ARIC Manuscript Proposal #2931

PC Reviewed: 02/13/17   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Prospective Study of Lung Function and Abdominal Aortic Aneurysm Risk: the Atherosclerosis Risk in Communities Study

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

2. Writing Group:
    Writing group members: Yasuhiko Kubota, Weihong Tang, Kunihiro Matsushita, David Couper, Aaron Folsom

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __YK___ **[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 analysis: 1-2 months from manuscript approval date.
First draft of the manuscript: 2-3 months from manuscript approval date.

4. Rationale:
Abdominal aortic aneurysm (AAA) is a common disease in Western populations, especially in elderly people, with a prevalence of 4–9% in men and 1% in women (1). Once rupture occurs, mortality rates can be as high as 65–85% (2). So far there is no treatment for AAA other than surgery. Since AAA is usually asymptomatic and AAA

growth is discontinuous, with periods of growth alternating with periods of stability, it is often difficult to estimate the prognosis of AAA or offer interventions (3). Thus, it is important to identify populations at high risk of AAA.

Chronic obstructive pulmonary disease (COPD) has been suggested to be associated with increased risks of AAA and its rupture (4-8). A previous clinical cross-sectional study showed that this association was independent of smoking, and mediated by inflammation and hemostasis (4). A prospective study has suggested that inflammatory and hemostatic markers are associated with AAA events (9), and thus, COPD may be a risk factor for AAA. In addition, if inflammation and hemostasis in fact increase the risk of AAA, other respiratory impairments, such as restrictive lung diseases (RLD), may also increase the risk of AAA via similar mechanisms. However, to the best of our knowledge, no epidemiological study has reported the prospective association between respiratory impairments, including COPD, and AAA.

The Atherosclerosis Risk in Communities Study (ARIC) has hospitalized AAA data through 2011. Therefore, using two important markers for respiratory impairment, lung function measured by spirometry and respiratory symptoms, we sought to prospectively investigate whether respiratory impairments (lung restriction, airway obstruction, and others) are related to the risk of AAA in a population-based study in the U.S.

5. Main Hypothesis/Study Questions:
To investigate the associations between respiratory impairments (lung restriction, airway obstruction, and others) and AAA 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).

Design
Prospective design.

Inclusions
Participants with spirometry data and information on respiratory symptoms at visit 1.

Exclusions
Those who had prior AAA surgery or aortic angioplasty at visit 1.

Main exposures
We will classify participants into 4 categories, "normal" was defined as those with $FEV_1/FVC \geq$ lower limit of normal (LLN), $FVC \geq LLN$ and no respiratory symptoms, "respiratory symptoms with normal spirometry" as those with respiratory symptoms but $FEV_1/FVC \geq LLN$ and $FVC \geq LLN$, 'restrictive lung disease pattern' as $FEV_1/FVC \geq LLN$ and $FVC < LLN$, and 'COPD pattern' as $FEV_1/FVC < LLN$ (10). We used this same classification for a recent ARIC publication on lung function and venous thromboembolism (11). We included 'respiratory symptoms with normal spriometry' in the present analysis because others have documented adverse health outcomes among

people in this category (11, 12), and this category may reflect lung diseases with preserved lung function or borderline RLD or COPD.

Statistical analysis
We will present the prevalences of potential AAA risk factors at visit 1 (age, sex, race, smoking status, pack-years of smoking, drinking status, height, hypertension, HDL-C, LDL-C and prevalent peripheral artery disease) (13) according to the 4 respiratory categories. Then, we will examine the association between respiratory impairments and AAA risk using Cox proportional hazard models adjusting for potential AAA risk factors. We will also examine the associations between spirometry measurements (FEV1, FVC and FEV1/FVC) and AAA risk. If sample size is adequate, we will rerun models among only non-smokers.

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)?

#1505: Risk Factors for Abdominal Aortic Aneurysm (PMID: 27834688)
#2633: Associations between Novel Biomarkers and Risk of Abdominal Aortic
      Aneurysm (PMID: 26085454)

#1295: Association of Chronic Obstructive Pulmonary Disease with Venous Thromboembolism in the Atherosclerosis Risk in Communities (ARIC) Study (PMID: 27696765)

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* 2009.18)
  ___   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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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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associated with activation of inflammation and hemostasis, not smoking or cardiovascular disease. J Vasc Surg. 2006 Mar;43(3):474-80.

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