

## ARIC Manuscript Proposal # 3360

PC Reviewed: 2/12/18  
SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Association between cholesterol levels and brain volumes: the ARIC-Neurocognitive (ARIC-NCS) Study

**b. Abbreviated Title (Length 26 characters):** Cholesterol and brain volumes

**2. Writing Group:** Kasra Moazzami, Melinda C. Power, Rebecca Gottesman, Thomas Mosley, Pamela Lutsey, Clifford Jack, Ron Hoogeveen, Nancy West, Alvaro Alonso

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

**First author: Kasra Moazzami**  
Address: 1516 Clifton Rd NE, Room 4053  
Rollins School of Public Health  
Emory University  
Atlanta, GA 30322  
Phone: 857-294-6186  
E-mail: kmoazza@emory.edu

**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).

Name: **Alvaro Alonso**  
Address: 1516 Clifton Rd NE, Room 3051  
Rollins School of Public Health  
Emory University  
Atlanta, GA 30322  
Phone: 404 727 8714  
E-mail: [alvaro.alonso@emory.edu](mailto:alvaro.alonso@emory.edu)

### **3. Timeline:**

Analysis to be started immediately. We expect a manuscript draft to be prepared over the next 6 months.

### **4. Rationale:**

The brain is the most cholesterol-rich organ, containing more than 20% of the whole body's cholesterol.<sup>1</sup> Cholesterol is not only an essential structural component for cellular membrane and

myelin synthesis, but also a required component for synapse formation and axonal guidance.<sup>2</sup> Cholesterol depletion in neurons results in impairments in neuronal activity and neurotransmission, leading to synapse degeneration.<sup>3-5</sup>

Higher levels of cholesterol, particularly low-density lipoprotein (LDL) cholesterol, are a well-established risk factor for developing cardiovascular disease and stroke. However, studies investigating the effect of cholesterol levels on risk of dementia and Alzheimer disease (AD) have yielded inconsistent and conflicting results.<sup>6-13</sup> While some studies suggested an association of high midlife cholesterol concentrations with increased risk of AD,<sup>6,7</sup> or cognitive decline,<sup>13</sup> others have not found such associations.<sup>8-12</sup>

Early alterations in specific regions of the brain structure in cognitively normal adults have shown to precede the clinical picture of AD by 5 to 10 years.<sup>14-18</sup> Diminished brain volumes in brain regions including the parahippocampal, entorhinal, and inferior parietal lobules; hippocampus; precuneus; and cuneus have been identified as early preclinical markers of AD risk.<sup>19,20</sup> However, few studies have investigated the relationship between cholesterol levels and brain volumes.<sup>21-23</sup> Moreover, there is no prior study investigating the association between longitudinal changes in cholesterol levels and early imaging biomarkers of AD.

Therefore we aim to investigate the association between midlife cholesterol levels at ARIC visit 2, as well as changes in cholesterol levels between visit 2 and 5, and total and regional brain volumes at ARIC visit 5.

## **5. Main Hypothesis/Study Questions:**

**Aim.** To investigate the association of blood cholesterol levels (total cholesterol, LDL-C, and high-density lipoprotein (HDL-C)) with total and regional brain volumes, adjusting for sociodemographic information, and cardiovascular risk factors (triglycerides, diabetes, hypertension, heart rate, obesity, smoking, and kidney function), inflammation (CRP), cholesterol lowering medications, and APOE4 status.

**Hypothesis:** We hypothesize that higher LDL levels at visit 2 as well as increases in LDL levels from visit 2 to visit 5 are associated with lower total and regional brain volumes, and that the association is independent of demographics, cardiovascular risk factors, cholesterol lowering medications, and APOE4 status.

## **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 population

We will include all participants who attended ARIC visit 2 and visit 5 and underwent brain Magnetic Resonance Imaging (MRI) scans. We included values in visit 2 since cognitive function testing was done during visit 2 in the ARIC cohort, and comparisons could be made with a previous study of ARIC showing a decline in cognition associated with higher cholesterol levels.<sup>13</sup>

Of these, we will exclude those with incomplete MRI data or poor image quality, those with prior stroke or cardiovascular disease, those with multiple sclerosis, brain tumor, surgery/radiation to the head, as well as those with missing values for cholesterol levels.

### Outcome of interest

The following brain volumes will be used as outcomes in our analysis:

1. Total brain volume
2. Lobar volumes (frontal, parietal, temporal, and occipital)
3. Total volume of deep gray subcortical structures defined as the total volume of the thalamus, caudate, putamen, and globus pallidum
4. Total volume of an Alzheimer disease signature region defined as the total volume of parahippocampal, entorhinal, and inferior parietal lobules; hippocampus; precuneus; and cuneus.

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### Covariates of interest

We will explore the following variables as potential confounders of the association between cholesterol values and brain volumes. Covariate information will come from visit 2, with the exception of static sociodemographic variables which were collected at baseline:

1. Sociodemographic variables: age, sex, race-center, education
2. Cardiovascular risk factors: triglycerides, diabetes, hypertension, heart rate, obesity, smoking, kidney function
4. Inflammation (CRP)
3. Cholesterol lowering medications
4. APOE4 status

### Statistical analysis

Adjusted multivariable linear regression models will be used to assess the associations between cholesterol levels and brain volumes.

We will perform 2 separate analyses:

First, we will explore the association between cholesterol levels at visit 2 and brain volumes.

Second, we will explore the association between changes in cholesterol levels between visit 2 and 5 and brain volumes

Model 1 will be adjusted for sociodemographic factors and total intracranial volume and APOE4 status

Model 2 will include all variables in model 2 in addition to cardiovascular risk factors, inflammation, and cholesterol lowering medications.

All analyses will be weighted to the ARIC visit 5 / NCS sample using weights provided by the Coordinating Center.

In addition, we will also use Inverse probability of attrition weighting in order to predict attrition from visit 2 to visit 5. Attrition due to mortality and other loss to follow-up (censoring) will be modeled separately. Weights will be based on the product of the probability of being alive and of remaining in the study for each individual, for each visit. Models predicting attrition from visit 2 to visit 5 will include: age, sex, race/center, education, hypertension, smoking, and, diabetes.

Among a total of 1968 participants who underwent brain MRI studies at visit 5, 1,860 subjects have cholesterol values at visit 2. This sample size will be adequate to detect any relationship between cholesterol levels and brain volumes.

We will also perform a sensitivity analysis excluding those who were taking lipid lowering medications at visit 2.

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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

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)?

MS3302 Lipids and Amyloid (Bennett/Power). Focus on amyloid deposition.

- MS2201r Lipids and cognitive change (Power). Focus on cognitive decline.
- MS2200r Lipids, statins and dementia (Power). Focus on incident dementia.

None of these manuscripts focus on brain volumes as an endpoint. Dr. Power is included as a coauthor in this proposal

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\* 2008.06 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 at <https://www2.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

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