1.a. Full Title: Alcohol consumption and subsequent risk of hypertension: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Alcohol & Hypertension risk

2. Writing Group:
   Writing group members: Yifei Lu, Mariana Lazo, Lyn Steffen, Edger Miller, Gerardo Heiss, Elizabeth Selvin, Lawrence Appel, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

_ Y.L. _____ [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: The analyses will use existing ARIC data, and manuscript preparation will be performed in the following 12 months.

4. Rationale:

Hypertension is a leading cause of cardiovascular and kidney diseases.\textsuperscript{1,2} Although we have a number of options to treat hypertension, given that a majority of adults develop hypertension during lifetime, efforts to prevent hypertension are important as well. Several lifestyle modifications such as increasing
physical activity, eating a healthy diet, and preventing or quitting smoking have been recommended in this regard. Another potential approach is limiting alcohol consumption. Possible pathophysiology linking alcohol to elevated blood pressure (BP) includes: enhancing vascular reactivity; stimulating the sympathetic nervous system or the renin-angiotensin-aldosterone system; or increasing endothelin release and cortisol levels.

However, previous epidemiological studies have reported conflicting results regarding the association of alcohol consumption with incident hypertension. Specifically, although elevated hypertension risk was generally seen among heavy alcohol users, results were not consistent for the light to moderate alcohol consumption, with a few showing each of positive, no, or inverse associations with incident hypertension. Also, many of these studies investigated specific populations (only white, male or female health professionals), had a short follow-up less than 10 years, assessed alcohol consumption only at baseline, or missed information regarding alcoholic type. Moreover, few studies assessed BP change over time, and none of them give a follow-up more than 10 years.

To overcome these caveats, we will comprehensively evaluate alcohol consumption (including current drinking patterns [i.e. drinking frequency, alcoholic type] and previous drinking patterns [i.e. quitting years, former drinking frequency, former drinking years]) using data from a biracial community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study and explore the associations of alcohol consumption with BP trajectory and incident hypertension at up to five time points during follow-up of ~30 years.

5. **Main Hypothesis/Study Questions:**

   1) Alcohol consumption will modify the BP trajectory over time, with steeper rate of BP increase among heavy drinkers.
   2) Heavy, but not light and/or moderate, alcohol consumption will be associated with incident hypertension.
   3) Alcohol cessation, particularly among heavy drinkers, will be associated with lower risk of incident hypertension.
   4) These associations will be generally consistent across alcoholic types.

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:**

Prospective cohort study

**Inclusion criteria:**

All black and white ARIC study participants free of prevalent hypertension at visit 1.

**Exclusion criteria:**

- Participants who identified themselves as non-white/non-black.
- Participants with cardiovascular diseases (defined as coronary heart disease, stroke, and heart failure) at baseline, and we will further exclude participants with prevalent hypertension for incident hypertension analysis.
- Participants with missing data on alcohol consumption, and covariates of interest.
- Participants with missing data on incident hypertension, BP measurement, and anti-hypertensive medication use.

Exposure:

Alcohol consumption was assessed at Visits 1-5 using an interviewer-administered dietary questionnaire. Current, former, and never drinkers were classified by answering yes/no questions: “Do you presently drink alcoholic beverages?” and, if not, “Have you ever consumed alcoholic beverages?”. Current drinkers were asked to specify how many 4-ounce glasses of wine (10.8g ethanol), 12-ounce bottles or cans of beer (13.2g ethanol), or 1.5-ounces shots of liquor (15.1g ethanol) they drank weekly. Total weekly alcohol consumption, and specific weekly alcohol consumption in wine, beer, or liquor then were calculated and converted into the number of standard drinks (1 standard drink = 14g ethanol) for each current drinker. According to the Dietary Guidelines for Americans, we will categorize total weekly alcohol consumption into: <1, 1-<8, 8-<15, and ≥15 drinks/week. 8 drinks/week and 15 drinks/week corresponds to the high-risk drinking cutoffs for female and male, respectively. We will categorize years since quitting into <5, 5-<10, 10-<15, ≥15 years, cumulative drinking years before quitting into <10, 10-<20, ≥20 years, and the number of standard drinks consumed per week before quitting into <8, 8-<15, ≥15 drinks/week. We will explore both time-fixed (visit 1) and time-varying (all visits 1-5) exposures.

Outcome:

The sitting arm blood pressure was measured at each Visit 1-5 using a standardized Hawksley random-zero sphygmomanometer except visit 5 where Omron oscillometric device was used. Three measures were taken for each individual, and the average of second and third readings will be used for evaluating BP trajectory and classifying hypertension (except visit 4 where only two measurements were obtained and those two were averaged). Whether “having high blood pressure or hypertension ever diagnosed” or “taking anti-hypertension medication within past 2 weeks” were asked to report by cohort participants at each visit, annual follow-up contacts after visit 4, and semi-annual follow-up contacts after 2012.

BP trajectory:

systolic BP (SBP) and diastolic BP (DBP) was measured and recorded at Visits 1-5. For those who self-reported the use of anti-hypertension medication, we will additionally add 10 mmHg for SBP and 5 mmHg for DBP, as done previously.

Incident hypertension:

Each participant was followed from baseline through the last semi-annual follow-up, for incident hypertension, which was defined as either of the following:
1) Newly self-reported hypertension (doctor diagnosis or medication use) at follow-up visits or annual/semi-annual follow-up contacts;
2) Newly measured hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) at follow-up visits.

**Covariates:**

- Sociodemographics: age, race, gender;
- Physical information: body mass index;
- Lab examination: total cholesterol, HDL cholesterol, creatinine-derived eGFR;
- Lifestyle: education level, smoking status, diet score (scores 0-5 based on the consumption of fruits and vegetables, fish, fiber-rich whole grains, sodium, sugar-sweetened beverages), physical activity (American Heart Associate defined physical activity category as recommended vs. intermediate vs. poor);
- Comorbidities: diabetes
- Medication: cholesterol-lowering medication

**Statistical analysis:**

Baseline characteristics will be compared across drinking status of never drinkers, former drinkers, and current drinkers at baseline.

**BP trajectory:**

To identify the SBP and DBP trajectories across 6 drinking groups (never drinkers [reference group], former drinkers, current drinkers [0-1, 1-<8, 8-<15, and ≥15 drinks/week]) over Visits 1-5, we will fit linear mixed effects regression models which account for the correlations of BP measurements at different time points within the same individual. Random slope and intercept will be employed to account for individual differences. Model 1 will include drinking groups updated at each visit, follow-up years, and interaction term of drinking groups with follow-up years; model 2 will adjust for age, gender, race, education level, smoking status, diet score, physical activity, and body mass index at baseline; model 3 will additionally adjust for baseline total cholesterol, HDL cholesterol, cholesterol-lowering medication, creatinine-derived eGFR, and diabetes.

**Incident hypertension:**

We will further exclude cohort participants with prevalent hypertension at baseline.

For the time-fixed analyses, we will use all the information collected at visit 1. We will primarily quantify the associations of 6 drinking groups (never drinkers [reference group], former drinkers, current drinkers [0-1, 1-<8, 8-<15, and ≥15 drinks/week]) with incident hypertension. Then we will secondarily explore more detailed categories of former drinkers based on years since quitting (<5, 5-<10, 10-<15, ≥15 years), cumulative drinking years before quitting (<10, 10-<20, ≥20 years), and weekly total alcohol consumption before quitting (<8, 8-<15, ≥15 drinks/week) for former drinkers. We will also investigate specific types of wine, beer, and liquor (counted as continuous number of standard drinks) for current drinkers.

For the time-varying analyses, we will run the same models with updated drinking and covariates data from follow-up Visits 2-5. We will carry forward the last available value for the missing data at follow-up visits.
All of the analyses will be conducted using Cox proportional hazards models with crude model for model 1; adjustments on age, gender, race, education level, smoking status, diet score, physical activity, and body mass index for model 2; additional adjustments on total cholesterol, HDL cholesterol, cholesterol-lowering medication, creatinine-derived estimated glomerular filtration rate (eGFR), and diabetes for model 3.

Finally, as sensitivity analyses to confirm robustness of our findings based on the aforementioned analyses, we will stratify by gender and race, and apply different definitions for incident hypertension (e.g., newly self-reported anti-hypertensive medication use only). All analyses will be performed with Stata version 14.0, and a p-value <0.05 will be considered statistically significant.

Limitations:

Alcohol consumption was based on self-report, subjecting to recall bias and misclassification.

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

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.cscn.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)?

#451: “Alcohol consumption and incident hypertension”. This proposal focuses on short follow-up time in ARIC, and a manuscript from this proposal has been already published (Hypertension. 2001; 37: 1242-50.)

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* __________)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __2014.05__ __________ __________)

*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 ____ No.

References:


