ARIC Manuscript Proposal # 3649

PC Reviewed: 6/9/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Mid-life, late-life, and 30-year cumulative exposure to traditional cardiovascular risk factors and zero coronary artery calcium: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Traditional CVD risk factors and zero CAC

2. Writing Group

Writing group members: Frances Wang, Shoshana H. Ballew, Aaron Folsom, Lynne Wagenknecht, Candace M. Howard-Claudio, Josef Coresh, Matthew Budoff, Michael Blaha, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **FW [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: These analyses will use existing ARIC data; thus, manuscript preparation will be conducted over the next 12 months.

4. Rationale:

Although age is one of the strongest risk factors of cardiovascular disease, vascular disease burden is very heterogeneous across older adults. Traditionally, studies have focused on the unhealthy end of the vascular aging spectrum, namely adverse outcomes such as cardiovascular death and myocardial infarction. However, the field of public health is shifting towards aiming to optimize cardiovascular health in addition to avoiding adverse events (eg. American Heart Association 2030 goals to extend health-adjusted life expectancies).[1]

Knowledge of cardiovascular health profiles linked to healthy vascular aging is important for understanding how to optimize cardiovascular health and extend healthy life expectancy in the population. Although it seems that predictors of healthy vascular aging will merely be the opposite of cardiovascular risk factors, this may not be the case when we evaluate the synergistic or longitudinal effect of risk factors.[2,3] Thus, information on what constitutes an optimal cardiovascular health profile is currently incomplete. Additionally, associations between long-term exposures to risk factors and ideal coronary artery health need to be better understood.

Coronary artery calcium, a marker of atherosclerotic plaque burden, is a strong predictor of cardiovascular risk in the general population and an established marker of arterial age.[4-7] Zero CAC, the absence of calcified plaque in the coronary arteries detected by non-contrast CT, is a powerful protective marker with a highly positive 10-year prognostic outlook, even in the 75+ age group, and a valuable parameter for assessing healthy vascular aging in older adults.[8,9] Studies on health vascular aging defined by zero CAC are limited. In one study, the risk factor burden in those with persistent zero CAC was found to be lower than for those who develop CAC.[2] However, the contribution of individual risk factors and their long-term (eg. >10 year) exposures to zero CAC in older adulthood have not been examined.

Leveraging over 30 years of data on exposure to time-varying traditional cardiovascular risk factors from the ARIC study, this study will assess the association between middle age, older age, and cumulative risk factor exposures with zero CAC at older age. Upon completion of this study, we will understand optimal cardiovascular risk factor profiles for healthy vascular aging, which may have implications on health promotion or clinical care of traditional cardiovascular risk factors throughout the life span.

5. Main Hypothesis/Study Questions:

Hypothesis 1.1: *Mid-life risk factors will be more strongly associated with zero CAC than late-life factors.*
Hypothesis 1.2: *By analyzing 30-year exposures, we will identify the relative importance of traditional cardiovascular risk factors for healthy vascular 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 methodologic limitations or challenges if present).

Study Design: Cohort study from ARIC Visit 1 to 7

Inclusion Criteria:

- Black and white ARIC participants who underwent coronary artery calcium scan at Visit 7

Exclusion Criteria:

- Prevalent coronary heart disease at Visit 7 (by design of the ARIC CAC ancillary study)
    - However, those with prevalent CHD will be included in a secondary analysis.

Exposures:

Traditional cardiovascular risk markers:

- Blood pressure
- Glucose
- Smoking
- Cholesterol

Covariates:

From Visit 7 data, we will consider:

- Sociodemographics: age, race, sex, education, income
- Physical information: body mass index
- Lifestyle: smoking status
- Clinical Factors: obesity, use of hypertensive, diabetes, and cholesterol lowering medication, family history of coronary artery disease
- Physical activity

Statistical analysis plan:

We will summarize the characteristics of the study population, all participants who underwent CAC scanning at ARIC Visit 7, by sex.

Middle-age risk factor exposure and healthy vascular aging

Using multivariable logistic regression to evaluate the association between middle age risk factors and zero CAC, we will use exposure data from ARIC Visit 1 in 1987-1989 when participants were age 45-64 and evaluate the strength of association between exposure to each cardiovascular risk factor (blood pressure, glucose, smoking, cholesterol) with the outcome of zero CAC during ARIC Visit 7 (2018-2019).

Older-age risk factor exposure and healthy vascular aging

Then, we will repeat the analysis to evaluate the association between risk factors at older age and zero CAC outcomes. We will use cardiovascular risk factors ARIC Visit 5 from 2011-2013 when participants were aged 66-90 as the exposure with zero CAC during ARIC Visit 7 as the outcome.

Cumulative risk factor exposure and healthy vascular aging

For the assessment on the association between cumulative exposures from middle to older age with zero CAC outcomes, we will leverage all risk factor exposure data before the Visit 7 CAC outcomes, ARIC Visits 1 to 6 (2016-2017), to evaluate cumulative risk factor burden in two ways.

First, we will evaluate total years of exposure to a high risk state, exposure-years, for each risk factor. Using hypertension as an example, we will assess the number of years in a hypertensive state defined by blood pressure >130/80 over the period of ARIC Visit 1-6 to calculate hypertension-years for each Visit 7 participant (**Figure 1**). This method for examining cumulative exposures is able to capture total exposure to high risk conditions over time; however, continuous factors such as blood pressure must be treated categorically with the necessity of defining cut-offs for high-risk thresholds.

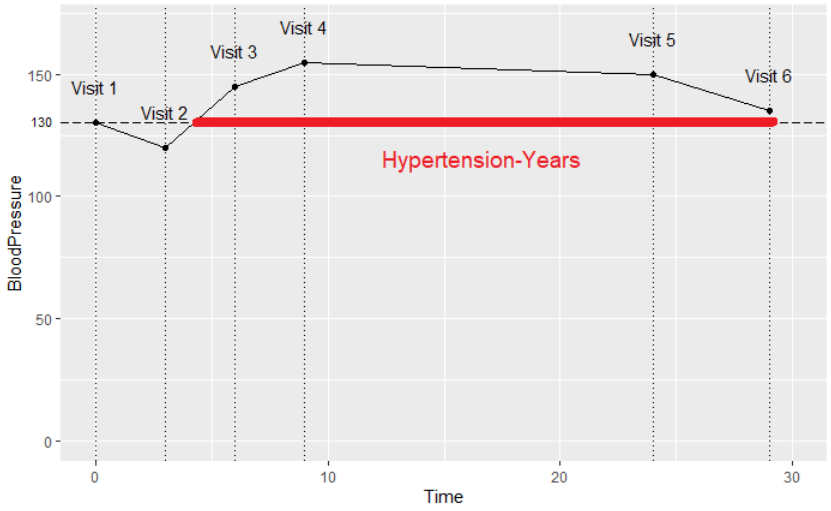

Figure 1. Example of estimating total hypertension-years using a systolic blood pressure cutoff of 130 mmHg.

Second, we will also evaluate a weighted average of exposure to each cardiovascular risk factor over time. Extending the earlier blood pressure example to the second method of assessing cumulative exposures, we will perform a weighted average of blood pressure across ARIC Visit 1-6 (**Figure 2**). A strength of this method is that it is able to capture exposures in a continuous manner, unlike the first methods; however, other than through this averaged number, it is not able to capture the duration of total exposure to the high risk state. For both methods of assessing cumulative exposure, multiple imputation by chained equations (MICE) will be used for missing observations in the analysis (eg. if a participant missed a study between Visits 1-6).

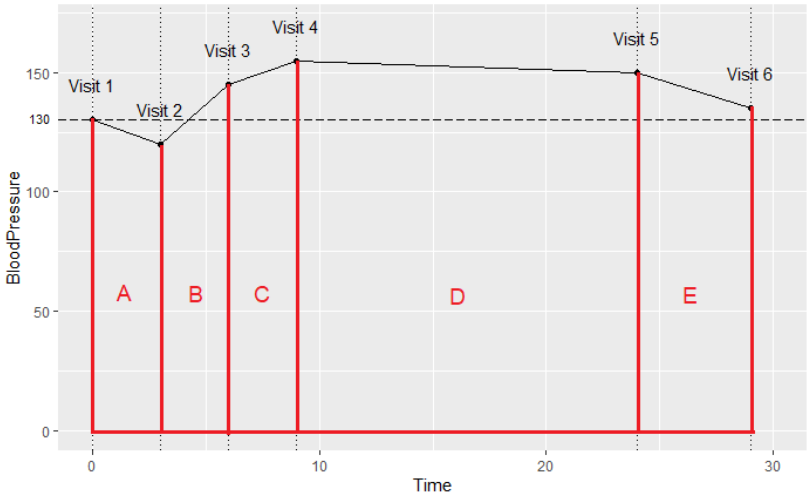

Figure 2. Example of estimating time-weighted average of systolic blood pressure.
Weighted average = ∑ Areas(A:E)/ΔT

Secondary and sensitivity analyses

We will conduct a few secondary analyses. First, we will repeat the analysis including individuals with prevalent CHD at Visit 7 in the CAC>0 category, comparing characteristics of individuals with zero CAC to those with CAC>0 or prevalent CHD. We will also repeat the analysis with an expanded definition of low CAC using cutoffs of CAC 0-9 and CAC <25 percentile instead of the conservative zero CAC as the outcome. Next, we will perform these analyses using the outcome of adverse vascular aging defined as high CAC (CAC>300[10], CAC>1000[10], CAC>75 percentile[11]). Additionally, we will examine the association between mid-life, late-life, and 30-year cumulative CVD risk factors with continuous CAC [ln(CAC+1)] using similar methods noted above and multivariable linear regression models instead of logistic regression models. Another secondary analysis will involve using inverse probability weighting to account for attrition during the 30-year follow-up using weights from all ARIC participants eligible for CAC in Visit 7 to evaluate the potential effect of selection bias (from differential characteristics between individuals who agreed to undergo CAC scanning and were part of the study versus those who refused) on our observed associations.

As a sensitivity analysis, we will exclude individuals at baseline with prevalent stroke, atrial fibrillation, and heart failure. Another sensitivity analyses will include stratifying analyses by medication usage (i.e, statins and antihypertensives for the analyses centered on cholesterol and blood pressure, respectively). Additional subgroup analyses will include stratifying by family history of coronary artery disease, sex, and race.

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

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 existing ARIC manuscript proposals for assessing the relationship between midlife proteomics and CAC outcomes in older adults or on related topics.

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

_X_ A. primarily the result of an ancillary study (list number* _2016.06_)

___ 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.

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