ARIC Manuscript Proposal #3689

PC Reviewed: 8/11/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Population based associations of change in cognitive function with brain changes assessed by multiple imaging modalities.

1.b. Abbreviated Title (Length 26 characters): Cognition and brain imaging

2. Writing Group: Alessandro Orlando, Richey Sharrett, Josef Coresh, Rebecca F Gottesman, David S Knopman, Andreea Rawlings, Andrea LC Schneider, Thomas Mosley, Clifford Jack, Dean Wong, James Pike.

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

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3. Timeline: Manuscript to be completed and submitted within 6-12 months.

4. Rationale:

According to the World Health Organization, the number of deaths due to dementia has doubled in the past six years.[1] It is now the fifth leading cause of death worldwide and the sixth leading cause of death in the United States.[1,2] Importantly, dementia is not an acute disorder, but a chronic one defined by cognitive abilities which decline over time.[3,4] Pathological abnormalities in the brain–including beta amyloid proteins and white matter hyperintensities—commonly present, and accumulate over decades prior to when overt dementia is likely to be diagnosed.[5–8]

Cognitive performance is ultimately dependent on the activity of neurons. As the concert of synaptic neuronal firings in the brain begins to become affected by the myriad of dementia-related pathological processes, reduced cognitive performance occurs.[9] Brain imaging studies have identified that general and region-specific atrophy, cerebral infarcts, and white matter abnormalities are associated with dementia and mild cognitive impairment–a precursor to dementia.[8,10,11] Nevertheless, little is known about the relationship between prior decline in cognitive functioning and brain characteristics in the elderly. This is due to the long preclinical period until dementia diagnosis and the dearth of studies with adequate long-term follow-up. Not surprisingly, many published studies are limited by small sample sizes or short follow-up.[4,12,13] Without long-term follow-up, data on long-term changes in cognition are unavailable.

It stands to reason that because dementia 1) is a result of pathological processes in the brain, 2) is a process that occurs over many years, and 3) is characterized by decreased cognitive function and deleterious brain characteristics, *long term changes in cognitive functioning* would be more strongly associated with dementia-related brain characteristics than would *level of cognitive functioning measured cross-sectionally at the time of imaging*. Several published studies have observed the association of prior cognitive decline with decreased brain volumes.[13–17] Again, these studies were limited. Therefore, associations between *long-term* cognitive *decline* and late-life brain morphology are needed in large, diverse cohorts with long follow-up. Contributing information to this gap in knowledge is the primary objective of our study.

Additionally, it is of great interest to identify early hallmarks of dementia before the pathological process leads to irreversible neuronal damage. Recent longitudinal population-based cohort studies that have examined changes in cognitive function in relation to brain morphology were conducted in subjects in late-life, and are lacking information about mid-life changes.[14–16,18] This begs the question: What is the relationship between short-term mid-life changes in global cognitive function, and late-life brain morphology? Answering this question will inform the potential utility of mid-life cognitive assessments for predicting late-life brain characteristics associated with cognitive impairment and dementia. Early identification can highlight individuals who are at risk or showing early signs of dementia, and who might benefit from early medical or lifestyle interventions. Contributing information to this gap in knowledge is the secondary objective of our study.

It is worth noting that previous ARIC investigators recently examined the relationship between long-term cognitive decline and brain morphology using different measures of cognitive change and brain morphology.[18] The main exposure of interest in the Schneider et al. study was isolated decline in specific measures of cognition (visit two to visit five). Comparison groups were created based on domain-specific declines (e.g. top 20% of decline in memory only), while brain imaging outcomes were limited to voxel-based and region of interest-specific gray matter volumes. In summary, Schneider and colleagues observed that subjects with the highest declines in memory-only also had significantly smaller brain volumes in limbic structures and sections of the temporal lobe, whereas subjects with highest declines in executive-only and language-only domains exhibited lower brain volumes in multiple, brain regions without identifiable pattern, as would be expected from “scatter-shot” small vessel lesions or other non-localizing pathogenic processes. We wish to augment, not supplement, the work done by Schneider and colleagues. This will be achieved by focusing on changes in general cognition and adding a broad set of

brain outcomes including white matter hyperintensities, white matter integrity, beta-amyloid deposition, and the presence of lacunes.

There is great value in leveraging the ARIC cohort to add to this growing body of literature. Specifically, the ARIC cohort is perfectly positioned to address our study objectives by having rich, 21-year data on mid-to-late life changes in cognition, and late-life detailed brain imaging data via magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and positron emission tomography (PET) in a biracial, population-based cohort. These features will allow for a deeper characterization of how long-term global cognitive changes relate to late-life brain morphologies, and how short-term cognitive changes in mid-life relate to late-life brain morphologies.

5. Main Hypothesis/Study Questions

Primary aim: Describe how long-term mid-life decreases in global cognitive factor scores across 21 years relates to brain morphology in late-life, in a longitudinal population-based cohort of black and white participants.

> Study Hypothesis 1: We hypothesize that long-term decreases in global cognitive factor scores will be associated with lower total brain volume, Alzheimer's disease signature region volume and other regional cortical volumes, larger white matter hyperintensity volume, loss of white matter integrity, more lacunes, and elevated brain beta-amyloid deposition (standardized uptake value ratio of florbetapir ^{18}F >1.2) at ARIC visit five.
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> Study Hypothesis 2: We hypothesize that the following variables will not significantly modify the effect of change in global cognitive factor scores and brain morphology: race [black/white], sex [male/female], initial baseline global cognitive factor scores [above/below median]; We also hypothesize that associations between change in global cognitive factor scores and brain morphology will be significantly stronger in participants of above, versus below, the median age. Note that age and baseline global cognitive factor scores will be explored as continuous variables, and also using different category definitions.

Secondary aim: Describe how short-term mid-life changes in global cognitive factor scores across six years relate to brain morphology in late-life, in a longitudinal population-based cohort of black and white participants.

> Study Hypothesis 3: We hypothesize that short-term decreases in global cognitive factor scores will not be significantly associated with total brain volume, Alzheimer's disease brain region volumes, white matter integrity, volume of white matter hyperintensities, or proportion of subjects presenting with brain beta-amyloid deposition or lacunes at ARIC visit five.

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
This study will use cognitive data collected via the main ARIC prospective observational cohort study and ARIC-NCS study. Cognitive data will be used from visits two, four and five, and imaging data are those collected at the visit five neurocognitive study (i.e. MRI and PET). The target population for this study will be middle-to-late aged adults of black or white race living in the United States between the early 1990s and early 2000s.

Inclusion and Exclusion Criteria
General inclusion criteria are as follows: 1) having completed the following three neurocognitive tests at visits two, four, and five (delayed word recall test, digit symbol substitution test, word fluency test); 2) having participated in and completed the visit five brain magnetic resonance imaging study. The following general exclusion criteria will be applied: 1) participants in Maryland or Minnesota who are not white; 2) participants in Mississippi who are not African-American; 3) participants in North Carolina who are not white or African-American; 4) participants whose level of education is unknown.
Exposures and Outcomes
The primary exposure variable will be change in global cognitive factor score as currently defined by the ARIC-NCS Analysis workgroup. Changes in global cognitive factor scores will be explored as continuous and categorical variables. For hypotheses one and two, changes in cognitive factor scores will be assessed between ARIC visits two and five. For hypothesis three, changes in cognitive factor scores will be assessed between ARIC visits two and four.

The primary outcomes for this study will be assessed at ARIC visit five and are as follows: total brain volume, Alzheimer's disease signature region volume, other regional cortical volumes, volume of white matter hyperintensities, white matter integrity (via mean diffusivity and fractional anisotropy), presence of lacunes and beta-amyloid by PET imaging. Similar to cognitive function, brain imaging measures will be explored as continuous and categorical variables, as appropriate.

Data Analysis
Due to the sampling scheme for the visit five brain MRI, all analyses will incorporate inverse probability sampling and non-response weights created by the coordinating center, except the beta-amyloid analyses.. Furthermore, variable transformations or categorizations might be necessary if normality assumptions are not met. All hypothesis testing will be two-sided with an alpha level of 0.05, with the exception of the interaction analyses in hypothesis 2 which will have an alpha level of 0.01.

<u>Hypothesis 1</u>
A 3 x 3 analysis will be done to determine how the starting and ending *global cognitive factor score* relates to the study outcomes (Table 1). Each participant will be categorized into tertiles of *global cognitive factor scores* based on their visit two and visit five value, separately. This categorization will provide information on whether relative *change* and relative *initial cognitive*

function scores are associated with our study outcomes. For example, comparing cells a, e, and i will compare participants across differing levels of initial cognitive function, and whose cognitive function relative to other participants has remained stable. Additionally, comparing cells g, h, and i will compare participants with the highest initial global cognitive function scores, but who had differing levels of long-term decline in global cognitive function scores. Cells a and g are of particular interest. Individuals in cell a, with low cognitive performance levels at the time of the imaging, are not expected to show the signs of brain pathology that will be seen in persons whose level, similarly low at the time of imaging, has declined substantially (i.e. cell g). Thus, examination of the 3 x 3 table will provide justification for the primary hypothesis 1. Each study outcome will have a 3 x 3 table constructed. Importantly, we will also analyze the margins of the table comparing brain measures by tertiles of global cognition at visit 5 and visit 2 to assess how longitudinal measures compare to cross-sectional measures.

Table 1. Total brain volume, by change in tertile of global cognitive factor score.

Mean volume (SD)		**Visit 5**		
		Tertile 1 (low)	Tertile 2	Tertile 3 (high)
Visit 2	Tertile 1 (low)	a	b	c
	Tertile 2	d	e	f
	Tertile 3 (high)	g	h	i

The results of the 3 x 3 analysis may help inform the interpretation of our primary method of analyzing hypothesis 1. A difference is to be noted, however: the 3 x 3 analysis examines change in tertile ranking, whereas our primary analysis of the first hypothesis examines level of absolute change. The table will help to make sure that zero change captures sufficient information as a comparator since we need to confirm that individuals with no change at low, middle and high function have similar brain metrics.

To analyze both of the first two hypotheses, we first need to derive the main independent variable, then use it in the final models. A linear mixed effects model will be used to derive a *change in global cognitive factor score* for each ARIC participant, adjusted for age and race. The dependent variable in this derivation model will be the *global cognitive factor score* at visits two, four, and five. The fixed effects in this model will be *age* and *race*; the random effects will be the *participant*, *years since visit two*, and a spline term for *years since visit two* at six years. Random intercepts and slopes will allow for the modeling of participant-specific trajectories of cognitive change. Unstructured and auto regressive correlation structures will be explored and assessed via Akaike's information criterion (AIC), and robust variance estimates will be used. Ultimately, this model will be used to estimate an adjusted change in global cognitive factor score (V5–V2) for each participant (using best linear unbiased predictors, BLUPs, which shrink estimates for measurement error). This derived value will then be used as the principal independent variable in subsequent models assessing the first two hypotheses of this study, which relate cognitive change to brain signs.

The primary analyses for hypothesis one will be evaluated using a multivariable linear regression model, adjusting for age, sex, race, education level, and volume of the cranial vault. The primary

independent variable will be *adjusted change in global cognitive factor score* from visit two to five; this variable will be explored as continuous and categorical. An example of categorical definition of tertiles of decline. The primary dependent variables (assessed at visit five) will be as follows: total, Alzheimer's disease-specific, and regional brain volumes, volume/proportion of white matter hyperintensities, mean white matter diffusivity and fractional anisotropy, and cortical PET-measured beta-amyloid. Multivariable logistic regression, adjusting for age, sex, race, education level, and volume of the cranial vault, will be used to compare adjusted odds of having lacunes present at visit five, by *adjusted change in global cognitive factor score* from visit two to visit five (continuous or categorical).

Hypothesis 2

The second hypothesis will use the final models used for the first hypothesis and will examine the interaction of following the variables collected at visit two: age, race, sex, and global cognitive factor score. Interaction variables will be assessed via likelihood ratio tests for their addition to the models in the first hypothesis, and via interaction effect estimate Wald test P-values.

Sensitivity analyses for hypotheses one and two: To address concerns of *regression to the mean* in the analysis of the interaction variable *baseline global cognitive factor score*, we will use a methodology suggested by Nesselroade.[19] Briefly, the *baseline global cognitive factor score* at visit two will be dichotomized based on its median value. Then, a simple *change in global cognitive factor score* will be calculated based on the difference between the global cognitive factor scores at visits four and five. The final linear regression model examining this interaction will have *change in global factor score* (V5-V4) as its main independent variable, other confounding variables, a dichotomized *baseline global cognitive factor score* as an interaction variable, and the study outcome of interest as the dependent variable.

Hypothesis 3

The analyses for hypothesis three will be done using a multivariable linear regression model adjusting for age, sex, race, education level, and volume of the cranial vault. The primary independent variable will be *change in global cognitive factor score* from visit two to four. Unlike the change variable created for hypothesis one, this change variable will be calculated based on simple subtraction (V4-V2) and will be explored as continuous and categorical. The primary dependent variables (assessed at visit five) will be as follows: total, Alzheimer's disease-specific, and regional brain volumes, volume/proportion of white matter hyperintensities, and mean white matter diffusivity and fractional anisotropy, and PET-measured cortical beta-amyloid deposition. Multivariable logistic regression, adjusting for age, sex, race, education level, and volume of cranial vault, will be used to compare adjusted odds of having lacunes present at visit five, by *change in global cognitive factor score* from visit two to visit four (continuous or categorical).

Sensitivity Analyses and Limitations

We plan to assess the robustness of aforementioned results by conducting multiple sensitivity analyses. First, all participants with incident strokes or traumatic brain injuries between visit two and visit five will be excluded. Second, we will exclude participants in $\leq 5^{th}$ percentile of baseline

global cognitive factor scores. Third, we will also supplant the global cognitive factor score with the global z-score and assess the consistency with our main analysis.

The first limitation of this analysis is that it does not establish temporality between cognitive decline and brain imaging measures, since MRI imaging was done only at follow up. This is an important limitation for brain volume outcomes (which do not specifically identify atrophy) but is of little concern for our other study outcomes (e.g. lacunes, white matter hyperintensity volume, beta-amyloid, diffusivity, and fractional anisotropy). Second, the Alzheimer's disease signature region of interest has been shown to be sensitive to changes in memory, not changes in language and executive functioning. Thus, a global cognitive factor score that incorporates memory, language, and executive functioning might not resolve differences in Alzheimer's disease signature region volumes. Lastly, because visit five PET imaging is only available for 346 participants, PET-based outcome analyses will be limited by small sample sizes.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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)?

a. Schneider ALC, Senjem ML, Wu A, et al. Neural correlates of domain-specific cognitive decline. *Neurology*. 2019;92(10):e1051-e1063.
b. Rawlings AM, et al. Cognitive Reserve in Midlife Is Not Associated With Amyloid-β Deposition in Late-Life. J Alzheimers Dis. 2019;68(2):517-521. PMID: 30775981

c. The following collaborators from the above studies are included in the current study proposal: Drs. Sharrett, Gottesman, Rawlings, Schneider, and Knopman.

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

_X__ A. primarily the result of an ancillary study (list number*):
1999.01, 2008.06, 2009.29

___ 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 https://sites.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.

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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