1.a. Full Title:
The association between ankle-brachial index and incident diabetes mellitus: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): ABI and incident diabetes

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. S.H. [please confirm with your initials electronically or in writing]

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3. Timeline:
We will use existing ARIC data to perform the analysis and prepare the manuscript in the following 12 months.
4. Rationale:

Lower extremity peripheral arterial disease (PAD), characterized by atherosclerotic stenosis or occlusion of leg arteries and typically diagnosed by ankle-brachial index (ABI) <0.9 [1], affects approximately 8 million people in the United States [2]. PAD increases the risk of cardiovascular disease and reduces quality of life due to ischemic leg pain and intermittent claudication [1][3]-[5].

Regardless of leg symptoms, patients with PAD experience functional decline and impairment [6]-[9], which can result in reduced level of physical activity [10][11]. As physical inactivity is a well-known risk factor for diabetes [12], it is possible that low ABI is associated with the development of diabetes. However, to the best of our knowledge, this association has not been studied, although the opposite direction (i.e., diabetes as a risk factor of PAD) is well-known [1][2]. Therefore, the aim of this study is to investigate the association of ABI and incident diabetes in a community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study. Shared pathophysiology between atherosclerosis and insulin resistance, such as the involvement of inflammation, may also contribute to the link of ABI to diabetes risk [13][14][15].

5. Main Hypothesis/Study Questions:
1. Low ABI will be independently associated with increased risk of incident diabetes.
2. High ABI, a condition seen in some individuals with PAD and vascular calcification, can be also associated with increased risk of incident diabetes.

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 from diabetes at baseline examination (visit 1) with data of ankle-brachial index.

Exclusion criteria
- Participants who identified themselves as non-white/non-black.
- Participants with diabetes at baseline defined by self-reported physician diagnosis or treatment of diabetes, fasting blood glucose ≥126 mg/dl or random blood glucose ≥200 mg/dl [16].
- Participants with missing variables of interest.

Exposure
- ABI at visit 1: defined as a ratio of systolic blood pressure (SBP) of ankle to that of arm [17]. The blood pressure of the upper extremity and lower extremity were measured by automated oscillometric device Dinamap Model 1846 SX as a part of ARIC Ultrasound Assessment of carotid and popliteal arteries [18]. Ankle SBP was measured four times in a randomly selected leg and the last non-missing value was used as numerator of ABI and brachial SBP was measured twice in the right arm and the first non-missing value was used as denominator of ABI [19]. ABI was also assessed at visits 3 and 4 in subsample, which will be used for sensitivity analysis.
Outcome

Incident diabetes: We will test a visit-based definition and an interview-based definition, as previously done in ARIC [20]. Visit-based diabetes cases will be defined as newly identified diabetes at follow-up visit 2 to 5 based on glucose measurements, self-reported diagnosis by physicians or diabetes medication use. Given a long elapsed time between visits 4 and 5 (~15 years), we will also investigate visit-based diabetes cases restricted to visits 2, 3 and 4. Interview-based cases are defined as newly identified diabetes based on self-reported diagnosis or diabetes medication use at annual phone interview during ~20 years of follow-up.

Other variable of interest:
(1) Age, gender, race
(2) Body mass index, sitting blood pressure, total cholesterol level, low-density and high-density lipoprotein cholesterol level, triglyceride level, fasting glucose level.
(3) Lifestyle: cigarette smoking and alcohol drinking habits.
(4) Physical activity/physical function: At visit 1, visit 3 and during annual phone interview, ARIC has collected various information on physical activity/function such as Baecke physical activity questionnaire, which recorded the duration, intensity and frequency of physical activity at work, in leisure time and during sports and produced an index score to represent level of physical activity [21]. We will treat physical activity/function as a time-fixed and time-varying covariate.
(5) Family history of diabetes.
(6) Medical history: hypertension, cardiovascular diseases.
(7) Inflammatory markers: white blood count, fibrinogen at visit 1 and hs-CRP at visit 2.

Data Analysis Plan

Primary analysis will use Cox proportional hazards models to examine the association between ABI with its spline terms (knots at thresholds of subsequent categories) and incident diabetes (visit-based diagnosis and interview based diagnosis separately). We will also treat ABI as a categorical variables using its quintiles as well as the following categories of ABI [22]: <0.5, 0.5~0.7, 0.7~0.9, 0.9~1.1, 1.1~1.3, and 1.3+. We will construct four models: Model 1 will only adjust for age, sex and race; Model 2 will include additional covariates mentioned above except for physical activity/physical function and inflammatory markers; Models 3 will further adjust for inflammatory markers. Model 4 will add physical activity/physical function as a potential mediator. For all four models, we will test models both with and without adjustment for baseline fasting glucose levels.

We will repeat the analysis in several key subgroups according to age, sex, race, smoking status, and history of cardiovascular disease. When visit 5 data are included for visit-based definition, we will conduct a sensitivity analysis with inverse probability of attrition weighting to account for participants who died before visit 5 or were alive at the initiation of visit 5 but did not attend. For this sensitivity analysis, we will use key demographic and clinical prognostic variables obtained at visit 4 or after that during
follow-up before visit 5 (e.g., incidence of cardiac disease). To explore the possibility of reverse causation, we will exclude incident diabetes that occurred in the first three years of baseline and also explore the association between ABI and development of impaired fasting glucose (IFG) (≥100 mg/dL) among those with normal fasting glucose (<100 mg/dL) at baseline.

Limitations and challenges
Although we will rigorously adjust for covariates in our models, we still could not rule out the possibility of residual confounding. In addition, diabetes is based on self-report during 15 years between visit 4 and 5, particularly for those who did not attend visit 5. However, we will test the impact of limiting to visit-based definition at visit 2 through 4 and also conduct inverse probability attrition weighting approach. ABI was measured at a randomly selected leg, which may affect the validity of exposure measurement. However, the effect size of ABI on cardiovascular risk in ARIC is similar to that from other cohorts [3]. Finally, the physical activity is predominantly based on self-report, which usually leads to an overestimate of actual physical activity [23].

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ 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  ____ 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.csc.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)?
There are no proposals investigating the association of ABI and future risk of diabetes.

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.cscce.unc.edu/aric/forms/](http://www.cscce.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/](http://publicaccess.nih.gov/) are posted in [http://www.cscce.unc.edu/aric/index.php](http://www.cscce.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

References


