ARIC Manuscript Proposal # 2970

PC Reviewed: 04/11/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title:
The American Heart Association's Life Simple 7 and Risk of Peripheral Artery Disease: The Atherosclerosis Risk in Communities (ARIC) Study
b. Abbreviated Title (Length 26 characters):
LS7 & incident PAD in ARIC

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. PKG **[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).

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3. Timeline:
April 2017 – Submit proposal
May-June 2017 – Complete primary data analysis
June 2017 – Submit as abstract to AHA Scientific Sessions
July-August-September-October 2017 – Additional data analysis/Manuscript preparation
November –December 2017 – Submit manuscript for publication committee review

4. Rationale:

Lower-extremity peripheral arterial disease (PAD) is associated with a high clinical and economic burden. 8 million people in the United States alone and over 200 million people worldwide are estimated to have PAD.[1,2] These individuals are at a much higher risk of cardiovascular and all-cause mortality compared to individuals without PAD.[3,4] Total annual Medicare PAD-related costs are estimated at nearly $4 billion, which is comparable to estimates of Medicare expenditures for cardiac arrhythmias, congestive heart failure, and cerebrovascular disease.[5] The mean 2 year hospitalization costs per patient in the Reduction of Atherothrombosis for Continued Health (REACH) registry range from nearly $7500 in asymptomatic PAD to over $10000 in those with a history of lower-limb amputation or revascularization.[6]

In 2010, the American Heart Association Strategic Planning Task Force and Statistics Committee identified metrics of ideal cardiovascular health known as Life's Simple 7 (LS7), including 7 modifiable health behaviors and biological factors (nonsmoking, body mass index <25 kg/m^2, physical activity, ideal diet, untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm Hg, and untreated fasting blood glucose <100 mg/dL), to target for the primary prevention of cardiovascular disease (CVD).[7] Attainment of ideal cardiovascular health has been associated with a reduced incidence of coronary heart disease, stroke, and heart failure.[8-11]

While PAD and other CVDs share many common risk factors included in the LS7, the association of the combination of these LS7 metrics with incident PAD has not been reported. Of note, 40% of people with PAD in the REACH registry had no concomitant coronary or cerebrovascular disease, suggesting the importance of specifically studying PAD in this context.[12] Considering the increased morbidity and mortality as well as healthcare costs associated with PAD, identifying strategies to reduce PAD incidence are important. Therefore, we will quantify the association between LS7 and incident PAD in the Atherosclerosis Risk in Communities (ARIC) study, a large biracial prospective cohort study of men and women.

5. Main Hypothesis/Study Questions:

1) To investigate the association of the LS7 with incident PAD.
2) To investigate whether associations of LS7 with risk of incident PAD differ when stratified by race and sex

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).

Data:

Study participants

Eligible participants will be from the ARIC cohort (n=15,792) with baseline examination data on all Life' s Simple 7 characteristics—food frequency questionnaire, physical activity, body mass index, smoking, total cholesterol, seated blood pressure after a 5-minute rest, and fasting glucose.

Exclusion criteria

Individuals without complete baseline LS7 data, with prevalent PAD, or without follow-up PAD data will be excluded. Prevalent PAD will be defined as ankle-brachial index

(ABI) ≤0.9 at visit 1, intermittent claudication based on Rose Questionnaire, or self-reported history of leg revascularization at visit 1.

Life's Simple 7

LS7 components were defined as published by the AHA.[5] Components were defined according to prior study in ARIC[13], and shown in Table (below). An overall LS7 score ranging from 0 to 14 will be calculated as the sum of the LS7 component scores (2 points for ideal, 1 points for intermediate, and 0 for poor). This score will be classified as inadequate (0–4), average (5–9), or optimum (10–14) cardiovascular health.

Component	Ideal	Intermediate	Poor
Smoking	Never or former >1 year	Former <1 year	Current
Physical activity	≥150 min/wk moderate or ≥75 min/wk vigorous or ≥150 min/wk mod + vig	1-149 min/wk moderate or 1-74 min/wk vigorous or 1-149 min/wk mod + vig	No physical activity
Body mass index	<25 kg/m^2	25-29.9 kg/m^2	≥30 kg/m^2
Healthy diet†	4-5 components	2-3 components	0-1 component
Blood pressure	<120/80 mmHg without medication	SBP 120-139 mmHg or DBP 80-89 mmHg or Treated to <120/80 mmHg	SBP≥140mmHg or DBP≥90mmHg
Total cholesterol	<200 mg/dl, without medication	200-239 mg/dl or Treated to <200 mg/dl	≥240mg/dl
Blood glucose	<100 mg/dl, without medication	100-125 mg/dl or Treated to <100 mg/dl	≥126mg/dl

†Responses to the Block FFQ were used for the 'healthy diet score' that is based on how many components of the 5 diet goals are met. Fruits and vegetables ≥ 4.5 cups/day; Fish 3.5 ounces ≥ 2 servings/week; Sodium <1500 mg/day; Sweets/sugar-sweetened beverages ≤ 450 kcal/week; Whole grains (1.1g of fiber in 10 gms of carbohydrates), 1-oz equivalent servings ≥ 3 services/day.

Incident PAD

Given the caveats of ABI measurements in ARIC (nearly all participants but only single leg at visit 1, only on a subsample and single leg [sometimes different leg than visit 1] at visits 3 and 4), PAD incidence will be primarily defined as a hospital discharge diagnosis consistent with PAD. Specifically, all records with an International Classification of Disease, Ninth Revision code 440.2 (atherosclerosis of native arteries and extremities), 440.3 (atherosclerosis of bypass graft of the extremities), 440.4 (chronic total occlusion artery extremities), 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below-knee amputation), 84.17 (above-knee amputation), 38.18 (leg endarterectomy), 39.25 (aorto-iliac-femoral bypass), 39.29 (leg bypass surgery), and 39.50 (PTA of non-coronary vessels) will be qualified as hospitalized PAD.

Other Variables of Interest

Demographic - Age, Race, Sex, Education, clinic site

Comorbidities – Baseline ABI, Coronary heart disease, Stroke, Heart failure, ECG-based left ventricular hypertrophy[14]
Laboratory data – eGFR
Medication use – Aspirin use
Others – Alcohol consumption

Analysis plan:

1) Comparison of baseline characteristics
   - Participants will be compared according to (1) development of PAD and (2) LS7 categories—inadequate, average, or optimum. The distribution of the LS7 components, number of ideal health factors, and overall LS7 score will be compared by race and sex.
2) Associations of LS7 with incident PAD
   - Poisson regression will be used to calculate incidence rates of PAD by LS7 categories adjusted for age, sex, race, education, and clinic site.
   - Hazard ratios (HRs) for incident PAD will be calculated (1) for each individual LS7 component (referent category=poor), (2) number of ideal LS7 components (referent category=0 ideal factors), and (3) across overall LS7 score categories (optimum or average versus inadequate). HRs for incident PAD will also be calculated for per a 1-point higher overall LS7 score and per increase in ideal component.
   - Multivariable cox proportional hazards rations will be used to compute HRs and 95% confidence intervals (CI). Multivariable models will be adjusted for as follows: Model 1 adjusted for age, sex, race, education, and clinic site; Model 2 will include covariates in Model 1 with the addition of alcohol consumption, aspirin use, coronary heart disease, congestive heart failure, eGFR, left ventricular hypertrophy, and stroke.
   - We will evaluate the effect modification by race and sex using a stratification technique and comparing models with and without interaction terms
3) Sensitivity analysis
   - Since the LS7 was designed for the setting of primary CVD prevention, we will repeat the analysis described in #2 excluding individuals with baseline clinical cardiovascular disease (coronary heart disease, stroke, and heart failure) to see if associations differ.

7.a. Will the data be used for non-CVD analysis in this manuscript? __XX_ 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?
_XX___ 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 __XX_ 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

__XX__ 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)?
The author identifies no significantly related manuscript proposals. Co-authors with extensive ARIC experience for prior proposals related to PAD have been contacted to collaborate

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