ARIC Manuscript Proposal #2370

PC Reviewed: 5/13/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Risk factors associated with kidney function trajectories: the Atherosclerosis Risk in Communities study

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

2. Writing Group:
Writing group members: Morgan Grams, W.H. Linda Kao, Elizabeth Selvin, Casey Rebholz, Josef Coresh. Others are welcome to join.

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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3. Timeline: Data analysis to start after approval of this manuscript proposal, abstract available by December 2014, first draft available by June 2015.

4. Rationale:

Kidney function trajectories have long been used in the estimation of time to end-stage renal disease (1). Recently, kidney function change over time has been related not only to end-stage renal disease 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 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.

Persons with proteinuria are at particularly high risk for chronic kidney disease progression (11). A recently discovered genetic variant of the *APOL1* gene may underlie this relationship, at least in part: APOL1 high-risk status has been associated with higher rates of proteinuria as well as higher rates of kidney function decline in persons with chronic kidney disease (12). However, whether this relationship holds true in the general population in not known. Some have argued that the presence of two high-risk variants of *APOL1* is not sufficient to cause accelerated kidney function decline, and that a "second hit" is necessary (13). Persons with renal risk variants in *APOL1* with chronic kidney disease may have already experienced a "second hit," and therefore their kidney function trajectories may exaggerate risk associated with *APOL1* risk variants.

Other risk factors may influence kidney function trajectories. There is some evidence that, compared with Caucasians, African-Americans experience an increase in eGFR in young adulthood followed by a more rapid decrease in eGFR. Most new cases of chronic kidney disease occur after the age of 70 (14). Whether the rate of kidney function decline is constant by age is uncertain. Cumulative exposure to high blood pressure, elevated blood glucose, or poor diet may correspond to trajectories in kidney function. Certain medications such as angiotensin converting enzyme (ACE) inhibitors are thought to slow kidney function decline, at least in the case of proteinuria (6).

Using 25 years of kidney function data in the Atherosclerosis Risk in Communities (ARIC) cohort, we propose to characterize kidney function trajectories in a community-based population as well as to evaluate risk factor associations with patterns of eGFR change over time.

5. Main Hypothesis/Study Questions:

Aim 1: Describe trajectories of kidney function across 25 years of follow-up.

Hypothesis 1: Participants with stable eGFR over time are more likely to attend study visits; persons with rapid kidney function decline are more likely to be captured through clinical creatinine data from hospitalizations or linkage with the

United States Renal Data System (USRDS) end-stage renal disease (ESRD) registry. Thus, careful exploration of trajectories using "scored" data (e.g., eGFR imputation of 15 ml/min/1.73 m2 at ESRD, supplementation with hospitalized eGFR values) will be important.

Hypothesis 2: Rates of eGFR change will not be normally distributed. Instead, certain participants, such as those with high genetic risk (e.g., APOL1 high risk, high genetic CKD scores) will exhibit much greater eGFR decline over time.

Aim 2: Evaluate associations of a) traditional, b) treatment-related, and c) novel participant characteristics with kidney function trajectories.

Hypothesis 1: Cumulative exposure to higher blood pressure and higher blood glucose will be associated with steeper eGFR decline. Black participants, including those of APOL1 low-risk status, women, and older participants will also have steeper rates of eGFR decline. Persons with proteinuria will have steeper eGFR decline

Hypothesis 2: Exposure to non-steroidal anti-inflammatory drugs and angiographic procedures will be associated with steeper eGFR decline. Exposure to angiotensin converting enzyme inhibitor medications will be associated with slower eGFR decline.

Hypothesis 3: Certain markers of diet quality, such as dietary acid load and animal-derived protein intake, will be associated with steeper declines in eGFR. *APOL1* high-risk status, variants of the *UMOD* gene, and a cumulative chronic kidney disease (CKD) genetic risk score will be associated with kidney function decline.

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 ARIC participants free of CKD Stage 5 (eGFR<15 ml/min/1.73 m^2) at visit 1 with measured baseline covariates who consented to the cardiovascular disease cohort surveillance (and genetic study, for aim 2 analyses of *APOL1* risk status, *UMOD*, and the CKD genetic risk score). We will also perform sensitivity analysis excluding participants with CKD Stage 3 and 4 (eGFR<60 ml/min/1.73 m^2).

Outcome variables: eGFR trajectories will be modeled using estimates based on creatinine (visits 1, 2, 4, and 5) and, separately, based on cystatin C (visits 2, 4, and 5). 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: Participant risk factors for eGFR decline will be grouped in three categories: a) traditional, b) treatment-related, and c) novel. We anticipate that explored traditional risk factors will include age, race, and sex, as well as diabetes and glucose control, hypertension and blood pressure control, and proteinuria. Treatment related risk factors will include known nephrotoxins such as non-steroidal anti-inflammatory drugs and angiographic dye as well as medications with theoretical renal preservation effects, such as antiotensin converting enzyme inhibitors. Novel risk factors will include dietary factors as well as genetic risk factors such as APOL1, UMOD variants, and a composite genetic risk score.

Summary of data analysis: eGFR trajectories will be estimated using linear mixed models with random intercepts and random slopes. In sensitivity analyses, we will also model the incorporation of the effect of survival using shared parameter models. Participant characteristics will be explored both in their association with baseline eGFR and their association with change in eGFR. Covariates for adjustment of multivariable regression models will include age, race, sex, and presence of diabetes, hypertension, and coronary heart disease. The latter three covariates will also be evaluated in a time-varying manner. Actual trajectories will be represented visually using spaghetti plots. Predicted trajectories given a specified set of covariates will be visualized in a similar manner. Best linear unbiased prediction (BLUPs) of the slopes will be plotted to demonstrate the distribution of slopes associated with participant characteristics.

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, as well using shared parameter models to evaluate the impact of the competing risk of death on trajectory estimates.

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)?**

#960: Individual and area-level life-course SES and decline in renal function: 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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