**ARIC Manuscript Proposal #3868**

**PC Reviewed: 6/8/21** **Status: _____** **Priority: 2**
**SC Reviewed: _____** **Status: _____** **Priority: ____**

**1.a. Full Title**:

Differences in brain volumes in individuals with mild cognitive impairment and normal cognition across different anatomical regions: The Atherosclerosis Risk in Communities (ARIC) study.

**b. Abbreviated Title (Length 26 characters)**:

MCI and brain volume differences

**2. Writing Group**:

Writing group members: Fernando Mijares Diaz, A. Richey Sharrett, Jennifer A. Deal, Alessandro Orlando, Andrea L. C. Schneider, James R. Pike, Clifford R. Jack.

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

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## 3. Timeline:

| Timetable | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Research activity** | May | June | July | Aug | Sep | Oct | Nov | Dec | Jan | Feb |
| Research proposal | | | | | | | | | | |
| Literature review | | | | | | | | | | |
| Data management/exploration | | | | | | | | | | |
| Data analysis – Aim 1 | | | | | | | | | | |
| Output organization (Tables, Figures – Aim 1) | | | | | | | | | | |
| Data analysis – Aim 2 | | | | | | | | | | |
| Output organization (Tables, Figures – Aim 2) | | | | | | | | | | |
| Manuscript preparation | | | | | | | | | | |
| Manuscript revision | | | | | | | | | | |

## 4. Rationale:

Despite much published research on mild cognitive impairment (MCI) during the last few years, for example[1-2], there continues to be a gap in knowledge of a broader range of volumetric brain changes in MCI vs. normal cognition (NC) in community-based samples,[3-5.] Less is published on differences in MCI subtypes, e.g., amnestic MCI (aMCI) vs. non-aMCI, and how these brain changes relate to lower performance in the 3 specific cognitive domains defined in ARIC NCS.[6-8] In particular, there is a paucity of precise, quantitative, imaging-based studies of the differences in regional brain volumes associated with MCI in representative Black and White resident populations of older age.[4, 9-11]

Current work by Orlando et al. (manuscript proposal #3689) characterizes the regional volume differences associated with prior 20-year decline in a 3-test combined cognitive score. Interestingly, the pattern was suggestive of that expected from memory loss more than a loss in other domains. In this proposal, we will determine whether this pattern is more characteristic of amnestic MCI than non-amnestic MCI.

Schneider et al. looked at regional differences in persons with isolated memory loss, language, and speed-executive function and found only memory to be associated with small volumes in the regions they expected to be affected.[12] However, their numbers were small, and single tests were used to identify cognitive domains. Our study builds on this work and will re-examine these relationships using multiple cognitive tests, which are better defined using several tests for each domain.

Research in ARIC and other studies has quantified the rate of cognitive decline associated with various exposures.[13-17] Still, reviewers often ask, "how important are the declines of the magnitude reported?". This study will provide a useful scale by which to answer that question. Specifically, we will quantify the level of 20-year decline that equals the difference between a recognized MCI syndrome and normal cognition, both estimates from the same population.

The current state of the published literature is constrained by small sample sizes, varying and sometimes imprecise ways to operationalize and diagnose MCI vs. normal cognition and unrepresentative populations.[1,9,18,19] There is a clear need to address and reduce this knowledge gap. The ARIC-NCS is primed to do so thanks to its 10-test battery of cognitive tests, well-developed criteria operationalized in advance of study initiation, large sample size and a biracial population.[20]

## 5. Main Hypothesis/Study Questions:

### Main Study Question

- What differences in regional brain volumes are associated with general and amnestic mild cognitive impairment (MCI, aMCI).

### Study questions

**Aim 1:**

- **1a.** To estimate differences in volume of selected brain regions in non-demented individuals with MCI vs. those who are cognitively normal.
- **1b.** To estimate the number of standard deviations of 20-year cognitive decline equivalent to the difference between mild cognitive impairment and normal cognition, using total cortical volume as the metric of comparison.

**Aim 2:**

- **2a.** To estimate differences in volumes of selected brain regions between amnestic vs. non-amnestic MCI.
- **2b.** To estimate differences in volumes of selected brain regions associated with standard deviation differences in memory, language, and speed-executive function domain scores.

## 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:** Cross-sectional

**Inclusion criteria:**

- Individuals in ARIC who participated in and completed visit 5 (2011-13).
- Having an ARIC diagnosis of mild cognitive impairment or normal cognition at visit 5.

- Having undergone a brain MRI scan at visit 5.

**Exclusion criteria:**

- Individuals with dementia at visit 5.
- Participants without data for education and race at visit 5.

**Outcome of interest:**

The primary outcome variables are those of Schneider et al and Orlando et al, consisting of total and regional brain volumes (cc)[12]. Specifically, brain volume of 22 anatomical regions associated with the following cognitive domains: memory (medial temporal lobe, posterior cingulate, amygdala, entorhinal cortex, hippocampus); language (left inferior frontal gyrus, left superior temporal gyrus); executive function/speed of processing (prefrontal cortex, anterior cingulate, subcortical); other (pericalcarine fissure, basal ganglia, fusiform gyrus, Heschl`s gyrus, insula, lingual gyrus, cuneus, precentral gyrus, precuneus, postcentral gyrus, paracentral gyrus, supramarginal gyrus, thalamus). We will also examine the volume of the "temporal lobe meta-ROI region" defined by the Mayo MRI reading center, because of its relationship to Alzheimer's Disease and other neurodegenerative diseases. Separately, we will be comparing volume differences for 5 ROIs (4 lobes and subcortical grey matter) as a second set of outcome variables.

All outcomes will be expressed in terms of percent differences in volume compared to the population mean.

**Exposure variables:**

Aim 1: diagnoses of mild cognitive impairment vs. normal cognition.
Aim 2a: diagnoses of amnestic vs. non-amnestic mild cognitive impairment.
Aim 2b: cognitive domain scores (memory, language, processing speed-executive function)

**Covariate variables:**

Age (years), sex (male vs. female), race (black vs. white), education (3 classes), intracranial volume (cc).

All diagnoses used as primary exposure variables will be derived from ARIC visit 5.

**Specific reference to the time of their collection, summary of data analysis and any anticipated methodologic limitations of challenges if present.**

All outcome and exposure variables will be collected from participants who completed ARIC visit 5 (2011-2013) with brain imaging. MCI diagnoses incorporate normative data developed within the ARIC study (except for normative data for the Boston naming test and digit span backward test, derived from data obtained from the National Alzheimer's Coordinating Center).[20,21] Moreover, we will consider the use of inverse probability sampling and non-response weights for the imaged population.

Given the large number of ROI's, a limitation of our analysis is the possibility of spurious associations due to type I error (multiple comparisons). Modeling each outcome of interest with a separate linear regression model increases the probability of type I error and, given that regional volumes within an individual are related to one another, fails to make full use of all available data. Therefore, to minimize multiple comparisons and maximize efficiency, we will use linear mixed models to estimate marginal differences in brain volumes associated with MCI (aim 1a), accounting for the correlation of regions within an individual using a subject-specific random effect. For aim 2a our exposure of interest will be aMCI vs. non-aMCI and for aim 2b, lower performance in a cognitive domain as defined by ARIC. Our first model will include 5 ROIs (4 lobes and subcortical grey matter) and our second model will include all 22 anatomical regions of interest (as was done in Schneider et al and is being done in Orlando et al). We will include both a subject specific random effect and a random effect for each region to allow estimated mean differences to vary across regions and within individuals. For the random effects, we will assume an unstructured correlation matrix. We will adjust for age, sex, race, education, and intracranial volume, and we will conduct sensitivity analysis excluding individuals with clinical depression and stroke. Additionally, we will consider cortical thickness as a sensitivity analysis for selected regions where thickness is measured accurately.

Since this study is meant to be descriptive, we do not think that the analysis's cross-sectional nature will limit the interpretation of the findings. Nonetheless, we will be comparing data from Orlando's (manuscript ##3689) analysis of the 20-year period under sub-aim 1b to understand the quantity of previous cognitive decline equivalent to the diagnosis of mild cognitive impairment in terms of total cortical brain volume difference.

There is a need to be aware of the general limitation that the construct of MCI poses and the current lack of a standardized set of diagnostic criteria.[22] Although the diagnostic criteria and approaches used to operationalize and diagnose MCI within ARIC are well-developed,[20,21] it is important to bear in mind that there is wide-ranging methodological variation in the literature and in research vs. clinical settings in how MCI is defined and diagnosed.[11,18,23-25]

**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)? Enter proposals here**

    - #3689 Alessandro et al. "Population based associations of change in cognitive function with brain changes assessed by multiple imaging modalities"

**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* _ARIC NCS___)**
**___ 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.

References:


1. Anderson N. State of the science on mild cognitive impairment (MCI). *CNS Spectr*. 2019;24(1):78-87. doi:10.1017/s1092852918001347.
2. Corlan AD Medline trend: automated yearly statistics of PubMed results for any query. 2004. http://dan.corlan.net/medline-trend.html. Accessed April, 2021.
3. Fotenos A, Snyder A, Girton L, Morris J, Buckner R. Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology*. 2005;64(6):1032-1039. doi:10.1212/01.wnl.0000154530.72969.11.

4. Tabatabaei-Jafari H, Shaw M, Cherbuin N. Cerebral atrophy in mild cognitive impairment: A systematic review with meta-analysis. *Alzheimers Dement.* 2015;1(4):487-504. doi: 10.1016/j.dadm.2015.11.002
5. Zhang J, Liu Y, Lan K et al. Gray Matter Atrophy in Amnestic Mild Cognitive Impairment: A Voxel-Based Meta-Analysis. *Front Aging Neurosci*. 2021;13:627919. doi:10.3389/fnagi.2021.627919.
6. Zhang H, Sachdev PS, Wen W, et al. Gray matter atrophy patterns of mild cognitive impairment subtypes. *J Neurol Sci*. 2012;315(1-2):26-32. doi:10.1016/j.jns.2011.12.011.
7. Roberts RO, Geda YE, Knopman DS, et al. The incidence of MCI differs by subtype and is higher in men. *Neurology.* 2012; 78(5):342–51. doi: 10.1212/WNL.0b013e3182452862.
8. Machulda M, Lundt E, Albertson S et al. Cortical atrophy patterns of incident MCI subtypes in the Mayo Clinic Study of Aging. *Alzheimers Dement*. 2020;16(7):1013-1022. doi:10.1002/alz.12108.
9. Driscoll I, Davatzikos C, An Y et al. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*. 2009;72(22):1906-1913. doi:10.1212/wnl.0b013e3181a82634.
10. Wu A, Sharrett A, Gottesman R et al. Association of Brain Magnetic Resonance Imaging Signs With Cognitive Outcomes in Persons With Nonimpaired Cognition and Mild Cognitive Impairment. *JAMA Netw Open*. 2019;2(5):e193359. doi:10.1001/jamanetworkopen.2019.3359.
11. Fletcher E, Gavett B, Harvey D, et al. Brain volume change and cognitive trajectories in aging. *Neuropsychology*. 2018;32(4):436-449. doi:10.1037/neu0000447.
12. Schneider A, Senjem M, Wu A et al. Neural correlates of domain-specific cognitive decline. *Neurology*. 2019;92(10):e1051-e1063. doi:10.1212/wnl.0000000000007042.
13. Schneider A, Sharrett A, Patel M et al. Education and Cognitive Change over 15 Years: The Atherosclerosis Risk in Communities Study. *J Am Geriatr Soc*. 2012;60(10):1847-1853. doi:10.1111/j.1532-5415.2012.04164.x.
14. Brown C, Sharrett A, Coresh J et al. Association of hospitalization with long-term cognitive and brain MRI changes in the ARIC cohort. *Neurology*. 2015;84(14):1443-1453. doi:10.1212/wnl.0000000000001439.
15. Schneider A, Jonassaint C, Sharrett A et al. Hemoglobin, Anemia, and Cognitive Function: The Atherosclerosis Risk in Communities Study. *J Gerontol A Biol Sci Med Sci*. 2015;71(6):772-779. doi:10.1093/gerona/glv158.
16. Lipnicki D, Crawford J, Dutta R et al. Age-related cognitive decline and associations with sex, education and apolipoprotein E genotype across ethnocultural groups and geographic regions: a collaborative cohort study. *PLoS Med*. 2017;14(3):e1002261. doi:10.1371/journal.pmed.1002261.
17. Walker K, Power M, Gottesman R. Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review. *Curr Hypertens Rep*. 2017;19(3):24. doi:10.1007/s11906-017-0724-3.
18. Petersen R, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med*. 2014;275(3):214-228. doi:10.1111/joim.12190.

19. D Smith C, J Van Eldik L, A Jicha G et al. Brain structure changes over time in normal and mildly impaired aged persons. *AIMS Neurosci*. 2020;7(2):120-135. doi:10.3934/neuroscience.2020009.
20. Knopman D, Gottesman R, Sharrett A et al. Mild cognitive impairment and dementia prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study. *Alzheimers Dement*. 2016;2(1):1-11. doi:10.1016/j.dadm.2015.12.002.
21. Schneider A, Sharrett A, Gottesman R et al. Normative Data for 8 Neuropsychological Tests in Older Blacks and Whites From the Atherosclerosis Risk in Communities (ARIC) Study. *Alzheimer Dis Assoc Disord*. 2015;29(1):32-44. doi:10.1097/wad.0000000000000042.
22. Petersen R. Mild Cognitive Impairment. *Continuum*. 2016;22(2 Dementia):404-418. doi:10.1212/con.0000000000000313.
23. Anstey K, Maller J. The role of volumetric MRI in understanding mild cognitive impairment and similar classifications. *Aging Ment Health*. 2003;7(4):238-250. doi:10.1080/1360786031000120732.
24. Roberts R, Knopman D. Classification and Epidemiology of MCI. *Clin Geriatr Med*. 2013;29(4):753-772. doi:10.1016/j.cger.2013.07.003.
25. Hansen A, Caselli R, Schlosser-Covell G et al. Neuropsychological comparison of incident MCI and prevalent MCI. *Alzheimers Dement*. 2018;10(1):599-603. doi:10.1016/j.dadm.2018.08.009.