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

b. Abbreviated Title (Length 15 characters):
Alcohol and PAD

2. Writing Group:
Writing group members: Samiha T. Khan, Yifei Lu, Steven Menez, Gerardo Heiss, Elizabeth Selvin, Kunihiro Matsushita,

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

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3. Timeline:
The analyses will use existing ARIC data, and manuscript preparation will be performed in the following 6 months.

4. Rationale:
Peripheral artery disease (PAD) affects more than 8 million Americans and over 200 million people around the world.1,2 PAD significantly increases the risk of mortality, cardiovascular events,1,3 reduced leg function (e.g., walking impairment), and amputation.4,5 Despite its high prevalence and impact on mortality and morbidity, PAD has generally received much less attention compared to coronary artery disease and stroke.6,7 This is an important caveat since risk factor profiles are not necessarily consistent across these three major atherosclerotic diseases.1

In this context, although there are a number of studies investigating the association of alcohol consumption with cardiovascular risk (often a J-shaped association with the lowest risk in low-to-moderate alcohol drinkers and elevated risk in both heavy and never drinkers),2,3 only a limited number of prospective studies have explored the association of alcohol intake with incident PAD8-11 and reported conflicting results with U-shape,5,8,11 inverse10 and positive associations.9 Also, most of these studies included selected populations of only physicians,8 only whites10 or Japanese Americans.9 Therefore, using data from the ARIC Study, we seek to quantify the association of alcohol intake with incident PAD. Given the large sample size and long follow-up of ARIC, we will be able to uniquely evaluate critical limb ischemia (CLI), the severe form of PAD, as an outcome as well.

5. Main Hypothesis/Study Questions:
- There will be a J-shaped association between alcohol intake and incident PAD and CLI.
- The association will be consistent across different alcohol 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:
Multi-center population-based prospective cohort study

Inclusion criteria:
All African American and white participants in the ARIC Study free of prevalent PAD (defined ABI ≤0.9, a history of leg revascularization, or intermittent claudication) at visit 1

Exclusion criteria:
- Participants who identified themselves as non-white/non-black
- Participants with prevalent PAD at baseline
- Participants with missing data on alcohol consumption and other covariates of interest, and incident PAD

**Exposure:**
- Alcohol consumption at Visit 1 will be the primary exposure, based on 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\(^{12}\)) for each current drinker. According to the Dietary Guidelines for Americans,\(^{12}\) 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 females and males, 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. To confirm robustness of our primary findings, we will repeat the analysis using data on alcohol intake at each of visits 2-4 as well.

**Outcome:**
- PAD-related hospitalizations, identified with the following ICD-9 codes based on previous literature:\(^{12-15}\) atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Among PAD cases, those based on 440.22, 440.23, and 440.24 and those with coexisting codes of leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4) will be considered CLI.

**Covariates:**
- Sociodemographic data: age, race, gender, education level
- Physical measurements: body mass index, systolic and diastolic blood pressure, ABI
- Associated medical comorbidities:
  - Hypertension, defined as systolic blood pressure ≥ 140mm Hg, diastolic blood pressure ≥90 mmHg, or taking any antihypertensive medication.
  - Diabetes, defined as fasting glucose level ≥126 mg/dL (≥7.0 mmol/L), non-fasting glucose level ≥200 mg/dL (≥11.1 mmol/L), self-reported physician diagnosis, or use of antidiabetic medications
  - Prevalent coronary heart disease at visit 1 based on self-reported clinical history and evidence of prior myocardial infarction by electrocardiogram.
- Prevalent stroke based on self-report
- Total and high-density lipoprotein cholesterols

**Social factors:**
- Smoking status

**Statistical analysis plan:**
- Baseline characteristics will be compared among all participants with quartiles of alcohol consumption (overall and by gender)
- Cox proportional hazards models will be used to quantify the association of alcohol intake with PAD outcomes. Alcohol intake will be modeled as continuous (using splines) and categorical variables based on the Dietary Guidelines for Americans.
  - Model 1 will be crude.
  - Model 2 will be adjusted for baseline variables of age, race, gender, BMI, and education level
  - Model 3 will be additionally adjusted for blood pressure, antihypertensive medications, total and high-density lipoprotein cholesterols, diabetes, prevalent coronary heart disease, and prevalent stroke
  - Model 4 will be adjusted for ABI.
- We will conduct subgroup analysis by age, gender, race, smoking status, and history of hypertension, diabetes, coronary disease, and stroke.

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.cscce.unc.edu/ARIC/search.php](http://www.cscce.unc.edu/ARIC/search.php)
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)?

#1445: Longitudinal relation between dietary intake and peripheral arterial disease in middle-aged adults: ARIC.
This proposal included alcohol intake as a part of dietary intake. However, a manuscript has been already published from this proposal (Am J Clin Nutr. 2017;105:651-659) and thus there is no risk that our new proposal interfere this existing proposal. Also, our proposal will focus on alcohol intake and comprehensively evaluate its association with PAD. In addition, this proposal will uniquely evaluate CLI as an outcome.

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* __2014.05___)
___ 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.csc.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.csc.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__
References