ARIC Manuscript Proposal #3228

PC Reviewed: 9/11/2018	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Metabolomics of coffee consumption and risk of kidney disease in the ARIC study

b. Abbreviated Title (Length 26 characters): Metabolomics of coffee and kidney disease

2. Writing Group:
Writing group members:

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Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _CMR____ **[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 is approved. We plan to have a manuscript ready for co-authors to review within one calendar year.

4. Rationale:
According to the 2015-2020 Dietary Guidelines for Americans, moderate coffee consumption (up to 3-5 cups/d or providing up to 400 mg/d of caffeine) is not associated with long-term health risks and therefore can be incorporated into healthy eating styles [1]. In fact, coffee consumption has been shown to be protective of chronic illnesses such as type 2 diabetes [2, 3], coronary heart disease [4], some cancers [5, 6] as well as total mortality [7]. We have recently shown that coffee consumption was associated with a reduced risk of kidney disease in the Atherosclerosis Risk in Communities study, with the most robust association for those consuming at least 3 cups of coffee per day [8]. Several other studies have also found an inverse association between coffee consumption and kidney disease risk in diverse populations [9, 10].

The beneficial effects of coffee on the kidney may be due to many of the compounds that can have an integral role in biological processes and mechanisms. Coffee contains essential compounds such as chlorogenic acid, lignans, quinides, trionelline, and magnesium, which may reduce insulin resistance and systematic inflammation [7]. Chlorogenic acid has been shown to reduce glucose absorption in the intestine by inhibiting glucose-6-phosphate translocase, which reduces oxidative stress and liver glucose output [11, 12]. Lignans, quinide, and trionelline may improve glucose metabolism [13]. Caffeine is a methylxanthine that alters kidney function through several mechanisms such as natriuresis, hemodynamics, and the renin-angiotensin-aldosterone (RAAS) system and has been hypothesized to be protective of glomerular injury. Caffeine and other metabolites in coffee (quinate, trigonelline) may therefore be in the pathway between coffee consumption and kidney disease.

Metabolomics allows for the comprehensive characterization of small metabolic compounds in biological specimens [14]. The metabolome is responsive to dietary intake and therefore is a useful method for detecting biomarkers of coffee and metabolic pathways that are potentially modifiable [15]. The untargeted and unbiased metabolomic approach maximizes the potential for discovery of novel markers of coffee consumption and could provide insights about metabolic pathways underlying the coffee-kidney disease relationship.

5. Main Hypothesis/Study Questions:
Aim 1: To identify metabolites associated with coffee consumption, as potential biomarkers of coffee.
Aim 2: To investigate whether the candidate biomarkers (metabolites) of coffee are associated with incidence of kidney disease.

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: The proposed project includes a cross-sectional analysis of metabolites and coffee (Aim 1) and a prospective analysis of coffee-related metabolites and incident kidney disease (Aim 2).

Eligibility: Approximately 4,000 African-American and Caucasian ARIC study participants with metabolomic profiling data from visit 1 serum specimens (ancillary study #2014.20 and 2008.16; two "batches")

Exposure: Metabolites were measured from stored fasting serum samples by Metabolon, Inc. (Durham, North Carolina) using an untargeted, ultra-performance liquid chromatography tandem mass spectrometry approach. This untargeted approach identified approximately 600-800 named and unnamed metabolites. In the present study, we will primarily focus on the ~200 named metabolites with limited missing values, reasonable reliability, and present in both batches. Metabolites will be log-transformed for the analysis.

Outcomes:
A. Acute kidney injury (AKI) defined by a hospitalization or death with ICD-9-CM code 584.X (ICD-10-CM code N17.x) in any position.

B. Incident CKD (composite) defined by at least 1 of the following 4 criteria [16]:

1) Development of reduced kidney function (eGFR <60 ml/min/1.73 m^2) accompanied by 25% eGFR decline at any subsequent study visit relative to baseline
2) International Classification of Diseases (IC)-9/10 code for a hospitalization related to CKD stage 3+ identified through active surveillance of the ARIC cohort
3) ICD 9/10 code for a death related to CKD stage 3+ identified through linkage to the National Death Index
4) End-stage renal disease identified by linkage to the US Renal Data System (USRDS) registry

C. ESRD cases identified by US Renal Data System (USRDS)

Covariates: We will use the following variables as covariates: age, sex, race-center, education, BMI, physical activity, total energy intake, eGFR, smoking, alcohol consumption, DASH diet score, and batch (when the metabolomics profiling was conducted).

Statistical Analysis: For Aim 1, we will use multivariable linear regression to estimate the cross-sectional association between metabolites and coffee consumption at baseline (visit 1). These models will be adjusted for age, sex, race-center, education, BMI, physical activity, total energy intake, eGFR, smoking, alcohol consumption, DASH diet score, and batch.

For Aim 2, we will use Cox proportional hazards models to estimate hazard ratios for the association between metabolites of coffee and risk of AKI, CKD, and ESRD. We will adjust for the following covariates in the Cox model: age, sex, race-center, education, BMI, physical activity, total energy intake, eGFR, smoking, alcohol consumption, DASH diet score, and batch. In a separate model, we will additionally adjust for diabetes, systolic blood pressure, and anti-hypertensive medication use. All analyses will be run in Houston, Texas using scripts provided by the first author.

Limitations: Given the large number of metabolites, there is a high likelihood of detecting a false positive association. We will adjust the significance threshold by the Bonferroni method (dividing by the number of metabolites) to account for multiple comparisons (0.05/number of metabolites) [17].

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? ____ 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 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/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)?

MS #2868: Coffee consumption and incident kidney disease in the ARIC study (first author: Hu; last author: Rebholz)

MS #3145: Serum Metabolomic Markers of Diet Quality (first author: Rebholz)

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
__X_ A. primarily the result of an ancillary study

2014.20: Genomics, Metabolomics, and Cardiovascular Disease (PI: Boerwinkle)

2008.16: Metabolomics & Heart Failure: A Novel Approach to Biomarker Discovery (PI: Nettleton)

___ 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

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