ARIC Manuscript Proposal # 1914

1.a. Full Title: Age-, gender-, and race-interaction on the association of chronic kidney disease with cardiovascular disease: the Atherosclerosis Risk in Communities Study

  b. Abbreviated Title (Length 26 characters): Demographic-CKD interaction

2. Writing Group:
   Writing group members: Xuan Hui, Kunihiro Matsushita, Yingying Sang, Josef Coresh

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

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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) is identified as a common condition that elevates the risk of cardiovascular disease as well as all-cause mortality. Accumulating evidence has been

shown that reduced eGFR and elevated albuminuria are independently associated with clinical risk (1, 2). Individuals with CKD are known to die of cardiovascular disease than to develop kidney failure (3). CKD is defined as either decrease in kidney function (glomerular filtration rate [GFR] <60 ml/min/1.73m^2) or presence of kidney damage (urinary albumin excretion of $\geq$ 30mg/day) (4). Once CKD is defined, CKD stages are determined by the level of glomerular filtration rate (eGFR) (2). Although GFR of 15, 30, 45, 60, and 90 are usually used as thresholds of CKD staging, some propose age-, gender-, and race-specific cut-points (5).

However, little is actually known whether the associations of GFR and albuminuria with clinical outcomes are consistent or not in different subgroups according to age, gender, and race. Regarding gender and race, most of the previous studies more focus on gender or racial disparities in risk among CKD population (6-13) and have not assessed whether the contribution of CKD to clinical risk is similar between genders and racial/ethnic groups (14). In terms of age, a recent meta-analysis has shown that, although relative risk of mortality is slightly lower in elderly (age $\geq$65 years) than young individuals (<65 years), the relationship between kidney measures and mortality was largely consistent in these two age groups (ref. CKD-PC phase 1 papers). These meta-analyses selected cardiovascular mortality as a cardiovascular outcome. Since mortality can be affected by healthcare system or different selection of treatment in subgroups by age, gender, and race, to assess biological interaction, it is preferable to assess cardiovascular disease with non-fatal events. Also, to our knowledge, no studies have assessed potential effect modification by age, gender, and race in the same study population, leaving uncertainty about relative importance between these demographic variables.

Therefore, the objective of this study is to investigate whether contribution of low eGFR to increased risk of cardiovascular disease is consistent or not among subgroups according to age, gender, and race in the middle-aged bi-ethnic cohort, with implications of age-, gender-, and race-specific thresholds of GFR for CKD staging. Since recent reports suggest using albuminuria in addition to GFR for CKD staging and risk classification (15, 16), we are particularly interested in eGFR-risk relationship in the context of albuminuria. Also, we will evaluate interaction between demographic variables and albuminuria. We will use the CKD-EPI equation in our analysis since clinical guidelines would recommend this equation and comprehensive assessment of interaction of demographic variables with CKD-EPI eGFR would be clinically relevant.

5.   Main Hypothesis/Study Questions:
The association of reduced GFR and high albuminuria with cardiovascular outcomes (coronary heart disease, heart failure, stroke) is consistent or not in subgroups according to age, gender, and ethnicity.

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 measured serum creatinine, albuminuria and variables required for GFR estimation (age, gender, and race).

Exclusion:
Ethnicity other than black and white.
Individuals with missing data of covariates.

Exposures:
eGFR: CKD-EPI eGFR
ACR: using albumin-to-creatinine ratio

Outcomes:
1. Coronary events including a hospitalized myocardial infarction (MI), fatal CHD, cardiac procedure
2. Heart failure: HF hospitalization or death from HF coded 428 according to the ICD-9 or I50 for ICD-10[17, 18]
3. Stroke: definite and possible incident stroke Composite cardiovascular disease: Coronary heart disease, heart failure and stroke.
4. All-cause mortality

We will conduct a series of stratified analysis to test interaction. To maximize statistical power for stratified analysis, our primary cardiovascular outcome is composite CVD. Specific cardiovascular disease will be analyzed as secondary outcomes.

Other variables of interest and covariates:
- Sociodemographic factors: age, gender, and ethnicity
- Physical information: systolic blood pressure, diastolic blood pressure, body mass index (BMI)
- Lifestyle: smoking habit
- Comorbidities: hypertension (defined as antihypertensive medication use & blood pressure ≥140/90 mmHg), diabetes, history of cardiovascular disease (coronary heart disease; heart failure; stroke at baseline)

Analytic plan:
We will conduct subgroup analysis stratifying by age, gender and ethnicity to see if the associations between kidney measures and cardiovascular disease are consistent in different subgroups according to age (< vs. ≥65 years), gender (female vs. male) and race (white vs. black). The primary analysis will use Cox proportional hazards models to quantify the association between eGFR and ACR with cardiovascular disease and all-cause mortality. First, both eGFR and ACR will be modeled as continuous variables with splines (knots at 30, 45, 60, 75, 105 mL/min/1.73 m^2 for eGFR and 10, 30, 300 mg/g for ACR). To evaluate interaction, models with and without product terms between kidney measures and potential effect modifiers will be tested. Using the model with the product terms, we will evaluate the ratio of hazard ratio between subgroup, reflecting multiplicative interaction, at each 1-unit of eGFR and ACR. Overall interaction will be

tested based on likelihood ratio test comparing those two models. We will also test interaction based on categories of the combination of eGFR (<30, 30-44, 45-59, 60-75, 75-89, 90-105, and 105+) and ACR (<10, 10-29, 30-299, and 300+).

Limitations:
We will not be able to rule out the possibility of residual confounding.
The single measure of serum creatinine and ACR might be another problem.

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

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)?
MP1123: Albuminuria and kidney function as pridictors of cardiovascular events mortality; Astor, B.

MP1362: Chronic kidney disease and risk of end-stage renal disease: The Atherosclerosis Risk in Communities Study; Bash, L.

MP1449: Comparison of a novel equation for estimated glomerular filtration rate with a conventional one regarding the association with coronary heart disease, stroke, and all-cause mortality: The Atherosclerosis Risk in Communities (ARIC) Study; Matsushita, K.

MP1823, "Interaction of chronic kidney disease with classical cardiovascular risk factors. Pooled analysis of general population cohorts"; Matsushita K.

These would be most relevant proposals. However, MP1123, 1362, and 1449 do not focus on interaction, and MP1823 does not deal with non-fatal CVD. Also, the key authors of these proposals 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.

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