ARIC Manuscript Proposal #1505

PC Reviewed: 5/12/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Risk Factors for Abdominal Aortic Aneurysm

b. Abbreviated Title (Length 26 characters): Aortic Aneurysm Risk

2. Writing Group:

Writing group members: Weihong Tang, Alvaro Alonso, Pam Lutsey, Frank Lederle, Lu Yao, Aaron Folsom; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _WT_ **[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: Finish by mid 2014

4. Rationale:

Abdominal aortic aneurysms (AAA) are an important manifestation of vascular disease in older age. Traditional atherosclerotic disease risk factors, particularly male sex, smoking and hypertension, contribute to the etiology of AAA. Rupture of an AAA is a life threatening condition, and a lot of research has been put into clinical guidelines for screening and revascularization of AAAs.

Epidemiologic studies of AAA have often been conducted as cross-sectional studies following population screening for AAA, for example the VA study by Lederle (1), our co-investigator, and those from CHS (2), Rotterdam (3), and Tromso (4). Fewer AAA studies have employed a prospective cohort design. Recently, Lederle et. al., reported risk factors for AAA (hospitalized symptomatic or repair) in the Women's Health Initiative Cohort (5). A study most akin to ARIC, by virtue of having risk factors in middle age and long follow up, was the Chicago Heart Association Detection Project in Industry cohort; AAA was found by linkage using Medicare and death certificate ICD codes.

ARIC's hospital ICD code database enables the identification of hospitalized AAA. A first pass counted, through 2004, approximately 260 people with hospitalized AAA, 124 of them with procedures, and perhaps 20 with rupture or dissection of the AAA. (Thoracic aneurysms excluded.) As a pilot study, we explored multiple hospitalizations of Minnesota ARIC participants who had any AAA code, and reviewed procedure codes and any hospital discharge summaries we had filed. Although we had relatively few discharge summaries, those that were available tended to confirm the diagnosis. Of 65 AAAs, 7 were ruptured, 32 had revascularization procedures, and most of the rest were asymptomatic AAAs. Only occasionally did a thoracic AA seem to be miscoded as an AAA.

We envision several stages to the analysis, with likely several papers. The first stage is to sort through the ICD code hospital and mortality data through 2011 to get a picture for all centers of three groups: Any AAA code (expect n=280), any AAA code plus revascularization code (expect n=135), and any AAA rupture (expect n=33). We hope to confirm at this stage that the data make sense for further analysis. If Medicare data were to become available soon, we could add cases from Medicare files. The second stage would be to analyze traditional risk factors and AAA incidence. A third stage would be to look at other nontraditional risk factors.

In addition, the finished ARIC Visit 5 exam has been ascertaining asymptomatic AAA cases by using abdominal aortic ultrasound, as part of the NIH-funded ARIC ancillary study (for grant information please see Q11). The abdominal ultrasound exam is expected to identify an addition of 100-150 asymptomatic AAA cases among participants who came to the Visit 5 exam.

5. Main Hypothesis/Study Questions:

-Modifiable risk factors measured in middle age will be associated with risk of AAA over the next 20 years.
-Nontraditional risk markers also will be identified that may be relevant in the etiology 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).

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

Endpoint: clinical/hospital AAAs and ultrasound AAAs as defined below.

1. Hospital AAAs 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.

2. Asymptomatic AAAs ascertained based on the Visit 5 abdominal aortic ultrasound exam. We will use a widely used definition for 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.

Exposures: Initially we will study traditional risk factors: age, gender, race, smoking, alcohol consumption, diet, BMI, waist, height, lipids, BP, hypertension, diabetes, fasting glucose, insulin, exercise, and peripheral arterial disease. Then, we will explore some of the novel risk factors measured in the entire ARIC cohort, including white blood cell count, fibrinogen, D-dimer, CRP, FVIIc, FVIIIc, and vWF.

Data Analysis: Cox proportional hazards models for clinical/hospital AAA analysis and logistic regression for ultrasound AAA analysis.

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 risk factors 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 will be pooled using meta-analysis techniques and the pooled results will also be reported. All models will be adjusted for potential confounders.

Subgroup analyses will be done by race, sex, and possibly other subgroups.

REFERENCES

1. Lederle FA et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Ann Intern Med 1997;126:441-9.

2. Alcorn HG, Wolfson SK Jr, Sutton-Tyrrell K, Kuller LH, O'Leary D. Risk factors for abdominal aortic aneurysms in older adults enrolled in The Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. 1996 Aug;16(8):963-70.

3. Pleumeekers HJ, Hoes AW, van der Does E, van Urk H, Hofman A, de Jong PT, Grobbee DE. Aneurysms of the abdominal aorta in older adults. The Rotterdam Study. Am J Epidemiol. 1995 Dec 15;142(12):1291-9.

4. Singh K, Bønaa KH, Jacobsen BK, Bjørk L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study : The Tromsø Study. Am J Epidemiol. 2001 Aug 1;154(3):236-44.

5. Lederle FA, Larson JC, Margolis KL, Allison MA, Freiberg MS, Cochrane BB, Graettinger WF, Curb JD; Women's Health Initiative Cohort Study. Abdominal aortic aneurysm events in the women's health initiative: cohort study. BMJ. 2008 Oct 14;337:a1724. doi: 10.1136/bmj.a1724.

6. Rodin MB, Daviglus ML, Wong GC, Liu K, Garside DB, Greenland P, Stamler J. Middle age cardiovascular risk factors and abdominal aortic aneurysm in older age. Hypertension. 2003 Jul;42(1):61-8.

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?

None

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 (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.cscc.unc.edu/aric/forms/

12. 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.