ARIC Manuscript Proposal #3735

PC Reviewed: 11/16/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1. a. Full Title: Association between Kidney Function and Lipid Levels in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Kidney Function and Lipid Levels in Older Adults

2. Writing Group:

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

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3. Timeline: We plan to submit the manuscript for ARIC review within one year from the

approval of the manuscript proposal.

4. Rationale: While cardiovascular disease (CVD) is the leading cause of mortality in those with chronic kidney disease (CKD)[1], the traditional risk factor for CVD, hypercholesteremia, is not clearly characterized in patients with kidney disease.

Previous studies examining the association between kidney function and lipid levels were limited by inclusion of only healthy participants, use of only serum creatinine to estimate GFR, and inconclusive relationships between eGFR and LDL or HDL cholesterol. [2, 3, 4, 5, 6] In addition, there is limited literature regarding the association between kidney function and lipid levels in the elderly population. Furthermore, most studies used serum creatinine to estimate glomerular filtration rate (GFR), a measure of kidney function. However, serum creatinine-based eGFR may underestimate kidney function in older adults because it is dependent on muscles mass and protein intake, which can be diminished in older adults.[7, 8]

The aim of our study is to describe the association of kidney function with the measures of lipid levels, including total cholesterol, triglycerides, LDL, and HDL, in older adults. We will use both serum creatinine-based eGFR (eGFRcr) and cystatin-C-based eGFR (eGFRcys) as measures of kidney function and compare the results.

We will also quantify the proportion of individuals in each atherosclerotic cardiovascular disease (ASCVD) risk category in older adults who are not on statin, stratified by CKD.

5. Main Hypothesis/Study Questions:

Aim 1. Evaluate the associations between eGFR and lipid levels (total, triglycerides, LDL and HDL) in older adults, stratified by statin use. We will use both eGFRcr and eGFRcys as measures of kidney function and compare the results.

Hypothesis 1: eGFRcys-lipid associations will be stronger than eGFRcr-lipid associations

Aim 2. Quantify the proportion of individuals at low (≤5%), borderline (5% - <7.5%), intermediate (≥7.5% - <20%), and high risk (≥20%) for ASCVD according to ACC/AHA ASCVD risk calculation (i.e., pooled cohort equation)[9] among those who were not on statin, free of coronary artery disease and stroke, and aged ≤75 years, stratified by CKD status, one of the risk enhancers.[10] We will use both eGFRcr and eGFRcys to define CKD as eGFR <60 ml/min/1.73 m^2, and compare the results. We will repeat analyses among those aged ≤79 years, as well as those aged 76-79 years since pooled cohort equation can be used up to this age.

Hypothesis 2: The proportion of high risk individuals will be greater in CKD as compared to non-CKD. This difference by CKD status will be greater when CKD was defined by eGFRcys than when it was defined by eGFRcr.

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:

- Cross-sectional study

Inclusion:

- All ARIC participants who have data on serum creatinine, cystatin-C and lipid levels at visit 5 (2011-2013) for Aim 1
- Participants not on statin for Aim 2.

Exclusion:

- Missing data on eGFR from serum creatinine or cystatin-C at visit 5
- Missing data on lipid levels (total, HDL, LDL, or triglycerides)
- Individuals on dialysis

Exposure:

- eGFR calculated with serum creatinine
- eGFR calculated with cystatin-C

Outcome:

- Lipid levels (total, LDL, HDL, TG): both continuous and categorical outcomes[11]
  Borderline high total cholesterol: ≥200 mg/dl; Very high total cholesterol: ≥240 mg/dl
  Borderline high LDL: ≥100 mg/dl; High LDL: ≥160 mg/dl; Very high LDL: ≥190 mg/dl
  Low HDL: <40 mg/dl in men and <50 mg/dl in women
  Borderline high TG: ≥150 mg/dl; High TG: ≥200 mg/dl; Very high TG: ≥500 mg/dl

Stratifying variable:

- Statin use

Other variables:

- Age, sex, race-center, education, income, history of coronary artery disease, heart failure, hypertension, diabetes, liver disease (ICD-based diagnosis up to visit 5), body mass index, physical activity, smoking, and alcohol use
- Variables to calculate ACC/AHA ASCVD risk: age, sex, race, systolic blood pressure, total cholesterol, HDL, diabetes, smoking, antihypertensive medication use

Statistical analysis:

- All analyses will be done separately by using eGFRcr or eGFRcys.

- We will summarize baseline characteristics across eGFR categories (<45, 45-60, ≥60 ml/min/1.73 m^2), stratified by statin use.

- Analysis with continuous outcome (lipid levels) and continuous exposure (eGFR)
  a. We will fit lineal regression models with linear splines with three knots at eGFR 90, 60, and 45 ml/min/1.73 m^2.
     - ✓ Model 1: unadjusted model
     - ✓ Model 2: age, sex, and race-center adjusted model

- ✓ Model 3: model 2 + education
- ✓ Model 4: model 3 + other covariates listed above **(other variables)**

- Analysis with binary outcome (lipid levels) and continuous (eGFR)
  a. After checking the distribution of categorical outcomes of lipid levels, we will choose cut-off values (e.g. total cholesterol: ≥200 mg/dl, or 240 mg/dl) for binary outcome.
  b. We will fit logistic regression models with linear splines with three knots at eGFR 90, 60, and 45 ml/min/1.73 m^2
     - ✓ Model 1: unadjusted model
     - ✓ Model 2: age, sex, and race-center adjusted model
     - ✓ Model 3: model 2 + education
     - ✓ Model 4: model 3 + other covariates listed above **(other variables)**

- Analysis with binary outcome (lipid levels) and categorical exposure (eGFR <45, 45-60, ≥60 ml/min/1.73 m^2)
  a. We will estimate prevalence of high levels in each outcome by eGFR categories.
  b. We will fit logistic regression models with eGFR categories as an exposure.
     - ✓ Model 1: unadjusted model
     - ✓ Model 2: age, sex, and race-center adjusted model
     - ✓ Model 3: model 2 + education
     - ✓ Model 4: model 3 + other covariates listed above (other variables)

- In sensitivity analyses, income will be further adjusted in the aforementioned models.

- Among individuals not on stain, without coronary artery disease and stroke, and aged ≤75 years, we will estimate proportion of individuals in each ASCVD risk category, and examine whether it differs by CKD (eGFR <60 or eGFR ≥60 ml/min/1.73 m^2). We will also repeat analyses among those aged ≤79 years, as well as among those aged 76-79 years.

Limitations:

- We cannot establish temporality between kidney function and lipid levels due to cross-sectional study design.
- Residual confounding is possible in all observational studies.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No

(The 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 current derived consent file ICTDER05 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

___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)?

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 https://sites.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.

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