ARIC Manuscript Proposal #3453

1.a. Full Title: Smoking, smoking cessation, and future risk of abdominal aortic aneurysm

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

2. Writing Group:

Writing group members: Ning Ding, Yingying Sang, Jeremy Van't Hof, Corey A. Kalbaugh, Michael Hall, Josef Coresh, Maya Salameh, Michael Blaha, Weihong Tang, Kunihiro Matsushita

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]

First author: Ning Ding
Address: Department of Epidemiology
         Johns Hopkins Bloomberg School of Public Health
         Welch Center for Prevention, Epidemiology, and Clinical Research
         2024 E. Monument St., Room B314, Baltimore, MD 21287
         Phone: (202) 769-6061  Fax:
         E-mail: nding3@jhmi.edu

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).

Name: Kunihiro Matsushita
Address: Department of Epidemiology,
         Johns Hopkins Bloomberg School of Public Health,
         2024 E. Monument St., Suite 2-600, Baltimore, MD 21287
         Phone: (443) 287-8766  Fax: (410) 367-2384
         E-mail: kmatsus5@jhmi.edu

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:

Abdominal aortic aneurysm (AAA) is often asymptomatic but is usually catastrophic when it is ruptured [1]. Thus, understanding of its risk factors and targeted screening are crucial. In this context, smoking is considered the strongest risk factor for AAA, and male ever smokers are
recommended to receive one-time screening for AAA with ultrasonography at age of 65 to 75 years [2]. These notions are based on a number of prospective studies reporting the positive association between smoking and AAA [3].

However, when we closely look at those studies, there are several important caveats. For example, only a few studies evaluated this association in men and women separately [4-10]. None of them independently investigated the intensity and duration of smoking, which have shown different contributions to some cardiovascular phenotypes [11]. Also, it is inconclusive as to how long the impact of smoking lasts on AAA after its cessation. Four studies tackled this topic but have some limitations such as a simple categorization of smoking cessation (≥10 years and <10 years) [8, 12], and a short follow-up time [13]. Only one study explored smoking cessation over 20 years and reported that AAA risk returns to baseline after 20 years of cessation in women but not in men [9].

To overcome these caveats, using data from the Atherosclerosis Risk in Communities (ARIC) Study, we will comprehensively evaluate the association of smoking (including smoking status [current, former, and never], pack-years, intensity, and duration) and smoking cessation over 30-40 years with incident AAA among men and women separately. Abdominal ultrasound data at ARIC visit 5 will also allow us to explore these smoking parameters and their associations with aortic diameter at older age. Since ARIC is a bi-racial cohort (white and black), we will be able to evaluate the potential racial difference in the smoking-AAA relationship.

5. Main Hypothesis/Study Questions:
Hypothesis 1: All smoking parameters (status, pack-years, duration, and intensity [pack/day]) will be strongly associated with an increased risk of AAA.
Hypothesis 2: Longer duration of smoking cessation will be associated with lower risk of AAA, but elevated risk will last over 20-30 years.
Hypothesis 3: There will be sex and race difference in the association between smoking and AAA.

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 (1987-89) and had AAA outcome information during follow-up.

Exclusions:
- Race/ethnicity other than black or white
- Missing data on smoking variables of interest or relevant baseline covariates
- Missing data on AAA

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) and duration (years) amongst current and former 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 years since quitting as a time-varying exposure over ~40 years.

Outcomes (dependent variables):
- Incident AAA: Incident AAA is identified by searching hospitalization records, death certificate, Medicare data, surveillance of local hospitals, and annual or semi-annual telephone interviews. Clinical AAA were based on the ICD-9 codes of 441.3 (AAA, ruptured), 441.4 (AAA, without rupture), 38.44 (AAA, resection with replacement) or 39.71 (AAA, endovascular repairment) or cause of death with the ICD-9 or 10 codes of 441.3, 441.4, I17.3 (AAA, ruptured) or I17.4 (AAA, without rupture) identified from the above sources or two outpatient claims at least a week apart in the Medicare data [10]. Participants were followed until an AAA event, date of death, date of the last contact, or through December 31, 2011, whichever came first.

- Aortic diameter at visit 5: Abdominal ultrasound was performed at visit 5 (2011-2013) using Philips iE33 high resolution duplex scanner and Philips C5-1 transducer (Philips Healthcare, Bothell, WA). Certified technicians measured the anterior-posterior and transverse aortic diameter at the proximal aorta (just below the superior mesenteric artery), the mid aorta (2 cm below the renal arteries), the distal aorta (1 cm above the bifurcation), and the place of maximal infrarenal aortic diameter. Any images with aortic diameter >2.8 cm or probable pathology, as well as a 5% random sample of the rest were reviewed by vascular imaging physicians to verify [14].

Covariates:
- Sociodemographics: age, race, gender, education level
- Physical information and lifestyle: body mass index, systolic blood pressure, dyslipidemia, alcohol habit, inflammatory markers (WBC, CRP)
- Comorbidities: 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 of several smoking measures with incident AAA.
- Pack-years, intensity, and duration 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 <5, 5-<10, 10-<20, 20-<30, 30-<40, and ≥40 years.
- We will adjust for the covariates listed above.
- When years since quitting is 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, hypertension and diabetes).
- Given the potential impact of the competing risk of death for estimating AAA risk, we will run Fine and Gray’s proportional subhazards models.
For aortic diameters, will run linear regression and logistic regression (e.g., diameter ≥3 cm as an outcome variable) 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  ____ X__ 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? ____ 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”? ____ X__ 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](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)?

The most relevant proposal is MP#1505 Risk Factors for Abdominal Aortic Aneurysm. However, this proposal has already published an article and reported the association of basic smoking parameters (i.e., smoking status, pack-years of smoking, and cessation [quitter before visit 1 and recent quitter]) with incident AAA [10]. The current proposal will extend to other smoking parameters (i.e., duration, intensity, and cessation as a time-varying variable during follow-up) and abdominal diameter as an outcome variable.
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* _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.cscce.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.cscce.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.

Reference


