ARIC Manuscript Proposal #2312

PC Reviewed: 2/11/14   **Status:** <u>A</u>   **Priority:** <u>2</u>
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: Ankle-brachial index and physical function and activity in older individuals: the Atherosclerosis Risk in Communities (ARIC) Study

   b. Abbreviated Title (Length 26 characters): ABI and physical function

2.   Writing Group:
     Writing group members: Kunihiro Matsushita, Shoshana Ballew, Yingying Sang, Corey Kalbaugh, Laura Loehr, Hirofumi Tanaka, Gerardo Heiss, B. Gwen Windham, Elizabeth Selvin, Josef Coresh, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _KM_ **[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).
     Name:
     Address:

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3.   Timeline: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4.   Rationale: Lower extremity peripheral artery disease (PAD), commonly defined as ankle-brachial index (ABI) <0.9, affects 8-10 million individuals in the US[1-3] and more than 200 million individuals around the globe.[2] The prevalence increases dramatically with age (from ~1% at age 40-49 to ~15% at age 70-79 years in the US).[4] Of note, its

prevalence increased by 24% globally in the last decade.[2] PAD increases mortality risk, mainly due to cardiovascular disease. Indeed, patients with PAD have 3-6 fold higher risk of 10-y mortality compared to those without.[5] PAD has been reported to also reduce quality of life due to limited mobility and leg pain or tiredness, particularly in older individuals.[6-9] However, these previous studies focusing on older population have been conducted in small samples (n <~1500) from selected populations (mainly PAD cases referred to vascular labs[6-8] or those with impaired physical function[9]), leaving uncertainty regarding the general impact of ABI on physical function or activity in older individuals in the community. Therefore, the aim of this study is to assess the association of ABI with physical function and activity using data from the ARIC Study visit 5.

5. Main Hypothesis/Study Questions:
Hypothesis 1: Low ABI will be associated with low physical function and activity independently of other comorbidities such as diabetes, hypertension, and history of cardiac disease or stroke

Hypothesis 2: High ABI, reflecting arterial stiffness, will be also associated with low physical function and activity independently of other comorbidities such as diabetes, hypertension, and history of cardiac disease or stroke

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).

Inclusions:
- All black and white ARIC subjects with data on ABI and physical function and activity at visit 5

Exclusions:
-Ethnicity other than black or white
-Missing data on ABI and physical function and activity at visit 5

Exposure (independent variables):
-ABI measured at visit 5: We will test both lowest value and mean value of ABI from both legs

Outcome (dependent variables):
-Physical function: The Short Physical Performance Battery (SPPB) was evaluated at visit 5 as a measure of physical function and consists of three domains: (1) gait speed (i.e. 4 meter walk), (2) chair stands (i.e. single chair stands and repeated chair stands), and (3) balance (semi tandem stand, side-by-side stand, and tandem stand). We will analyze global SPPB score (range: 0-12: ≥10 ideal function, 6-9: intermediate, and <6 poor), summary score of each domain (range: 0-4), and score or exact value of each constituent.

-Physical activity: Physical activity levels (work, leisure, and sports) were assessed at the ARIC visit 5 using physical activity questionnaire (form code: PAC).

Other variables of interest and covariates:
-Sociodemographics: age, race, gender, education level
-Physical information: body mass index, waist circumference, blood pressure, heart rate
-Lifestyle: smoking status and alcohol habit
-Comorbidities: diabetes, hypertension, dyslipidemia, chronic kidney disease (defined by kidney function and albuminuria), depression, cognitive impairment, and history of cardiac disease (coronary heart disease and heart failure), stroke, and fracture (from discharge code and/or CMS data).

Statistical Analysis Plan:
We will use linear and logistic regression models to quantify the association of ABI and physical function and activity as continuous and/or dichotomous outcome variables, as appropriate. ABI will be treated as a continuous variable with splines and a categorical variable based on clinical categories (ABI: <0.5, 0.5-0.7, 0.7-0.9, 0.9-1.1, 1.1-1.4 [reference], and ≥1.4)[10] in the models (another cutoff for high ABI, 1.3,[11] will be also tested). We will adjust for the covariates listed above. We will repeat the analysis after stratifying the study sample by age, gender, race, and presence/absence of comorbidities such as diabetes, obesity, and history of cardiac disease and stroke. The interaction will be tested by likelihood ratio test.

　　　We will conduct a sensitivity analyses with inverse probability of attrition weighting to account for participants who 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., diabetes and incidence of cardiac disease).

Limitations:
　　　A cross-sectional design will not allow us to evaluate causality of the associations. As with any observational study, we will not be able to rule out the possibility of residual confounding. The results may not be generalizable to ethnic groups other than whites and blacks.

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)?
There are no proposals investigating the association of ABI and physical function/activity.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?   _____ Yes   __X__ 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.

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report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. 2006;113:e463-654