ARIC Manuscript Proposal # 3222

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SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: The Relationship of Functional Endurance with Cognitive Status: The ARIC Study.

b. Abbreviated Title (Length 26 characters): functional endurance and cognition

2. Writing Group:
Writing group members: B. Gwen Windham, Sara B. Parker, Kirby Parker, Kelley Gabriel, Priya Palta, Dave Knopman, Rebecca Gottesman, Michael Griswold, Thomas Mosley others welcome

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

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3. Timeline: Project will begin with ARIC approval. Manuscript completion expected within 2 years.

4. Rationale:
A growing body of literature suggests changes in gait, including gait speed, are predictive of cognitive decline and dementia primarily over a few years.[1-5] One relatively small study of 200 cognitively normal older adults reported greater gait speed declines up to 12 years before the onset of mild cognitive impairment (MCI) compared to persons who maintained a normal cognitive status;[6] the changes were small, 0.02m/sec, difficult to detect without a gait lab or expensive technology. Most recognizable changes in gait, however, may only begin to develop after substantial pathology has developed, limiting its utility to predict dementia during a time when interventions would be effective. For example, pre-clinical cognitive and structural changes in the brain are strongly associated with gait abnormalities and gait speed decline in dementia-free older adults,[7-13] but are not generally considered reversible. The combination of gait speed slowing and concurrent subjective memory loss is also predictive of incident

dementia, especially non-Alzheimer dementia.[14,15] Although gait speed remains an attractive predictor of dementia risk due to the ease of administration in clinical and research settings and its predictive utility, identifying other markers that triage "high risk" individuals to interventions, especially pre-clinical, high functioning adults.

Functional endurance is the ability to sustain effort that requires conjoint work capacities from cardiopulmonary, biomechanical and neuromuscular function. Improved cardiopulmonary function and fitness are associated with healthier cardiovascular risk profiles[16] which are, in turn, associated with better cognition.[17-19] A growing body of literature suggests cardiorespiratory fitness may be important for brain health in terms of brain structure, cognitive function, and vascular function.[20-26] However, studies have been limited by sample size, lack of racial diversity or limited cognitive evaluations. Small trials support habitual aerobic exercise, which improves cardiorespiratory fitness and endurance, as an intervention to preserve cognition.[27-29] Gaps remain regarding potential effects of cardiorespiratory fitness and endurance on clinical cognitive outcomes such as MCI and dementia and on structural, vascular and functional changes in the brain, which could benefit cognition. The Framingham Offspring Study demonstrated associations of higher cardiorespiratory fitness with higher brain volumes 20 years later.[25] However, there are limited data that replicate these findings or that report on relations of cardiorespiratory fitness with systematically assessed dementia and MCI outcomes.

Although the relationship of cardiovascular risk factors in middle-age with late-life cognition is well established, the mechanisms explaining this relationship remain to be elucidated. Relationships of cardiopulmonary fitness and endurance with healthier cardiovascular risk profiles,[16,30] which are associated with better cognition and less small vessel disease in the brain, suggest that cardiorespiratory fitness and endurance may protect against progression to MCI and/or dementia through effects on brain structure. There is a dearth of information on the relationship of cardiorespiratory fitness or endurance with the spectrum of cognitive status including normal cognition, MCI, and dementia or progression to MCI/dementia. Existing studies that reported associations of cardiorespiratory fitness with late-life dementia were conducted in databases of selected clinic patient populations, including healthy patients seeking preventive care[22,31] and veterans[32] and lacked systematic assessments of dementia outcomes. Cardiorespiratory fitness assessed with maximal or submaximal graded exercise test (GXT) protocols are difficult to measure in large populations and in many older adults with limited functional abilities or have established medical contraindications to exercise testing. There are also issues of cost, inadequate space (for treadmill or cycle ergometer), and participant burden.

Field-based measures of functional endurance, measured by extended timed walks, are alternatives to GXT protocols because they moderately approximate cardiorespiratory fitness[33] and are predictive of cardiovascular events and mortality.[34,35] The distance walked during a two minute period at one's maximal pace without running, as assessed using the Two-Minute Walk (TMW) is the recommended measure of endurance from the NIH Toolbox.[36] The TMW has a 0.97 correlation with the six minute walk and a 0.94 correlation with the twelve minute walk;[33,37] furthermore, the TMW has similar correlations as the longer 6- and 12-minute walk tests with submaximal exercise tests (r=0.45 to 0.51 with vO2 max obtained from a symptom limited maximal GXT).[33] The ARIC study affords a unique opportunity to examine relations of functional endurance with cognitive status (normal, MCI and dementia), and progression to MCI or dementia in a biracial older cohort. Associations of functional endurance with MCI/dementia, but even more importantly, with progression to MCI and/or dementia, would support the hypothesis that interventions to improve endurance could mitigate age-associated cognitive decline and progression to cognitively impaired states.

Self-reported physical activity is a candidate alternative predictor; since cardiorespiratory fitness is a physiological consequence of higher intensity physical activity, self-reported physical activity may approximate objective measures of endurance. These detailed self-reported physical activity questionnaires, however, have limited utility in clinical settings due to the time required to administer them, especially among more active persons. In most clinical settings, only single-item global questionnaire is feasible. Other potential candidate measures include briefer measures of self-reported physical activity and sedentary behaviors and brief objective assessments of physical performance, such as gait speed. Although such measures are unlikely to perform as well as objective assessments of endurance in higher functioning persons, quantifying advantages of simpler, feasible measures is an important step in translating meaningful information into clinical practice.

This study will examine the association of endurance using the TMW, with cognitive status cross-sectionally and with progression to MCI/dementia and whether these relationships are mediated through brain volumes, microbleeds, and markers of small vessel disease (white matter hyperintensities, microstructural integrity, infarcts). We will also examine associations of gait speed with cognitive status and progression to MCI/dementia in ARIC; we will determine whether or not endurance provides additional information on relations to MCI/dementia than gait speed. We will compare findings to analyses using other clinically feasible measures (self-report) of physical activity.

5. Main Hypothesis/Study Questions:

Aim 1: (A) To examine relations of TMW with concurrent cognitive status and progression to MCI and/or dementia in the Atherosclerosis Risk in Communities (ARIC) study (Visit 6 cross sectional; (B) Visit 6 to Visit 7).

Aim 2: To examine and compare the additional value, if any, of the TMW beyond simpler, more clinically feasible measures of physical activity and physical performance with brain measures, cognitive status, and progression to MCI and/or dementia.

Aim 3: To examine relations of TMW with brain volumes and markers of small vessel disease (white matter hyperintensities, microstructural integrity, infarcts and microbleeds) and potential mediating effects of these brain measurements on the relationship of endurance with cognitive outcomes.

Aim 4: (a) To examine associations of self-reported measures of physical activity with MCI/dementia; **(b)** To compare relations of MCI/dementia and TMW to relations of MCI/dementia and self-reported physical activity (determined from Aim 4a)

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

1. Cross-Sectional: V6 TMW associations with V6 Cognition and Cognitive Status
2. Longitudinal: V6 TMW associations with V6-V7 Cognitive change and transitions to MCI/Dementia

Inclusion Criteria:

1) Attended ARIC visit 6 with available data (including completion/non-completion status) of TMW

Exclusion Criteria:

1) Participants missing TMW response at visit 6 for primary analyses
2) Participants with documented clinical stroke before visit 6
3) Blacks from MN and MD due to small numbers

Outcome: Adjudicated cognitive status at visit 6 and visit 7: normal, MCI, and dementia. Progression to MCI or dementia from visit 6 to visit 7.

Predictor(s): TMW distance measured will be the primary predictor of interest. We will also construct categories of TMW performance to incorporate non-completers: Unable, Attempted but unable to complete; completers and/or completers split into tertiles.

For alternative clinical predictors (all from visit 6), we will also assess associations of the following with brain measures, cognitive status and progression to MCI/dementia.

1) The ARIC/Baecke Sport and Leisure Index (total MET-min/wk), a validated measure of physical activity
2) An abbreviated measure of 4 questions assessing activity and sedentary activity also from the ARIC/Baecke Sport and Leisure Index:
    a. In comparison with others of your own age do you think your physical activity during leisure time is much less, less, the same, more, or much more?
    b. During leisure time, do you sweat Never, Seldom, Sometimes, Often or Very Often?
    c. During leisure time, do you watch television
    d. During leisure time, do you walk?
3) Usual 4m gait speed (cm/sec), faster of two trials

Covariates
Demographic variables, including race-site, sex, and education will be extracted from visit 1.
The primary adjustor set will include age, race-site, education, and ApoE4.
Additional analyses will examine conditions and biomarkers such as BMI, hypertension, diabetes, heart disease, and stroke, systolic and diastolic blood pressure, diabetes, and smoking taking in to consideration these may be in the pathway to better functional endurance and cognition. When examining potential variables in the pathway of interest, we will also incorporate related medications, including anti-hypertensive medications (with systolic and diastolic blood pressure levels) and lipid lowering drugs extracted from visit 6.

***Statistical Analysis*:**
Exploration:
Initial stages of analyses will involve data cleaning, variable development, and exploratory data analyses (EDA). Graphical EDA will examine the nature and extent of potential nonlinear relationships using smoothing splines and surfaces. Correlations between the TMW and the alternative clinical predictors will be examined.

Primary analyses:
We will use multinomial regression models to examine cross-sectional associations of TMW distance or self-reported predictors (Aims 1, 2 and 4) with cognitive status (normal, MCI, dementia) adjusted for covariates listed above. When examining potential additional utility of TMW over and above alternative clinical predictors, predictors will be included along with TMW in regression models. In addition, TMW will itself be regressed on the alternative clinical predictors to extract residuals of remaining information not explained by the alternative clinical predictors. These TMW residuals will then be included in the

regression models with the alternative clinical predictors to examine whether the remaining TMW information carries any additional utility over and above that already covered by the alternative clinical predictors while avoiding potential collinearity issues. Similar approaches will be used to examine TMW versus self-reported physical activity associations. Longitudinal analyses will incorporate inverse probability for attrition weighting (IPW) to examine potential selection bias due to cohort attrition across visits (missingness).

Mediation analyses: TMW-brain pathology -> cognitive outcomes
In Aim 3, we will examine potential effects of TMW on cognitive outcomes that may operate through brain pathology (WMH, atrophy, infarcts, and microstructural integrity) in cross sectional analyses. Hence, we will further examine effects of visit 5 brain pathology on TMW-cognitive outcomes using structural equation model (SEM) mediation pathway approaches. Because only a subset of participants underwent V5 brain imaging, the mediation analysis will be conducted only on V6 participants with V5 imaging, both with and without sampling weights included. We will compare primary results of TMW to cognitive outcomes models in the whole cohort to results of TMW to cognitive outcomes models that are limited to the subset with brain imaging and re-weight if necessary to ensure similarity of findings between the full dataset and brain imaging subset dataset. Additional analyses that consider potential mediators or variables in the pathway, e.g. BP → endurance → cognition, will use this same mediation approach.

Limitations: We will use brain imaging most proximal to the visit 6 TMW assessment; for most participants, brain imaging will come from visit 5, and so brain pathology may have progressed. We will acknowledge this in the manuscript. If data from imaging ancillary studies are available, we will also consider using these imaging studies instead. Older people with cognitive impairments are less mobile/active, so reverse causality is an important limitation which we will include in the discussion of the manuscript. We also included plans to examine endurance associations with progression to MCI/dementia. Specifically, we will include additional analyses limited to participants with normal cognition at Visit 6 and examine associations of endurance with progression from normal cognitive status to MCI/dementia at Visit 7. We will also examine relationships of interest among those with MCI (or normal or MCI) at Visit 6 who progress to dementia (or MCI/dementia). Other limitations include selection bias; physically and cognitively healthier participants are more likely to return to visits and to participate in the TMW. Our analyses will incorporate techniques to examine potential influences of missingness. In addition, brain imaging was conducted in a subset of participants so comparing results from models without brain imaging variables to results from models with brain imaging may not be appropriate. To address this, we will also limit analyses of TMW relations to cognitive outcomes (without brain imaging variables) to the same analyses/results among the subset with imaging data to determine the degree to which imaging selection influence the relationship of TMW with cognitive outcomes. ARIC lacks data of peripheral contributors to mobility impairment such as vision problems, arthritis and musculoskeletal abnormalities in the overall cohort. We will examine physical reasons for not completing the TMW that were collected during the TMW protocol (e.g. joint pain). We will acknowledge these limitations.

7.a. Will the data be used for non-CVD analysis in this manuscript? _x_ 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? __x_ 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? __x_ Yes ____ No

APOEe4 will be used as a covariate

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"? __x_ 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)?

MP#2310. Physical activity and change in cognition and incidence of dementia: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Palta P et al.

MP#3035. Physical activity in adulthood and subclinical brain MRI markers: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Palta P et al.

MP#3012. Resting Heart Rate and Cognitive Change Over 20-years: the Atherosclerosis Risk in Communities (ARIC) Study. Wang S.

MP#3075. Association between white matter microstructural integrity and cognitive decline, MCI, and incident dementia. Power MC.

MP#1018r. Physical activity and cognitive decline (2004). Dubbert P et al.

MP#1088. Physical Activity and Cerebral Abnormalities on MRI. Dubbert P et al.

MP#3054. Brain Structural MRI Abnormalities Predict Dementia, MCI and Cognitive Decline in an Older Population. Wu A et al.

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

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

___ 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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