

ARIC Manuscript Proposal #3092

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

- 1.a. Full Title:** Associations of Subclinical vascular burden among Middle-Aged Adults with Change in Functional Status Later in Life

- b. Abbreviated Title (Length 26 characters):** Subclinical disease, functional status

2. Writing Group:
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Michelle C. Odden, Kunihiro Matsushita, Rebecca Gottesman, others welcome

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

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3. Timeline:

	From	To
Planning & Data Acquisition	October, 2017	January, 2017
Analysis	January, 2017	May, 2018
First Draft	May, 2018	July, 2018
Submission of Final Report	July, 2018	August, 2018

4. Rationale:

Functional status—the ability to perform usual daily activities—is a key component of quality of life and well-being, a strong risk factor for mortality, and a crucial factor in ensuring the proper management of chronic conditions.¹⁻⁵ With a few exceptions,^{6,7} studies examining risk factors for decline in functional status have been conducted in populations of older adults (≥ 65 years of age). We propose that middle adulthood (45-64 years of age) is a critical period of risk accumulation; alternations to the cardiovascular system occurring in midlife may induce impairments across multiple organ systems, leading to a more rapid deterioration in functional status in older adulthood. The prevalence of cardiovascular disease (CVD) in midlife is low ($<10\%$).⁸ Subclinical vascular disease (SVD), known to be predictive of future CVD and mortality,⁹⁻¹³ can capture small alterations in structure and function of the cardiovascular system among asymptomatic persons and, therefore, may be an informative measure of risk in middle-aged adults. SVD may therefore provide additional risk stratification of functional decline beyond clinically recognizable CVD. A better understanding of the role of midlife SVD measures on changes in functional status offers opportunities for intervention earlier in the course of functional decline.

The primary aim of this proposed study is to examine the association of midlife SVD measures with trajectories of functional status. We are uniquely positioned to address these questions in the Atherosclerosis Risk in Communities (ARIC) Study due to its availability of midlife SVD, repeated measures of functional status measures over 15 years, and large sample size.

5. Main Hypothesis/Study Questions:

- **Aim:** To identify the association of midlife SVD measures with functional trajectories.
Hypothesis 1a: Persons with higher SVD burden (ankle-brachial index, intima-media thickness, carotid distensibility, electrocardiography abnormality, and overall SVD burden) will have lower baseline levels of functional status.
Hypothesis 1b: Persons with higher SVD burden (ankle-brachial index, intima-media thickness, carotid artery distensibility, electrocardiography abnormality, and overall SVD burden) will have more rapid functional decline over time.

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).

Exclusion criteria:

- Participants with self-reported race other than black or white.
- Black participants from the Minnesota and Maryland study communities.
- Had prevalent CVD (myocardial infarction [MI], heart failure [HF], or stroke) before the first functional measure.
- Missing all subclinical measures of interest (ankle-brachial index, carotid intima-media thickness, carotid artery distensibility, and electrocardiography) at Visit 1.
- Missing any functional status measures.

Outcome:

Functional status: will be measured as a sum score of four questions (yes=1 and no=0), “Are you able to do your usual activities, such as work around the house or recreation?”, “Are you able to

walk up and down stairs without help?”, “Are you able to do heavy work around the house, such as shoveling snow or washing windows?”, and “Are you able to walk half a mile without help?” The total score of functional status will range from 0 (lowest) to 4 (highest). All four questions were administered to participants during the annual telephone interviews conducted in 1993-2007 (up to 15 annual assessments). The appropriateness of using the sum score of functional status has been demonstrated in the ARIC.¹⁴

Predictors:

- **Ankle-brachial index (ABI)** measured in Visit 1. The details of how ABI was measured in the ARIC has been previously documented.¹⁵ ABI will be categorized as low risk (1.01-1.40), intermediate risk (0.90-1.00 or >1.40), and high risk (<0.90).
- **Carotid artery intima-media thickness (IMT; mm)** measured in Visit 1. The details of how IMT was measured in the ARIC has been provided previously.¹⁶ IMT will be modeled both continuously and in categories with cutoffs 0.6 and 1.0 mm, based on previous research in the ARIC.¹⁶
- **Carotid artery distensibility (CAD; mm)** measured in Visit 1. The details of how CAD was measured in the ARIC has been previously documented.^{19,20} CAD will be modeled both continuously and in tertiles.
- **Electrocardiography (ECG) abnormality** measured in Visit 1. ECG findings will be classified as no, minor (1-2-6, 1-2-8, 1-3-x, 2-1, 2-2, 2-4, 3-1, 3-3, 4-3, 4-4, 5-3, 5-4, 6-3, 6-5, 7-3, 7-5, 7-6, 8-1-2, 9-1), or major abnormalities (1-1-x, 1-2-x [except 1-2-6 and 1-2-8], 4-1-1, 4-1-2, 4-2, 5-1, 5-2, 6-1, 6-2, 6-4-1, 6-4-2, 6-8, 7-1-x, 7-2-x, 8-3-1, 8-3-2) according to Minnesota Codes.²¹
- **Subclinical vascular disease (SVD) burden index:** each of four SVD measures (ABI, carotid IMT, CAD, and ECG abnormalities) will be scored as 0 (no abnormalities), 1 (minor abnormalities), or 2 (severe abnormalities). The SVD burden index will be calculated as the total score of four measures, ranging from 0 (lowest burden) to 8 (highest burden).

Covariates:

- Race-study center (MN-whites, MD-whites, NC-whites, NC-blacks, MS-blacks) in Visit 1
- Age (in years) in Visit 1
- Sex (male or female) in Visit 1
- Education (<high school, high school or equivalent, or >high school) in Visit 1
- Body mass index ([BMI]; <25, 25-30, ≥30 kg/m²) in Visit 1
- Smoking status (current, previous, never) in Visit 1
- Physical activity assessed by the Baecke questionnaire in Visit 1; total minutes/week
- Diabetes mellitus (yes or no), defined as fasting glucose ≥126 mg/dL, non-fasting serum glucose ≥200 mg/dL, self-reported use of hypoglycemic medications, or self-reported physician diagnosis within the previous two weeks, in Visit 1
- Systolic and diastolic blood pressure (mmHg) in Visit 1
- Anti-hypertensive medication use (yes or no) in Visit 1
- Hospitalized cardiovascular events—MI, HF, and stroke—that occurred during the follow-up period (1993-2007) will be identified through the ongoing surveillance of medical

records and thorough participants' self-report of prior hospitalizations provided using an annual telephone follow-up interview.²² A composite variable will be created to indicate the presence of any of three CVD events.

Data Analysis:

We will describe the baseline demographic and health characteristics of the participants by categories of SVD measures (choice of cut-points for the CVD burden score [0-8] will be determined by its sample distribution) using means and standard deviations for continuous variables and counts and proportions for categorical variables. Analysis of variance (or non-parametric equivalent) and χ^2 test will be used to compare continuous and categorical variables, respectively.

We will first use the LOWESS plot to visually depict the trajectories of functional status over up to 15 years. We will then use generalized estimating equation models (Poisson distribution) with robust variance and unstructured correlation matrix to identify the association of baseline SVD measures with repeated functional status measures over time. All available functional status measures will be used. Missing functional status measures will be imputed as the average of two neighboring values (one year before and after). All available functional status prior to death will be used. The remaining missing functional status data will be treated as missing at random.¹⁴ Five individual SVD measures (ABI, carotid IMT, CAD, and ECG abnormalities) and the SVD burden index (both continuously and in categories) will be modeled separately, with the healthiest group being the reference. Model 1 will adjust for a combined race-study center variable, age (continuous), age squared (will be dropped if $P > 0.2$), and sex. Model 2 will additionally adjust for education (<high school, high school or equivalent, or >high school), smoking status (current, former, or never), physical activity (continuous), BMI (<25, 25-30, or ≥ 30 kg/m²), diabetes (present or not), and hypertension (present or not) in the fully adjusted models. Linear spline terms will be used to represent time since baseline if the trajectories of functional status are observed to be non-linear.

In sensitivity analyses, we will examine interactions on the association of SVD with trajectories of functional status differs across two important demographic variables: age and sex. A second sensitivity analysis will exclude incident CVD (MI, HF, or stroke) cases occurring between 1993-2007.

All tests will be two-sided with a significance level of $P < 0.05$. Analyses will be performed using Stata version 15.0 (StataCorp IC, College Station, TX).

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

Cardiovascular Disease and Patterns of Change in Functional Status Over 15 Years: Findings from the Atherosclerosis Risk in Communities (ARIC) Study. Anna Kucharska-Newton, Michael Griswold, Zhihao Howard Yao, et al.

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* _____)

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/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.csc.c.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 X No.

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