ARIC Manuscript Proposal #3781

PC Reviewed: 2/9/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of cigarette smoking and coronary artery and extracoronary calcification in older adults: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Smoking and vascular calcification

2. Writing Group:

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

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3. Timeline: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Smoking is a major risk factor for atherosclerosis [1], but its contribution may vary across different vascular beds. For example, several studies including ours have demonstrated that smoking is a stronger risk factor for peripheral artery disease (PAD) than coronary heart disease or stroke [2, 3]. A recent Mendelian randomization study has confirmed stronger causality of smoking for PAD than other atherosclerotic diseases [4].

However, whether the association of cigarette smoking with vascular calcification is consistent across different vascular beds is uncertain. Many studies have shown a consistent dose-response association between smoking and coronary artery calcium (CAC) [5-10], but inconsistent results were found for thoracic aortic calcification [5, 11-14] and aortic valve calcification [5, 15-18]. Also, most studies used a simple categorization of smoking status (current, former, or never), and it is inconclusive whether and how long the impact of smoking on vascular calcification lasts across different vascular beds after its cessation [14].

To comprehensively quantify the association of cigarette smoking and smoking cessation with calcification of different vascular beds in older adults, we will study data in the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:
Aim: to quantify the association of cigarette smoking with calcification of different vascular beds (coronary arteries, thoracic aorta, and cardiac valves) independent of traditional cardiovascular 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:
We will quantify the association of cigarette smoking with calcification of different vascular beds using data from visit 7.

Inclusions:
- All black and white ARIC participants with data on smoking, calcification scores of vascular beds, and other variables of interest.

Exclusions:
- Race other than black or white
- Prevalent atherosclerotic cardiovascular disease (coronary heart disease and stroke)
- Missing relevant data on smoking and covariates
- Missing data on calcification scores of vascular beds

Exposures (independent variables):

- Current vs. former vs. never smokers at visit 7
- Cumulative pack-years of cigarette smoking at visit 7: the average number of cigarettes per day times the years of smoking, divided by 20. Pack-years of smoking will be modeled categorically (<20, 20-<40, ≥40 pack-years).

- Years since quitting in former smokers at visit 7: age at visit 1 minus the recalled age of quitting smoking (for former smokers at visit 1) plus years not smoking during visit 1 to visit 7. Years since quitting will be modeled categorically (current smoker or quit<5, 5-<25, ≥25 years).

Outcomes (dependent variables):
Calcification of vascular beds: coronary artery, aortic valve, aortic valve ring, mitral valve, ascending thoracic aorta, and descending thoracic aorta.
- Measured by non-contrast CTs and scored using the Agatston method.
- Calcification score at each vascular bed will be modeled as a binary outcome (e.g., >0 vs 0; >100 vs. ≤100; >400 vs. ≤400) and continuously (ln[score+1] to account for its non-normal distribution).
- Number of calcified vascular beds: We will create a score from 0-6 reflecting the number of vascular beds with calcification.

Covariates:
- Sociodemographics: age, race, sex, education level
- Physical information: body mass index, systolic blood pressure, total cholesterol, HDL cholesterol, C-reactive protein
- Lifestyle: alcohol habit
- Comorbidities: diabetes, antihypertensive medication use, cholesterol-lowering medication use, kidney function
- Family history of coronary artery disease

Statistical Analysis:
- The prevalence of calcification of each vascular bed across categories of pack-years will be compared.
- We will quantify the association of cigarette smoking (smoking status, pack-years of smoking, and years since cessation) and calcification score of each vascular bed.
- Linear regression models: the calcification score (ln[score+1]) of each vascular bed as continuous outcome.
- Logistic regression models: the calcification score of each vascular bed as binary outcome.
- Ordinal regression models: the number of calcified vascular beds as ordinal outcome.
- We will construct 2 models. Model 1 will adjust for age, race, and sex. Model 2 will further adjust for education level, body mass index, systolic blood pressure, total cholesterol, HDL cholesterol, C-reactive protein, alcohol status, diabetes, antihypertensive medication use, cholesterol-lowering medication use, kidney function, and family history of coronary artery disease.
- We will use likelihood ratio test to test for interaction by key demographic and clinical factors (e.g., age, sex, race, alcohol use, hypertension, anti-cholesterol medication, and diabetes).
- We will also characterize traditional risk factor profile in heavy smokers (≥20 pack-years) with low vs. high calcification scores.
- We will use seemingly unrelated regression to compare the strength of associations with different vascular beds.
- The data will be analyzed in Stata 14.

Limitations:

- There is potential survival bias because some of the sickest smokers might have already developed atherosclerotic cardiovascular disease before visit 7.
- There may be potential measurement errors in self-reported smoking status.
- The intensity of smoking data was only available at visit 1-4. There may be misclassification when we use smoking intensity data at visit 4 to calculate cumulative pack-years if participants remained to be current smokers at visit 5 and 6.
- We will not be able to eliminate the possibility of residual confounding as is the case in any observation study.
- ARIC predominantly included whites and blacks, so the results may not be generalizable to races other than whites and blacks.

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)?

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
___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

References:

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