ARIC Manuscript Proposal #4099

PC Reviewed: 8/9/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Prevalence and progression of CKD in an older community-based population

b. Abbreviated Title (Length 26 characters): Older adults and CKD

2. Writing Group:

Writing group members: Shoshana H Ballew, Aditya Surapaneni, Jesse Seegmiller, Josef Coresh, Morgan Grams, *others welcome* (order TBD).

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MG___ **[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: Analyses will begin once the manuscript proposal has been approved. We anticipate that the manuscript will be written and submitted to the ARIC Publications Committee within one year of the manuscript proposal being approved.

4. Rationale: The prevalence of CKD is high, at 14.4% of the US population with CKD based on decreased eGFR or high albuminuria.[1] Older adults have an exceptionally high prevalence of CKD, with some studies estimation >50% prevalence at age 70 and older.[2] Serum creatinine is recommended as the primary filtration marker for eGFR in current KDIGO guidelines[3], although this marker is affected by non-kidney determinants such as muscle mass, which raises concerns of misclassification in older individuals. In response to the controversial use of race coefficients in clinical algorithms, the CKD Epidemiology Collaboration developed a

new creatinine -based eGFR equation without adjustments for race[4] that has been recommended for immediate implementation.[4,5]

In addition to this new equation, interest in using cystatin C, which is another major filtration marker, is growing because it is not affected by muscle mass and its GFR equation does not use a race coefficient and may be more strongly associated with adverse outcomes.[6,7] However, cystatin C can also be affected by non-GFR determinants, including inflammation, adiposity, type 2 diabetes, and thyroid dysfunction.[8,9] Another marker, beta-2-microglobulin, does not have these non-GFR determinants and has also been shown to be strongly associated with outcomes.[10-12] The differences in prevalence by age and filtration marker (creatinine vs. cystatin vs. beta-2-microglobulin) and the risk of CKD progression (40% decline in eGFR) is less well known.

5. Main Hypothesis/Study Questions:

Aim 1: To estimate the prevalence of CKD in a population of older community-dwelling adults and sensitivity to adding cystatin C as a filtration marker.
Aim 2: To compare differences in estimates of eGFR by filtration markers in a population of older community-dwelling adults.
Aim 3: To estimate risk of CKD progression in a population of older community dwelling adults.

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: We will conduct analyses of the ARIC cohort, treating Visit 5 as the baseline visit.

Study Population: The study population will consist of white and African-American ARIC participants with data on kidney function from Visit 5 and follow-up for kidney outcomes.

Exposure: We will evaluate prevalence of CKD stages (by eGFR and urine albumin-to-creatinine ratio) stratified by 5-year age category. We will look at persistence of CKD from the lab repeat visit on a subsample of visit 5 participants. Other covariates will include sex, race, diabetes, blood pressure, BMI, prevalent CVD, and heart failure.

Outcomes: Creatinine-based and/or cystatin-based Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equations will be used to estimate GFR.[13,14] CKD progression will be defined as having a 40% decline in eGFR at the subsequent visit 6 (may also look at visit 7 as well) or ESRD as identified by the US Renal Data System (USRDS) registry.[15-17] We will also evaluate eGFR defined by creatinine alone, cystatin alone, creatinine and cystatin, and a multimarker approach to estimating GFR (e.g., creatinine, cystatin C, beta-2-microglobulin).

Statistical Analysis: We will use descriptive statistics, including means, medians, and proportions to compare kidney function by age categories at Visit 5. For CKD progression, we

will analyze the association of age with CKD progression, adjusting for other demographic characteristics as well as, in subsequent models, additional comorbidities and kidney function at baseline. We will also evaluate the competing risk of death using multinomial models. We will also look at the risk factors for discordance between progression by different eGFR equations.

Limitations: We acknowledge that our proposed study has a few limitations. First, we are only using data from Visit 5 onwards in order to capture an older population. We will only have a single visit for prevalence. Second, the risk of death is high and can preclude the development of CKD progression.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X__ 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? __X__ 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)?
No manuscript proposals examining the prevalence of CKD by different filtration markers in the visit 5 and older population. Some related proposals looking at kidney function in older adults and alternative filtration markers are listed below:

MS#3853: Testican-2 and CKD progression
MS#3735: Association between Kidney Function and Lipid Levels in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study
MS#3730: Diabetes and estimated glomerular filtration rate decline in older adults: The Atherosclerosis Risk in Communities (ARIC) Stud
MS#3052: Association between Kidney Function and Lipid Levels in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study

MS#2919: The association of kidney disease measures with physical function in older adults: The Atherosclerosis Risk in Communities (ARIC) Study
MS#2444: Blood biomarkers as predictors of end-stage renal disease and mortality – meta-analysis

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __ __ Yes _X___ No

11.b. If yes, is the proposal

_ __ A. primarily the result of an ancillary study (list number*_____)
_ _ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __2011.03_(Selvin for funding on visit 6 labs, Matsushita for funding of visit 3 labs))

*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, approved manuscripts using 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 __**X**__ No.

References

1. United States Renal Data System. *2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States.* National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2021.
2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA.* 2007;298(17):2038-2047.
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney inter, Suppl.* 2013;3(1):1-150.
4. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med.* 2021;385(19):1737-1749.
5. Delgado C, Baweja M, Crews DC, et al. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *J Am Soc Nephrol.* 2021;32(12):2994-3015.
6. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367(1):20-29.
7. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med.* 2013;369(10):932-943.
8. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int.* 2009;75(6):652-660.
9. Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Measured and estimated glomerular filtration rate: current status and future directions. *Nat Rev Nephrol.* 2020;16(1):51-64.
10. Astor BC, Shafi T, Hoogeveen RC, et al. Novel Markers of Kidney Function as Predictors of ESRD, Cardiovascular Disease, and Mortality in the General Population. *Am J Kidney Dis.* 2012;59(5):653-662.
11. Inker LA, Mondal H, Greene T, et al. Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis. *Am J Kidney Dis.* 2016;68(3):392-401.
12. Foster MC, Coresh J, Hsu CY, et al. Serum beta-Trace Protein and beta2-Microglobulin as Predictors of ESRD, Mortality, and Cardiovascular Disease in Adults With CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis.* 2016;68(1):68-76.
13. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.
14. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367(1):20-29.
15. Rebholz CM, Selvin E, Liang M, et al. Plasma galectin-3 levels are associated with the risk of incident chronic kidney disease. *Kidney Int.* 2018;93(1):252-259.
16. Sumida K, Kwak L, Grams ME, et al. Lung Function and Incident Kidney Disease: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis.* 2017;70(5):675-685.
17. Tin A, Scharpf R, Estrella MM, et al. The Loss of GSTM1 Associates with Kidney Failure and Heart Failure. *J Am Soc Nephrol.* 2017;28(11):3345-3352.