1. **Full Title**: The Association of Height with PAD Outcomes in the Atherosclerosis Risk in Communities (ARIC) Study

2. **Abbreviated Title** (Length 26 characters):
   Height and PAD

3. **Writing Group**:
   Writing group members: Steven Menez, Lucia Kwak, Ning Ding, Caitlin Hicks, Morgan Grams, Aaron Folsom, Gerardo Heiss, Elizabeth Selvin, Bernard Jaar, Kunihiro Matsushita

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

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**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) is the third leading cause of atherosclerotic vascular morbidity after coronary heart disease and stroke, and this disorder affects more than 200 million individuals around the world.[1] The current standard of care measure for evaluation of patients with suspected peripheral arterial disease is the ankle-brachial index (ABI), with a cutoff of 0.9 as a sensitive and specific marker for presence of disease.

However, it is known that ABI tends to be lower among individuals with shorter height due to less progressive ankle blood pressure increase, related to distance from the heart.[2] This potential misclassification of ABI related to height has not been widely recognized in the literature and may explain some previous findings of shorter height as a risk factor for PAD, and counterintuitively similar prevalence of PAD between men and women.[3-7]

If height is pathophysiologically associated with the development of PAD beyond ABI misclassification, height should prospectively be associated with clinical PAD including leg amputation. However, to our knowledge, no previous studies have looked at the exposure of height with the development of clinical PAD outcomes. Therefore, using data from the ARIC Study, we seek to identify if differences in height have an association with clinical PAD.

5. Main Hypothesis/Study Questions:
Are differences in height associated with clinical PAD outcomes?

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[8]

Inclusion criteria:
All African American and white participants in the ARIC Study free of prevalent PAD at Visit 1 who have measured height and ABI.

Exclusion criteria:
- Participants who identified themselves as non-white/non-black.
- Participants with prevalent PAD at baseline (i.e., ABI ≤0.9, self-reported peripheral revascularization, intermittent claudication based on the Rose questionnaire).
- Participants with missing data on height and other covariates of interest, and PAD

Exposure:
- patient height

Outcome:
PAD-related hospitalizations, identified with the following ICD codes based on previous literature: 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.[9, 10]

Covariates:
- Sociodemographic data: age, race, gender, education level
- Physical measurements: body mass index, systolic and diastolic blood pressure, ABI
- Associated medical comorbidities:
  - Hypertension
  - 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
- Social factors:
  - Smoking status
  - Alcohol status

Statistical analysis plan:
- Baseline characteristics will be compared among all participants with quartiles of height (overall and by gender)
- Cox proportional hazards modeling will be used to analyze PAD-related outcomes based on height as continuous (using splines) and categorical (quartiles) variables.
  - 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 adjusted further for hypertension, diabetes, prevalent coronary heart disease, and prevalent stroke
- 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.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)?

To the best of our knowledge, there are no ARIC proposals tackling height as a predictor of PAD.

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.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


