ARIC Manuscript Proposal #2922

PC Reviewed: 01/10/2017	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Obesity measures and the risk of peripheral artery disease

b. Abbreviated Title (Length 26 characters): Obesity and PAD

2. Writing Group:

Writing group members: Caitlin Hicks, Chao Yang, Shoshana Ballew, Chiadi Ndumele, Aaron Folsom, Gerardo Heiss, James Black III, Elizabeth Selvin, Kunihiro Matsushita

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

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3. Timeline: Data to be used in this proposal are available. Analyses and manuscript preparation will be performed over the next 12 months.

4. Rationale:

Peripheral arterial disease (PAD) affects 8-10 million individuals in the United States and more than 200 million individuals worldwide [1]. The most severe form of PAD is critical limb ischemia (CLI), which is characterized by rest pain, ulcers, or gangrene. Even with surgical intervention, as many as 40% of patients with CLI will require major amputation at one year [2]. Individuals with PAD also have twice the risk of overall mortality, cardiovascular mortality, and major coronary events over 10 years compared to the general population [3].

Prospective data from the Framingham Heart Study have shown that age, sex, serum cholesterol, hypertension, cigarette smoking, diabetes, and coronary heart disease are associated with an increased risk of claudication [4]. Similarly, a recent report from the Health Professionals Follow-up Study also identified smoking, hypertension, hypercholesterolemia, and type 2 diabetes as major risk factors for clinically significant PAD [5]. While body mass index (BMI) has also been shown to be significantly higher in patients with more risk factors for PAD [5], there is currently no quantitative assessment of the association between obesity and incident PAD. Furthermore, the association between obesity and CLI has not previously been reported.

To address this knowledge gap, we aim to analyze data from the Atherosclerosis Risk in Communities (ARIC) Study to assess the independent association between a range of obesity measures and PAD and CLI. We hypothesize that obesity will be positively associated with risk of PAD, and that the association will be magnified for CLI risk.

5. Main Hypothesis/Study Questions:

Obesity measures will be independently associated with risk of PAD, and the magnitude of these associations will be greater for CLI risk.

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 variables of interest

Exclusions:

-Ethnicity other than black or white
-Missing data on variables of interest
-Participants with a history of PAD at baseline visit of interest (determined by ankle-brachial index <0.9 and self-report of intermittent claudication or leg artery revascularization at visit 1)

Exposures:

Our primary exposure of interest will obesity at visit 1, which was assessed in various measures:

i. Body mass index (visit 1)
ii. Waist circumference (visit 1)

iii. Waist-to-hip ratio (visit 1)
iv. Body fat measures
    a. Triceps skin fold (visit 1)
    b. Subscapular skin fold (visit 1)

Our secondary analysis will incorporate obesity measures assessed at other visits and will treat obesity measures as time-varying exposures as well as cumulative exposures:

i. Body mass index (visits 2-5)
ii. Waist circumference (visits 2-5)
iii. Waist-to-hip ratio (visits 2-5)
iv. Self-reported weight at age 25 years

Although the number of cases may be an issue, we will explore whether body fat percentage measured at visit 5 is associated with PAD and CLI outcomes.

Outcomes:

PAD-related hospitalizations will be identified according to the following ICD codes based on previous literature [6, 7]: 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); peripheral vascular disease, unspecified (443.9); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of these, 440.22, 440.23, and 440.24 will be considered CLI. Also, we will consider any cases with the above code as CLI when the following codes coexist: leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4).

Other variables of interest and covariates:

Sociodemographics: age, race, gender, education, and insurance
Physical information: blood pressure including ankle-brachial index (ABI) obtained at visit 1 (whole study), 3 and 4 (subsample), presence/absence of left ventricular hypertrophy by electrocardiogram, and carotid atherosclerosis by ultrasound
Lifestyle: smoking status/amount and alcohol habit
Comorbidities: diabetes, dyslipidemia, hypertension, kidney function, coronary heart disease, stroke, heart failure, atrial fibrillation
Laboratory values: fasting glucose, Hemoglobin A1c (visit 2)

Statistical analysis plan:

Our primary analysis will focus on the association between obesity at visit 1 and 1) incident PAD and 2) incident CLI. We will use Cox proportional hazards models adjusting for the covariates listed above to quantify the association between obesity and incident PAD- and CLI-related hospitalizations over time. We will evaluate the measures of obesity outlined in our exposure section as both continuous variables and categorical variables based on quartiles and pre-defined clinical categories. To evaluate whether

obesity measures have uniquely strong associations with CLI, we will compare HR for PAD without CLI vs. that for CLI using seemingly unrelated regression.

We will implement a few models to account for the impact of potential confounders and mediators for obesity-PAD relationship. Model 1 will be crude. Model 2 will be adjusted for demographic variables (age, gender, race, and center). Model 3 will further adjust for potential confounders, education levels, smoking, and physical activity. Model 4 will include potential mediators, diabetes, lipids, blood pressure, antihypertensive medications, kidney dysfunction, and other cardiovascular diseases.

Our secondary analysis will investigate the association between obesity measures as time-varying covariates over time and 1) incident PAD and 2) incident CLI. We will also investigate whether changes in obesity provide additional predictive value for PAD and CLI risk beyond obesity at a single time point.

In addition, we will conduct sensitivity analyses by stratifying the study sample into key clinical subgroups to assess whether the associations identified above are consistent across an array of populations. Specifically, we will analyze the interaction between obesity, PAD/CLI, and diabetes, both as a clinical entity and as measured by glycemic markers (i.e. hemoglobin A1c), using the likelihood ratio test. Finally, given the potential impact of the competing risk of death for estimating PAD and CLI risk, we will run Fine and Gray's proportional subhazards models [8].

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 several ARIC proposals with PAD as an outcome as listed below (only recent ones are listed). Of these, #1832 would be most relevant since it includes obesity as a potential predictor for PAD risk. However, the lead investigator of #1832, Dr. Matsushita, will play an important role in the current proposal as well and thus will be responsible for any coordination.

#1832: Risk prediction model for incident PAD in the ARIC cohort
#1915: Improvement of cardiovascular risk prediction using non-traditional risk factors in the chronic kidney disease (CKD) population
#2479: Serum 25-hydroxyvitamin D and incident peripheral arterial disease: The Atherosclerosis Risk in Communities Study (ARIC)
#2497: Microvascular disease measures and the risk of peripheral artery disease

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

_X__ 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.

References:

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3. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197-208.
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6. Bekwelem W, Bengtson LG, Oldenburg NC, et al. Development of administrative data algorithms to identify patients with critical limb ischemia. Vasc Med 2014;19:483-490.
7. Wattanakit K, Folsom AR, Selvin E, et al. Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol 2007;18:629-636.
8. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 1999;94:496-509.