ARIC Manuscript Proposal # 3647

PC Reviewed: 6/9/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Physical frailty, cognition, and neurodegenerative brain changes

b. Abbreviated Title (Length 26 characters): Frailty and Neurodegeneration

2. Writing Group:

Writing group members: Emma L. Ducca, Gabriela Gomez, Priya Palta, Kevin Sullivan, Cliff Jack, David Knopman, Rebecca Gottesman, Jeremy Walston, B. Gwen Windham, Keenan Walker (senior author)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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3. Timeline:

The proposed manuscript would be completed within one year of approval. The data needed to complete the proposed manuscript have been collected. The first author is currently enrolled as a doctoral student at St. John's University and is proposing the current manuscript for completion of dissertation requirements. The first author will serve as principal investigator for the proposed research, under the guidance of Dr. Walker, and

will be responsible for overseeing all aspects of this project, including data extraction, data analysis, and preparation of manuscripts. Research timeline is provided below.

Research Timeline	Q1	Q2	Q3	Y4
Determine study inclusion and exclusion criteria	√			
Creation of data set needed for analysis	√			
Data management and cleaning	√			
Data analysis		√		
Drafting of manuscripts			√	
Internal peer review and journal submission			√	√

4. Rationale:

Frailty is a complex health condition in older adults that results in diminished physiologic reserve due to the decline in function across multiple physiologic systems[1]. Estimates of frailty and prefrailty prevalence among community-dwelling older adults varies from 4.9-27.3% and 34.6-50.9% respectively [2]. Frailty is associated with increased vulnerability to health sequelae including falls, disability, chronic illness, increased health care utilization, and premature death [3,4].

Although there is considerable evidence suggesting that frailty and cognitive decline are linked, there is some conflicting evidence regarding the etiopathogenesis of these conditions. Large cohort studies have found that frailty is associated with increased rates of cognitive decline [5,6] as well as Alzheimer's disease (AD) [7] and vascular dementia (VaD) [8]. However, there have been other studies suggesting that cognitive impairment may increase risk for developing frailty [9–11]. While there is evidence that suggests that poorer cognitive functioning may be linked to the development of physical frailty, both frailty and cognitive decline share underlying mechanisms and as such, the relationship between these conditions may be bidirectional or have overlapping etiologies [12]. To address this research question, the first and second aims of this project will to explore the potential bidirectional relationship between cognition and frailty. More specifically, we propose to examine the degree to which cognitive functioning influences the longitudinal progression of physical frailty and conversely, to which frailty status may affect cognitive decline.

Existing literature suggests an association between neurodegenerative brain changes and frailty status [13–15]. However, the specific neurologic pathways which contribute to frailty remain unclear. Furthermore, there is no consensus as to whether brain abnormalities in non-demented older adults are associated with increased frailty risk. Identifying the neurobiological changes that put individuals at increased risk for frailty and dementia could aid in developing intervention and prevention strategies for these conditions. Thus, the third and fourth aims of the proposed research will examine whether neuroimaging markers associated with neurodegenerative disease, including reduced brain volume, poorer white matter integrity, and greater cortical amyloid, are associated with incident frailty.

5. Main Hypothesis/Study Questions:

Aim 1: Determine if physical frailty is associated with poorer performance on measures of cognitive function and cognitive decline.

- *H1:* Non-demented, frail older adults will have poorer performance and greatest declines on processing speed/executive function and memory/language measures compared to non-demented non-frail older adults.

Aim 2: Determine if cognitive function is associated with increased risk for physical frailty in a sample of non-frail, non-demented older adults.

- *H1:* Older adults with poorer performance on memory and processing speed/executive function measures will have increased incidence of physical frailty as compared to those with greater scores on these domain measures.
- *H2:* Processing speed/executive function measures will be more predictive of physical frailty than memory/language measures among non-demented participants at V5.

Aim 3: Determine if physical frailty status is associated with brain amyloid level, lower total and regional brain volume, and greater white matter hyperintensity volume in a sample of non-demented older adults.

- *H1:* Non-demented, frail older adults will have greater levels of cortical amyloid, smaller total and regional brain volumes, and reduced white matter integrity, compared to non-demented non-frail older adults.

Aim 4: Determine if neuroimaging markers of neurodegenerative disease are associated with incident physical frailty status.

- *H1:* Older, non-demented non-frail adults with greater levels of cortical amyloid, smaller total and regional brain volumes, and reduced white matter integrity, compared to non-frail older adults will have increased incidence of physical frailty.

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).

Aim 1: Determine if physical frailty is associated with poorer performance on measures of cognition and cognitive decline.

Study design: Cross-sectional and longitudinal.

Inclusion/exclusion criteria: We will consider all non-demented participants who have cognition and frailty status measured at visit 5. Participants missing essential covariates (e.g., education) will be excluded from all analyses.

Aim 2: Determine if cognitive function is associated with increased risk for physical frailty.

Study design: cross-temporal.

Inclusion/exclusion criteria: We will consider all participants who are non-frail and non-demented at visit 5 who completed cognitive testing visit 5. Participants missing essential covariates (e.g., education) will be excluded from all analyses.

Aim 3: Determine if physical frailty status is associated with brain amyloid level, markers of neurodegeneration including lower total and regional brain volume, and greater white matter hyperintensity volume in a sample of non-demented older adults.

Study design: Cross-sectional.

Inclusion/exclusion criteria: All participants who completed frailty assessment and received MRI at visit 5 will be considered. A separate analysis will be done on a subset of participants (N=346) who completed Positron Emission Tomography (PET) imaging.

Aim 4. Determine if neurodegenerative disease markers are associated with incident physical frailty status.

Study design: Cross-temporal.

Inclusion/exclusion criteria: All participants non-frail at visit 5 who received an MRI at visit 5 and underwent frailty assessment at visit 6 or 7. A separate analysis will be done on a subset of participants (N=346) who completed Positron Emission Tomography (PET) imaging.

Exposure and Outcome Variables

***Frailty*:** Nearly all participants who attended visits 5, 6, and 7 of the ARIC Neurocognitive Study (NCS) have been categorized as *frail, pre-frail,* or *robust* based on the frailty phenotype definition operationalized by the Cardiovascular Health Study (CHS)[1] and validated in the ARIC study[16]. This definition of frailty is based on 5 components: exhaustion, slowness, low physical activity, and unintended weight loss. Participants are categorized as "frail" if they met 3 or more of the criteria listed below. Participants meeting none, one, or two of the frailty criteria will be classified as "non-frail."

1. *Exhaustion*: Participants who answered "some of the time" or "most of the time" to the following two questions on the Center for Epidemiological Study's-Depression (CES-D) scale [17] (administered at visit 5 and visit 7) were classified as positive exhaustion: "I felt everything I did was an effort" and "I could not get 'going'".
2. *Slowness*: Walking speed was measured at visit 5 and visit 7 as the time needed to walk 4 m at a usual pace. Slow walking speed was defined as a time within the lowest 20th percentile, adjusted for gender and height, as defined in CHS.
3. *Low Physical Activity*: Physical activity was measured at visit 5 and visit 7 using the modified Baecke questionnaire. Low physical activity was defined as reported physical activity in the lowest 20th percentile stratified by gender.

4. *Weakness*: Grip strength in the participant's preferred hand was measured at visit 5 and visit 7 using an adjustable, hydraulic grip strength dynamometer. Weakness was defined as grip strength in the lowest 20th percentile, adjusting for gender and BMI according to established norms. Grip strength measures were not obtained for participants with bilateral surgery in hands or wrists in the previous 3 months.
5. *Weight Loss*: Weight loss was defined as a 10% weight loss from visit 4 to visit 5 or a body mass index (BMI) at visit 5 less than 18.5kg/m^2. The criteria for weight loss changed for participants after visit 6. For both visit 6 and visit 7, weight loss was defined as the percent change in weight from visit 5/6 to visit 6/7.

Cognitive variables of interest: We will use data from the comprehensive cognitive assessment, which has been described previously [18]. We will examine global and domain-specific factor scores.

Neuroimaging variables of interest:
MRI Variables. 3T MRIs were conducted in approximately 2,000 participants at visit 5 as part of the ARIC Neurocognitive Study (NCS). The acquisition sequence for the ARIC visit 5 MRI has been described previously[19]. At each ARIC site, a common set of sequences were performed for all participants: MP-RAGE, Axial T2*GRE, Axial T2 FLAIR, and Axial DTI.

We will examine total and regional brain volume with a focus on several ROIs, including the Alzheimer's disease signature region and the hippocampus. Additionally, VBM will be used to identify regional group differences in gray matter (GM) and white matter (WM) density among frail and non-frail participants using voxel-wise parametric statistical tests. We will correct for multiple comparisons using the FDR threshold. We will generate maps based on voxel-based associations. Generalizations will be drawn from these maps. These analyses will be used to compare participants with and without frailty at visit 5.

White Matter Hyperintensity (WMH) Volume. WMH volume (mm^3) was be assessed quantitatively from FLAIR images using a computer-aided segmentation program (FLAIR-histoseg) to assess the total volumetric burden [21]. We will compare groups described above on measures of total WMH volume. All analyses of WMH volume and regional brain volume will be adjusted for total intracranial volume.

Diffusion Tensor Imaging (DTI). Fractional anisotropy (FA) and mean diffusivity (MD) have been calculated from the DTI sequences, as has been described in detail elsewhere[22]. In addition to examining specific white matter tracts (e.g., corpus callosum, fornix, hippocampal cingulum bundle), we may also examine FA and MD in four white matter networks: limbic, commissural, association, and projection tracts[24].

Positron Emission Tomography (PET). Florbetapir, a ligand that binds to Aβ, is used to help estimate the total amount of Aβ deposition in the brain, with greater uptake of the compound used as a representation of greater accumulation of Aβ. Global cortical florbetapir uptake has been calculated as a weighted average of the following regions:

orbitofrontal, prefrontal, superior frontal, lateral temporal, parietal, occipital cortices as well as the precuneus, anterior cingulate, and posterior cingulate. Cerebellar gray matter will be used as a reference region. In accordance with previous methods, we will examine amyloid both as a dichotomous and a continuous variable.

***Covariates**:* For all study aims, analyses will be adjusted for the following potential confounding variables, including demographic and clinical variables, selected based on knowledge of the existing literature. Specifically, demographic variables of interest will include age (extracted at visit 5), race-center, sex, education, center (extracted at visit 1), and *APOE*e4 status. Cardiovascular risk factors (i.e., hypertension, diabetes, coronary heart disease) will also be used as covariates.

Summary of data analysis

Aim 1: Determine if physical frailty is associated with accelerated rate of cognitive decline. We will use multivariable linear regression and generalized estimating equations or linear mixed models to examine how frailty status is associated with cognitive function at visit 5 and cognitive decline between visits 5 and 7. Analyses will be adjusted for demographic and cardiovascular risk factor variables. We will first examine results in an unadjusted model (Model 1). Next, we will adjust for demographic variables including age, education, sex, study center-race, and *APOE*e4 status (Model 2). Finally, we will examine a third model which includes demographic characteristics as well as cardiovascular risk factors (i.e., hypertension, diabetes, coronary heart disease) (Model 3). Methodologic challenges include selective attrition between visit 5 and visit 7. Sensitivity analyses using multiple imputation and inverse probability weighting will be used to address these limitations.

Aim 2: Determine if cognitive function is associated with increased risk for incident physical frailty. Multivariable logistic regression analysis will be used to determine the relationship between V5 performance on cognitive measures and frailty status by visit 7. We will use Models 1-3 described above. Methodologic challenges include selective attrition between visit 5 and visit 7 as well as differing frailty definitions between visit 5 and visit 7. Sensitivity analyses using inverse probability weighting will be considered to address the former limitation. Additional sensitivity analyses will also be performed, including repeating analyses including only participants who are robust (i.e., meet no frailty criteria) at visit 5, and repeating analyses using a cumulative frailty index score as an outcome rather than the binary frailty definition.

Aim 3. Determine if physical frailty status is associated with brain amyloid level, markers of neurodegeneration including lower total and regional brain volume, and greater white matter hyperintensity volume in a sample of non-demented older adults. We will use multivariable linear regression to examine how frailty status is associated with markers of neurodegenerative disease at visit 5. Analyses will be adjusted for demographic and cardiovascular risk factor variables as described above in Models 1-3. We will use sampling weights to account for selected sampling for neuroimaging ascertainment. As the number of participants who completed PET imaging is relatively

small, we may not have sufficient statistical power to detect an association of amyloid deposition with frailty status.

Aim 4. Determine if neurodegenerative disease markers are associated with incident physical frailty status. We will use multivariable logistic regression analysis to assess the relationship of visit 5 neuroimaging markers with incident frailty status through visit 7. We will use sampling weights to account for selected sampling for neuroimaging ascertainment. As described above, methodologic challenges include selective attrition after visit 5 will be addressed in sensitivity analyses using inverse probability weighting. Additionally, differing frailty definitions between visit 5 and visit 6/7 represents a challenge to data analysis. To address this methodological challenge, we will examine frailty status using a cumulative index score as described above.

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.cscc.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)?
We are aware of an ancillary proposal currently under review that proposes to examine frailty and dementia, the aims of which are included below. The current proposal is unique in its aims, which propose to focus on the underlying neurobiological mechanisms associated with frailty and cognitive decline.

Aim 1. To assess temporal patterns of occurrence in the development of physical frailty and dementia.
Aim 2. To assess whether the pattern of onset was different between dementia cases that were attributable primarily to AD and those that were attributable to either primarily vascular or mixed AD/vascular factors.
Aim 3. To estimate the combined effects of physical frailty and dementia for: (i) incident hospitalization, (ii) incident falls, and (iii) all-cause mortality while accounting for the patterns of occurrence, primary pathway, and time-dependent multimorbidity confounding.

Other related ARIC proposals include:
#2791: Association of Life's simple 7 at mid-life with frailty in older adults

#2215: Development of longitudinal measures of general and domain-specific latent factors for cognitive performance

#2288: Associations of brain imaging with cognitive change over 20 years

#2671: Cardiovascular characterization of frailty in the elderly: The ARIC study

#2465: Operationalizing frailty in the ARIC cohort

#2303: Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities Study

#3574: The association of motoric cognitive risk with neuroimaging and incident dementia: The ARIC Study

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.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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