ARIC Manuscript Proposal # 3074

PC Reviewed: 11/14/2017	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between obesity and kidney function trajectories: the Atherosclerosis Risk in Communities study

b. Abbreviated Title (Length 26 characters): Obesity and eGFR decline

2. Writing Group:
Writing group members: Zhi Yu, Morgan Grams, Chiadi Ndumele, Eric Boerwinkle, Kari North, Josef Coresh

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

F**irst author**: Zhi Yu, MS
Address: 2024 E. Monument, B-314E
Baltimore MD 21287

Phone: 617-583-3861
E-mail: zyu33@jhmi.edu

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).

Name: Josef Coresh, MD PhD
Address: Welch Center for Prevention, Epidemiology & Clinical Research
2024 E. Monument St., Suite 2-600
Baltimore, MD 21287

Phone: 410-955-0495 Fax: 410-955-0476
E-mail: coresh@jhu.edu

3. Timeline: Data analysis to start after approval of this manuscript proposal, abstract available by January 2018, first draft available by June 2018.

4. Rationale:
Kidney function trajectories have long been used in the estimation of time to end-stage renal disease (ESRD) (1). Recently, kidney function change over time has been related not only to ESRD but also to all-cause mortality and cardiovascular disease risk (2-4). Evidence presented at a Food and Drug Administration conference in 2012 suggests that a decline in estimated glomerular filtration rate (eGFR) of 30%-40% may be a suitable surrogate endpoint in clinical trials (5). Rapid chronic kidney disease (CKD) progression,

defined as a sustained decline in eGFR by more than 5 ml/min/1.73 m^2 per year according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (6), has been associated with increased risk of death, heart failure, myocardial infarction, peripheral artery disease, and death from stroke (4, 7-10). Understanding risk factors for different patterns of kidney function trajectories is important so that individuals at risk for rapid progression may be targeted for interventions to slow kidney disease progression and to decrease risk for associated adverse outcomes.

Obesity is associated with increased risk of incident CKD (11), ESRD (12), and mortality (13), according to some studies. Recent evidence suggested that higher body mass index (BMI) categories are associated with greater decline in kidney function trajectories among young and healthy adults (14). However, the relationship between obesity and eGFR decline in an older population, among whom the prevalence of kidney disease is highest and increasing most rapidly, is not known. There may be difference given previous findings that the association between BMI and rapid loss of kidney function attenuated among older subjects (15).

Using 29 years of kidney function data in the Atherosclerosis Risk in Communities (ARIC) cohort (1987–1989 (baseline) to 2016–2017), we propose to examine the association between obesity and patterns of eGFR change over time in a community-based population. Obesity status will be assessed by BMI at baseline, BMI at age 25, cumulative weight history using trapezoidal rule, waist-hip-ratio, waist circumference, as well as genetic risk score of obesity. GFR will be estimated using serum creatinine, cystatin C, combination of serum creatinine and serum cystatin C (16), and Beta 2 microglobulin (17). We will evaluate the relationships between obesity and incidence of CKD and ESRD as secondary analyses.

5. Main Hypothesis/Study Questions:

Aim 1: Update trajectories of kidney function across 29 years of follow-up.

Hypothesis: Trajectories of kidney function will be steeper at older age using cystatin C compared to serum creatinine eGFR.

Aim 2: Evaluate associations of obesity with kidney function trajectories.

Hypothesis 1: Overweight and obese participants will have steeper rates of eGFR decline. Overweight and obesity measured by BMI at baseline, BMI at age 25, and cumulative weight history will be associated with steeper eGFR decline. Participants with higher waist-hip-ratio and waist circumference will also have steeper rates of eGFR decline. Genetic risk score of obesity will be associated with eGFR decline, providing evidence for a causal relationship.

Hypothesis 2: The associations between obesity with kidney function trajectories will be stronger using cystatin compared to creatinine.

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: Prospective cohort analysis beginning at ARIC visit 1

Inclusion/Exclusion Criteria: The study population will consist of all diabetes-free ARIC participants with eGFR>60 ml/min/1.73 m^2 at visit 1 and measured baseline BMI.

Outcome variables: eGFR trajectories will be modeled using estimates based on creatinine (visits 1, 2, 4, 5, and 6), cystatin C (visits 2, 4, 5, 6), combination of serum creatinine and serum cystatin C, and Beta 2 microglobulin (visits 2,4,5,6) separately. For persons with additional available creatinine values, such as those hospitalized for coronary heart disease or heart failure since 2005, or those who were known via linkage to the United States Renal Data System to progress to end-stage renal disease, we will separately estimate eGFR trajectories using both study visit and clinically captured data.

Exposure variables: Obesity will be measured by BMI at baseline, BMI at age 25, cumulative weight history using trapezoidal rule, waist-hip-ratio, waist circumference, as well as a composite genetic risk score of obesity. All these variables will be categorized after we examine their distributions.

Summary of data analysis:
eGFR trajectories modeled using estimates based on creatinine, cystatin C, combination of serum creatinine and serum cystatin C, and Beta 2 microglobulin will be separately estimated using mixed models with random intercepts and random slopes. We will evaluate slopes as linear and with knots (at 3 years, 9 years, and 23-24 years when using time of follow-up as time metric; at age 55 when using age as time metric). Because persons with ESRD are much more likely to miss subsequent follow-up visits, we will impute eGFR as 15 ml/min per 1.73 m2 at the time of ESRD onset in the primary analysis. Unbiased prediction estimates of eGFR slope over time will be obtained for each group of each obesity measurement in unadjusted and adjusted analyses. Risk factors will be used in adjustment are age, sex, race-center, hypertension (systolic BP and medication), HDL cholesterol, prevalent cardiovascular diseases, smoking status, uric acid, incorporating interaction terms of each risk factor with time. All continuous risk factors will be centered. We will further adjust for APOL1 risk status in sensitivity analysis. We will also try evaluating some of the risk factors in a time-varying manner or excluding participants who develop diabetes during follow-up in sensitivity analyses.

We will also analyze CKD (defined as eGFR<60 or hospitalization) and ESRD incidence (using USRDS linkage) as secondary outcomes and compare their associations with obesity to those of eGFR trajectories. We hypothesize that obesity may be more strongly associated with eGFR decline and CKD incidence than ESRD due to secondary weight loss, particularly at visits more proximal to the onset of ESRD (e.g. reverse causation).

Potential limitations: Anticipated methodologic limitations include the effect of informative drop-out. Those who miss follow-up study visits are more likely to have baseline CKD, and they may be more likely to have rapid declines in eGFR. We will

address this issue by modeling several different ways – imputing GFR for those who develop ESRD, using additional eGFR from creatinine abstracted from hospitalization data, and evaluating eGFR trajectories using Washington County Hospital data. Our measures of BMI are only at age 25 (by self-report which has limitations) and study visits (with a long gap between visit 4 and visit 5).

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? _X__ Yes ____ 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.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)?

#2370: Risk factors associated with kidney function trajectories: the Atherosclerosis Risk in Communities study

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
_X__ 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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