ARIC Manuscript Proposal #3223

PC Reviewed: 08/14/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
The relationship between systemic inflammation in mid- to late-life and late-life mobility: The ARIC Study

b. Abbreviated Title (Length 26 characters):
Inflammation and mobility

2. Writing Group:
Writing group members: Kirby Parker, Keenan Walker, Sara Parker, Xiaoqian Zhu, Chad Blackshear, Hoogeveen Ron C, Ballantyne CM, Anna Kucharska-Newton, Priya Palta, Liz Selvin, Thomas H. Mosley, Michael E. Griswold, B Gwen Windham, 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]

First author: **Kirby Parker, Keenan Walker (Co-first authors)**
Kirby Parker Address: School of Medicine, UMMC
2500 N. State St
Jackson, MS 39216
Email: kgparker@umc.edu

Keenan Walker Address: Johns Hopkins Hospital, Department of Neurology
Phipps 446
600 North Wolfe St.
Baltimore, MD 21287
Phone: 626-840-6216 Fax: 410-955-0672
E-mail: kwalke26@jhmi.edu

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).
Name: **B. Gwen Windham**
Address: Department of Medicine, Division of Geriatrics
2500 N. State St
Jackson, MS 39216
Phone: 601-984-5645 Fax: 601-984-5783
E-mail: gwindham@umc.edu

3. Timeline:
Writing and analyses to begin immediately following manuscript approval.

4. Rationale:

Poor physical function, such as slower walking speed, leads to poorer quality of life, institutionalization, incident disability, higher costs and mortality in community-dwelling older adults.(1-4) The underlying mechanisms contributing to physical function impairments are poorly understood; consequently, optimal interventions and timing of interventions to preserve mobility in later life remain unknown. Two mechanisms have emerged as favored processes that contribute to mobility decline. These are inflammation and, perhaps less modifiable, abnormalities in the brain, such as cognitive processes(5-7) and structural changes, for example, atrophy and small vessel disease, (8-11). In older adults, higher C-reactive protein (CRP) is associated with poorer strength, slower gait speeds and higher rates of disability, which are partially explained by lower strength and/or gait speed.(12) Longitudinal studies have also reported associations of higher inflammation in late life with incident disability and steeper declines in gait speed.(13, 14) Several lines of data suggest the effects of inflammation operate directly on muscle tissue. Epidemiologic studies demonstrate higher levels of interleukin-6 (IL-6), CRP, and tumor necrosis factor alpha (TNFα) or soluble receptors for TNFα are associated with slower walking speed and may directly affect muscle strength in late-life.(13, 15-17) Mouse models have shown that IL-6 transgenic mice have decreased skeletal muscle mass, and anti-mouse IL-6R antibody inhibits muscle atrophy.(18) In vitro studies demonstrate TNF-α inhibits myogenic differentiation via the ubiquitin-proteasome system (UPS) pathway, which promotes both TNF-α and IL-6 production.(19) TNF-α has also been shown to interfere with myocyte differentiation, promote catabolism of cultured muscle cells through reactive oxygen species and nuclear factor–κβ pathways(20) and impair contractile force of muscle contraction in murine models.(21) These data strongly support inflammatory mediated effects on muscle that could lead to aging associated declines in mobility.

Chronic conditions, such as obesity and diabetes, occur with increasing frequency in older age and are associated with poorer mobility (22, 23) and with higher inflammation. At the muscle level, greater amounts of intramuscular calf adipose tissue are associated with higher inflammation and with poor mobility in older adults.(24) Obesity may be an early target for interventions to reduce or avoid inflammation and preserve mobility. In support of this, inflammation partially mediates relationships of obesity with mobility. (25) Although other chronic conditions may also contribute to mobility impairments in older age, obesity is an especially attractive condition to study because obesity is associated with higher levels of inflammatory biomarkers including cytokines in the UPS pathways that is linked to slowing of gait speed and muscle impairments.(26-28) Obesity is also a precursor to other medical conditions (e.g. diabetes, hypertension), and to subsequent gait disturbances.(23) Diabetes, which is strongly linked to obesity, is also associated with cytokines involved in UPS pathways and is associated with poorer mobility, mobility disability and declines in mobility in late life.(29-31) Preventing obesity could eliminate multiple pathways to mobility disability, including prevention of mechanical joint trauma, reducing inflammation, and diabetes prevention.

ARIC and other studies, however, have shown cerebral small vessel disease is associated with inflammation,(32-37) with mobility in older adults,(9, 11, 38-41) and may partially mediate the relationship of inflammation to aging-associated mobility impairments.(17, 42) One small study (n=179) of older adults suggested that cumulative measures of inflammation in late life contribute to greater declines in function in late life and may be partially explained by cerebral small vessel disease. (42) Other studies with inflammation, gait and brain imaging data had limited characterization of brain features, cross-sectional design, or limited generalizability.(43) Therefore, whether the effects of inflammation operate through the brain, e.g. promoting atrophy or small vessel disease, or peripherally, in the muscle, remains unclear. In addition, the relationship of chronic exposures to inflammation or different trajectories of inflammatory exposures (cumulative, sustained higher levels, brief exposures to high levels) earlier in life, when treatment or prevention strategies may be more effective, with late life

mobility is not known. These gaps hinder development and timely implementation of interventions that would help preserve mobility in late life.

There is growing interest in developing approaches to reduce mobility disability with aging that include lifestyle interventions, cognitive training and pharmacological approaches, particularly through anti-inflammatory effects.(44-48) Effective interventions could involve single or multiple approaches, including prevention of chronic conditions such as obesity that promote inflammation; treatment of conditions, e.g. hypertension and/or diabetes, that lead to cerebral small vessel disease; and interventions/pharmacotherapy to reduce inflammation. However, there is little evidence to guide focused interventions that might be most effective in preventing gait disturbances in late life. For example, it is unclear if effects of inflammation on mobility could be better mitigated by treating or preventing chronic disease, such as obesity, or by controlling inflammation. ARIC provides unique opportunities to fill these gaps in knowledge. This study will examine temporal associations of mid- to late-life inflammatory marker trajectories with late-life mobility and mobility decline and the modifying effects of chronic conditions, namely obesity, and anti-inflammatory medications.

5. Main Hypothesis/Study Questions:

1) Higher levels of circulating inflammatory markers in midlife (visit 2 and visit 4) will be associated with slower gait speed in late-life (visit 5) and with greater gait speed decline (visit 5 to visit 6).

2) Associations between CRP exposure across mid- to late-life and late-life mobility and gait speed decline will be examined and compared in cross-sectional, cross-temporal, cumulative inflammatory burden, and inflammation trajectory models. We anticipate having a greater number of visits with high inflammation will be associated with poorer gait speed than having no visits with high inflammation or only 1 mid-life visit with high inflammation.

3) The association of high inflammation (determined from trajectory analyses in Hypothesis 2) across mid- to late life with slower gait speed will be stronger in the presence of obesity compared to obesity alone or high inflammation alone.

4) Anti-inflammatory medications will attenuate the association of inflammation and obesity with gait speed

5) The associations of inflammation with gait speed will be independent of cerebral small vessel disease.

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

Inclusion Criteria: Attended ARIC visit 2 and had available CRP measures for CRP level associations with gait speed; Attended visit 2 with CRP measures across visits 2-5 for trajectory associations.

Exclusion Criteria: We will exclude blacks from MN and MD due to small numbers.

Outcome: Gait speed measured at one's usual pace over 4 meters (faster of two trials; if only trial was completed, we will use the single measure)

Predictor(s)
Continuous and categorical CRP will be implemented in several modelling frameworks:

1. Midlife CRP exposure (cross-temporal and longitudinal)
    a. V2 CRP level associations with V5 Gait (cross-temporal)
    b. V2 CRP level associations with V5-V6 Gait change (longitudinal)
    c. V4 CRP level associations with V5 Gait (cross-temporal)
    d. V4 CRP level associations with V5-V6 Gait change (longitudinal)
2. Late-life CRP exposure (cross-sectional and longitudinal)
    a. V5 CRP level associations with V5 Gait (cross-sectional)
    b. V5 CRP level associations with V5-V6 Gait change (longitudinal)
3. 21-year CRP exposure history (longitudinal)
    a. V2-V4-V5 CRP trajectory associations with V5 Gait
    b. V2-V4-V5 CRP trajectory associations with V5-V6 Gait change
    c. Cumulative CRP associations with V5 Gait
    d. Cumulative CRP associations with V5-V6 Gait change

Dichotomized CRP: Each participant will be categorized as having "low" or "high" CRP levels at each visit using a clinical cut-off of 3 mg/L. Levels of 3 mg/L or higher are suggestive of low-grade systemic inflammation at the time of that visit.(49)

V2-V4-V5 CRP trajectory: We will conduct trajectory analysis similar to our team's previous work.(50, 51) Using the "low" versus "high" CRP dichotomization, participants will be categorized into one of four groups (see below), each group representing a distinct degree of chronicity of mid to late-life systemic inflammation.

- *Stable low*: low CRP levels (<3 mg/L) at all three visits
- *Unstable low*: low CRP levels (<3 mg/L) at 2/3 visits
- *Unstable high*: high CRP levels (≥3 mg/L) at 2/3 visits
- S*table high*: high CRP levels (≥3 mg/L) at all three visits

Cumulative CRP: Similar to previous work, the 21-year average CRP level will be derived using the log transformation of arithmetic mean of observed CRP levels at visits 2, 4, and 5. (18)

Covariates
Time-invariant demographic variables, including race-site, sex, and education will be extracted from visit 1. Primary covariates will include age, sex, race-center, and education or income.(52, 53) Modifiers of interest are obesity and anti-inflammatory medications which will include use of any of the following: aspirin, NSAIDS, statins (recognizing use may be primarily limited to visit 4 and visit 5), and potentially glucophage for analyses among diabetics only. If evidence for modification is not supported, the proposed potential modifying conditions have been associated with inflammation and with mobility so these will be included as covariates. We may also consider other chronic conditions as potential effect modifiers including diabetes, heart failure, heart disease, stroke and hypertension. Additional covariates

for the primary analysis of the relationship of inflammation with mobility will be considered including heart disease, systolic and diastolic blood pressure, anti-hypertensive medications, alcohol use, and stroke history. Covariates will be extracted from visit 2, incorporating time-varying covariates and conditions, as feasible.

***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.

Primary Analyses: cross-sectional / cross-temporal

Gait speed is fairly normally distributed. We will use linear regression models to examine cross-sectional cross-temporal and exposure history relationships between CRP and gait speed at visit 5. Cumulative measures will use AUC approaches similar to our team's and others' previous work.(42, 50) Cross-temporal and exposure history regression models will incorporate inverse probability for attrition weighting (IPW) to examine potential selection bias due to cohort attrition across visits (missingness). In addition joint (shared parameter) model approaches will be used to examine longitudinal predictor submodels coupled with visit 5 outcome submodels.

Secondary Analyses: Longitudinal

We will use linear mixed effects models (LMM) to examine associations between CRP predictors and gait speed decline from Visit 5 to Visit 6. Additionally we will examine joint modelling of longitudinal inflammatory predictor information with outcomes similar to previous ARIC work.(54)
Missingness effects will also be examined using IPW and either multiple imputation (MI) or shared parameter model (SPM) approaches.

Additional analyses: Chronic disease and medication effects

In addition to individual and joint effects, we will introduce interaction terms to assess potential modifying effects of chronic disease (i.e., obesity, hypertension, diabetes) and/or anti-inflammatory medication use (steroidal and nonsteroidal). In additional post-hoc analyses we will add interaction terms for orthopedic surgeries and fractures which may have occurred prior to Visit 5. This information will be obtained from hospitalization records and from the CMS Medicare claims for inpatient and outpatient care.

Additional analyses: Brain-Body relationships

In additional analyses, we will examine potential effects of inflammation on mobility that may operate through inflammation effects on the brain. Hence, we will further examine effects of visit 5 WMH volume, WM volume (WM at risk), hippocampal/AD signature region volume, total precentral gyrus volume, total frontal lobe volume, and total intracranial volume(55, 56) on CRP-Gait analyses. Visit 5 stage 3 sampling weights will additionally be incorporated in these analyses.

Limitations

Brain imaging was only conducted in a subset of ARIC participants. 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 cumulative CRP and CRP trajectory relations to gait speed (without brain imaging variables) to the subset with imaging data to determine the degree to which

imaging measures influence the relationship of inflammation with gait speed. We were not able to adjust for arthritis, vision, other musculoskeletal problems or pain in ARIC.

Conditions other than obesity are also associated with inflammation and gait disturbances and will be considered in this proposal, although the initial focus will be obesity. Some of these, for example, diabetes and hypertension may lie in the pathway of obesity to gait; we will be cautious in interpreting models that adjust for these variables.

We are limited to CRP as a marker of inflammation; although small subsets have other biomarkers, CRP provides the largest sample and also the only measure with repeated measures of inflammation. CRP is a non-specific acute phase reactant, but tends to increase and decrease rapidly. We acknowledge that both increases and decreases in inflammatory markers tend to be blunted with older age. Having multiple visits with elevated CRP measures increases our confidence that a participant has exposures to chronic inflammation.

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? ____ 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.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#2791 Association of Life's simple 7 at mid-life with frailty in older adults. Palta, et al.

MP# 2865. Inflammatory biomarkers at midlife and late-life and brain atrophy in older adults: The ARIC Study. Walker et al.
MP# 2866. The association of midlife and late-life inflammatory biomarkers with cerebral small vessel disease and white matter integrity in the elderly: The ARIC Study. Walker et al.
MP#2254 Relationship of Adiposity Trajectories to Later Life Physical Function and Strength. Windham et al.

MP#2930 Systemic inflammation in midlife as a predictor of frailty in late-life: The ARIC Study. Walker et al.

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 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.

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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