

ARIC Manuscript Proposal #3543

PC Reviewed: 1/14/20
SC Reviewed: _____

Status: _____
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Priority: 2
Priority: _____

1.a. Full Title: Associations Between Mid-life Vascular Risk Factors and Late-life Physical Function Decline in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Mid-life Vascular Risk Factors & Late-life Physical Function Decline

2. Writing Group:

Writing group members: Laura Skow, A. Richey Sharrett, Rebecca Gottesman, Josef Coresh, Priya Palta, Kevin Sullivan, Michael Griswold, Jennifer Schrack, B. Gwen Windham, and others welcome.

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

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3. Timeline:

Analysis: 6 months. Manuscript: 6 months.

4. Rationale:

Vascular risk factors have been related to late life physical function. Within the ARIC cohort, better cardiovascular health in mid-life (Visit 1) as measured by the Life Simple 7 score has been shown to predict both higher performance on the Short Physical Performance Battery (SPPB) and greater chances of having a SPPB score indicating normal physical function in late-life (Visit 5)¹. Additionally, cardiovascular risk factors (smoking, poor diet, and low physical activity) in mid-life have been associated with slower gait speeds and reduced grip strength in late-life^{2,3}. Similarly, in a recent cross-sectional analysis of 1,451 older Chinese adults the number of vascular risk factors linearly increased the risk of physical function dependence⁴

Physical function decline is a useful outcome that is less susceptible to confounding by participants' stable characteristics than is a single physical function measurement. Few studies have adequate duration to evaluate the connections between mid-life risk factors and late-life outcomes. Cognitive function is recognized as a key contributor to mobility outcomes, and is also influenced by mid-life vascular risk factors^{5,6}. Yet the vascular contribution to late-life physical decline, including patterns of key vascular risk factor combinations and persistence, are not well understood. This proposal will focus on a mid-life vascular risk profile (presence, combinations, and persistence), and its association with decline in physical function between visits 5 and 7.

The now well-established association between physical function and cognitive status in older age adds plausibility to the view that physical and cognitive declines may have shared precursors⁷⁻¹⁰. Late-life physical dysfunctions, such as reduced gait speed, are associated with cognitive decline^{11, 12}, mild cognitive impairment¹³, and dementia¹⁴, and cognitive status is likewise associated with greater functional declines¹⁵. Several mid-life vascular risk factors predict late-life dementia¹⁶, cognitive decline¹⁷, and reduced brain volumes¹⁸. Thus, vascular risk factors in mid-life could represent a common contributor to both cognitive and physical declines in late-life.

This study aims to investigate mid-life vascular risk factors (V1) and mid-life vascular risk factor persistence (V1-4) as predictors of decline in late-life physical function (V5-7). Specifically, we propose to assess how mid-life blood pressure, blood glucose, smoking status, and cholesterol levels, the key modifiable risk factors for several vascular conditions, may predict late-life physical function outcomes. These four vascular risk factors are well-established predictors of cardiovascular disease and poor cognitive outcomes, representing a proximal assessment of aggregate vascular risk in mid-life for which targeted interventions could be effective in preserving physical health. Other lifestyle risk factors such as BMI, physical activity, and diet are known to effect levels of these proximal vascular risk factors (e.g. physical activity alters blood pressure, diet influences cholesterol levels) such that some of their potential associations with late-life

outcomes would be expected to work through the proposed risk factors. Thus, they may lie in the pathways of interest and are therefore not the focus of this proposal but will be considered, however, as described in the analysis section.

5. Main Hypothesis/Study Questions:

1. Mid-life vascular risk factors (V1) will be associated with **greater physical function declines** in late-life (V5-7).
2. **Presence of vascular risk factors throughout** mid-life (V1-4) will be associated with greater physical function decline in late-life (V5-7).

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).

Participants:

Exclusions: Participants who are neither Black nor white. Non-whites in Washington Co. and Minneapolis. Participants with Parkinson's and participants with stroke will also be excluded. We will also exclude participants with no baseline (visit 5) measures of physical function.

Predictors

We propose to look at the vascular risk factors which, in ARIC NCS, were more strongly associated with cognitive outcomes and are considered strong precursors leading to vascular disease, namely hypertension (and blood pressure), diabetes (and blood glucose), pack years of smoking, and cholesterol, individually and together in multivariable analyses. In view of its weaker associations with brain disease, we believe cholesterol less likely to be important here. We anticipate the combination of diabetes with hypertension will be associated with the steepest decline in physical function.

Outcomes

Late-life physical function measures will be examined starting at V5, and we will use V6 & V7 to assess subsequent decline. We propose to study both the composite Short Physical Performance Battery (SPPB) and its individual components (chair stands, gait speed, standing balance), and grip strength.

Covariates

Proposed covariates include age, race-site, sex, BMI, education (3 groups), baseline alcohol use, coronary heart disease, and heart failure.

Statistical Analysis:

We propose to use mixed models to measure the associations of predictors, both individually and together, as both categorical and continuous measures with the change between V5 and V7 in physical function measures. Analyses will be considered in persons with and without cognitive impairment (MCI or dementia) at visit 5. Since associations may be affected by the failure of persons to be examined post-baseline, multiple imputation by chained equations (MICE) and other techniques will be explored to address missing data issues. Variables expected to help with imputing missing post visit 5 physical function measures include, among others, unintended weight loss and any available physical function measures in participants examined at visit 6 or visit 7 and, for those who miss those visits, self-reported health and functional health scale from AFU interviews.

Participants with the poorest function may not show substantial decline in follow-up visits. We will consider techniques to examine floor effects including removing participants with the lowest function, e.g. worse 5 or 10%, or below some threshold such as gait speed <0.6m/s.

Predictors will be considered individually and combined in multivariable equations, such as:

- a. Categorical V1: Aim 1a. Mid-life vascular risk factors from Visit 1 will be categorized using previously defined thresholds. Derived variables include Rx information (e.g. those on antihypertensive medications for hypertension are classified as hypertensive).
 - a. Blood pressure (as previously used in ARIC¹⁹)
 - i. 0=Normal (not pre- or hypertensive)
 - ii. 1=Pre-hypertension (systolic above 120 mm Hg and diastolic above 80 mm Hg, but not qualifying as hypertensive)
 - iii. 2= Hypertension (systolic above 140 mm Hg, diastolic above 90 mm Hg, or use of antihypertensive medication)
 - b. Blood glucose (as previously used in ARIC²⁰)
 - i. 0=Normal
 - ii. 1=Pre-diabetes
 - iii. 2=Diabetes
 - c. Smoking status (self-report)
 - i. 0=Never smoker
 - ii. 1=Former smoker
 - iii. 2=Current smoker
 - d. Cholesterol (according to AHA guidelines²¹)
 - i. 0=Normal (total cholesterol <200 mg/dL)
 - ii. 1=Borderline (total cholesterol 200-239 mg/dL)
 - iii. 2=Hypercholesterolemia (total cholesterol >240 mg/dL)
- b. Continuous V1: Aim 1b. Mid-life vascular risk factor levels from Visit 1 will be modeled continuously.
- c. Categorical & persistence: Aim 2a. Mid-life vascular risk factors will be modeled categorically as described above at each of Visits 1-4 and summed as a count (from 0-24 [0-6 for each visit X 4 visits]), as done by Gottesman *et. al*¹⁷.

- d. Continuous & persistence: Aim 2b. Each of the mid-life vascular risk factor levels from Visit 1-4 will be individually averaged to one overall value to represent that 9-year period in midlife per risk factor and modeled continuously.
- e. Combinations: Exploratory data analysis will elucidate sample sizes of various combinations of the four primary vascular risk factors. If sample sizes permit, such analyses may guide analyses of combinations. Existing literature suggests diabetes and hypertension, particularly among healthier older adults, are adversely associated with physical function. We anticipate coexistence of two or more conditions, particularly combinations with diabetes and hypertension, will be most detrimental on physical function.

Outcomes

- a. **SPPB** will be modeled as both ordinal and categorical.
 - a. Ordinal: The SPPB ranges from 0-12, with higher scores indicating greater function.
 - b. Categorically: Good function will be defined as a score ≥ 10 ; intermediate function will be defined as between 6 and 9; poor function is a score ≤ 5 .
- b. **Gait speed** will be modeled continuously, and by established cutpoints for low function (<1.0 m/s) and disability (<0.8 m/s).^{22, 23} and “dismobility” (<0.6 m/s)²⁴.
- c. **Grip strength** will be modeled continuously and by established cutpoints for clinical weakness (<26 kg men, <18 kg for women).²⁵

Limitations:

The continuous and categorical models for mid-life vascular risk factors do not take into account trajectories of change in mid-life. The analyses do not account for extraneous effects on physical function such as arthritis or physical injuries other than stroke (exclusion); however, using late-life function declines better accounts for fixed differences between people (e.g. mid-life physical ability or injuries) compared to using late-life physical function levels alone. These analyses do not assess treatment effects. These are important, but we believe that inferences regarding statins, hypoglycemic medications or antihypertensive drugs require a thoughtful analysis (including perhaps propensity score methods) beyond the scope of the current undertaking.

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.csc.unc.edu/ARIC/search.php>

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)?

#2254 – Windham; Adipose Trajectories & Function

#2383 – Windham; Mid-life LS7 Risk Factors and Late Life Physical Function

#3501 – Juraschek; Subclinical CVD & Physical Function

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2008.06)

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.csc.unc.edu/anic/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.csc.unc.edu/anic/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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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

No.

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