ARIC Manuscript Proposal #3583

PC Reviewed: 3/10/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Arterial stiffness and subsequent changes in kidney disease measures: The Atherosclerosis Risk in Communities (ARIC) Study.

1b. Abbreviated Title (Length 26 characters): Arterial stiffness & CKD changes

2. Writing Group:
Esther Kim, Shoshana H. Ballew, Yingying Sang, Hirofumi Tanaka, Michelle Meyer, Josef Coresh, Gerardo Heiss, Kunihiro Matsushita, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. EK **[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: Once the proposal is approved, we will begin analysis using available data from the ARIC study visit 7. A manuscript will be completed within 6 months after approval.

4. Rationale:
Arterial stiffness is implicated as a potential mediator of cardiorenal interaction. Indeed, several previous studies including ours reported cross-sectional associations between measures of chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] or albuminuria) and arterial stiffness (mainly central stiffness).[1-10] For example, we recently reported that measures of central arterial stiffness, carotid-femoral pulse wave velocity (cfPWV) in particular, were strongly associated with lower eGFR.[1] However,

those cross-sectional studies were unable to examine temporality between arterial stiffness and reduced kidney function.

In this context, a handful of studies have conducted longitudinal studies examining changes in kidney function and arterial stiffness.[2, 5, 6, 10, 11] The results, however, have been inconclusive, with some studies reporting positive associations while others reporting no associations. Moreover, the studies were limited by examining only one measure of CKD (eGFR), but not albuminuria, and limited arterial segments (cfPWV or baPWV) in mostly small study populations (n<1000).

With the recently available visit 7 data from the ARIC study, we propose to address the limitations of the past longitudinal studies by examining PWV at six arterial segments (carotid-femoral [cfPWV], heart-carotid [hcPWV], heart-femoral [hfPWV], heart-ankle [haPWV], brachial-ankle [baPWV], and femoral-ankle [faPWV]) at visit 5 with subsequent changes in both measures of CKD (eGFR and albumin-creatinine ratio [ACR]) measured through visits 5-7. We hypothesize that higher arterial stiffness (particularly central arterial stiffness) contributes to greater changes in eGFR and ACR over time. The ARIC study data at visits 5, 6, and 7 will therefore provide a unique and timely opportunity for us to elucidate the potential temporality in the association between arterial stiffness and CKD among older adults.

5. Main Hypothesis/Study Questions:
Greater arterial stiffness (cfPWV, hfPWV, hcPWV, haPWV, baPWV, faPWV) are associated with decreased eGFR and increased ACR over time, independent of other conventional cardiovascular and kidney 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 PWV and kidney disease measures (serum creatinine and cystatin C and albuminuria) at visits 5, 6, and 7

Exclusions:
- Race other than black or white
- Missing data on kidney disease measures
- Missing PWV
- Missing covariates of interest

Exposure (independent variables):

Arterial stiffness measures at visits 5:
- cfPWV (indicates central arterial stiffness)
- hfPWV (indicates central arterial stiffness)
- hcPWV (indicates central arterial stiffness)

- haPWV (indicates composite of central and peripheral arterial stiffness)
- baPWV (indicates composite of central and peripheral arterial stiffness)
- faPWV (indicates peripheral arterial stiffness)
- Ankle-brachial index (ABI) (we will also explore ABI since high ABI is considered as a marker of lower extremity arterial stiffness[12])

Outcome (dependent variables):

- eGFR: eGFR will be calculated using the recently proposed CKD-EPI equation[13, 14] incorporating data of cystatin C, age, gender, and race at visits 5, 6, and 7 and measured in ml/min/1.73 m^2. We will be using cystatin C as a filtration marker to avoid misclassification of kidney function with creatinine in older adults.

- Albuminuria: As recommended in clinical guidelines,[15] urinary albumin-to-creatinine ratio (ACR) will be used as a measure of albuminuria at visits, 5, 6, and 7.

Other variables of interest and covariates:

- Sociodemographic factors: age, race, gender, education level
- Physical information: body mass index, blood pressure
- Lifestyle: smoking status, alcohol habit
- Comorbidities: Diabetes, history of cardiovascular disease (coronary heart disease, stroke, and heart failure), total cholesterol, high density lipoprotein
- Medication: antihypertensive medication

We will have updated covariate values at visits 5, 6, and 7 for body mass index, blood pressure, smoking status, alcohol habit, comorbidities, and medication.

Statistical analysis plan:

The primary analysis will use generalized estimating equation (GEE) to estimate the marginal effect of each arterial stiffness measure on the rates of eGFR and ACR change over the study visits (5-7), since we are interested in the population-level effect of arterial stiffness on kidney disease. Also, due to the highly variable nature of ACR, examining the within-participant difference in ACR may not capture a true change in ACR related to arterial stiffness measures. We will also run mixed-effects models with random intercept and slopes, but we anticipate that the mixed-effects models will most likely provide similar marginal estimates as the GEE approach.

We will graph and generate correlation and variance matrices of eGFR and ACR residuals over time to estimate the appropriate working correlation structure. We will adjust for the covariates listed above (with time-updated covariate values if available). We will test for potential interactions between arterial stiffness and age, gender, race, and presence/absence of comorbidities such as diabetes and cardiovascular disease.

To address potential bias due to attrition of participants after visit 5, we will re-run our analyses using inverse probability of attrition weighting (IPAW) methods as a sensitivity analysis.[16] Similar to IPAW methods used in previous ARIC publications,[17-19] we will

estimate the marginal and conditional probability of remaining in the study to generate base and stabilized weights using data prior to visit 5 (mainly visit 4 data and follow-up data [annual/semiannual and hospitalization]).[17]

As the relationship between arterial stiffness and CKD is most likely bidirectional, as a secondary analysis, we will also examine the marginal effect of eGFR and ACR at visit 5 on the rates of change in PWV over the study visits (5-7).

Limitations:

- Possibility of residual confounding
- The results may not be generalizable to younger population or ethnic groups 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 ____ 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)?

There are no proposals looking at the association between PWV measures and CKD in ARIC using visit 5 and visit 7 data. We have previously examined the cross-sectional relationship between PWV measures and CKD at visit 5 (MP #2241).

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* _____)

_X__ 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.

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