ARIC Manuscript Proposal # 3202

PC Reviewed: 7/10/2018	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Clinical Determinants of Healthy Cardiovascular Aging: Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Determinants of CV Aging

2. Writing Group:
Writing Group Members:

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

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3. Timeline: Analysis is anticipated to begin as soon as approval is obtained. The manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation is anticipated to take place within one year of approval of the proposal.

4. Rationale:
Aging is one of the strongest risk factors in the development of atherosclerotic cardiovascular diseases (ASCVD) as well as heart failure (HF). In previous epidemiological studies, adults 65 years or older accounted for over 80% of all cardiovascular disease (CVD) related deaths in the United States (Lloyd-Jones DM, Circulation. 2009 Jan 27;119(3):e21–181). This is likely a result from age-related physiologic changes of the cardiovascular system and the cumulative effects of risk factors over time. Conversely, healthy cardiovascular aging may be thought of as aging without the clinical manifestation of CVD. The determinants of healthy cardiovascular aging likely involve a combination of genetic and environmental factors. With respect to the latter, important elements of ideal cardiovascular health, as defined by the American Heart Association, include 4 lifestyle factors – smoking (never or quit >12mo ago), body mass index (BMI) (<25kg/m^2), physical activity (≥150min/wk moderate intensity or ≥75min/wk vigorous intensity or combination), diet (healthy diet score 4-5 components), as well as 3 risk factors – total cholesterol (<200mgdL), blood glucose (<100mg/dL), blood pressure (<120/<80mmHg) (Lloyd-Jones DM, Circulation. 2010;121:586-613). However, even among a “healthy” population without clinical CVD, these factors may play a role in driving the pathogenesis that lead to sub-clinical disease (Fretz A, Am J Cardiol. 2018 Feb 15;121(4):430-436).

Serum biomarkers serve as a potential window to the pathophysiologic processes in the development of CVD. Biomarkers, such as troponins in myocardial infarction (Amsterdam EA, Circulation.2014;130:2354-2394) and brain natriuretic peptide (BNP) in heart failure exacerbation (Yancy CW, Circulation. 2017;000:e000–e000. DOI: 10.1161/CIR.0000000000000509), have long been used in the setting of acute cardiovascular events.

Measurement of biomarkers in asymptomatic adults can be a marker of subclinical cardiac damage, stress, fibrosis, and inflammation in older adults. High sensitivity cardiac troponins T (hs-cTnT) has been shown to be a sensitive biomarker for subclinical myocardial damage (Reichlin T, N Engl J Med. 2009 Aug 27;361(9):858-67) and detectable levels via high sensitivity assays are associated with incident coronary heart disease (CHD), HF and death in individuals without known CVD (Sauders JT, Circulation. 2011 Apr 5; 123(13): 1367–1376). Temporal increases in hs-cTnT are independently associated with CHD, cardiovascular mortality and HF (deFilippi CR, JAMA. 2010 Dec 8; 304(22): 2494–2502; McEvoy JW, JAMA Cardiol. 2016 Aug 1; 1(5): 519–528).BNP is a hormone secreted by ventricular cardiomyocytes in response to increased ventricular wall stress (Kim HN, Circulation. 2011 May 10;123(18):2015-9).

Circulating serum levels of N-terminal prohormone brain natriuretic peptide **(**NT-proBNP), the prohormone to BNP, have been found to be elevated in symptomatic and asymptomatic individuals with left ventricular dysfunction (Hartmann F, Circulation. 2004 Sep 28;110(13):1780-6; Macheret F, J Am Coll Cardiol. 2011 Mar 22;57(12):1386-95). Incremental levels of NT-proBNP have been associated with increased risk of incident HF in numerous cohort studies including the ARIC study (Ndumele CE, Circulation. 2016 Feb 16;133(7):631-8) (Choi EY, Circ Heart Fail. 2012 Nov;5(6):727-34).

Many individuals live to very old age and never develop CVD. Biomarkers related to cardiac function such as NT-proBNP and hs-TnT increase with age. Older adults as in ARIC study visit 6 can enable us to identify which individuals do not develop clinical symptoms of MI, stroke, or HF and also continue to have "normal" levels of hs-TnT, NT-proBNP. With data collected over the previous 3 decades, we will be able to identify major midlife factors that lead to "healthy cardiovascular aging" and examine the association between healthy cardiovascular aging

The aim of the proposed study is to identify how clinical and lifestyle factors at midlife (in particular modifiable factors) and their trajectories over time are associated with healthy cardiovascular aging.

5. Main Hypothesis/Study Questions:

Hypothesis: Midlife clinical and lifestyle factors as well as their trajectories are associated with healthy cardiovascular aging.

Study questions:

1. Among older adults without a history of clinical cardiovascular disease, what proportions of the population meet criteria (based on absence of CVD, subclinical CV damage and high physical function) for healthy cardiovascular aging?

2. Which identifiable major midlife clinical and lifestyle factors are associated with “healthy cardiovascular aging,” defined as the absence of clinical CVD events or subclinical CVD and adequate functional status?

3. What is the longitudinal impact (trajectory) of clinical and lifestyle factors on healthy cardiovascular aging?

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 methodological limitations or challenges if present).

Study Design:
Data from the prospective cohort study ARIC up to visit 6 will be used to identify major midlife factors that are associated with *healthy* versus *non-healthy* cardiovascular aging.

Health cardiovascular aging – Individuals in ARIC visit 6 will be categorized as having healthy cardiovascular aging if they meet the following criteria:

1) No known history of prevalent cardiovascular disease (MI, revascularization, HF, peripheral arterial disease, cerebral vascular disease).
2) Lower biomarker evidence of subclinical CVD: For NT-proBNP, we will use a relative cutoff of less than or equal to 91pg/mL for male individuals and less than or equal to 110pg/mL for female individuals, which corresponds to the lowest tertile in the study population at visit 6 for the respective genders. For hs-cTnT, we will use a cutoff of less than or equal to 13ng/L for male individuals and less than or equal to 9 for female individuals, which again represents the lowest tertile of hs-cTnT measurements in the study population at visit 6 for the respect genders. Participants must satisfy both cutoffs to meet the biomarker criteria. We elected to used relative cutoffs instead of hard cutoffs (ie lowest quantifiable biomarker levels) as too few participants at visit 6 would have met a more stringent biomarker criteria.
3) High physical functioning as assessed by ability to achieve average speed of ≥1.0 m/s (2 trials) walking 4 m at normal pace. As gait speed is correlated to height, we will adjust for height in our analysis.

Non-healthy cardiovascular aging - Patients will be classified as non-healthy cardiovascular aging if, at ARIC visit 6, criteria for healthy cardiovascular aging as outlined above are not met. Since we are interested in healthy cardiovascular aging, those patients who were recruited in visit 1 but who died before visit 6 will be able to contribute to the analysis as representing non-healthy cardiovascular aging. We also propose to perform separate analyses that incorporate 1) patients who died from cardiovascular causes and 2) patients who died from all causes prior to visit 6 as part of the non-healthy cardiovascular aging group. Cardiovascular mortality is defined as death attributable to MI, HF, or stroke.

Study measures and Statistical Analysis:

For the included patients, data on risk factor and lifestyle metrics (as outlined below) from ARIC visit 1 will serve as the baseline exposures. The same measures from clinic visit 2-6 will also be assessed in order to evaluate for trajectories of exposure. For patients who died prior to visit 6, data up to the most proximal visit to death will be used.

Assessing for determinants of healthy cardiovascular aging

First, association between midlife factors (risk factors and lifestyle metrics from clinic visit 1) and healthy cardiovascular aging will be assessed in univariate logistic regression models. Multivariable regression models will then be constructed to identify major predictors of healthy cardiovascular aging. Tentatively, we propose the following models:

1) Ideal Cardiovascular Health Components (Life's Simple 7 score) - Study measures for lifestyle and risk factors are based off previous AHA definition of ideal cardiovascular health (Lloyd-Jones DM, Circulation. 2010;121:586-613). These measures include

smoking, body mass index, physical activity, healthy diet score, blood pressure, fasting glucose, and total cholesterol. Based on the Life's Simple 7 score (LS7), metrics will be assessed and scored as ideal (2), intermediate (1) and poor (0). Total score will be classified as optimal (10-14 pts), intermediate (5-9 pts), and poor (0-4 pts).

2) An individual risk factor and lifestyle metrics model – In this model, we propose to adjust for the individual variables in the LS7 in addition to LDL-cholesterol, HDL-cholesterol, triglyceride level, use of cholesterol-lowering medication (yes or no), use of antihypertensive medication (yes or no), hemoglobin A1c, estimated glomerular filtration rate.

Assessment of trajectories

To better understand how time-varying exposures between visits 1 and 6 is associated with cardiovascular health later in life, we will identify trajectories of these lifestyle/clinical factors, assess for subgroups within the study population with similar trajectories of risk factors and determine the association of these subgroups with healthy versus non-healthy cardiovascular aging. The lifestyle/clinical factors that we are interested in analyzing are: overall LS7 score, BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglyceride, fasting blood glucose, hemoglobin A1c, eGFR and current smoking.

Latent class trajectory analysis will be used to identify subgroups with similar trajectory for each of the above variables. Continuous data will be modeled using a censored normal distribution while binary data will be analyzed using a logistic model. The optimal model fit will be determined by adjusting for different numbers of trajectories classes and trajectory shapes – ie linear, quadratic, cubic. To do this, we will start with 5 trajectory classes and try to find the optimal model with 1–7 trajectory classes using Bayesian Information Criterion (BIC) to guide improvement in the model fit. We will then repeat analyses adjusting for trajectory shapes to determine the best parsimonious model based on BIC. Individual participants will then be grouped into each of the trajectory classes based on the calculated posterior predicted probabilities for belonging to each group. Finally, to determine the association of these trajectory classes to healthy cardiovascular aging, we will perform logistic regression analyses with the trajectory classes for each of the lifestyle/clinical factors serving as exposures and healthy cardiovascular aging as the dependent variable. Each analysis will be adjusted for age, sex, race, education level and the other lifestyle/clinical factors.

Accounting for drop-out and no attendance at visit 6

To account for drop out and no attendance, we will employ an inverse probability of attrition weighting (IPAW) approach to account for potential informative missingness effects. In addition, we will employ the use of multiple imputation by chained equations (MICE), a statistical technique whereby missing values are replaced with plausible values. MICE is carried out through a series of univariate imputation prediction models in which each variable containing missing data is regressed on all other variables, including previous imputations of the missing variables.

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.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)?

Relation of Lifestyle Factors and Life's Simple 7 Score to Temporal Reduction in Troponin Levels Measured by a High-Sensitivity Assay (from the Atherosclerosis Risk in Communities Study)

Fretz A, Am J Cardiol. 2018 Feb 15;121(4):430-436

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study *
___ 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-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.