ARIC Manuscript Proposal #3712

PC Reviewed: 9/8/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Physical Function and Subsequent Risk of Cardiovascular Events in Older Adults

b. Abbreviated Title (Length 26 characters): SPPB & CVD risk in elderly

2. Writing Group: Xiao Hu, Yejin Mok, Ning Ding, Kevin Sullivan, Pamela L Lutsey, Jennifer A. Schrack, Priya Palta, Kunihiro Matsushita

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

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3. Timeline: The analysis will use existing ARIC data, and manuscript preparation will be performed in the following 12 months.

4. Rationale: Traditional cardiovascular risk factors such as lipids are known to have limited prognostic value among older adults,[1] and thus there is an interest in identifying novel predictors in this population.[2] Indeed, several circulating biomarkers such as cardiac troponin (TnT) have been shown as potent predictors of cardiovascular disease in older adults.[3-6]

In this regard, reduced physical function is recognized as a representative phenotype of aging,[7] has been associated with cardiovascular disease in a number of previous studies,[8-36] and thus may be promising. However, most of these studies were conducted in selected populations (e.g. hospitalized patients,[11-15,20,23,24] patients with pre-existing cardiovascular disease[8,10-16,19-22,24]), had small study samples (<1000 participants),[8,10,12-16,18-21,23-24] or investigated mortality which is an unspecific outcome.[8,10-11,13-14,16-21,22-23,25-30] Importantly, few studies have formally tested cardiovascular risk prediction improvement by adding physical function.

To overcome these caveats of previous literature, we will investigate the association of physical function, evaluated by a validated instrument, the Short Performance Physical Battery (SPPB),[37] with the subsequent risk of fatal and non-fatal cardiovascular events using data from community-dwelling older adults in the Atherosclerosis Risk in Communities Study. We will also assess whether SPPB can improve cardiovascular risk prediction beyond traditional risk factors (e.g., predictors in the Pooled Cohort Equation) and other promising novel predictors such as TnT.

5. Main Hypothesis/Study Questions:

- Lower SPPB score is associated with increased risk of cardiovascular events.
- SPPB scores improves cardiovascular risk prediction beyond traditional risk factors and other representative novel predictors.

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 at baseline examination (visit 5) with data on SPPB.

Exclusion criteria:

- Participants who identified themselves as non-white/non-black
- Participants with missing variables of interest

Exposure: SPPB at visit 5: SPPB was implemented by trained and certified staff following instructions in ARIC protocol.[38] Three components of the SPPB - chair stands, standing balance and gait speed – were conducted in sequence.

- Participants were asked to stand up with arms folded across their chest. If participants successfully finished a single chair stand, they were asked to do 5 repeated chair stands as fast as possible and the time to complete 5 chair stands was recorded. An ordinal score was given based on completeness and time used (0 - unable to accomplish, 1 - 16.7 to 60 seconds, 2 - 13.7 to <16.7 seconds, 3 - 11.2 to <13.7 seconds, and 4 - <11.2 seconds). A higher score indicates better performance.
- For standing balance test, participants first attempted a semi-tandem test. Those who held their balance for at least 10 seconds were assumed able to finish a side-by-side test and continued to a full tandem test. Those who failed the semi-tandem test were

assumed unable to finish a tandem test and continued to do a side-by-side test. A score was given based on completeness and time used (1 point for completing each of side-by-side stand test and semi-tandem stand test, 1 point for holding tandem stand 3 to <10 seconds, 2 points for holding tandem stand 10 seconds). A higher score indicates better performance.

- For the gait speed test, participants were asked to walk 4 meters at their usual pace two times, and the result of the faster trial was recorded. An ordinal score was given based on time used (0 - unable to accomplish test, 1 - ≥8.70 seconds, 2 - 6.21 to <8.70 seconds, 3 - 4.82 to <6.21 seconds, and 4 - <4.82 seconds). A higher score indicates better performance.

SPPB score is the sum of the three test scores, ranging from 0 to 12 (a higher score indicates better performance).

Outcome:

Cardiovascular event, after visit 5 through December 31, 2018.

Primary outcome:

- A composite of coronary heart disease (CHD), stroke, or heart failure (HF)
    - CHD: a definite or probable myocardial infarction or definite coronary death (as a sensitivity analysis we will include coronary revascularization procedure)
    - Stroke: definite or probable cases of sudden or rapid onset of neurologic symptoms lasting for 24 hours or leading to death in the absence of another cause
    - HF: a definite or probable acute decompensated HF

Secondary outcome:

- Individual outcomes of CHD, stroke, and HF
- All-cause mortality

Covariates (visit 5 unless otherwise noted):

- Socio-demographics: age, race, gender, education level (at visit 1)
- Physical information: body mass index (BMI), systolic blood pressure (SPB), diastolic blood pressure (DPB), high-sensitivity TnT (hs-TnT), N-terminal pro-BNP (NT-proBNP)
- Lifestyle information: smoking status, alcohol drinking habit and physical activity levels
- Comorbidities: diabetes, hypertension treatment, total cholesterol, HDL cholesterol, cholesterol-lowering medication use, kidney function, chronic obstructive pulmonary disease (COPD), and history of CHD, stroke, or HF

Statistical analysis plan:

The SPPB score will be analyzed as continuous (with splines or as a linear term after linearity is confirmed) and categorical variables with 3 categories (0-6 low performance, 7-9 intermediate performance, 10-12 high performance [reference][39]) or tertiles depending on the data distribution. We will compare time to event in different SPPB categories using Kaplan Meir analysis and will use Cox proportional hazards models to quantify the prospective association of

SPPB at visit 5 with each of the outcomes listed above. To account for competing risk of mortality, we will also run Fine and Gray subdistribution hazard regression models.

We will assess confounding by building several models. Model 1 will be crude. Model 2 will adjust for age, sex, and race. Model 3a will additionally account for other traditional predictors in the Pooled Cohort Equation (i.e., blood pressure, smoking status, diabetes, lipids, and relevant medications). Model 3b will further include BMI, education level, and physical activity status. Model 4 will additionally adjust for kidney function, COPD and history of cardiovascular disease.

We will repeat the analysis in major subgroups by demographics (age, gender, and race) and clinical subgroups (e.g., the status of diabetes, smoking, and prevalent cardiovascular disease). The interaction will be tested by likelihood ratio tests comparing models with and without interaction terms between SPPB and stratified variables.

We will also run similar analyses with each component (chair stands, standing balance and gait speed) of SPPB as an exposure. In this analysis, we will build models with and without the other two components as covariates (e.g., adjusting for standing balance and gait speed when analyzing chair stands as an exposure). Each component will be analyzed as both continuous variable (time required for chair stands test, time held for stand balance test, walk velocity in gait speed test) and categorical variable(each component score from 0 to 4[reference]).

Subsequently, if SPPB is found to be significantly associated with primary outcome, we will examine whether the addition of SPPB (as both continuous and categorical variable) improves Harrell's c-statistics beyond traditional cardiovascular predictors as included in Pooled Cohort Equation (PCE). We will also assess whether SPPB improves Harrell's c-statistics after being added to a model including both traditional risk factors as in PCE and promising novel predictors of cardiovascular disease such as hs-TnT and NT-proBNP.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

____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)?
To our knowledge, there are no ARIC proposals exploring SPPB and subsequent risk of cardiovascular outcomes. A few potential relevant proposals would be:

MS#2815 "Muscle strength and incident cardiovascular outcomes in community-dwelling older adults: the Atherosclerosis Risk in Communities (ARIC) Study" exploring grip strength and subsequent risk of CVD (already published in JACC 2020)

MS#3566 "Association of coronary artery and extracoronary calcification with reduced physical function and frailty in older adults: the Atherosclerosis Risk in Communities (ARIC) Study" exploring physical function and coronary artery calcification

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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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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