ARIC Manuscript Proposal #2934

PC Reviewed: ___/___/16 **Status: _____** **Priority: ____**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Coffee consumption and risk of liver disease in the ARIC study.

b. Abbreviated Title (Length 26 characters): Coffee and liver related hospitalization

2. Writing Group:
Writing group members:

Emily A. Hu, BA
Mariana Lazo, MD, PhD
Elizabeth Selvin, PhD, MPH
Josef Coresh, MD, PhD, MHS
Lyn M. Steffen, PhD, MPH, RD
James Hamilton, MD
Casey M. Rebholz, PhD, MS, MPH
Others welcome

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]**

First author: Emily A. Hu
Address: MHS Student
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St.
Baltimore, MD 21218

Phone: 781-866-9200 Fax:
E-mail: ehu6@jhu.edu

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).

Name: Casey M. Rebholz
Address: Johns Hopkins Bloomberg School of Public Health
2024 E. Monument Street, Suite 2-600
Baltimore, MD 21287

Phone: 410-502-2049 Fax:
E-mail: crebhol1@jhu.edu

3. Timeline: We aim to have a complete draft of the manuscript for the co-authors to review by 9/1/17.

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, 8). Recent studies have found that coffee consumption may be protective of liver disease.

Liver-related mortality has become a growing burden in the US, accounting for approximately 34,000 deaths per year (9). The 3 most common causes of chronic liver disease are viral hepatitis, alcohol consumption, and obesity. Few studies have examined the association between coffee and hepatitis B (10). One study that evaluated the clinical effect of coffee in HBV-positive patients found no influence of coffee on the severity of hepatitis B (11). A study on hepatitis C patients found a beneficial effect of coffee on the disease progression in these patients (12). They found lower incidence of fibrosis and cirrhosis in coffee drinkers compared to non-coffee drinkers. In a cross-sectional study, high coffee consumption was associated with a lower prevalence of clinically significant fibrosis (8.8% vs. 16.3%). Liver disease that is related to obesity and diabetes, also known as nonalcoholic fatty liver disease (NAFLD) is largely tied to type 2 diabetes as part of metabolic syndrome (13). Currently, there is mixed evidence on the association between coffee consumption and NAFLD. There are a number of studies worldwide that have found coffee to be protective against the development of metabolic syndrome as well as NAFLD (14-17). On the other hand, another study found that coffee was associated with less severe fibrosis in patients with NAFLD, but did not find an association between coffee and new onset NAFLD (18). Some studies suggest that the biological mechanisms stem from the caffeine in coffee (17). Others suggest that antioxidants, which are present in both caffeinated and decaffeinated coffee, have a role in reducing liver disease (16). In general, most of these studies have been cross-sectional and there is a need for more cohort studies that look prospectively at the incidence of fibrosis and clinical outcomes such as liver related hospitalizations.

Our study seeks to examine the association of regular coffee consumption with risk of clinical and subclinical liver disease in a community-based setting.

5. Main Hypothesis/Study Questions: We hypothesize that higher coffee consumption is associated with a lower risk of incident liver disease (liver disease-related hospitalizations and elevated non-invasive markers of fibrosis) after adjustment for major confounding factors among ARIC study participants.

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 December 31, 2013 or most recent follow-up available.

Exposure: The primary exposure will be coffee consumption, measured by an interviewer-administered food frequency questionnaire (FFQ) at the baseline and year 6 visits. Participants reported usual consumption over the past year. Participants were 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. In order to report more precise and etiologically relevant levels of intake, we will use the cumulative average of coffee consumption, by calculating the mean of 2 assessments (visits 1 and 3).

Outcomes:
Our two main outcomes are liver-related hospitalizations and elevation in liver enzymes. For the assessment of incident elevated liver enzymes, we will use measurements of liver enzymes at visit 2 and visit 4.

1. Liver-related hospitalizations and deaths identified through recent cohort surveillance files that include one of the following ICD-9 codes based on prior reports (19): "571.0 Alcoholic fatty liver", "571.2 Alcoholic cirrhosis of the liver", "571.3 Alcoholic liver damage, unspecified", "571.40 Chronic hepatitis, unspecified", "571.41 Chronic persistent hepatitis", "571.49 Other chronic hepatitis", "571.5 Cirrhosis of liver without mention of alcohol", "571.6 Biliary cirrhosis", "571.8 Other chronic nonalcoholic liver disease", "571.9 Unspecified chronic liver disease without mention of alcohol"
2. We will examine the individual enzymes. Incident elevated enzymes at visit 4 will be assessed among participants without prevalent elevated enzymes at visit 2.
    a. Alanine amino-transferase (ALT), aspartate amino-transferase (AST), gamma glutamyl-amino-transferase (GGT)
    b. Elevated enzyme levels: ratio of ALT/AST>1, ALT > 40 U/l, AST > 40 U/l, GGT > 60 U/l (20, 21).

<u>Sensitivity analyses for the outcome definitions:</u>

1. For liver-related hospitalizations, restrict the outcome definition to hospitalizations and deaths with liver-related code as the primary code.
2. Non-invasive liver fibrosis score (FIB-4), an accepted score with proven validity across liver diseases of different etiologies (22-24):
    a. FIB-4 will be calculated at visit 2 and visit 4 from age, AST (U/l), platelet (10^9/L), and ALT (U/l), according to the published formula: FIB-4 = (age [years] x AST [U/L])/(PLT [10^9/L] x (ALT [U/L])$^{1/2}$) (24, 25).

b. Non-invasive liver fibrosis score (FIB-4) will be defined using the published cut-off of FIB-4>2.67 at visit 4 among participants without prevalent elevated FIB-4 at visit 2 (26).

Exclusions: We will exclude participants who are missing >10 FFQ items at each visit or who have extreme values for total energy intake (<500 or >3,500 kcal/d for women; <700 or >4,500 kcal/d for men).

Covariates: We will use the following variables as covariates: sex, race-center, age, physical activity, smoking, education level, diabetes status, BMI, added sugar consumption, total energy intake, alcohol consumption, baseline liver enzymes (visit 2).

Main Analyses:

1) We will assess differences in socio-demographic risk factors and liver-related risk factors according to categories of coffee consumption.
2) We will estimate the hazard ratios and associated 95% CIs for incident risk of liver disease associated with different categories of coffee intake (low, moderate, high) using Cox regression models.
    a. Model 1: Adjusted for total energy intake
    b. Model 2: Adjusted for model 1 plus sex, race-center, age, education
    c. Model 3: adjusted for model 2+ physical activity, smoking,
    d. Model 4: Model 3 plus alcohol, sugar sweetened beverages, and other food and beverage groups
    e. Model 5: Model 4+ diabetes status, BMI
    f. Model 6: Model 5+baseline liver enzymes (visit 2)
3) We will also estimate the risk of liver disease by coffee consumption category within subgroups of people by race (black/white), smoking (current/former/never), BMI categories (obese vs. not obese), diabetes status (yes/no), and alcohol consumption levels (former and heavy alcohol consumers vs. moderate alcohol consumers vs. never alcohol consumers). We will test for interactions between these factors and coffee consumption to see whether they may be effect modifiers. Variables such as diabetes status will be treated as time-varying.
4) We will estimate competing risk of all-cause mortality prior to development of liver disease using cumulative incidence function (stcrreg, stcurve command)

Limitations:

1) There may be measurement error in the assessment of dietary intake (coffee, alcohol, added sugar, total energy intake) due to the use of self-reported 66-item food frequency questionnaires. It should also be noted that several strategies were employed to minimize reporting error, including the administration of the food frequency questionnaires by trained interviewers and the use of visual representations of serving sizes. To obtain a more precise estimate, we will use the cumulative average in coffee intake incorporating dietary data collected at visit 1 and visit 3.

2) The liver disease outcome based on hospitalizations and deaths may underestimate the number of individuals who developed liver disease. We will additionally use liver enzyme data for the ascertainment of liver disease due to the lack of liver biopsy data.
3) Our exposure and outcome do not align perfectly in terms of timeline for the analysis of liver enzymes. Coffee consumption will be based on visit 1 dietary data, while our baseline measure for prevalent liver disease will be based on measurement of liver enzymes at visit 2. Coffee intake, as reported on the food frequency questionnaire, represents usual intake over the past year. Therefore, we can use dietary data from visit 1 to approximate diet in visit 2.
4) The FIB-4 score has only been validated in populations with HIV and liver disease (24-27). Therefore, using this score may not be suitable to be used in a general population like ARIC. However, this score is a relevant clinical outcome and would strengthen our study. We have included it in this proposal as a sensitivity analysis.

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
#2065: Epidemiology of Liver-Related Hospitalizations in a community-based population
#2868: Coffee consumption and incident kidney disease in the ARIC study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __ x __ Yes __ __ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
__X_ 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/

Ancillary Study #2009.16; Title: Short-term markers of glycemia and long-term outcomes; PI: Dr. Elizabeth Selvin – measurement of liver enzymes at visit 2

Ancillary Study #2008.10; Title: Measurement of NT-pro-BNP and troponin T at visit 4 for the full ARIC cohort; PI: Dr. Christie Ballantyne - measurement of liver enzymes at visit 4

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. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015-2020 Dietry Guidelines for AmericansDecember 2015; (8th Edition). Available from: http://health.gov/dietaryguidelines/2015/guidelines/.
2. Floegel A, Pischon T, Bergmann MM, Teucher B, Kaaks R, Boeing H. Coffee consumption and risk of chronic disease in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Germany study. Am J Clin Nutr. 2012;95(4):901-8.

3. Ding M, Bhupathiraju SN, Chen M, van Dam RM, Hu FB. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. Diabetes Care. 2014;37(2):569-86.
4. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation. 2014;129(6):643-59.
5. Bhoo-Pathy N, Peeters PH, Uiterwaal CS, Bueno-de-Mesquita HB, Bulgiba AM, Bech BH, et al. Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Breast Cancer Res. 2015;17:15.
6. Zhou Q, Luo ML, Li H, Li M, Zhou JG. Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. Sci Rep. 2015;5:13410.
7. Ding M, Satija A, Bhupathiraju SN, Hu Y, Sun Q, Han J, et al. Association of Coffee Consumption With Total and Cause-Specific Mortality in 3 Large Prospective Cohorts. Circulation. 2015;132(24):2305-15.
8. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R. Association of coffee drinking with total and cause-specific mortality. N Engl J Med. 2012;366(20):1891-904.
9. Hoyert DL, Xu J. Deaths: preliminary data for 2011. Natl Vital Stat Rep. 2012;61(6):1-51.
10. Wadhawan M, Anand AC. Coffee and Liver Disease. J Clin Exp Hepatol. 2016;6(1):40-6.
11. Ong A, Wong VW, Wong GL, Chan HL. The effect of caffeine and alcohol consumption on liver fibrosis - a study of 1045 Asian hepatitis B patients using transient elastography. Liver Int. 2011;31(7):1047-53.
12. Freedman ND, Everhart JE, Lindsay KL, Ghany MG, Curto TM, Shiffman ML, et al. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. Hepatology. 2009;50(5):1360-9.
13. Forlani G, Giorda C, Manti R, Mazzella N, De Cosmo S, Rossi MC, et al. The Burden of NAFLD and Its Characteristics in a Nationwide Population with Type 2 Diabetes. J Diabetes Res. 2016;2016:2931985.
14. Hino A, Adachi H, Enomoto M, Furuki K, Shigetoh Y, Ohtsuka M, et al. Habitual coffee but not green tea consumption is inversely associated with metabolic syndrome: an epidemiological study in a general Japanese population. Diabetes Res Clin Pract. 2007;76(3):383-9.
15. Catalano D, Martines GF, Tonzuso A, Pirri C, Trovato FM, Trovato GM. Protective role of coffee in non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci. 2010;55(11):3200-6.
16. Gutierrez-Grobe Y, Chavez-Tapia N, Sanchez-Valle V, Gavilanes-Espinar JG, Ponciano-Rodriguez G, Uribe M, et al. High coffee intake is associated with lower grade nonalcoholic fatty liver disease: the role of peripheral antioxidant activity. Ann Hepatol. 2012;11(3):350-5.
17. Birerdinc A, Stepanova M, Pawloski L, Younossi ZM. Caffeine is protective in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2012;35(1):76-82.
18. Zelber-Sagi S, Salomone F, Webb M, Lotan R, Yeshua H, Halpern Z, et al. Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. Transl Res. 2015;165(3):428-36.
19. Kim WR, Brown RS, Jr., Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. Hepatology. 2002;36(1):227-42.
20. Schneider AL, Lazo M, Ndumele CE, Pankow JS, Coresh J, Clark JM, et al. Liver enzymes, race, gender and diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. Diabet Med. 2013;30(8):926-33.
21. Sanyal AJ, Brunt EM, Kleiner DE, Kowdley KV, Chalasani N, Lavine JE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. Hepatology. 2011;54(1):344-53.
22. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317-25.
23. Adler M, Gulbis B, Moreno C, Evrard S, Verset G, Golstein P, et al. The predictive value of FIB-4 versus FibroTest, APRI, FibroIndex and Forns index to noninvasively estimate fibrosis in hepatitis C and nonhepatitis C liver diseases. Hepatology. 2008;47(2):762-3; author reply 3.
24. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7(10):1104-12.
25. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010;59(9):1265-9.
26. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology. 2013;57(4):1357-65.

27. Adams LA, George J, Bugianesi E, Rossi E, De Boer WB, van der Poorten D, et al. Complex non-invasive fibrosis models are more accurate than simple models in non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2011;26(10):1536-43.