ARIC Manuscript Proposal # 3373

PC Reviewed: 4/9/19       Status: _____       Priority: 2
SC Reviewed: _________       Status: _____       Priority: ____

1.a. Full Title:
Modification of the association between \textit{APOL1} risk variants and incident chronic kidney disease by diet

b. Abbreviated Title (Length 26 characters):
Diet, \textit{APOL1}, and CKD

2. Writing Group:
Anam Tariq, Teresa K. Chen, Lyn M. Steffen, Josef Coresh, Morgan E. Grams, Casey M. Rebholz, 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]

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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:
Analyses will begin immediately after the manuscript proposal has been approved. The first author will complete the analysis and prepare a manuscript as a Master’s thesis project by the
end of the 2019-2020 academic year. We anticipate that a manuscript will be submitted to the ARIC Publications Committee within one year of approval of the proposal.

4. Rationale:

Apolipoprotein L1 (APOL1) variants are associated with increased risk of chronic kidney disease (CKD) (1, 2). The APOL1 high-risk genotype, defined as having 2 copies of the risk variants, has been associated with higher risk of ESRD and with faster decline in estimated glomerular filtration rate (eGFR) (3). However, not everyone with high-risk APOL1 genotypes develops overt kidney disease. Environmental factors, e.g. diet, may serve as a “second hit” to induce kidney function decline in those with APOL1 risk alleles.

There is evidence suggesting that a healthy dietary pattern may be associated with lower risk of incident CKD. In the ARIC study, higher adherence to a DASH-style diet was associated with lower risk for kidney disease independent of demographic characteristics, socioeconomic status, total energy intake, lifestyle factors, comorbid conditions, antihypertensive medication use, and baseline kidney function (4). In the Jackson Heart Study, there was a stronger association between APOL1 risk alleles and prevalent CKD among those with higher adherence to a fast food diet and among those with higher adherence to a Southern diet relative to those with lower adherence to these derived dietary patterns (5). In addition, those with moderate adherence to a prudent dietary pattern had a stronger association between APOL1 risk alleles and CKD status.

However, the role of dietary patterns as a modifier of the association between APOL1 risk alleles and CKD risk has not been investigated prospectively. Identifying factors associated with the onset of CKD according to APOL1 risk status may help to uncover potentially modifiable environmental second hits.

5. Main Hypothesis/Study Questions:

We hypothesize that mid-life dietary patterns will modify the association between APOL1 risk status and incident CKD.

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 study, using ARIC study visit data from visit 1 (1987-1989) through December 31, 2017.

Inclusion:
- African-American participants with APOL1 genotyping and all Caucasian participants. We will impute low-risk APOL1 status for whites given the low prevalence of APOL1 risk alleles in this group, as previously done in the ARIC study (3, 6).
- Those with dietary intake data collected at study visit 1 (baseline, 1987-1989).

Exclusion:
- Participants with baseline eGFR ≤60 mL/min/1.73 m² or prevalent ESRD, as identified by linkage to the US Renal Data System (USRDS) registry, at baseline (visit 1).
- Those with missing dietary intake data.

**Exposure:** As detailed in a previous ARIC publication, APOL1 risk alleles were directly genotyped using Taqman assays for 3,757 blacks who gave informed consent for genetic studies (7). The G1 risk allele was defined by missense mutations at rs73885319 and rs60919145, and the G2 allele was the 6-bp deletion at rs71785313. Using a recessive genetic model, APOL1 high-risk status was defined as the presence of two risk alleles (G1/G1, G1/G2, or G2/G2). APOL1 low-risk status was defined as zero or one risk allele. All whites were characterized as APOL1 low-risk due to the low prevalence of APOL1 alleles in whites (3, 6).

**Modifier:** Dietary intake was assessed using a semi-quantitative 66-item food frequency questionnaire (FFQ), modified from the Willett questionnaire. For this analysis, we will assess adherence to a DASH-style diet using a score that ranks participants according to intake of red and processed meat, sweetened beverages, sodium, fruit, vegetables, whole grains, nuts and legumes, and low-fat dairy (4, 8). In addition, we will use factor scores for a Western dietary pattern and a prudent dietary pattern which were derived in the ARIC study using principal component analysis (9).

**Outcome:** The primary outcome is incident CKD defined as eGFR <60 mL/min/1.73 m² accompanied by ≥25% eGFR decline from baseline, an International Classification of Diseases (ICD), Ninth/Tenth Revision code for a kidney disease-related hospitalization or death, or ESRD (dialysis or transplantation) identified by linkage to the USRDS registry between baseline (study visit 1, 1987-1989) and December 31, 2017.

**Covariates:**
- In multivariable regression models, we will adjust for the following baseline covariates: age (continuous), gender (binary), race-center (categorical), socioeconomic status (categorical), education level (categorical), physical activity (continuous), smoking status (categorical), body mass index (continuous), systolic blood pressure (continuous), hypertension status (binary), diabetes status (binary), and eGFR (continuous).
- Baseline kidney function (eGFR) will be assessed using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation for eGFR.
- In a sensitivity analysis, we will additionally adjust for urine albumin-to-creatinine ratio measured at study visit 4.

**Data analysis:** Baseline characteristics of the study participants will be described according to APOL1 risk status [high-risk (2 alleles) vs. low-risk (0 or 1 allele)] using descriptive statistics (mean, standard deviation, frequency, proportion). We will test for differences in baseline characteristics according to APOL1 risk status using chi-squared and analysis of variance for categorical and continuous variables, respectively. Cox regression will be used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between APOL1 risk status and incident CKD after stratifying by tertiles of adherence to the DASH-style dietary pattern, a Western dietary pattern, and a prudent dietary pattern using a series of nested models.
We will test for interaction between dietary pattern and *APOL1* on the association with incident CKD using likelihood ratio tests.

**Limitations:** Potential measurement error due to self-reported dietary intake. Another limitation is the long time interval between dietary assessments (visit 1 and visit 3) and the end of follow-up (2017) considering that diet may change over time. However, while generally overall dietary patterns do not change considerably over time, they may change in older adults due to physical and social limitations. In the ARIC study, we have demonstrated that there is little change in diet quality between visit 1 and visit 3 (manuscript under revision). In addition, the dietary assessments at visit 1 and visit 3 do not reflect the current food supply in the U.S.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ 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  ____ 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/mantrack/maintain/search/dtSearch.html](http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html)

____ 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 #3169 (first author: Teresa Chen) – “*APOL1* risk variants in a community-based older population” – There is no overlap between the two proposals. Nonetheless, given that Teresa is actively working on *APOL1* in ARIC, we have invited her to join our writing group.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  ____ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

 References