ARIC Manuscript Proposal #2998

PC Reviewed: 06/06/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association Between Brain β-Amyloid Deposition and Physical Function Decline in a Community-based Cohort without Dementia: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

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

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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).

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3. Timeline: Analysis to begin at visit 6 data close-out, 2018; planned manuscript preparation and submission 6-12 months after

4. Rationale:
Mobility impairments affect 1/3 of older adults, are associated with falls, disability, institutionalization, premature mortality[1-5] and are costly.[6] The brain is emerging as an important contributor to aging-related mobility decline, and abnormalities in brain structure may modify responses to gait rehabilitation strategies.[7] Prior studies have shown that white matter hyperintensities (WMH), atrophy, infarcts, and executive function are associated with poor gait.[8-11] Furthermore, these brain structural alterations are also associated with cognitive decline and

dementia. Relationships of changes in gait and cognition are bidirectional, i.e., changes in gait may predict incident dementia and cognitive decline may precede mobility decline.[12,13] Shared mechanisms may explain these relationships and, if elucidated, could lead to earlier identification of persons at risk for gait and cognitive decline. Identifying pathological changes associated with decline in gait and cognition could lead to novel preventive therapies and interventions.

Recent data also suggest that β-amyloid deposition across all or specific regions (e.g., posterior and anterior putamen, occipital cortex) of the brain is associated with slower gait speed.[14-16] These studies were limited by cross-sectional designs and, for one, a lack of brain imaging markers of cerebral small vessel disease known to be associated with mobility and cognition. Due to this latter limitation, contributions of amyloid independent of small vessel disease markers could not be determined. This is especially relevant in racially diverse populations who tend to have more or more severe cerebral small vessel disease and are at greater risk for physical disability.[17-19] Only one small study reported associations between brain β-amyloid deposition and ***decline*** in gait speed, the first to demonstrate temporal associations between β-amyloid and mobility decline. The Baltimore Longitudinal Study of Aging NeuroImaging (BLSA-NI) Study highlighted that among 59 participants (mean age 75 years; 50% women; and 83% white race), Aβ burden in global or specific brain regions (e.g., cortex, putamen, and dorsolateral prefrontal cortex and lateral temporal lobe) was associated with greater decline in gait speed over a median follow-up of 5 years.[20] However, BLSA participants tend to be healthier, white, more educated and of higher socioeconomic status than the general US population. Because amyloid deposition generally occurs more in non-motor control regions, we will examine the influences of cognition on the relationships of amyloid deposition with mobility and potential synergistic effects of cerebral small vessel disease.

This study will examine the relationship of cerebral β-amyloid deposition globally and by regions, with a specific interest in regions involved in motor control, with gait speed and gait speed decline from Visit 5 to Visit 6, and whether the associations differ by race. We will also examine other physical function outcomes including performance on chair stands and balance tasks and the Short Physical Performance Summary Battery (SPPB) score, falls, and postural instability.

5. Main Hypothesis/Study Questions:

Hypothesis 1 - In non-demented adults, higher cerebral β-amyloid deposition globally and in motor control regions will be associated with slower gait speed (cross-sectionally) and greater decline in physical performance (gait speed, SPPB, chair stands, and balance).

Hypothesis 2 - these associations will be partially mediated through cognition.

Hypothesis 3 –β-amyloid deposition and brain structural markers will have interactive effects on physical function decline among older adults. The ability to detect these interactions may be limited because of our limited sample size. Nevertheless, we consider that knowing the presence or absence of these interactions, even if only trends, will be valuable for planning future studies.

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).

Design:
Longitudinal analysis of all participants in completed ARIC-PET study (N= 346 completed scans).

Inclusion criteria:
Participants in the ARIC-PET sub-study with measures of gait speed at Visit 5 and Visit 6.

Exclusions:
Missing data for β-amyloid imaging at Visit 5 and gait speed at Visit 5. One participant with dementia who underwent PET imaging will be excluded. Additional analyses will be conducted to examine differences between PET and non-PET participants.

Outcomes:
Primary outcome: Gait speed
Secondary outcome: SPPB and each component (i.e., chair stands and balance), falls, postural instability from Unified Parkinson's Disease Rating Scale.

Exposures:
β-amyloid PET SUVR. The SUVR's will be evaluated as a continuous and standardized variable (global SUVR and in pre-specified regions of interest) as well as a binary variable based on the published ARIC-PET cut-point of SUVR > 1.2. We will also assess regional β-amyloid deposition as the exposures, including orbitofrontal cortex, prefrontal cortex, superior frontal cortex, lateral temporal lobe, medial temporal lobe, combined med temporal/ amygdala/ hippocampus, amygdala, hippocampus, parietal lobe, posterior precuneus, occipital lobe, anterior cingulate, caudate, putamen, thalamus, midbrain, pons, medulla, centrum semiovale, and this composite global cortical measure.

Covariates:
Covariates may include age, BMI, sex, race, site, educational level, clinical characteristics at Visit 5 (smoking, diabetes, systolic blood pressure, diastolic blood pressure, antihypertensive medications), brain MRI variables at Visit 5 (infarcts, WMH, global atrophy, or total brain volume), and cognitive function at Visit 5. A basic model will include age, BMI, sex, race-site, selected *a priori* because they have known associations with β-amyloid deposition in the brain and are risk factors for physical functional decline.

Analysis:
Associations of brain β-amyloid deposition globally and by regions of interest with physical functional change will be examined by linear mixed effects models or generalized estimating equations using Stata version 14.0 (StataCorp; College Station, TX). We will verify the model assumptions of linearity, normality of residuals, homoscedasticity, and absence of collinearity. The amount of β-amyloid deposition in the brain, time (years between visits 5 and 6), and the amount of β-amyloid deposition × time will be modeled as fixed effects. The intercept and interval will be allowed to vary between individuals and modeled as random effects. We will also include an interaction term between β-amyloid deposition and brain MRI variables to test an interactive effect of amyloid and other MRI markers on decline in gait speed or SPPB.

In sensitivity analyses, analyses for heterogeneity of effect between brain β-amyloid deposition (global or in specific regions) and outcomes by sex, race, or apolipoprotein E ε4 allele will be performed, with inclusion of interaction terms. If the interaction is observed, stratified analyses will be conducted. To examine both effects of attrition and biasedness in the PET subsample on our findings, we will conduct sensitivity analyses as recommended by the ARIC analysis committee to account for missing data using IPAW or shared parameter models where appropriate.

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"? __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)?
ARIC Manuscript Proposal #2729, "Neurocognitive correlates of mobility."
ARIC Manuscript Proposal #2511, "Vascular risk factors and brain amyloid deposition: The ARIC-PET Study".

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* _____)
__X B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____2009.29_____ _____)

*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 ____ No.

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