ARIC Manuscript Proposal #3901

PC Reviewed: 7/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Polygenic Coronary Heart Disease Risk with CAC=0 and CAC >1000 in Adults ≥75 Years Old: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Polygenic Risk & CAC in Old Age

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. OD [please confirm with your initials electronically or in writing]

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3. Timeline: Since data is available, manuscript preparation is expected to be complete within 12 months after approval.

4. Rationale:

Approximately one in eight (30.1 million) United States adults will be 75 years of age or older by 2040[1]. In the setting of an aging population, the focus of public health and clinical research has expanded beyond disease management and prevention toward improving long-term healthy aging in the population, as noted for example in the American Heart Association 2030 Impact Goal of extending healthy life expectancy[2].

The absence of coronary artery calcium (CAC=0) has been identified as a marker of healthy vascular aging[3], conferring a highly favorable 10-year prognostic outlook even among adults ≥75 years old. Likewise, CAC=0 has also been associated with relative protection from non-cardiovascular chronic diseases, including cancer, and thus may reflect a more global healthy aging phenotype[4,5]. Conversely, an extremely elevated CAC (≥1000) is increasingly being appreciated as an adverse vascular aging phenotype, as the presence of CAC ≥1000 substantially increases the risk for atherosclerotic cardiovascular disease (ASCVD), non-ASCVD disease, and all-cause mortality regardless of age[6,7]. However, prediction of these two CAC phenotypes (0 and ≥1000) at older age remains elusive, with lifestyle factors and traditional risk factors incompletely describing the prevalence of these phenotypes in adults >75 years of age.

Indeed, there is substantial heterogeneity between individual ASCVD risk factors and CAC burden. For example, approximately 40% of individuals with diabetes and/or metabolic syndrome have CAC=0 through 60 years of age[8], whereas nearly one-third of individuals with a mean age of 57 years and zero traditional risk factors develop incident CAC[3]. While a lower ASCVD risk factor burden certainly increases the probability of healthy vascular aging throughout the life course and vice-versa, the significant heterogeneity between traditional ASCVD risk and the presence/absence CAC warrants the investigation of more fundamental mechanisms (i.e. genetics) underlying arterial aging phenotypes.

Genomic risk assessment of coronary heart disease (CHD) may be a particularly useful approach. Meta-analyses of genome-wide association studies have identified numerous and common single nucleotide polymorphisms (SNPs) that robustly associate with CHD[9]. Although the effect size of each variant is small, collectively they work in aggregate (polygenic), together with the contribution of lifestyle, to influence the manifestation and expression of CHD[10]. Prior studies have assessed the utility of CHD polygenic risk scores (PRS) for predicting incident CAC and downstream ASCVD outcomes[11–14]; however, this work has largely been applied in middle age populations.

Overall, CHD-based PRSs have inconsistently improved risk prediction of ASCVD outcomes[11–14], which may be due to the fact that the value of genomic information is modified by age[15]. Genetics may provide prognostic information more effectively early versus later in life, prior to the accumulation of environmental[16] and clinical risk factors which may have a larger magnitude relative association with subclinical atherosclerosis burden as individuals age. While middle-aged adults with a higher genetic predisposition to CHD experience a larger risk reduction associated with adherence to a healthy lifestyle compared to individuals with a lower genetic risk[16], the interaction of genetics, physical activity, and diet among older individuals remains incompletely understood. Identifying the association of a CHD PRS with CAC-based vascular aging phenotypes in older persons can provide insight into the pathobiology of vascular aging and atherosclerotic plaque development, considering the contributions of genetics vs. lifestyle vs. traditional risk factors. Additionally, this proposal has implications for identifying a potential age-specific utilization of genomic information in CHD risk stratification.

5. Main Hypothesis/Study Questions:

*A PRS for CHD will provide a modest clinically meaningful improvement beyond that of lifestyle behaviors and traditional ASCVD risk factors for identifying older persons with healthy vascular aging (CAC=0) or adverse vascular aging (CAC ≥1000).

* There will be moderate modification of the strength of association for the cumulative burden of lifestyle behaviors and traditional ASCVD risk factors with CAC by the PRS.

What is the prevalence of CAC=0 (or CAC ≥1000) in very high PRS with little to no risk factors?
What is the prevalence of CAC=0 (or CAC ≥1000) in low PRS with high 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: This is a (shifted timed) prospective study that leverages time-weighted cumulative measures of lifestyle and traditional risk factors (Visits 1-7) as well as ARIC genetic data and CAC outcomes at Visit 7.

Inclusion criteria:
- ARIC participants with sufficient genetic data to calculate the CHD PRS
- Underwent CAC scan at Visit 7

Exclusion criteria:
- Inability to calculate the polygenic risk score for CHD[9]
- No information on CAC scores, which includes those with prevalent coronary heart disease at Visit 7 (by design of the ARIC CAC ancillary study).
- Missing key covariates

Exposures:
Polygenic risk score for CHD as derived by Khera et al.[9]

Primary analyses will be conducted among white and black ARIC participants together. Subgroup analyses will then be conducted separately among individuals of European and African ancestry.

A PRS based on over six million genetic variants was previously developed using LDPred[9]. PRS scores will be computed among ARIC participants using the per-allele weights provided by Khera et al. The score will be analyzed both as a continuous and categorical variable. As a categorical variables, participants who scored in the lowest 20th percentile will be considered to have low genetic susceptibility, while participants who scored in the top 20th percentile will be considered to have high genetic susceptibility. All other participants will be considered to have intermediate genetic susceptibility.

Outcomes (collected at Visit 7): CAC

- Healthy vascular aging (Primary Outcome)

Primary definition: CAC 0

Alternative definitions: CAC 0-9, CAC < 25th percentile

- Adverse vascular aging (Secondary Outcome)

Primary definition: CAC 1000+ (extensive coronary calcification)

Covariates

- Sociodemographic: age, race, sex, education, income
- Anthropometric: body mass index
- Lifestyle: physical activity and diet

    Physical activity will be measured through the Baecke questionnaire[17]. Adequate physical activity will be defined according to current guidelines and Life's Simple 7 definition[18] as ≥150 min/week of moderate physical activity or ≥75 min/week of vigorous physical activity

    *Diet will be measured through the 66-item Harvard food frequency questionnaire[19]. Optimal diet will be defined as adherence to 4 out of 5 components of a healthy diet pattern, defined by Life's Simple 7 (≥4.5 cups/day of fruits and vegetables, ≥2 servings/week of fish, ≥3 servings/day of whole grains, no more than 36 oz/week of sugar sweetened beverages, <1500 mg/day of sodium) [18].

- Clinical Factors: total cholesterol, HDL-C, hypercholesterolemia, systolic blood pressure, diastolic blood pressure, hypertension, glucose, diabetes, triglycerides, hypertriglyceridemia, smoking status, obesity, use of blood pressure-, lipid-, and/or glucose-lowering lowering medication, family history of coronary heart disease, glomerular filtration rate

*For lifestyle factors, anthropometric, and clinical ASCVD risk factors, we will use cumulative-based estimates from Visits 1-7. These cumulative-based estimates will be modeled in two different ways (A and B). Using total cholesterol and hypercholesterolemia as an example, we will calculate the time-weighted average of total cholesterol across Visits 1-7 (A) as well as the number of hypercholesterolemia-years (total cholesterol ≥200 mg/dL) that an individual has the presence/absence of LDL-C ≥100 mg/dL across Visits 1-7 (B).

As a sensitivity analysis, we will also adjust for raw lifestyle and ASCVD risk factor variables leveraging only cross-sectional measures at Visit 7.

Statistical analysis plan:

Baseline characteristics of study participants will be summarized and stratified according to low versus intermediate versus high polygenic CHD risk as Table 1.

Healthy Vascular Aging

Multivariable logistic regression will be utilized to evaluate the relationship between the CHD PRS and healthy vascular aging in older adults, defined as CAC=0. For all logistic regression models listed below, we will model the PRS as the independent variable and CAC=0 as the dependent variable. Clinical risk factors (covariables) will be tested continuously and categorically.

- Model 1: demographic variables (age, sex, race, visit center)
- Model 2: Model 1 + cumulative burden of lifestyle behaviors (physical activity and diet)

- Model 3: Model 2 + cumulative burden of cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, hypertriglyceridemia, family history of coronary heart disease, diabetes) + kidney function (glomerular filtration rate)

Additionally, we will replicate these methods using an expanded definition of low CAC using CAC 0-9 and <25th percentile, rather than zero CAC as the marker for healthy vascular aging. As a sensitivity analysis, we will further exclude individuals at baseline with prevalent stroke, atrial fibrillation, and heart failure.

Adverse Vascular Aging:
We will apply the same statistical modeling approach listed above to the adverse vascular aging phenotype. We will repeat these genetic analyses to assess the association of the continuous CHD PRS with adverse vascular aging (CAC ≥1000), beyond traditional risk factors and lifestyle variables measured in old age. Comparisons will be made for the strength of association for the PRS with healthy vascular aging versus adverse vascular aging.

Genetics of Continuous Coronary Artery Calcium:
We will examine PRS associations with continuous CAC [ln(CAC+1)] leveraging multivariable linear regression models while using a similar methodological approach as noted above.

Contributions of Lifestyle Behaviors and Traditional Risk Factors with Vascular Aging
Lastly, we will assess whether lifestyle and traditional risk factors modify the relationship of the CHD PRS with CAC=0 and/or CAC ≥1000. In particular, we will test whether the strength of association of lifestyle behaviors and normal values of traditional risk factors with CAC=0 and/or CAC ≥1000 varies across low, intermediate, and high polygenic risk for CHD. Multivariable model 3 will be applied to the specific CHD PRS groups below:
- Low polygenic CHD risk (bottom 20th percentile of CHD PRS)
- Intermediate polygenic CHD risk (middle 60th percentile of CHD PRS)
- High polygenic CHD risk (top 20th percentile of CHD PRS)

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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? __X__ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ 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/mantrack/maintain/search/dtSearch.html

___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 PRS for CHD and CAC outcomes in very old age adults or on related topics.

Among the proposal from the last few years, #2742 and #3616 are the most related regarding genetics. The biggest differences between the proposals are that #2742 and #3616 focuses on atherosclerotic cardiovascular disease (ASCVD) and CHD as an outcome and that #2742 and #3616 aim to describe differences between the performance of a genetic risk score between European and African Americans. This proposal will uniquely evaluate PRS for CHD versus traditional risk factors in very old age for long-term healthy versus unhealthy vascular aging, assessed using coronary artery calcification (CAC).

Other ARIC manuscript proposals related regarding CAC scoring include:
Proposal #3649 - 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
Proposal #3566 - Association of coronary artery and extra-coronary calcification with reduced physical function and frailty in older adults: The Atherosclerosis Risk in Communities Study
Proposal #3582 - The association of regional pulse wave velocity with vascular calcification: The Atherosclerosis Risk in Communities (ARIC) Study
Proposal #3728 - Physical activity and calcification of coronary arteries, aorta, and cardiac valves: The Atherosclerosis Risk in Communities (ARIC) Study

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* AS2016.06, AS2017.27**)**

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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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