

ARIC Manuscript Proposal #2487

PC Reviewed: 1/13/15
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Kidney disease measures and risk of abdominal aortic aneurysm: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:

Writing group members: Kunihiro Matsushita, Shoshana Ballew, Morgan Grams, Elizabeth Selvin, Aaron Folsom, Josef Coresh, Weihong Tang, Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. KM [please confirm with your initials electronically or in writing]

First author: Kunihiro Matsushita
Address: Department of Epidemiology,
Johns Hopkins Bloomberg School of Public Health,
615 N. Wolfe Street, Baltimore, MD 21205
Phone: (443) 287- 8766 Fax: (443) 683-8358
E-mail: kmatsush@jhsph.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:
Address:

Phone: Fax:
E-mail:

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:

Chronic kidney disease (CKD), defined as reduced kidney function or kidney damage, is a major global public health problem,^{1,2} affecting 10-20% of adults in the world³⁻⁶ and

increasing risk of various adverse outcomes.^{7,8} Approximately half of individuals with CKD die from cardiovascular disease (CVD),⁹ and thus it is crucial to better understand the epidemiological link between CKD and CVD. Indeed, numerous studies have investigated the association of kidney function and/or damage with major CVDs such as CVD mortality, coronary heart disease, stroke, and heart failure.¹⁰ However, data are much sparse for other subtypes of CVD, despite their potential impacts on prognosis and quality of life.¹¹

In this context, abdominal aortic aneurysm (AAA) is an important CVD subtype, as it constitutes the 14th leading cause of death in the US (10th in older men).¹² Of note, prevention and early detection of AAA is critical given its continued enlargement and catastrophic case fatality risk of 65-85% when it is ruptured.^{12,13} Regarding its association with CKD, conflicting results have been demonstrated for reduced kidney function in a few cross-sectional studies.¹⁴⁻¹⁶ Furthermore, to our knowledge, there are no studies investigating albuminuria, a representative measure of kidney damage, regarding its relation to AAA.

Therefore the main aim of this study is to prospectively and comprehensively assess the association of kidney function and damage with future risk of AAA in a community-based cohort, the ARIC Study. We will also conduct cross-sectional analysis focusing on abdominal aortic ultrasound data at visit 5.

5. Main Hypothesis/Study Questions:

Both kidney dysfunction and damage are associated with risk of AAA independently of each other and traditional CVD risk factors.

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 subjects with data on kidney disease measures (see below for details) at visit of interest and data on AAA during follow-up and at visit 5

Exclusions:

-Ethnicity other than black or white
-Missing data on kidney disease measures or AAA outcome

Exposure (independent variables):

- Kidney function measures
 - Estimated glomerular filtration rate (eGFR) based on serum creatinine and/or cystatin C (available at visit 1 [only serum creatinine], 2, 4, and 5)
 - Cystatin C (visit 2, 4 and 5), β 2 microglobulin (B2M) (visit 2 and 4), and beta trace protein (BTP) (only visit 4).
- Kidney damage measure
 - Urinary albumin-to-creatinine ratio (ACR) (visit 4 and 5)

Outcome (according to MP #2367):

- Clinical AAAs will be ascertained based on the following ICD diagnostic or procedure codes on discharge record or death certificates from visit 1 until the latest event data available at the time of analysis: 441.3 (abdominal aneurysm, ruptured), 441.4 (abdominal aneurysm without mention of rupture), 441.02 (dissection of aorta, abdominal), 38.44 (resection of vessel with replacement, aorta, abdominal) and 39.71 (endovascular implantation of other graft in abdominal aorta), I71.02 (dissection of abdominal aorta), I71.3 (abdominal aortic aneurysm, ruptured), and I71.4 (abdominal aortic aneurysm, without rupture). These diagnoses would include both symptomatic and asymptomatic AAAs that were medically documented. The CMS data will be used to identify additional hospital and outpatient AAAs. Identification of outpatient AAAs from the CMS data requires two claims that were at least seven days apart.
- Visit 5 AAAs will be 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 ≥ 30 mm.¹²

Other variables of interest and covariates:

Sociodemographics: age, race, gender, education, parental history of hypertension

Physical information: blood pressure, body mass index, presence/absence of left ventricular hypertrophy by electrocardiogram and carotid atherosclerosis by ultrasound

Lifestyle: smoking status/amount and alcohol habit

Comorbidities: diabetes, dyslipidemia

Statistical analysis plan:

The primary analysis will use Cox proportional hazards models to quantify the prospective association of kidney function measures and ACR with incident AAA. Given that we are interested in simultaneous associations of kidney function and damage measures with AAA, our primary analysis will use visit 4 data as baseline but will repeat the analysis with data from other visits to confirm robustness of our findings. Kidney function measures and ACR will be treated as categorical (quantiles and clinical categories) and continuous variables with splines respectively in the models. We will adjust for the covariates listed above. We will repeat the analysis after stratifying the study sample by key demographic and clinical subgroups according to age, gender, race, and the presence/absence of diabetes and hypertension. We are particularly interested in subgroups by gender and diabetes status, as there is an evident gender difference in the risk of AAA (more common in men but more deadly in women)¹⁷ and several studies demonstrate paradoxically lower risk of AAA among those with diabetes compared to those without.¹⁸ We will formally test interaction using likelihood ratio test.

We will conduct a few sensitivity analyses. Firstly, we will censor aortic dissection cases and try to specifically focus on aneurysm cases. Secondly, we will repeat our analysis restricting the outcome to hospital AAAs, with implications on more severe AAA cases. Thirdly, we will conduct cross-sectional analysis for kidney measures and visit 5 AAAs. As an extension of this analysis, we will also investigate abdominal aortic diameter as a continuous outcome variable. For this cross-sectional analysis, we will assess whether the implementation of inverse probability of attrition weighting provides

consistent results. We will use key demographic and clinical prognostic variables obtained at visit 4 or after that during follow-up before visit 5 (e.g., diabetes and incidence of cardiac disease) for attrition weighting.

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)?

There are a few proposals to investigate risk factors of AAA (MP#1505, #2248, and #2374) but none of them include kidney disease measures in the current proposal.

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* 2006.16 and 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.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.

References

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