1.a. **Full Title**: Clinically recognized varicose veins and infectious disease in older individuals

b. **Abbreviated Title (Length 26 characters)**: Varicose veins and infections

2. **Writing Group**:
   Writing group members: Yejin Mok, Junichi Ishigami, Anna Kucharska-Newton, Maya Salameh, Priya Palta, B. Gwen Windham, Pamela Lutsey, Kunihiro Matsushita

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

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3. **Timeline**: Analyses and manuscript preparation will be performed over the next 6 months.

4. **Rationale**:
   Varicose veins of the lower extremities, which are part of the spectrum of chronic venous disease, have been estimated to affect approximately 23% of adults in the US, with especially high prevalence in women and older adults.\(^1\) Varicose veins affect approximately 22 million women and 11 million men between 40 to 80 years old.\(^1,2\) Of these, 2 million men and women progress to serious morbidity including venous ulceration.\(^1,2\)
Patients with venous ulceration are at high risk of infections such as cellulitis.\textsuperscript{3} Even when there is no evident ulceration chronic venous disease is known as a risk factor of cellulitis.\textsuperscript{4} However, limited data are available from longitudinal cohort studies to comprehensively investigate varicose veins and the subsequent risk of infections. Quantifying the association of varicose veins with infection risk would be important to acknowledge potential importance of this underdiagnosed and underrecognized venous disease.

Therefore, we will investigate whether varicose veins are associated with subsequent risk of infections (e.g., cellulitis, bloodstream infection, pneumonia, and urinary tract infection) using data from the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:
   - Varicose veins will be associated with higher risk of infectious disease independently of comorbidities such as diabetes, or history of cardiovascular disease.
   - The associations will be more evident for lower extremity infectious disease (e.g., cellulitis).

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
   - We will quantify the association of varicose veins at visit 5 as baseline with subsequent risk of infection.

   Inclusions:
   - All ARIC participants with data on covariates of interest at visit 5

   Exclusions:
   - Race other than black and white
   - Missing data on covariates of interest at visit 5
   - Each of prevalent cases (e.g., prevalent cellulitis at visit 5 will be excluded in the analysis for incident cellulitis)

Exposure: Clinically recognized varicose veins
   - We will capture all ARIC participants who had diagnosis of varicose veins prior to visit 5.
   - Varicose veins will be defined by relevant diagnosis during hospitalization or outpatient visits.
     - Hospitalization due to varicose veins will be identified from ARIC hospitalization data and CMS Medicare data (ICD-9 codes: 454.xx).
     - Outpatient visits for varicose veins will be identified from CMS Medicare data (ICD-9 codes: 454.xx) (at least two visits for varicose veins as primary exposure and at least a visit as secondary exposure)

Outcomes:
• Outcome of interest will be hospitalization or outpatient with four types of infection (cellulitis, pneumonia, urinary tract infections, and bloodstream infections) after visit 5 (2011-2013) through December 31, 2016.
• Infections will be defined based on ICD-9 codes (cellulitis [040.0, 681, 682, and 730.0-2], pneumonia [480-486]; urinary tract infections [590.1, 599.0, and 601.0], and bloodstream infections [038, 054.5, 785.52, 790.7, 995.91, and 995.92]) or corresponding ICD-10 codes
  - Hospitalization due to infections will be identified from ARIC hospitalization data and CMS Medicare data
  - Outpatient visits for infections will be identified from CMS Medicare data (at least two visits for infections as primary exposure and at least a visit as secondary exposure)

Covariates: socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, history of cardiovascular disease (coronary heart disease, stroke or heart failure), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication), diabetes (fasting blood glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, reported history of diabetes, or use of anti-diabetes medication), lipid parameters (Total cholesterol, HDL cholesterol and LDL cholesterol), antidyslipidemia medications, ankle-brachial index, and health insurance status (besides Medicare) at visit 5.

Statistical analysis
1. We will summarize baseline characteristics by absence and presence of varicose veins.
2. Cumulative incidence of overall infections will be estimated by absence and presence of varicose veins using the Kaplan-Meier method.
3. We will quantify the association of varicose veins with overall infections using Cox proportional hazards models. Those models will adjust for covariates listed above.
4. Subsequently, we will repeat analysis for four subtypes of infections.
5. We will conduct a few sensitivity analyses
   a. To compare the contribution of varicose veins to infections in subgroups, we will perform subgroup analysis according to age, gender, race, smoking status, health insurance status (besides Medicare) and clinical conditions (diabetes, hypertension, and history of cardiovascular disease).
   b. Since we cannot capture outpatient visits for varicose veins and infectious disease outside of Medicare fee-for-service beneficiaries aged ≥65 years, we will restrict to ARIC participants enrolled continuously in Medicare Parts A and B through a fee-for-service plan within 2 years prior to visit 5 and repeat analysis. We will also repeat analysis for inpatient- and outpatient-based infectious disease, separately.

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
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)?
#3056: Ankle-brachial index and short-term risk of cardiovascular events in older adults
#2871: Cardiac Markers and Risk for Hospitalization with Infection: The Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ 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)* __________ __________ __________)

*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.
References