ARIC Manuscript Proposal #4017

PC Reviewed: 3/8/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Metabolites and CKD Progression

b. Abbreviated Title (Length 26 characters): Metabolomics and CKD progression

2. Writing Group:
Morgan Grams, Josef Coresh, Adi Surapaneni, Bing Yu, Eugene Rhee, *others welcome*

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

First author: MG
Address:

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: Analysis will begin upon receipt of the data and approval of the manuscript proposal. Manuscript will be written and submitted for ARIC Publications Committee review within one year of manuscript proposal approval.

4. Rationale:

Metabolomic profiling in individuals with CKD has the potential to identify novel biomarkers and provide insight into disease pathogenesis. We examined the association between blood metabolites and CKD progression, defined as subsequent development of ESRD or eGFR halving, in 1773 participants of the Chronic Renal Insufficiency Cohort (CRIC) study and 962 participants of the African American Study of Kidney Disease and Hypertension (AASK). In CRIC, more than half of measured metabolites were associated with CKD progression in minimally adjusted Cox proportional hazards models, but the number and strength of associations was markedly attenuated by serial adjustment for covariates, particularly eGFR. Ten metabolites were significantly associated with CKD progression in fully adjusted models in CRIC; five of these metabolites were also significant in fully adjusted models in AASK, highlighting potential markers of glomerular filtration (e.g. methylguanidine, pseudouridine) or azotemia (homocitrulline). Our findings also nominate N-acetylserine as a potential marker of kidney tubular function, although its association with CKD progression was significant in CRIC only. We propose to use ARIC as a third cohort by which to measure the association of the 10 implicated metabolites. Because of

genetic associations linking *ACY1* to N-acetylserine metabolism, we will also evaluate for these associations in ARIC.

5. Main Hypothesis/Study Questions:

Aim 1: To replicate observed associations between metabolites and CKD progression observed in CRIC and AASK.
Aim 2: To replicated observed genetic associations between SNPs in ACY1 and N-acetylserine.

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: We will conduct a prospective analysis of the ARIC cohort, using study visit 5 with follow-up through December 31, 2018 (or the most recent surveillance year).

Study Population: The study population will include all members of the ARIC cohort with consent to participate in cardiovascular research and available metabolomics data. All analyses will exclude those with ESKD at the study visit. For the GWAS of N-acetylserine, we will only evaluate participants who have consented to genetic research.

Exposure: The exposure for aim 1 will be metabolites. We will perform imputation for metabolites missing <80% of the time. A priori, we plan to impute missing data with the lowest value, as done in previous studies. Metabolites will be log-transformed. For aim 2, SNPs will be the exposure. We will perform analyses separately within the European-American and African-American populations.

Outcomes:

The main outcome will be CKD progression, defined as GFR decline more than 50% using subsequent visit data or incident ESKD.
Incident ESKD will be defined as the initiation of renal replacement therapy (either dialysis or transplant) and cases will be defined through linkage of the ARIC study with the United States Renal Data System (USRDS) registry.

Statistical Analysis:

We will evaluate the association between metabolites and outcomes using Cox proportional hazards model for CKD progression/ESRD. We will test associations in unadjusted models, demographic- and study-center adjusted models, and fully-adjusted models, which include known risk factors for adverse kidney outcomes (demographics, study center, cardiovascular disease, smoking, eGFRcrcys, urine albumin-to-creatinine, hypertension, diabetes). For N-acetylserine, we will evaluate genetic associations separately in whites and Blacks, adjusting for age, sex, and genetic principal components.

Limitations:

At visit 5, ARIC is a relatively older population, very different from the participants in AASK and CRIC.

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? __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)?

ARIC Manuscript Proposal #3533: Proteomics and kidney disease in a community based population
ARIC Manuscript Proposal #1182: A longitudinal Study of Metabolomics and Kidney Function among African Americans 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? __X__ Yes ____ No

11.b. If yes, is the proposal
_X__ A. primarily the result of an ancillary study (list number* 2017.27, 2013.21)
___ 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, approved manuscripts using 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.