

## ARIC Manuscript Proposal #2216

PC Reviewed: 9/10/13  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Association between Subclinical Carotid Atherosclerosis and Abdominal Aortic Aneurysm: the Atherosclerosis Risk In Community (ARIC) Study

**b. Abbreviated Title (Length 26 characters):** Carotid Atherosclerosis & AAA

**2. Writing Group:** Lu Yao, Weihong Tang, Aaron Folsom, Alvaro Alonso, Pamela Lutsey, TBA

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. X

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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 analyses will begin immediately. Goal completion is June 2014.

**4. Rationale:**

An abdominal aortic aneurysm (AAA) is a condition of progressive and irreversible dilatation of the abdominal aorta. The prevalence of AAA ranges from 1.3% and 0% in men and women 45-54 years of age, to 12.5% and 5.2% in men and women 75-84 years of age<sup>1</sup>. The in-hospital treatment of acute AAA only results in about 50% survival rate, and the most recent figure showed that life-threatening bleeding resulting from ruptured aortic aneurysms (mostly AAA) causes approximately 17,000 deaths in the U.S. each year<sup>2,3</sup>. Thus, AAA is an important public health issue.

Prospective cohort studies, including the ARIC Study, have suggested that traditional and novel risk factors for ischemic atherosclerotic diseases, including smoking, hypertension, dyslipidemias, age, male gender, and fibrinogen, were associated with increased risk of AAA<sup>1,4-8</sup>. In addition, angiotensin-2 and oxidative stress which are involved in the development of atherosclerotic diseases, are also related to increased risk of AAA<sup>9,10</sup>. The phenomenon that AAA and atherosclerosis share some mechanisms and common risk factors encourages us to explore the intrinsic relationship between them.

However, it is still a debate whether there is any causal relationship between atherosclerosis and AAA<sup>1</sup>. Data from early animal studies showed that aneurysms only form after prolonged exposure to atherogenic conditions<sup>11</sup>. Atherosclerotic plaques in aortic wall include matrix fibers; and the expansion of plaques may simultaneously dilate and weaken aortic walls which support mural tension and then lead to aneurysmal enlargement<sup>11</sup>. Recent studies further demonstrated that atherosclerosis, although initially occurs in the intima, promotes the dilation or shrinkage of the tunica media and adventitia; this in turn aggravates the obstruction and results in vascular remodeling via the disturbance in the synthesis and degradation of matrix proteins<sup>12, 13</sup>. In addition, one study showed that atherosclerosis lipid plaques were associated with later expansive remodeling of the vessel and arterial dilation<sup>14</sup>. To date, only one population-based follow-up study in Europe examined the relationship between baseline carotid plaque, plaque growth and growth of abdominal aortic diameter over 6 years; however, this study has limited number of AAA cases (26 in each category of aortic diameter)<sup>15</sup>.

To better understand this issue, therefore, we will use data from a large population-based cohort study to prospectively examine the association between baseline carotid atherosclerosis and AAA. Positive findings in the proposed study will help determine whether atherosclerosis is a risk factor for AAA, also define a high-risk population for AAA, which might benefit from early detection and early repair.

Carotid intima-media thickness (cIMT) is an easily accessible, non-invasive, and objective marker of subclinical atherosclerosis, and it has been shown to be related positively to coronary heart disease and myocardial infarction incidence<sup>16-19</sup>. In ARIC, cIMT as well as the presence of plaque, which also predicts coronary heart disease, were obtained in Visit 1<sup>20</sup>. ARIC also has measures of carotid artery distensibility in Visit 2, which could be used to complement the analysis of cIMT and plaque<sup>21, 22</sup>. ARIC's hospital ICD code and death certificate database enabled the identification of clinical AAAs. Also, the ongoing ARIC Visit 5 exam is ascertaining asymptomatic AAA cases by using abdominal aortic ultrasound, as part of the NIH-funded ARIC ancillary study: *Identifying Epidemiological Risk Factors for Abdominal Aortic Aneurysm* (R01HL103695, PI: Dr. Weihong Tang).

## **5. Main Hypothesis/Study Questions:**

We hypothesize that baseline carotid atherosclerosis is positively associated with the risk of 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)**

### Study Design

Prospective cohort from visit 1 through the 2011 events follow-up and the abdominal aortic ultrasound exam at Visit 5.

### Inclusion/Exclusion

We will include participants who had measures of carotid ultrasound measures at ARIC Study Visits 1 (baseline) or 2 (baseline only for analysis on carotid artery distensibility) and data on AAA from hospitalization records, death records, and/or abdominal aortic ultrasound scanning. We will exclude those who had prevalent AAA at baseline (if there was any) and those who were in other race groups than white or black.

### Variables

*Exposures:*

1. cIMT at Visit 1, measured bilaterally in the extracranial carotid arteries in the areas of the common carotid artery (1 cm proximal to the dilatation of the carotid bulb), the carotid bifurcation (1 cm proximal to the flow divider), and the internal carotid artery (1 cm distal to the flow divider). The mean cIMT, produced by combining the averages of two cIMT measures at the six carotid sites, will be grouped into quantiles and used as a categorical variable.

2. The presence of atherosclerotic plaque at any of the 6 segments was recorded by ARIC ultrasound readers as wall thickness in excess of 1.5 mm or the presence of lumen encroachment or irregular intimal surface and/or image characteristics indicative of structural heterogeneity of the arterial wall.

3. Carotid artery distensibility measures at Visit 2. This separate analysis will use Visit 2 as baseline. Carotid artery distension (e.g., Young's elastic modulus) will also be grouped into quantiles and used as a categorical variable.

*Outcomes:*

1. Hospital AAAs were ascertained through hospital discharge diagnoses and death certificates from Visit 1 to 2011 events follow-up. Hospital AAAs were defined using the definite ICD diagnostic codes 441.3, 441.4, 441.02, 38.44 and 39.71, and mortality code I71.02, I71.3, I71.4, 441.3 and 441.4. Other diagnostic codes that indicate probable diagnosis of AAA will be investigated case-by-case to clarify or rule out AAA diagnosis (such as thoracic aortic aneurysm, ICD diagnostic codes 441.0, 441.00, 441.5, 441.9, 39.52 and 38.64, and mortality code I71.0, I71.00, I71.8, I71.9, 441, 441.0, 441.5, and 441.9).

2. Asymptomatic AAAs were ascertained based on the Visit 5 abdominal aortic ultrasound exam. We will use a widely used definition of asymptomatic AAA, which is infrarenal abdominal aortic diameter  $\geq 30$  mm.

Overlap between the hospital and asymptomatic ultrasound AAAs: we expect a small overlap between the two groups because 1) a majority of clinical AAAs had symptoms, surgical repair or rupture, 2) clinical AAAs who had a history of rupture or surgical repair have been excluded from the abdominal ultrasound exam.

*Possible confounders:*

Age, gender, race, other cardiovascular disease risk factors including serum lipids, smoking, fibrinogen, history of cardiovascular disease, hypertension, peripheral artery disease, lipid-lowering medications, anti-coagulates, and antihypertensive medications. Since it is a debate whether type-2 diabetes is associated with AAAs, we do not consider it as a confounder but will perform a sensitivity analysis by adding it in the model.

Data analysis

Visit 1 will serve as baseline for the analysis of cIMT and presence of atherosclerotic plaques. Visit 2 will serve as baseline for the analysis of carotid artery distensibility measures. Participant characteristics at baseline will be described using means and proportions stratified by levels of cIMT, atherosclerotic plaques, or carotid artery distensibility.

The associations between baseline risk factors and AAA will be examined and reported separately for clinical and ultrasound-detected AAAs. For analyses on hospital AAAs, we will examine the proportionality assumption and use an appropriate form of Cox regression model to examine the association between baseline categorical ultrasound measures and subsequent clinical AAAs. For analyses on ultrasound-detected asymptomatic AAAs, we will exclude participants with known incident clinical AAA, and use logistic regression model to estimate the odds ratios for the associations, on the condition of fixed lengths of follow-up time. If a test of the homogeneity of associations for the two case groups is not rejected, results could be pooled using

meta-analysis techniques and the pooled results will also be reported. All models will be adjusted for the aforementioned confounders after being formally tested using stratified analysis.

In addition, subgroup analyses will be conducted to explore gender and/or race differences in the association, regardless of whether gender or race modifies the association statistically. The sensitivity analysis will be performed using a model further adjusting for type-2 diabetes.

**Limitations:** The incident hospitalized AAA analysis is limited in that prevalent AAA was not measured at baseline. The analyses of ultrasound-detected AAA will be restricted to ARIC participants attending the Visit 5 exam. The loss to follow-up will bias the OR estimate if loss is differential with regard to exposure and AAA outcome. We will attempt to limit this potential bias by adjusting for all variables potentially related both to the outcome and the probability of being censored. In addition, we will perform sensitivity analyses that apply the inverse-probability-weighting method where the observed responses are weighted by the inverse of the probability of participating in Visit 5 given their covariates at baseline.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**  Yes  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  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>**

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)?**

MP1505. Risk Factors for Abdominal Aortic Aneurysm. PI: Aaron Folsom

**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**  
(AS 2009.18: "Identifying Genetic and Epidemiological Risk Factors for Abdominal Aortic Aneurysm", R01HL103695, PI Weihong Tang)

\_\_\_\_ **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](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

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