ARIC Manuscript Proposal #3728

PC Reviewed: 11/16/20 **Status: _____** **Priority: 2**
SC Reviewed: _________ **Status: _____** **Priority: ____**

1.a. Full Title: Physical activity and calcification of coronary arteries, aorta, and cardiac valves: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Physical activity and coronary artery calcification

2. Writing Group:

Writing group members: Yejin Mok, Shoshana H. Ballew, Jennifer Schrack, Candace M. Howard-Claudio, Kenneth R Butler, Lynne Wagenknecht, Aaron Folsom, 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. _YM_ **[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: Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Regular physical activity has been associated with reduced risk of coronary heart disease (CHD) (1,2) through its beneficial effects on multiple cardiovascular risk factors, including lipids, diabetes, blood pressure, and obesity (3-6). However, conflicting results have been reported regarding the association between physical activity and coronary artery calcification (CAC), a representative measure of subclinical atherosclerosis (7-17). For example, the Multi-Ethnic Study of Atherosclerosis (MESA) showed no significant associations cross-sectionally (11), but inverse associations (i.e., less CAC in more active participants) prospectively (14). In contrast, CARDIA showed that higher physical activity from young to middle age was positively associated with a higher CAC (12).

Although these null or positive associations between physical activity and CAC seems counterintuitive, several studies suggested potential underlying mechanisms for this. An increase in mechanical stress on the coronary arteries due to high heart rate and blood pressure during exercise may contribute to accelerated coronary atherosclerosis (18-20). Analysis of morphologic features has shown that the most active persons have more often calcified plaques (18,21).

To better understand this complex association of physical activity with CAC, we propose to comprehensively evaluate contributions of physical activity at midlife and late-life to CAC using Atherosclerosis Risk in Communities (ARIC) study. We will also examine the association of physical activity with extra-coronary calcification (ECC) (e.g., aortic calcification, mitral valve calcification, etc.), which has not been extensively studied (22,23).

5. Main Hypothesis/Study Questions:

- What are the relationship of physical activity at middle age and older age with CAC at older ages?
- Is there the association of physical activity with calcification of vascular beds other than CAC? Is physical activity differently associated with CAC and ECC?

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: Prospective study

- We will evaluate whether physical activity assessed at middle age and older age is associated with CAC and ECC at visit 7. The primary analysis will use physical activity data at visit 1 and visit 3 to allow us to explore the beneficial effect of physical activity at middle-age, and a relatively longer follow-up (~25 years). Also, since physical activity can vary over time, and it may be related to cardiovascular outcomes (12), we will use the summary score or average physical activity at visit 1 and visit 3. The secondary analysis will include physical activity data at visit 5 to confirm the robustness of our findings, and results will potentially differ in older adults.

Inclusion:

- All ARIC participants who have information on physical activity at visit 1 and 3 (or visit 5) and CAC at visit 7 will be included in the analyses

Exclusion:

- Individuals with prevalent coronary heart disease at visit 7 (study design of ARIC CAC ancillary)- they will be included as a sensitivity analysis

- Missing CAC data
- Missing data on physical activity and covariates of interest
- Race other than black and white

Exposures:
Physical activity in ARIC was assessed via a modified interviewer-administered Baecke Questionnaire. We will consider the current American Heart Association (AHA) physical activity guidelines and total volume of activity. Participants itemized leisure time exercise activities and answered questions regarding the frequency of participation in each, hours per week and months per year performing each activity. Each activity is converted into a metabolic equivalent of task (MET) based on its intensity, as per the Compendium of Physical Activities (24). No exercise or light intensity will be defined as those involving a workload of <3 METs, moderate-intensity as those involving a workload of 3-6 METs, and vigorous-intensity as those involving a workload of >6 METs.

1. The American Heart Association (AHA) physical activity guideline (25)
    a. Physical activity levels will be categorized by current AHA recommendation
        i. Ideal: ≥75 min/week of vigorous-intensity exercise or ≥150 min/week of moderate-intensity exercise, or ≥150min/week of any combination of moderate + vigorous intensity exercise
        ii. Intermediate: 1-74 min/week of vigorous-intensity exercise or 1-149 min/week of moderate-intensity exercise, or 1-149 min/week of any combination of moderate + vigorous intensity exercise
        iii. Poor: 0 min/week of moderate or vigorous exercise
    b. The score of AHA physical activity guideline at middle-age (between visit 1 and visit 3; approximately interval 6 years)
        i. To comprehensively characterize physical activity over six years between visit 1 and visit 3, we will create a summary score by providing 2 points for ideal, 1 point for intermediate, and 0 points for poor at both visit 1 and visit 3, separately, and then sum the scores across the two visits. The summary score will range from 0 to a maximum of 4 points, with a higher score indicating higher levels of physical activity over the six years between visits 1 and 3 (e.g., 4 points indicates meeting 'ideal' levels of physical activity at both visits 1 and 3.
    c. Continuous min/week of physical activity
        i. We will also use continuous min/week of vigorous-intensity exercise, moderate-intensity exercise, or moderate-vigorous intensity exercise
2. The total volume of activity (a continuous variable of MET*min/week; a multiplicative combination of intensity, duration, and frequency of physical activity)
    a. We will create distribution-based tertiles of the total volume of physical activity intensity (MET*min/week)
    b. The score of the total volume of physical activity at middle-age (between visit 1 and visit 3; approximately interval six years)
        i. The score of the total intensity of the activity will be calculated by providing 2 points for the third tertile, 1 point for the second tertile, and 0 points for the first tertile at both visits 1 and 3. The summary score will

range from 0 to a maximum of 4 points, with a higher score indicating a higher total volume of physical activity over the six years between visits 1 and 3 (e.g., 4 points indicates being in the highest tertile at both visits 1 and 3).

c. Weighted average MET*min/week at middle-age

    i. We will also use weighted average MET*min/week at visit 1 and visit 3 (e.g., [(MET*miin/week at visit 1 X follow-up duration between visit 1 and visit 3) + (MET*min/week at visit 3 X follow-up duration between visit 3 and visit 7)] / [overall follow-up duration (visit 1 to visit 7)] as continuous variable for each of total, moderate and vigorous exercise). Each MET*min/week will be scaled in 200 MET*min/week, corresponding to moderate-activity of 60 minutes (3 METs*60 minutes) or vigorous-activity of 30 minutes (6 METs*30 minutes) (26).

Covariates of interest: socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, history of stroke, history of heart failure, hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, reported a history of hypertension, or use of antihypertensive medication), diabetes (fasting blood glucose ≥126mg/dl, non-fasting glucose ≥200mg/dl, reported a history of diabetes, or use of diabetes medication), use of anti-diabetes medications, lipid parameters (Total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride), and lipid-lowering therapy.

Outcomes:

- **Calcification of coronary artery and vascular beds other than coronary arteries**
    - CAC measured by non-contrast CTs were calculated using the Agatston method. CAC will be modeled as binary outcome (e.g., >0 vs. 0, >100 vs. ≤100, >500 vs. ≤500, >1000 vs. ≤1000, and >75^{th} percentile vs. ≤75^{th} percentile) and continuous outcome (ln[CAC+1]) to include participants with CAC=0.
    - ECC includes calcification at five sites: aortic valve, aortic valve ring, mitral valve, ascending aorta, and descending aorta. This will also be modeled as the binary outcome and continuous outcome.

Statistical Analysis:

1. We will summarize characteristics at both visits across categories of physical activity at each visit and the summary score of physical activity at middle age (between visit 1 and visit 3) and older age.
2. Subsequently, we will quantify the association of physical activity (as detailed above) with high CAC and ECC (binary outcomes) using a logistic regression model. We will also use a linear regression model to assess the association of physical activity with continuous CAC and ECC.
3. We will plot odds ratios of high CAC and ECC with a linear spline model of min/week and MET*min/week at each visit, and weighted average MET*min/week at middle-age and older-age to see whether there is a linear association. We will also repeat the same analysis for continuous CAC using a linear regression model.
4. For sensitivity analysis

a. We will perform subgroup analysis according to demographic (age, sex, and race), and clinical conditions (e.g., diabetes, hypertension, hyperlipidemia, etc.). Interactions will be tested using the likelihood ratio test comparing models with and without product terms of interest.
b. We will consider prevalent CHD at visit 7 as CAC>0, and repeat analysis.
c. To account for attrition, we will implement an inverse probability attrition weight.
d. We will repeat our analysis using physical activity data at visit 5 to confirm the robustness of our findings.

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)?

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _________)
___ 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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