1.a. Full Title: The association of kidney disease measures with physical function in older adults: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): Kidney & physical function

2. Writing Group:
   Writing group members: Yugo Shibagaki, Shoshana H. Ballew, Priya Palta, Beverly Gwen Windham, Josef Coresh, Kunihiro Matsushita, Others welcome

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

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3. Timeline: Analysis will begin following proposal approval and compilation of visit 5 data. A manuscript will be completed within 6 months after receiving necessary data for this proposal.

4. Rationale:
Chronic kidney disease (CKD) is highly prevalent among older adults in the US, with one third of US population experiencing CKD during the lifetime\(^1\). CKD increases the risk of various outcomes such as mortality, cardiovascular disease, and infectious disease\(^2\). Moreover, in the last decade, a number of studies have reported that CKD is also related
to reduced physical function. However, most of those studies examined only reduced kidney function\textsuperscript{3-33} but not the other key measure of CKD, albuminuria. Given that the KDIGO (Kidney Disease Improving Global Outcomes) CKD guideline emphasizes the characterization of CKD with both glomerular filtration rate (GFR) and albuminuria\textsuperscript{34}, it is of importance to quantify the associations of these two CKD measures with physical function. Although there have been a few studies investigating GFR and albuminuria in this context\textsuperscript{6,8,32,33}, those were either small\textsuperscript{8,32} or examined limited measures of physical function (e.g., walking speed)\textsuperscript{6,33}. In addition, none of those previous studies explored whether cognitive function, a condition tightly related to physical function as represented by the concept of “motoric cognitive risk syndrome”\textsuperscript{35-38}, modifies the association between CKD and physical function (i.e., lower cognition will intensify the association between physical function and CKD). Therefore, we will quantify the associations of GFR and albuminuria with a comprehensive objective measure of physical function, the Short Physical Performance Battery (SPPB)\textsuperscript{39}, and grip strength and then test whether cognitive function modifies these associations mainly using data from visit 5 of the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:
Both CKD measures, GFR and albuminuria, will be associated with reduced physical function, and these associations may be modified by cognitive function.

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 participants with data on kidney disease measures (serum creatinine and cystatin C and albuminuria) and physical function (SPPB and grip strength) at visit 5

Exclusions:
- Race other than black or white
- Missing data on kidney disease measures, SPPB, or grip strength

Exposure (independent variables):
- estimated GFR (eGFR)
  eGFR will be primarily calculated using the recently proposed CKD-EPI equation by cystatin C 11) to avoid confounding by muscle mass on serum creatinine and physical function. Nonetheless, we will secondarily investigate eGFR based on serum creatinine or both serum creatinine and cystatin C. Although we will first focus on eGFR at visit 5, we will also assess the association of eGFR overtime (cumulative exposure and change across visits 1 through 5 [cystatin C is available at visits 2, 4, and 5 and serum creatinine was additionally available at visit 1]) with measures of physical function at visit 5.
As recommended in clinical guidelines, we will use urinary albumin-to-creatinine ratio (ACR) as a measure of albuminuria. As will be done for eGFR, our primary exposure will be ACR at Visit 5, but we will also assess ACR overtime (from visit 4 to visit 5).

**Outcome (dependent variables):**
- Physical function by Short Physical Performance Battery (SPPB) at Visit 5
  - Chair stands
  - Standing balance
  - Four-meter walk
- Grip strength

**Other variables of interest and covariates:**
- Sociodemographics: age, race, gender, education level
- Physical information: body mass index, waist circumference, blood pressure, heart rate
- Lifestyle: smoking status, alcohol habit, and physical activity
- Comorbidities: Diabetes, hypertension, dyslipidemia, and history of CVD (coronary heart disease, stroke, and heart failure), cognitive function, inflammation (high-sensitivity C-reactive protein)
- Medication: number of medications, medications can interfere with cognitive function
- Cognitive function at visit 5: 1) memory—Delayed Word Recall Test (DWRT), Incidental Learning Test, and Logical Memory Test I and II; 2) language—Word Fluency Test, Animals Naming Test, and Boston Naming Test; 3) processing speed/attention—Digit Symbol Substitution Test (DSST), Digit Span Backwards Test, and Trail Making Test Parts A and B; and 4) global function Mini Mental State Examination (MMSE).

As done in previous ARIC projects, these cognitive function parameters will be treated as continuous and categorical variables (e.g., continuous Z score and level of impairment [normal, mild cognitive impairment, dementia]).

**Statistical Analysis Plan:**
The primary analysis will use linear regression models to quantify the association between kidney disease measures and physical function measures. eGFR and ACR will be treated as continuous variables with splines and categorical variables based on clinical categories (eGFR: <15, 15-29, 30-44, 45-59, 60-89, and 90+ ml/min/1.73m² and ACR: <10, 10-29, 30-299, and 300+ mg/g) in the models. We will also run logistic regression models with dichotomized dependent variables (e.g., SPPB score ≤6 as reduced overall physical function and ≤2 point for each of SPPB component). We will adjust for the covariates listed above.

To assess potential effect modification by cognitive function (overall as well as each domain), we will conduct stratified analysis by cognitive function and test interaction by incorporating its product terms with kidney disease measures. We will repeat the analysis after stratifying the study sample by age, gender, race, and presence/absence of comorbidities such as diabetes and cardiovascular disease.

We will conduct a few sensitivity analyses. Firstly, to evaluate the impact of extreme values, we will exclude individuals with CKD stage 5 (eGFR <15) or ESRD prior to visit...
5. Similarly, we will evaluate whether the exclusion of participants with significant impairment of cognition (MMSE < 10) alter our main results.

Limitations:
A cross-sectional design will not allow us to evaluate temporality of the associations or potential effect modifications. As with any observational study, we will not be able to rule out the 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?  __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”?  ____X____
      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.cscu.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)?

      A published ARIC article about CKD and frailty (Am J Kidney Dis. 2016 Nov 21. pii: S0272-6386(16)30525-X) based on ARIC MP# 2303 would be most relevant. However, the current proposal will be uniquely investigate the SPPB summary score as well as chair stand and standing balance. Also the key authors from that project are included in this proposal.
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)* __________ __________)

*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.

References


