:

We will exclude participants taking AV-nodal blocking medications at any visit.

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

Yes – Cognitive research, but we believe that this is directly related to the impact of CVD risk factors.

b. If Yes, is the author aware that the file ICTDER02 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? **__X__ Yes ____ No**
(This file ICTDER02 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**

We will assess differences by APOE4 genotype.

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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)?

#2433 Heart Rate Variability and its Association with Cognitive Decline over 20 years: The ARIC Neurocognitive Study (ARIC-NCS). This proposal is looking at HRV assessed by time domain measures of HRV [SDNN (ms) – standard deviation of all normal RR intervals] and r-MSSD (ms) [root mean square successive difference, the square root of the mean of the squared differences between adjacent normal RR intervals], not RHR per se. We have included (and discussed with) Alvaro Alonso, the senior author on that proposal, here to ensure no overlap. We have also included the first author Faye Norby.

#2294 Changes in heart rate over time and its relation to cardiac structure and function and prognosis in ARIC study. That proposal is a different outcome. We are looking at cognitive decline over 20 years.

#2175 Midlife blood pressure and 20-year cognitive change: The ARIC Neurocognitive Study. The exposure here is blood pressure, we have a different exposure. We have included first author Rebecca Gottesman here to ensure no overlap.

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

We will use some data from the ARIC-NCS at visit 5. We have included several ARIC-NCS investigators to participate in this proposal.

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _*ARIC-NCS*_____)

___ B. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

12. 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.

Understood

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