ARIC Manuscript Proposal #3037

PC Reviewed: 9/12/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Physical activity and subsequent risk of hospitalization with peripheral artery disease (PAD) in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Physical activity & incident PAD

2. Writing Group:

Writing group members: Yifei Lu, Shoshana Ballew, Elizabeth Selvin, Moyses Szklo, Corey Andrew Kalbaugh, Jennifer Schrack, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _Y.L.____ **[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 9 months.

4. Rationale:

Peripheral artery disease (PAD) is an atherosclerotic disease, limiting blood flow in the lower extremities.[1] PAD affects approximately 200 million adults worldwide and its prevalence

increased by 24% between 2000 to 2010.[2] PAD induces leg pain (typically as intermittent claudication), may progress to critical limb ischemia, and may result in leg amputation.[1] Also, patients with PAD have a 2-5 fold higher risk of death compared to those without PAD.[3] All of these indicate the importance and potentially huge benefit of preventing PAD.

Some studies have suggested a protective effect of physical activity in reducing atherosclerotic risk factors[4,5] and potentially preventing cardiovascular disease such as coronary heart disease.[5-7] However, whether and how physical activity is associated with incident PAD remains unclear. Even though a number of articles reported a link between physical activity and PAD,[8-21] most of them were cross-sectional[8-18] or confined to high risk populations (i.e. prevalent diabetes[14] or adults with borderline ABI of 0.90-1.00[19]). Of a few limited prospective studies, most were small (sample sizes <500)[19,20] or had short follow-up of less than 3 years.[20,21] Thus, we aim to explore prospective associations of physical activity with subsequent risk of PAD over 25 years in ARIC.

5. Main Hypothesis/Study Questions:
Higher level of physical activity is associated with lower risk of incident PAD.

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 of prevalent PAD at visit 1 with data on physical activity, covariates, and incident PAD.

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 prevalent CVD at baseline (defined as coronary heart disease, stroke, and heart failure)
- Participants with missing data on physical activity, covariates of interest, and PAD outcomes.

Exposure:
Physical activity data:
Physical activity level was assessed by a modified Baecke physical activity questionnaire at visit 1 and visit 3. The questionnaire evaluated the amount of physical activity and yielded a score ranging from 1(low) to 5 (high) during each of leisure, sport, and work times.

We will additionally assess physical activity using minutes per week of exercise solely based on Baecke sports questions. Also, as done in previous studies,[6,22,23] up to four sports in the previous year were specified and assigned metabolic equivalents of task (METS) values according to the

Compendium of Physical Activities.[24] Then minutes per week of moderate (3-6 METS) or vigorous (≥6 METS) physical activity were estimated for each participant. We will either treat METS score as a categorical variable according to the AHA guidelines (recommended: ≥150 min/wk of moderate intensity or ≥75 min/wk of vigorous intensity or ≥150 min/wk of moderate plus vigorous intensity; intermediate: 1-149 min/wk of moderate intensity or 1-74 min/wk of vigorous intensity or 1-149 min/wk moderate plus vigorous intensity; poor: 0 min/wk of moderate or vigorous exercise) or model it continuously (METS*minutes per week).

In this study, we will mainly investigate sport score and METS score but, to provide a complete picture, will also explore leisure and work scores. We will primarily analyze physical activity at visit 1 but repeat the analysis using visit 3 physical activity and their average as sensitivity analyses.

Outcome:

Incident PAD:

Incident PAD will be primarily defined as PAD-related hospitalizations with the following ICD codes based on previous literature[25]: 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). Of PAD cases, those with 440.22, 440.23, and 440.24 as well as any cases with the coexisting code of leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4) will be considered as critical limb ischemia (CLI).

As a sensitivity analysis, we will seek whether the addition of peripheral vascular disease, unspecified (443.9), which is controversial due to its unspecific property will change our results or not.

Covariates:

- Sociodemographics: age, race, gender, education level, insurance status;
- Physical information: body mass index, systolic blood pressure, diastolic blood pressure, walking ability
- Lab examination: total cholesterol, HDL cholesterol, triglycerides, fasting glucose, kidney function based on creatinine-derived eGFR, and inflammatory markers including white blood cell, albumin, fibrinogen;
- Lifestyle: smoking status (we will explore a few parameters such as pack-years and smoking status of never, former, and current; among the former smokers, how long since they quit) and alcohol habit
- Comorbidities: dyslipidemia, diabetes, and hypertension
- Medication: antihypertensive medication use, cholesterol-lowering medication use, diabetes medication use, aspirin use

Statistical analysis:

- Baseline characteristics will be compared across different physical activity categories.

- Kaplan-Meier estimates will be used to quantify PAD-free survival by physical activity categories.
- Cox proportional hazards models will be performed to quantify the prospective association of physical activity with incident PAD. Follow-up time will be defined as years from baseline visit to the date of incident PAD, death, loss to follow-up, or administrative censoring on December 31, 2014, whichever comes first. Physical activity will be initially treated as a categorical variable (recommended, intermediate, poor). To see if there is a non-linear dose-response relationship between physical activity and incident PAD, a restricted spline cubic model will be applied with physical activity as a continuous exposure (METS*min/wk).
- Models will be progressively adjusted as follow:

    Model 1: unadjusted

    Model 2: adjust for age, gender and race;

    Model 3: + education, insurance status, smoking status, alcohol intake, and walking ability (primary model);

    Model 4: + leisure score, work score (when we analyze leisure score or work score as a main exposure, sport score will be included as a covariate)
- We will also conduct mediation analysis on potential mediating variables – body mass index, systolic blood pressure, antihypertensive medication use, total and HDL cholesterol, triglycerides, cholesterol-lowering medication use, diabetes, creatinine-derived eGFR, an inflammatory marker (white blood cell, albumin, and fibrinogen in turn), and aspirin use, to see the extent to which these risk factors mediate the effect of physical activity on incident PAD.
- Although we will primarily evaluate physical activity as a single time exposure, we will also assess whether changes in physical activity from visit 1 to visit 3 will be associated with incident PAD beyond baseline physical activity measures. Participants who developed PAD before visit 3 will be excluded from this analysis. Physical activity changes will be modeled in two ways:

    Physical activity category change from visit 1 to visit 3: poor to poor, poor to intermediate, poor to recommended, intermediate to poor, intermediate to intermediate, intermediate to recommended, recommended to poor, recommended to intermediate, recommended to recommended;

    By subtracting METS minutes per week in visit 1 from those in visit 3, physical activity changes will be defined as increased group (increase more than 1 SD of difference between two visits), stable group (the changes are located within 1 SD of difference), or decreased group (decrease more than 1 SD of difference between two visits). We will also repeat analysis using the change in total minutes of physical activity per week regardless of intensity.
- We will perform subgroup analysis stratified by age, gender, race, obesity, diabetes, dyslipidemia, hypertension and smoking status.
- We will evaluate whether physical activity is differently associated with incident PAD vs. its severe form of CLI. We will formally test the difference in effect size using seemingly unrelated regression.
- To account for the possibility of reverse causation, we will check whether the exclusion of PAD cases in the first 1-5 years will yield considerably different results compared to the main analysis.

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)?
MP #2970, "The American Heart Association's Life Simple 7 and Risk of Peripheral Artery Disease: The Atherosclerosis Risk in Communities (ARIC) Study" includes physical activity as a part of seven factors consisting of Life Simple 7. However, the project will merely analyze three categories (ideal, intermediate, or poor) of physical activity. As noted above, the current proposal will explore physical activity in much finer and comprehensive ways. Dr. Matsushita participates to #2970 as "ARIC author" and will make sure the coordination between the two projects.

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* _____)
_X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __2014.05___ _____ _____)

*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 ____ No.

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