ARIC Manuscript Proposal #3467

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

1.a. Full Title: Psychosocial buffers of amyloid PET and MRI CSVD/neurodegeneration markers on cognition

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: Keenan Walker (first and corresponding author); Priya Palta; B. Gwen Windham; Lisa Barnes; Anna Kucharska-Newton; Thomas Mosley; Rebecca Gottesman; Mario Sims; Alison Huang; Miguel Arce; Jennifer Manly; others welcome

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

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3. Timeline: 3-9 months; manuscript submission winter 2019/2020.

4. Rationale:

While changes in brain volume, white matter hyperintensity (WMH) volume, and β-amyloid deposition are risk factors for dementia and cognitive decline, there is a great deal of individual variation in the degree to which these structural and molecular brain changes affect cognitive decline among older adults.[1] Accumulating evidence suggests that certain psychosocial factors may be protective against cognitive decline in the context of neurodegenerative, vascular, and Alzheimer'-specific brain changes. For example, greater education,[2] intellectual enrichment activities,[3] and occupational complexity[4] have each been associated with preserved cognition in the face of neurodegenerative disease.

Although this concept of preserved cognitive function in the context of disease (commonly referred to as cognitive reserve)[5] has been previously characterized, the majority of this research has been conducted using studies of non-Hispanic white older adults. Little is known about what factors may act as buffers against cognitive decline in African American older adults who may 1) be exposed to a differing set of life experiences and risk/protective factors and 2) have at older age a different burden of neurodegenerative and cerebrovascular disease, as compared to their non-Hispanic white counterparts.[6,7] Low socioeconomic position (SEP) and psychological risk factors, such as loneliness, depression, and stress, have been associated with a number of adverse outcomes in African Americans, including lower late-life cognition and cognitive decline.[8–10] However, whether these psychosocial factors are directly related to neurodegenerative and cerebrovascular disease, and whether they modify the association between pathological brain changes and cognitive function remains unclear.[11]

The current study will examine whether psychosocial factors, including childhood and adult SEP, and social support in adulthood, depressive symptoms, and stress moderate the relationship between pathogenic structural brain changes and cognitive function in African American older adults. Additionally, we will examine whether these psychosocial factors moderate the relationship between cortical amyloid deposition and cognitive function in a subset of African Americans with available florbetapir (amyloid) PET imaging. The current study will use psychosocial data collected as part of the baseline Jackson Heart Study (JHS) and neuroimaging and cognitive outcomes from individuals who are co-enrolled in the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study and the ARIC-PET Study. We hypothesize that psychosocial factors will modify the association of brain volume, WMH volume, and cortical amyloid levels with cognition and cognitive decline. Specifically, we hypothesize that the association between brain abnormalities and cognition will be weaker among African Americans with greater childhood SEP and adulthood social support, and lower levels of late-life depressive symptoms and global stress.

5. Main Hypothesis/Study Questions:

H1. The association of lower total and regional brain volume with lower late-life cognition and greater late-life cognitive decline will be stronger among participants with low (vs. high) childhood SEP and low adulthood social support, and high (vs. low) late-life levels of depressive symptoms and global stress.

H2. The association of high WMH volume with low late-life cognition and late-life cognitive decline will be stronger among participants with low (vs. high) childhood SEP and low adulthood social support, and high (vs. low) late-life levels of depression and global stress.

H3. The association of greater cortical amyloid with lower late-life cognition and greater late-life cognitive decline will be stronger among participants with low (vs. high) childhood SEP and adulthood social support, and high (vs. low) late-life levels of depression and global stress.

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

The JHS is a prospective, observational, community-based study of African American adults. Between 2000 and 2004, 5,306 individuals between ages 21 and 94 were recruited to be a part of the study from the Hinds, Madison, and Rankin counties in the Jackson Mississippi metropolitan area. Exposure/moderator information for this analysis was collected at JHS Visits 1 (2000-04) and 3 (2009-13). Participants co-enrolled in the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study received a brain MRI and completed a comprehensive cognitive assessment at ARIC Visit 5 (2011-13).

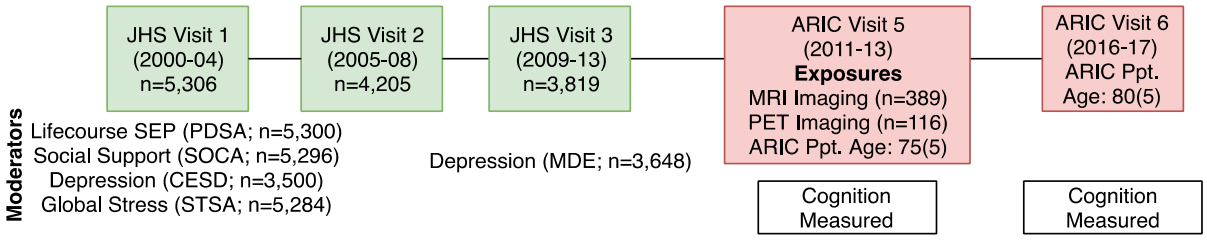

Figure 1. Study timeline.
CESD, Center for Epidemiological Studies-Depression; MDE, Major Depressive Episode; Ppt., participant; SEP, socioeconomic position.

Inclusion/Exclusion Criteria*:* Participants enrolled in the Jackson Heart Study will be included on the basis of 1) having received a brain MRI at ARIC Visit 5, and 2) having information available for one or more exposure/moderator variables of interest (i.e., measures of SEP, social support, depression, or stress). Participants missing Visit 5 global cognition or essential covariate information (e.g., age, education, sex) will be excluded. Analyses of cognitive decline will exclude participants with missing Visit 6 cognition.

Exposure Variables

Total brain volume. Total brain volume will be used as an overall measure of parenchymal volume loss. Total brain volume will be extracted from the ARIC-NCS MRI scans obtained at Visit 5. All analyses using this variable will include adjustment for total intracranial volume.

Regional gray matter volume: Several gray matter structures known to be susceptible to atrophic changes in the earliest stages of Alzheimer's disease will be specified as regions of interest

(ROIs). ROIs will include the hippocampus and a composite variable, the Alzheimer's Disease Signature Region, which is a composite measure of brain regions vulnerable to atrophy in the earliest phase of Alzheimer's disease (combined volume of the parahippocampal, entorhinal, inferior parietal lobules, hippocampus, and precuneus). Regional gray matter volumes will also be extracted from ARIC-NCS MRI scans obtained at Visit 5. Gray matter volumes were calculated using a semi-structured parcellation program. All analyses using regional gray matter volume will include adjustment for total intracranial volume.

White matter hyperintensity volume (WMH): WMH volume was derived from proton density-weighted images extracted from the ARIC-NCS MRI scans obtained at Visit 5. WMH burden was determined using a quantitative computer-aided segmentation program which uses an algorithm to segment fluid-attenuated inversion recovery (FLAIR) images (FLAIR-histoseg) to measure the volumetric burden of leukoaraiosis.[12] All analyses using WMH will include adjustment for total intracranial volume.

Flobetapir PET. 346 non-demented ARIC participants were enrolled at ARIC Visit 5 to undergo florbetapir PET imaging to measure cortical amyloid levels as part of the ARIC-PET Study.[6] Standardized uptake volume ratio (SUVR) was measured based on florbetapir (amyloid) uptake in prespecified regions of interest. Global mean cortical SUVR was calculated based on a weighted average (based on region-of-interest (ROI) volumes) of regions known to be typically impacted in Alzheimer's disease. The SUVR's will be evaluated at a cut-point of 1.2, with values >1.2 considered positive. Alternatively, we will examine SUVR as a continuous variable.

Buffer/Moderator Variables

Childhood Socioeconomic position (SEP). A summary score of childhood SEP has been created from information about parental education (of parent with highest level of education) before the time the participant reached 16 (rated 0 [low] to 2 [high] based on three groups: <high school (HS), HS/GED, and >HS), parental home ownership before the participant reached age 10 (rated 0 [no] to 1 [yes]) and childhood access to amenities while growing up until age 10 (rated 0 [low] to 2 [high] based on the number of amenities categorized into tertiles).[13] The summary childhood SEP score (range, 0 to 5) will be dichotomized at the sample median (low, high) or categorized into tertiles (low, medium, high).

Adult socioeconomic position (SEP). A summary of adult SEP has been created from information about participant education categorized into 4 groups (HS/GED or less, vocational certification/some college, associate/bachelor's degree, or postgraduate degree) and rated from 0 to 3; participant self-reported family income measured from 13 brackets which range from <$5,000 to >=100,000, which has been subsequently categorized into four groups for the analysis (<$25,000, $25,000 to $39,999, $40,000 to $74,999, or >=$75,000) and rated from 0 to 3; a score of wealth rated from 0 to 2 based on three assets (1. participant/family home ownership, 2. car ownership, and 3. amount of liquid assets ranging from $0 to >=$200,000, indicating the total amount of money the participant and their spouses could raise in an emergency by cashing in all possessions, stocks, bonds, or real estate); and a measure of use of public assistance rated from 0 to 2 based on the participant responses to three questions about use of food stamps, use of other welfare programs, and supplemental security income (SSI).[13] The

summary adult SEP score (range, 0 to 10) will be dichotomized at the sample median (low, high) or categorized into tertiles (low, medium, high).

Functional and structural social support. We will determine level of functional and structural social support from the Interpersonal Support Evaluation List (ISEL) instrument administered at JHS Visit 1. This instrument includes four domains of functional social support: appraisal, belonging, self-esteem, and tangible. Individuals can earn up to 12 points for each of the four domains. Individuals can receive a score ranging from 0 to 48, which we will dichotomize at 32, below which has been used to indicate low functional social support. We will also examine structural social support, the size of one's social network, using information from three items adapted from the Berkman Social Network Index. This index of structural social support has been previously validated.[14] A social network size < 8 will be used to categorize participants as having low structural social support.[15]

Depressive Symptoms. Depressive symptoms were measured at JHS Visit 1 using the 20-item Center for Epidemiologic Studies Depression Scale (CESD).[16] The CESD is a measure of depressive symptoms commonly used in epidemiological research.[17] The CESD will be evaluated as a continuous parameter and dichotomized at a score of 16, which is consistent with clinically significant depression symptoms (range 0 to 60; higher scores reflect greater levels of depressive symptoms).[18,19] The presence of a current and past major depression disorder will be examined at JHS Visit 3 using the Major Depressive Episodes (MDE) questionnaire. For analytic purposes, participants will be grouped as having a current or past major depressive episode (yes/no).

Global stress. We will use a measure of perceived global stress adapted from the Survey of Recent Life Experiences and Perceived Stress Scale, which was administered at JHS Visit 1. On this self-report measure, participants rated the extent of stress perceived in 8 domains (e.g., employment, relationships, meeting basic needs) over a twelve-month period. After summing each item, a total score ranging from 0 to 24 is derived for each participant.

Outcome Variable

Cognition and cognitive change: We will examine how ARIC Visit 5 imaging variables relate to cross-sectional cognition and cognitive change from Visit 5 to Visit 6 in domains of memory, language, and processing speed and executive function. Additionally, we will examine global cognition and global cognitive change as an outcome variable. We will use a latent variable approach (i.e., ARIC factor scores), described previously,[20] for the measurement of cognitive domains and global cognition.

NCS Comprehensive Cognitive Battery

Memory Composite
Delayed Word Recall Test (DWRT)
Logical Memory I & II
Incidental Learning

Language Composite

Word Fluency Test (WFT)
Animal Naming
Boston Naming Test

Processing Speed/Executive Function Composite
Digit Symbol Substitution Test (DSST)
Digit Span Backwards
Trail Making Test-A
Trail Making Test-B

Analytic Plan

Multivariable linear regression will be used to examine cross-sectionally the association of brain volume, WMH volume, and florbetapir PET with ARIC Visit 5 cognition. To test whether SEP, social support, depressive symptoms, or global stress modify the association of brain volume, WMH volume, and florbetapir PET with Visit 5 cognitive status, a multiplicative interaction term (imaging variable*psychosocial variable) will be added to the model as a predictor. For significant interaction, post-hoc analyses stratified by levels of the psychosocial variable of interest will be examined to determine the direction of the associations. Models will adjust for age, sex, education, and intracranial volume. Models that examine adult SEP will not adjust for education, as education is a part of the adulthood SEP composite score. However, we will consider a sensitivity analysis which includes education as a covariate.

Cognition_V5 ~ neuroimaging + age + sex + education + intracranial volume

Cognition_V5 ~ neuroimaging*psychosocial_buffer + neuroimaging + psychosocial_buffer + age + sex + education + intracranial volume

To examine the association of brain volume, WMH volume, and florbetapir PET with cognitive change from ARIC Visit 5 to Visit 6, we will use generalized estimating equations (GEE) with an exchangeable correlation matrix and robust variance. We will examine changes in global cognitive functioning as well as domain-specific cognitive change. To test whether SEP, social support, depressive symptoms, or global stress modify the association of brain volume, WMH volume, and florbetapir PET with cognitive change from ARIC Visit 5 to Visit 6, a multiplicative interaction term (imaging variable*time*psychosocial variable) will be added to the model as a predictor. For significant interactions, post-hoc analyses stratified by levels of the psychosocial variable of interest will be examined to determine the direction of the associations. Models will adjust for age, sex, education, and intracranial volume, and the interaction between these variables and time. Models that examine adult SEP will not adjust for education, as education is a part of the adulthood SEP composite score. However, we will consider a sensitivity analysis which includes education as a covariate.

CogChange_V5_V6 ~ neuroimaging*time + neuroimaging + time + age + sex + education + intracranial volume

CogChange_V5_V6 ~ neuroimaging*time*psychosocial_buffer + neuroimaging*time + psychosocial_buffer*time + neuroimaging*psychosocial_buffer + neuroimaging + time + psychosocial_buffer + age + sex + education + intracranial volume

Sample Size and Power Analysis
In total, 514 African American ARIC participants received a brain MRI at the Jackson, MS study site. A subset of these participants are co-enrolled in the JHS and will thus be included in the current set of analyses. In total, 141 African American ARIC participants underwent florbetapir PET imaging at the Jackson, MS study site. A subset of these participants are/were co-enrolled in the JHS and will thus be included in the current set of analyses.

For this power analysis, we calculated the smallest association detectable given a fixed sample size, 80% power, and an α of 0.05. Using a sample of 500 participants, we will have adequate power to detect an R^2 of at least 0.02 using multivariable linear regression with 7 covariates. Using a sample of 300 participants, we will have adequate power to detect an R^2 of at least 0.03 using multivariable linear regression with 7 covariates. Using a sample of 100 participants, we will have adequate power to detect an R^2 of at least 0.07 using multivariable linear regression with 7 covariates.

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/mantrack/maintain/search/dtSearch.html

___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# 3207. Minimum cognitive decline

MP# 3119. Vascular risk factors, brain amyloid deposition, and cognitive decline: The ARIC-PET Study

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

MP# 2211. Midlife psychosocial factors and cognitive decline

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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

Understood

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.

Understood

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