ARIC Manuscript Proposal #2619

PC Reviewed: 9/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Interaction of chronic kidney disease with obesity

b. Abbreviated Title (Length 26 characters): **CKD and obesity**

2. Writing Group:

Writing group members: Alex Chang, Morgan Grams, Shoshana Ballew, Kunihiro Matsushita, Mark Woodward, and others for the CKD prognosis consortium.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. M.G. **[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:

Data analysis will start immediately. A manuscript is expected to be prepared within 12 months.

4. Rationale:

The CKD Prognosis Consortium (CKD-PC) in an international consortium established in 2009 after a controversies conference sponsored by the Kidney Disease: Improving Global Outcomes (KDIGO). Since then CKD-PC has been aiming to conduct sophisticated meta-analyses to inform CKD clinical guidelines and improve CKD clinical practice and research. Indeed, several articles from CKD-PC have been cited in the

KDIGO 2012 clinical guidelines for CKD and create a basis for new CKD staging system based on both glomerular filtration rate (GFR) and albuminuria. CKD-PC will continue to explore clinically important questions surrounding nephrology care.

In order to expand on previous consortium papers regarding the interaction of CKD and several factors,[1-4] we will evaluate whether the impact of eGFR and albuminuria on clinical outcomes (mortality, cardiovascular disease, and kidney outcomes) is modified by obesity or not. This will address the clinically relevant questions of whether CKD staging and prognosis need to be tailored according to adiposity or body composition. For the obesity parameter, we will expand beyond BMI to look at other measures of anthropometry including waist circumference and waist-hip ratio.

5. Main Hypothesis/Study Questions:
Evaluation of and potential interaction of CKD with obesity in the risk of mortality, cardiovascular disease, and kidney outcomes.

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).
Population: All ARIC participants at Visit 4 with data on estimated glomerular filtration rate (eGFR) and albuminuria will be included. CKD will be defined as eGFR (using serum creatinine or cystatin C[5]) < 60 mil/min/1.73 m^2 or urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g.

Exposure Variables from ARIC visit 4:
- eGFR (serum creatinine). eGFR will be assessed by CKD-EPI epi equation.[6]
- Albuminuria (urinary albumin-to-creatinine ratio). Albuminuria will be expressed as urinary albumin-to-creatinine ratio (ACR).

Interacting/Confounding Variables from ARIC visit 4 or closest exam:
- Demographics: Age, sex, race, socioeconomic status, geography
- Medical history/comorbidities: history of cardiovascular disease (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, stroke, or peripheral artery disease), hypercholesterolemia, hypertension, diabetes mellitus
- Laboratory variables: cholesterol levels (total, HDL, LDL), triglycerides, glucose levels with fasting status, smoking (current, former, never), hemoglobin A1c
- Vital measurements: systolic blood pressure, diastolic blood pressure, heart rate, anthropometry (BMI [height, weight], waist circumference, waist-hip ratio)
- Interfering medication: antihypertensive medications including ACE inhibitors /ARB, cholesterol-lowering medication (Statins), as well as glucose lowering medication.

Outcome Variables:
- All cause mortality + Follow-up time

- Cardiovascular mortality (death from myocardial infarction, sudden cardiac death, heart failure, stroke) + Follow-up time
- End-stage renal disease (initiation of dialysis, kidney transplantation, death coded due to kidney disease) + Follow-up time
- Coronary heart disease + Follow-up time
- Heart failure + Follow-up time
- Stroke + Follow-up time
- Peripheral artery disease + Follow-up time
- Sudden cardiac death + Follow-up time

Brief analysis plan and methods:
Various cohorts from North America, Europe, Asia, and Australia will be pooled on individual participant level. Both continuous and categorical representations of eGFR and albuminuria will be explored, using Cox proportional hazards models. In predicting both renal and cardiovascular outcomes, interaction of albuminuria and eGFR with obesity will be assessed.

A. First, we will use categorical analysis, with CKD being defined according to the clinically relevant categories that were evaluated in the phase 1 meta-analysis of the CKD-PC collaboration:

- eGFR > 105
- eGFR 90–105 (reference category)
- eGFR 75–90
- eGFR 60–75
- eGFR 45–60
- eGFR 30–45
- eGFR 15–30
- eGFR <15, because the expected number of subjects in this category will probably very low, these individuals might be excluded from the analysis.

The association of eGFR and albuminuria with outcomes will be reported according to BMI categories.

B. We will evaluate the continuous association of eGFR and albuminuria with incidence rates of renal and cardiovascular outcomes using Cox proportional hazard models incorporating spline terms for eGFR with knots at 45, 60, 75, 90 and 105 mL/min/1.73 m^2 and albuminuria with knots at 10, 30, 300mg/g with and without adjustment for age, sex, race, BMI, anthropometry, and other atherosclerosis risk factors. These will be presented according to BMI categories.

C. Potential effect modification by obesity status will be evaluated by formally meta-analyzing statistics indicating the difference in hazard ratios across subgroups (e.g., beta for interaction term).[1-4]

Summary/conclusion:
By pooling various cohorts, from all over the world, on individual participant level; we will be able to rigorously assess potential interaction of CKD with obesity in the risk of mortality, cardiovascular disease, and kidney outcomes. These results will serve as key work for future guidelines and patient care.

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)?
MP#594: Body mass and renal function in ARIC
MP#1823: Interaction of chronic kidney disease with classical cardiovascular risk factors. Pooled analysis of general population cohorts
MP#2369: Obesity, weight distribution and risk of acute kidney injury in the Atherosclerosis Risk in Communities (ARIC) Study

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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. Mahmoodi BK, Matsushita K, Woodward M, et al. Effect modification by hypertensive status of the association of chronic kidney disease measures with mortality and end-stage renal disease: meta-analysis of 1,127,656 individuals from 45 cohorts. Lancet In Press.
2. Fox CS, Matsushita K, Woodward M, et al. Associations of Kidney Disease Measures with Mortality and End-Stage Renal Disease in Individuals With and Without Diabetes: A Meta-analysis of 1,024,977 Individuals. Lancet In Press.
3. Grams ME, Sang Y, Ballew SH, et al. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex With Acute Kidney Injury. Am J Kidney Dis 2015;Epub ahead of print.
4. James MT, Grams ME, Woodward M, et al. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Diabetes Mellitus, and Hypertension With Acute Kidney Injury. Am J Kidney Dis 2015;Epub ahead of print.
5. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis 2008;51:395-406.
6. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.