

ARIC Manuscript Proposal #2940

PC Reviewed: 02/14/2017

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Priority: _____

1.a. Full Title: Smoking, its cessation, and future risk of peripheral artery disease

b. Abbreviated Title (Length 26 characters): smoking and PAD

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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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: 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 cardiovascular disease (CVD) [1]. Several noxious components of cigarette smoke damage arteries by promoting endothelial dysfunction and by altering lipoprotein metabolism, coagulation, and platelet function [2, 3]. Smoking is also

associated with early biomarkers of CVD, such as markers of inflammation and thrombosis [4]. Although the prevalence of cigarette smoking declined in the past decade, 40 million US adults (16.8%) were still smoking in 2014 [5].

Smoking is considered as a particularly strong risk factor for peripheral artery disease (PAD) [6]. Indeed, numerous epidemiological studies have reported a positive association between smoking and PAD [7-21]. However, most of them are cross-sectional [7-16] and thus susceptible to bias by smoking cessation due to PAD or missing severe PAD cases. Although there have been a few prospective studies evaluating the association of smoking with incident PAD, they have some caveats such as an inclusion of only women [17] or men [18], a simple categorization of smoking status (current, former, or never) [19], short follow-up time of ≤ 5 years [20], or limited information about duration of smoking cessation [21].

Therefore, to comprehensively quantify the association of smoking and its cessation with incident PAD, we will study longitudinal data in the Atherosclerosis Risk in Communities (ARIC) Study. To determine whether the risk related to smoking is uniquely strong for PAD, we will also investigate coronary heart disease (CHD) and stroke.

5. Main Hypothesis/Study Questions:

Hypothesis 1: Smoking is strongly associated with an increased risk of incident PAD, and we will observe a dose-response relationship with pack-years and intensity (pack/day) [22] as an exposure.

Hypothesis 2: Duration of smoking cessation is inversely associated with incident PAD in a graded manner.

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).

Inclusions:

- All black and white ARIC participants who provided data on smoking status at visit 1, did not have a history of PAD, and had outcome information during follow-up.

Exclusions:

- Ethnicity other than black or white
- Missing data on smoking status, intensity (pack/day), or recalled age of quitting at visit 1
- Preexisting PAD at baseline (defined as a history of leg revascularization, ankle-brachial index ≤ 0.9 , or intermittent claudication)
- Missing data on PAD and relevant baseline covariates

Exposures (independent variables):

- Time-fixed exposures:
 - Current vs. former vs. never smokers at visit 1
 - Pack-years of smoking at visit 1 as the average number of cigarettes per day times the years of smoking, divided by 20.
 - Intensity (cigarettes/day) amongst current smokers
 - Years since quitting in former smokers at visit 1 based on baseline age minus the recalled age of quitting smoking

- Time-varying exposures: By incorporating information at other visits and annual follow-up data, we will be able to assess current, years since quitting, and never smoking as a time-varying exposure over ~25 years.

Outcomes (dependent variables):

- PAD and critical limb ischemia (CLI): PAD-related hospitalizations will be identified according to the following ICD codes based on previous literature [23,24]: atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); peripheral vascular disease, unspecified (443.9); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of these, 440.22, 440.23, and 440.24 will be considered CLI. Also, we will consider any cases with the above code as CLI when the following codes coexist: leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4).

- CHD:

-Adjudicated events: definite and probable myocardial infarction, fatal coronary heart disease

- Coronary revascularization

- Stroke: Adjudicated events of definite and probable stroke

Covariates:

- Sociodemographics: age, race, gender, education level

- Physical information: body mass index, systolic blood pressure, diastolic blood pressure

- Lifestyle: alcohol habit

- Comorbidities: obesity, dyslipidemia, diabetes, hypertension, antihypertensive medication use, cholesterol-lowering medication use, kidney function, and history of coronary heart disease or stroke

Statistical Analysis:

- The data will be analyzed in Stata 14.

- We will use Cox proportional hazards regression models to quantify the association between smoking status (e.g., current vs. former vs. never) or parameters (pack-years of smoking or years since quitting) and incident PAD and CLI.

- Pack-years of smoking among ever smokers will be categorized into quartiles as well as groups used in previous studies.

- Years since quitting will be categorized by every 3 to 6 years given triennial follow-up visits up in the first nine years of the ARIC Study.

- We will adjust for the covariates listed above.

- When current, years since quitting, and never smoking are modeled as time-varying variables, we will also treat covariates as time-varying variables whenever possible. In the case of missing data in either of visit or annual follow-up, we will carry forward relevant data from a prior visit or annual phone interview until available subsequently.

- We will use likelihood ratio test to test for interaction by key demographic and clinical factors (e.g., age, sex, race, alcohol use and diabetes).
- We will use seemingly unrelated regression to compare strength of association for PAD, CLI, coronary heart disease, and stroke.
- Given the potential impact of the competing risk of death for estimating PAD and CLI risk, we will run Fine and Gray's proportional subhazards models.

Limitations:

- Potential measurement errors in assessment of smoking status because the information is self-reported.
- There may be misclassification when we carry forward prior data in the case of missing updated information when performing time-varying analysis.
- 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.csc.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 several ARIC proposals with incident PAD as an outcome as listed below (only recent ones are listed). Of these, #1832 would be most relevant since it includes smoking as a potential predictor for PAD risk. However, the lead investigator of #1832, Dr. Matsushita, will play an

important role in the current proposal as well and thus will be responsible for any coordination. Also, a key analysis of time-varying smoking exposure is completely unique for this proposal.

#1832: Risk prediction model for incident PAD in the ARIC cohort

#1915: Improvement of cardiovascular risk prediction using non-traditional risk factors in the chronic kidney disease (CKD) population

#2479: Serum 25-hydroxyvitamin D and incident peripheral arterial disease: The Atherosclerosis Risk in Communities Study (ARIC)

#2497: Microvascular disease measures and the risk of peripheral artery disease

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* 2014.05)

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.csc.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.csc.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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