ARIC Manuscript Proposal # 2958

PC Reviewed: 03/14/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Moderate alcohol consumption and the risk of incident chronic kidney disease

b. Abbreviated Title (Length 26 characters): **Alcohol and CKD**

2. Writing Group:
Writing group members:
Sarah D Rosenberg, Natalie Daya, Elizabeth Selvin, Morgan Grams, Cheryl Anderson, Mariana Lazo, Casey M. Rebholz, Sarah Jones, others welcome (order TBD)

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

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3. Timeline: Data preparation, analysis, and manuscript drafting will begin upon approval and is expected to be finalized within a year.

4. Rationale:
The role of alcohol consumption in chronic disease risk is complex, exhibiting positive and negative associations depending on the chronic disease outcome of interest. Previous studies have shown moderate alcohol consumption to increase the risk for hormone sensitive tumors, upper gastrointestinal malignancies, and high blood pressure.[1] Other reports document protective associations between alcohol consumption and cardiovascular outcomes, including myocardial infarction and congestive heart failure.[1] Research investigating the association between alcohol and chronic kidney disease is still very limited and previous studies have reported inconsistent

results. The biological mechanisms for the effect of alcohol on the kidney is also unclear, but demonstrated a negative association between alcohol consumption and hyalinization of renal arterioles.[10]

One study investigated the association of alcohol consumption and CKD using 5,475 participants 28-75 years of age in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study.[2] With an alcoholic serving size being defined as 10 grams of alcohol regardless of the type, moderate alcohol consumption (defined as 2-7 drinks/week or 10-69.9 g/week) relative to nondrinkers was associated with a reduced risk of incident CKD.[2] In an analysis of the AusDiab cohort including 6,259 adults 25 years of age and older, moderate (≥10-<30 g/day) and heavy (≥30 g/day) alcohol consumption relative to <10 g/day was associated with an elevated risk for the onset chronic kidney disease.[3] In a cross-sectional study of 27,253 Taiwanese participants, the occasional and frequent drinking groups were associated with lower odds of stage 3 CKD than the non-drinking group among men, but there was no significant association among women.[4]

Given the conflicting findings in prior studies and the modifiable aspect of this exposure, additional research is needed to investigate the association between alcohol consumption and incident chronic kidney disease.

5. Main Hypothesis/Study Questions:

Hypothesis: Moderate alcohol consumption compared to low and no consumption is associated with a lower risk of incident chronic 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: We will conduct a prospective analysis using the data from the Atherosclerosis Risk in Communities (ARIC) study.[7] Participants with missing baseline data on covariates being analyzed (exposure, confounders, and effect modifiers), prevalent CVD or GI conditions at visit 1, or a baseline estimated GFR (eGFR) <60 mL/min/1.73 m^2 will be excluded from the analysis. Baseline for the proposed analysis is study visit 1 and the participants will be followed prospectively for the development of CKD through December 31, 2013 (or the most updated follow-up data).

Exposure: Alcohol consumption will be assessed based on responses during baseline visit 1 (1987-1989). Individuals were asked, “do you presently drink alcoholic beverages?” and “have you ever consumed alcoholic beverages?” If “no” was the response for both questions, they would be categorized as never drinkers.[8] If they answered “no” to the first and “yes” to the second, they would be classified as former drinkers.[8] For current drinkers, three additional questions were asked to assess how many drinks they consume per week.[8] One drink was defined as either 4 oz. of wine, 12 oz. of beer, or 1.5 oz. of liquor.[8] For the purpose of this analysis, total ounces of weekly alcohol consumption will be used to categorized as ≤1 drink/week, 2-7 drinks/week, 8-14 drinks/week, and ≥15 drinks/week.[8]

We will conduct a sensitivity analysis after restricting the study population to current drinkers only, since reverse causality could be an issue with the former drinkers' exposure category.

Outcome: Incident chronic kidney disease (CKD) will be measured as a binary variable and assessed between baseline visit (1987-1989) and the end of follow-up (December 31, 2013).[6] The primary outcome of incident CKD will be defined as meeting at least 1 of the following[6]:

- Reduced kidney function with an eGFR <60 mL/min/1.73 m^2 along with 25% eGFR decline at any succeeding study visit compared to baseline.
- ICD- 9/10 code for CKD stage 3+ hospitalizations identified by through active surveillance of hospitalizations in the ARIC study.
- ICD- 9/10 code for CKD stage 3+ deaths per the National Death Index.
- End-stage renal disease identified by the US Renal Data System registry.

Secondary outcomes to be assessed are end-stage renal disease (ESRD) and acute kidney injury. (AKI).

Covariates: The covariates to be included in this analysis are age, gender, race-center, smoking status, BMI, total energy intake, education, income, health insurance status, hypertension, and diabetes. Age will be analyzed as a continuous variable. BMI will be modeled as a time varying variable and will be calculated by dividing the weight (in kilograms) over the height (in meters) squared.[9] Categories for BMI will be underweight (≤18.5), normal (18.5-24.9), overweight (25-29.9), and obese (≥30). Education will be analyzed as an ordinal variable: less than high school, high school degree, and some college and above. Income will be analyzed as an ordinal variable: under $24,000, $24,000 to $49,999, and $50,000 or more. And smoking status will also be an ordinal variable: current, former, never. The following covariates will be dichotomized: gender (male/female), race (black/white), health insurance status (insured, not insured), presence of hypertension (yes/no), and presence of diabetes (yes/no). Hypertension will be classified as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mm Hg, or use of anti-hypertension medication within the past two weeks. Diabetes will be classified as glucose ≥126 mg/dl, non-fasting glucose ≥200 mg/dl, history of diagnosed diabetes, or reported use of diabetes medication within the past two weeks. The influence of hypertension and diabetes on the association between alcohol and kidney disease will be evaluated in separate regression models.

Data Analysis:

Baseline characteristics will be examined across five different alcohol categories: never drinker, former drinker, ≤1 drink/week, 2-7 drinks/week, 8-14 drinks/week, and ≥15 drinks/week. Analyses will be stratified by sex given the different classification of moderate alcohol consumption for men vs. women.

Incidence rates for CKD will be calculated for each category of alcohol consumption. A Kaplan-Meier survival curve will be used to evaluate survival free of CKD according to alcohol consumption categories.

Cox proportional hazard models will be used to evaluate time to event (incident CKD) for the categories of alcohol consumption. Person-time will be calculated as the number of years of observation from visit 1 (1987-1989) (when the alcohol exposure was classified) until incident CKD or censoring either from death, loss to follow-up, or administrative censoring on December 31, 2013. Alcohol consumption will be treated as a time varying variable. Model 1 will be

unadjusted. Model 2 will adjust for age, gender, BMI, race-center, education, income, and health insurance status.

Potential effect modifiers include diabetes, hypertension, smoking status, gender, and race. To evaluate the impact of these factors on the association between alcohol and CKD, the study population will be stratified by these factors and we will test for interaction. Based on the outcome of this analysis, we will either adjust for or stratify on these factors.

History of excessive drinking will be examined in former drinkers and current drinkers to access robustness of the findings and provide a description of study sample.

Anticipated Methodological Limitations:

Difficulty in differentiating between chronic kidney disease and acute kidney injury may be a possible limitation, but the method of defining CKD for this study had previously been shown, when compared to medical chart reviews, to have high specificity (96%).[6]

Measurement of alcohol consumption can be underreported and there may be recall bias when reporting how much is consumed on average per week for current drinkers. Alcohol consumption is also a chronic exposure; people may change drinking habits over time.[11,12] To determine if there was a history of excessive alcohol consumption (ever/never), the total amount of alcohol ingested weekly for past alcohol consumption was calculated during visit 1 and then again during visit 3 when they were asked "was there ever a time in your life when you consumed 5 or more drinks of any kind of alcoholic beverage almost every day?"[7,8]. This information can be used to assess robustness of the findings.

Residual confounding is also a limitation in any observational study that can result from lack of measurement or inadequate measurement of confounding factors.

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)?

ARIC Manuscript Proposal #2442 ("Alcohol consumption and myocardial biomarkers"): Dr. Mariana Lazo examined the cross-sectional and prospective association between alcohol consumption and cardiac biomarkers, but did not examine risk of kidney disease.[8] She is a member of the writing group for the present manuscript proposal.

ARIC Manuscript Proposal #1187 ("Effect of Alcohol Consumption (and Type of Alcoholic Beverage Consumed) on Lipid Levels: The ARIC Study"): Dr. Kelly Volcik examined the effects of total alcohol consumption and types of alcohol, stratified by sex, on plasma lipid levels. In her published manuscript, regular low-to-moderate alcohol consumption resulted in a beneficial effect on the lipid profile, i.e. increases in high density lipoprotein cholesterol and reduction in triglycerides, total cholesterol, and low density lipoprotein cholesterol.[14]

ARIC Manuscript Proposal #2290 ("Association of Smoking, Alcohol, and Obesity with Cardiovascular Death and Ischemic Stroke in Atrial Fibrillation: The ARIC Study"): In his published article, Dr. Kwon observed no significant association between alcohol consumption and cardiovascular disease.[15]

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.

References

1. Mukamal, K. J., Clowry, C. M., Murray, M. M., Hendriks, H. F.J., Rimm, E. B., Sink, K. M., Adebamowo, C. A., Dragsted, L. O., Lapinski, P. S., Lazo, M. and Krystal, J. H. (2016), Moderate Alcohol Consumption and Chronic Disease: The Case for a Long-Term Trial. Alcohol Clin Exp Res, 40: 2283–2291. doi:10.1111/acer.13231

2. Koning, S.H., Gansevoort, R.T., Mukamal, K.J. et al, Alcohol consumption is inversely associated with the risk of developing chronic kidney disease. Kidney Int. 2015;87:1009–1016.

3. Sarah L. White, Kevan R. Polkinghorne, Alan Cass, Jonathan E. Shaw, Robert C. Atkins, Steven J. Chadban; Alcohol consumption and 5-year onset of chronic kidney disease: the AusDiab study. *Nephrol Dial Transplant* 2009; 24 (8): 2464-2472. doi: 10.1093/ndt/gfp114

4. Hsu Y-H, Pai H-C, Chang Y-M, Liu W-H, Hsu C-C. Alcohol consumption is inversely associated with stage 3 chronic kidney disease in middle-aged Taiwanese men. *BMC Nephrology*. 2013;14:254. doi:10.1186/1471-2369-14-254.

5. Haring B, Selvin E, Liang M, Coresh J, Grams ME, Petruski-Ivleva N, Steffen LM, Rebholz CM. Dietary Protein Sources and Risk for Incident Chronic Kidney Disease: Results From the Atherosclerosis Risk in Communities (ARIC) Study. J Ren Nutr. 2017 Jan 5. pii: S1051-2276(16)30179-0. doi: 10.1053/j.jrn.2016.11.004.

6. Rebholz CM, Coresh J, Grams ME, Steffen LM, Anderson CA, Appel LJ, Crews DC. Dietary Acid Load and Incident Chronic Kidney Disease: Results from the ARIC Study. Am J Nephrol. 2015;42(6):427-35. doi: 10.1159/000443746.

7. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687-702.

8. Mariana Lazo, Yuan Chen, John W. McEvoy, Chiadi Ndumele, Suma Konety, Christie M. Ballantyne, A. Richey Sharrett, Elizabeth Selvin. Alcohol Consumption and Cardiac Biomarkers: The Atherosclerosis Risk in Communities (ARIC) Study. Clinical Chemistry Sep 2016, 62 (9) 1202-1210; DOI: 10.1373/clinchem.2016.255778

9. CDC. About adult BMI. https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/. Updated May 15, 2015. Accessed February 26, 2017.

10. Cecil M. Burchfiel, Richard E. Tracy, Po-Huang Chyou and Jack P. Strong. Cardiovascular Risk Factors and Hyalinization of Renal Arterioles at Autopsy. Arteriosclerosis, Thrombosis, and Vascular Biology. April 1997;17:760-768

11. Parekh RS, Klag MJ. Alcohol: role in the development of hypertension and end-stage renal disease. Curr Opin Nephrol Hypertens. 2001 May;10(3):385-90.

12. J. Rehm, H. Irving, Y. Ye, W. C. Kerr, J. Bond, T. K. Greenfield; Are Lifetime Abstainers the Best Control Group in Alcohol Epidemiology? On the Stability and Validity of Reported Lifetime Abstention. *Am J Epidemiol* 2008; 168 (8): 866-871. doi: 10.1093/aje/kwn093

13. Platt A, Sloan FA, Costanzo P. Alcohol-Consumption Trajectories and Associated Characteristics Among Adults Older Than Age 50. *Journal of Studies on Alcohol and Drugs*. 2010;71(2):169-179.

14. Khanh N. Vu, Christie M. Ballantyne, Ron C. Hoogeveen, Vijay Nambi, Kelly A. Volcik, Eric Boerwinkle, Alanna C. Morrison. Causal Role of Alcohol Consumption in an Improved Lipid Profile: The Atherosclerosis Risk in Communities (ARIC) Study. PLoS One. 2016 Feb 5;11(2):e0148765. doi: 10.1371/journal.pone.0148765. eCollection 2016.

15. Kwon Y, Norby FL, Jensen PN, Agarwal SK, Soliman EZ, Lip GY, Longstreth WT Jr, Alonso A, Heckbert SR, Chen LY. Association of Smoking, Alcohol, and Obesity with Cardiovascular Death and Ischemic Stroke in Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS). PLoS One. 2016 Jan 12;11(1):e0147065. doi: 10.1371/journal.pone.0147065. eCollection 2016.