1.a. Full Title: Coffee consumption and incident kidney disease in the ARIC study.

b. Abbreviated Title (Length 26 characters): Coffee and Kidney Disease

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __EH___ [please confirm with your initials electronically or in writing]

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3. **Timeline:** We aim to complete analyses by 1/1/17 and have a complete draft of the manuscript for the co-authors to review by 4/1/17.

4. **Rationale:**

   According to the 2015-2020 Dietary Guidelines for Americans, moderate coffee consumption (up to 3-5 cups/day or providing up to 400 mg/day of caffeine) is not associated with long-term health risks and therefore can be incorporated into healthy dietary patterns [1]. In fact, coffee consumption has been shown to be strongly inversely associated with major chronic diseases such as type 2 diabetes [2-4], coronary heart disease [5], some cancers [6, 7] as well as total mortality [8].

   Diabetes and cardiovascular disease share several risk factors for the development of kidney disease; therefore, it may be possible that coffee could also protect against kidney disease. Coffee contains many compounds that can have an integral role in biological processes and mechanisms, affecting health. Coffee contains essential compounds such as chlorogenic acid, lignans, quinines, trionelline, and magnesium [9], which may reduce insulin resistance and systemic inflammation [8]. 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 [10, 11]. Lignans, quinidines, and trionelline may improve glucose metabolism [12].

   It would be of great interest to examine whether coffee consumption has any significant effects on kidney disease, a disease with growing prevalence and costs. Few studies have investigated the association between coffee consumption and incident chronic kidney disease. Recently, a study found that coffee consumption was associated with a slightly higher estimated glomerular filtration rate (eGFR) in participants ages 46 and older [13]. This result was unexpected since coffee is a mild diuretic, which would be expected to lower GFR. Our study seeks to examine the risk of incident chronic kidney disease and incident end-stage renal disease across different levels of coffee consumption. Additionally, we will explore the risk of kidney disease by coffee consumption among different categories of BMI and status of diabetes, CVD, hypertension, and smoking status.

5. **Main Hypothesis/Study Questions:** We hypothesize that higher levels of coffee consumption, compared to low coffee consumption, will be associated with a reduced risk of incident chronic kidney disease and incident end-stage renal disease after adjustment for major covariates among adults in the ARIC study.

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 study, including participants from baseline (Visit 1, 1987-1989) through Dec 31, 2013 or latest follow-up available. We will exclude participants who are missing FFQ data, already have kidney disease at baseline, or who have extreme values for total caloric intake (<500 or >3,500 kcal/d for women; <700 or >4,500 kcal/d for men).

**Exposure:** The primary exposure will be a cumulative average of coffee consumption from visits 1 and 3, measured by a food frequency questionnaire (FFQ) during an interview. Participants are asked how frequently they consume an 8-ounce cup of regular (non-decaffeinated) coffee. Frequency options included “almost never,” “1-3 cups per month,” “1 cup per week,” “2-4 cups per week,” “5-6 cups per week,” “1 cup per day,” “2-3 cups per day,” “4-6 cups per day,” and “6 cups per day.” We will re-categorize these consumption levels into low, moderate, and high.

**Outcome:**
A. Incident CKD (composite) defined by at least 1 of the following 4 criteria:
   1) Development of reduced kidney function (eGFR <60 ml/min/1.73 m²) 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

B. Incident CKD using visit-based measures (development of reduced kidney function (eGFR <60 ml/min/1.73 m²) accompanied by 25% eGFR decline at any subsequent study visit relative to baseline) as a sensitivity analysis for the incident CKD composite definition (A)

C. Incident ESRD identified by the US Renal Data System (USRDS) registry

D. Kidney failure – composite definition to use as a sensitivity analysis for the incident ESRD definition (C) [14]
   1) USRDS data to identify treated kidney failure
   2) ICD-9-CM and ICD-10-CM codes from hospitalizations and deaths that represented kidney failure, transplantation, and dialysis
   3) A study visit eGFR<15 mL/min/1.73 m² calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation

**Covariates:** We will use the following variables as covariates: sex, race-center, age, health behaviors (physical activity, smoking), socioeconomic status (education, income), family history of CVD, medical data (blood pressure, serum glucose, baseline eGFR), diabetes status, hypertension status (medication use and BP), BMI, energy intake, overall diet quality. Overall diet quality will be measured by the PCA method and/or the Alternative Healthy Eating Index.
Main Analyses:

1) We will assess differences in demographic risk factors and other kidney disease risk factors according to categories of coffee consumption.

2) We will estimate the hazard ratios and associated 95% CIs for incident risk of CKD and ESRD associated with different categories of coffee intake using Cox regression models. Specifically, we aim to evaluate whether the different consumption levels (low, moderate, high) have different levels of risk for chronic kidney disease and ESRD.
   a. Model 1: Unadjusted
   b. Model 2: Adjusted for race-center, age, and sex, and energy intake
   c. Model 3: Model 2 + adjusted for physical activity, smoking, family history of CVD, overall diet quality, and education
   d. Model 4: Model 3+ adjusted for blood pressure, fasting blood glucose, diabetes status, hypertension status
   e. Model 5: Model 4 + adjusted for baseline eGFR
   f. Model 6: Model 5 + adjusted for BMI

3) In addition to these categories of consumption (low, moderate, high), we will use similar models as in #2 except with coffee consumption as a continuous variable assuming linearity and expressing the hazard ratio as per one additional cup of coffee per day.

4) We will repeat the 6 models in #2 using linear splines to more flexibly evaluate the shape of the association between coffee and kidney disease across the spectrum of coffee consumption.

5) We will also estimate the risk of kidney disease within population subgroups, i.e. by BMI categories, smoking status, hypertension status, diabetes status, and CVD status.

6) We will estimate competing risk of all-cause mortality prior to development of kidney disease (stcrreg command)

7) Our primary two outcomes for all analyses are incident CKD and ESRD. For incident CKD, we will use the composite definition and visit-based measures as a sensitivity analysis. For ESRD, we will use USRDS data and the kidney failure definition as a sensitivity analysis.

Limitations:
A potential limitation of this study is that there was a gap in study visits between 1998 and 2011. However, we have supplemented visit-based data with surveillance efforts for the identification of deaths and hospitalizations as well as linkage to the USRDS registry in order to ascertain incident kidney disease proximal to the time of onset. In addition, there may be measurement error in dietary assessment due to self-reported intake through the use of food frequency questionnaires. To obtain a more precise accurate, we will use the cumulative average in coffee intake as assessed at two time points (visits 1 and 3). Further, reported coffee consumption is most likely accurate since ‘coffee drinkers’ reliably drink their usual intake daily [15]. As with any observational study, there remains the possibility of residual confounding.

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)?

Manuscript proposals:
#2825: Coffee and Risk of Subclinical Myocardial Damage and Cardiovascular Events

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 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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**References**


