ARIC Manuscript Proposal #3817

PC Reviewed: 4/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Coronary Artery Calcium Scores of Zero and ≥1000 and Aging Phenotypes: The Atherosclerosis Risk in Communities(ARIC) study

b. Abbreviated Title (Length 26 characters): **CAC and aging phenotypes**

2. Writing Group:

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

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3. Timeline: Analyses and manuscript preparation will be completed over the next 6 months.

4. Rationale:

Coronary artery calcium (CAC) is an important marker of atherosclerosis that has been found to strongly predict coronary heart disease events, cardiovascular disease events, and all-cause mortality.[1,2] CAC scores of 0 have been proven to have high negative predictive value for events and mortality, particularly among middle-aged adults.[3,4] Importantly, CAC=0 is also associated with relative protection from non-cardiovascular chronic diseases, and thus may be thought to be a vascular marker of overall healthy aging- a process that starts early in life and is generally defined as preserved physical, social and mental well-being through life transitions.[5] Healthy aging is largely dependent on 2 major components: an innate capacity comprised of the interplay between genetics, risk factor exposure and clinical conditions; and environmental exposure.[6,7]

Although some amount of CAC is common with aging, 10-20% of individuals go their whole lives without developing any CAC.[8] Notably, a study done among the Tsimane people of Bolivia- a group with hunter-gather diet, high physical activity, and minimal traditional cardiovascular risk factors- showed that among adults 75 years and older, 65% had no CAC.[9] As CAC scores of 0 are associated with significantly reduced incidence of both cardiovascular and non-cardiovascular events,[3,10,11] exploring the breadth and correlates of this phenotype among older adults will add value to further defining healthy cardiovascular and non-cardiovascular aging.

Conversely, extremely elevated CAC scores ≥1000 have been associated with substantially increased risk of cardiovascular disease (including coronary heart disease), non-cardiovascular disease, and all-cause mortality, warranting aggressive preventive therapy.[12] CAC≥1000 is increasingly considered to represent an unhealthy vascular aging phenotype. As such, in this proposed analysis, we will use CAC≥1000 to explore the breath and correlates of CT-defined unhealthy aging.

Evaluating these phenotypes is especially important among older adults, for whom limited information is available on the prevalence and implications of zero and low CAC scores for individuals aged>75 years. With an average life expectancy of approximately 79 years in the U.S., 16.5% of the population is comprised of older adults aged >65 years- a percentage projected to reach 22% by 2050.[13,14] While much of the research findings on imaging derived vascular aging done in adults are extrapolated to this demographic group, they have unique characteristics and clinical profiles, and thus research focused on this age group is necessary.

In line with the goals of the United Nations Research Agenda on Ageing for the 21st century to prioritize research into the healthy determinants of aging,[15]more research is required to define aging phenotypes in this group. Thus, we propose to use the ARIC study to describe the degree to which healthy (CAC=0) and unhealthy (CAC≥1000) CT-derived aging phenotypes correlate with other characteristics, specifically across 7 key domains of aging, detailed below.

5. Main Hypothesis/Study Questions:

Hypotheses:

- A CAC score of 0 will be strongly associated with favorable values of other markers of healthy aging and cardiovascular risk

- Extremely elevated CAC scores ≥1000 will be associated with markers of adverse aging and cardiovascular risk

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 will primarily be a cross-sectional analysis of extant data from ARIC visit 7. However, as 2 variables of interest (pulse wave velocity and ankle brachial index) were collected at either visit 6 or 7, we would include information about these from visit 6.

Inclusion criteria: All ARIC participants who have available information on their CAC score.

Exclusion criteria:

- Individuals with prevalent coronary heart disease at visit 7(by design of the ARIC CAC ancillary study), or no information on CAC scores.
- Individuals with missing variables of interest

Independent variable: CAC score

Dependent variables:

- 7 domains of aging:
    1. **Cognitive function**: NCS cognitive status diagnosis (modeled as a categorical variable)
    2. **Vessel condition**: Right and left ankle-brachial index (ABI) (modeled as a continuous variable), right and left carotid-femoral pulse wave velocity(PWV) (modeled as a continuous variable)
    3. **Physical function**: Short Physical Performance Battery (SPPB) summary score (modeled as a continuous variable and as a categorical variable)
    4. **Physical strength**: Grip strength, mean of 2 trials (modeled as a continuous variable)
    5. **Physical activity**: Physical activity during leisure time excluding sport (modeled as a continuous variable)
    6. **Hearing loss**: Hearing loss category based on pure tone audiometry (modeled as a categorical variable)
    7. **Pulmonary function:** Predicted forced vital capacity (FVC) (modeled as a continuous variable)
- **Potential confounders for multivariable analyses:** sociodemographic variables (age, sex, race*center), statin therapy

Other variables of interest (For analysis of baseline characteristics)*: Comorbidities (History of diabetes, dyslipidemia, and hypertension); Medication use for cholesterol lowering, hypertension, and diabetes; Lipids (Low density lipoprotein cholesterol, Triglycerides, High density lipoprotein cholesterol, Total cholesterol), Body mass index (BMI), Smoking history, Alcohol use pattern.

* These variables will not be included in our primary multi-variable analyses because we are primarily interested in exploring the potential physiologic link between CAC and the pre-specified aging phenotypes regardless of comorbidities that are often rife in our population of interest.

Data analysis plan:

- CAC will be categorized as 0, 1-999 (reference category as regular aging) and ≥1000
- Baseline characteristics will be summarized by CAC category. Means and proportions will be reported for continuous and categorical values respectively. Differences between continuous variables will be tested using ANOVA and differences between categorical values will be tested using χ^2 statistic.
- The domains of aging will be explored among individuals with CAC score of 0 and raw values using descriptive analyses and compared with individuals in our reference category. Similar analyses will be conducted among individuals with extremely elevated CAC scores ≥1000.
- The association between CAC category and each measure of aging will be assessed separately using linear regression models, restricted cubic splines, logistic and ordinal logistic regression models as required. The relationships will be assessed using 2 models: Model 1 will be crude, Model 2 will be adjusted for potential confounders listed above (age, sex, race*center, statin therapy).
    - For sensitivity analyses, a larger model adjusting for all confounders and the additional variables of interest listed above will be used to assess the relationship between CAC category and each measure of aging.
- Additionally, for sensitivity analyses, markers of aging will also be assessed among individuals with low CAC scores of 0-10 and individuals with CAC <25th centile, as well as individuals with CAC >75th centile.
    - CAC will also be analyzed as a continuous variable and the reference group will be broken up into smaller subgroups as sample size allows.
    - Indices of vessel condition (ABI and PWV) will also be analyzed using only data from visit 7.

Limitations: As this is an observational study, there could be potential residual confounding. Also**,** due to the cross-sectional nature of this study, we are not able to assess the temporal relationship of the development of these aging domains, thus limiting causal inference. However, this study is designed as a descriptive study, and does not seek to define causality or predict incident events.

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? ____ 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 current derived consent file ICTDER05 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/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)?
Related ARIC manuscript proposals 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* 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 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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