1.a. Full Title: Associations between carotid plaque characteristics and cognitive function: The ARIC Carotid MRI Study

b. Abbreviated Title (Length 26 characters): Carotid plaque and cognition

2. Writing Group:

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

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3. Timeline:

We plan to analyze the data as soon as approval is obtained, and the manuscript will be prepared as soon as analyses are finished. We plan to conduct analyses and prepare the manuscript for submission within one year.

4. Rationale:
Existing literature has documented varied cross-sectional and longitudinal associations between carotid atherosclerosis and cognitive function and decline. Included in this literature are several informative papers based on ARIC data (Cerhan et al., 1998, *Gerontology*; Knopman et al., 2001, *Neurology*; Knopman et al., 2009, *Alzheimer's & Dementia*). Correlated systemic atherosclerosis and cerebrovascular changes are thought to be the most likely mechanisms.

Most published studies have utilized B-mode ultrasonography to assess carotid wall characteristics. Carotid intimal medial thickness (IMT) is one of the most widely studied measures, but IMT is known to be an imperfect standalone index of atherosclerosis, in that it can be affected by non-atherosclerotic factors such as hypertension and flow turbulence. Further, when ultrasound studies incorporate carotid plaque assessment, they have typically relied on gross indices such as presence/absence, or in some cases, plaque height. Assessment of carotid atherosclerosis via MRI technology provides more comprehensive information about plaque characteristics, such as presence of a lipid rich core, fibrous cap characteristics, and intraplaque hemorrhage (Virani et al., 2011, *Atherosclerosis*; Volcik et al., 2010, *Atherosclerosis*; Wasserman et al., 2010, *J Magn Reson Imaging*). The ARIC Carotid MRI ancillary study thus represents a unique opportunity to understand the association between more detailed carotid wall characteristics and concurrent cognitive function. To our knowledge, no study to date has examined the association between MRI-assessed carotid atherosclerosis and cognition.

There is no clear consensus regarding which cognitive domains of function are most correlated with carotid atherosclerosis. Most studies have utilized only gross cognitive screening measures. Of the studies that have included neuropsychological tests, some find associations between carotid atherosclerosis and attention/executive function, which is consistent with the current conceptualization of vascular cognitive impairment. However, other studies have identified stronger associations with memory function, which is consistent with recent literature that suggests a role of vascular risk factors in the development of Alzheimer’s disease. Either way, the three cognitive tests administered in the ARIC Carotid MRI sub-study, which assess memory, verbal fluency/executive function, and speed/executive function, are well poised to investigate whether associations between carotid wall characteristics, if present, differ across these aforementioned cognitive domains.

The proposed study carries the potential to improve our understanding substantially of the association between carotid atherosclerosis and cognitive function. Better characterizing cardiovascular risk for brain-related outcomes is critical for future public health efforts to delay onset of cognitive decline and dementia, both of which represent important threats to our aging population.

### 5. Main Hypothesis/Study Questions:

1. Are MRI-assessed carotid wall characteristics associated with concurrent reductions in cognitive performance?

2. Do different patterns of association arise across different cognitive domains? Specifically, we hypothesize that carotid wall and plaque characteristics carry the
strongest relationships with the Digit Symbol Substitution Test (DSST), which tests executive function (a domain that is often involved in vascular cognitive impairment).

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).

The planned study is cross-sectional and correlational in design. In the Carotid MRI ancillary study, carotid MRIs were performed on 2,066 participants in 2004-2006 using a stratified sampling plan. Approximately 1200 of these participants had carotid artery intima media thickness (CIMT) ≥68th percentile, as previously measured by B-mode ultrasound on visit 3 or 4. The CIMT cutoffs varied slightly across field centers and were 1.35, 1.00, 1.28, and 1.22 millimeters at Forsyth County, Jackson, Minneapolis, and Washington County, respectively. These values correspond to the 73rd, 69th, 73rd, and 68th percentiles of maximal CIMT, respectively. A random sample of approximately 800 participants with CIMT <68th percentile was also studied. The carotid MRI procedure included measurements of multiple plaque characteristics (listed below under variables of interest) using gadolinium-enhanced 1.5T MRI on the thicker internal carotid artery. Three cognitive tests were administered at the same visit. The Delayed Word Recall Test (DWRT) assesses verbal learning and memory. The Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale-Revised assesses processing speed and executive function. Lastly, the Word Fluency Test (WFT), also known as the Controlled Oral Word Association from the Multilingual Aphasia Examination, assesses verbal fluency. Covariates will be evaluated from the Carotid MRI ancillary study visit.

Inclusion/Exclusion:

Inclusion: ARIC Carotid MRI cohort participants with available carotid MRI and cognitive testing data.

Exclusions: Participants with conditions that could affect cognitive performance including stroke, dementia, multiple sclerosis, Parkinson’s disease, epilepsy, brain tumor, brain surgery, head radiation, and other neurologic disorders. Participants taking medications that may impact cognitive performance, including neuroleptics and benzodiazepines.

Variables of interest:

Carotid wall thickness:
Total wall volume (GDSICA_TOTALWALLVOLUME3ADJ)
Maximum wall thickness (GDSICA_MAXWALLTHICK_MAXCORE2)
Lumen area (LUMENAREA_MAXMEANWALL1)
Vessel wall area (VESSELWALLAREA_MAXMEANWALL1)
Normalized wall index (NWI: wall area/total vessel wall area) = 
(VESELWALLAREA_MAXMEANWALL1 / TOTALVESSELAREA_MAXMEANWALL1)

Lipid core:
Total lipid core volume (GDSICA_TOTALLIPIDCOREVOLUME2_NEW2)
Mean lipid core area (GDSICA_MEANLIPIDCOREAREA_NEW2)
Maximum lipid core area (GDSICA_MAXLIPIDCOREAREA_NEW2)
Lipid core, present/absent (LIPID_CORE)
Lipid core present in two adjacent slices (CORE_IN_2)

Fibrous cap thickness:
Mean cap thickness (MEAN_CAP_THICKNESS_2ADJACENT1)
Mean minimum cap thickness (MEAN_MIN_CAP_THICKNESS_2ADJACENT1)

Other plaque characteristics:
Intra-plaque hemorrhage (IPQHEM)
Maximum calcium area (GDSICA_MAXCALCIUMAREA)

Cognitive function:
Delayed word recall score (DWRT)
Word fluency test score (WFT)
Digit Symbol Substitution Test score (DSST)

Data analysis plan:
All statistical analyses will be weighted to account for the stratified random sampling design of the ARIC Carotid MRI sub-study. Following inspection of the data for outliers and assumption violations, individual multiple linear regression analyses will be used to examine the association between each plaque characteristic and each continuous cognitive outcome variable. Covariates will include age, sex, race-center, education, systolic blood pressure, total cholesterol, body mass index, smoking status, alcohol intake, antihypertensive medication use, lipid-lowering medication use, depressive symptoms, history of diabetes, history of coronary heart disease, history of heart failure. Lipid core characteristics will be additionally adjusted for wall thickness.

Anticipated methodologic limitations:
A primary methodologic limitation is its cross-sectional design, which cannot be used to draw causal conclusions. In addition, due to resolution constraints of the carotid MRI scan, analyses examining lipid core measurements will need to be limited to only those participants with maximum wall thickness ≥1.5 mm.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes ___X__ 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  ___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.cscce.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)?


   MS# 1339: Ballantyne, Virani, Nambi, Boerwinkle, Wasserman, Sharrett, Heiss, Folsom, Chambless. Does carotid intima-media thickness (CIMT)/plaque characteristics on carotid ultrasound predict the presence of high-risk plaques on carotid MRI in ARIC cohort.


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* _Carotid MRI study_)  

____  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 [http://www.cscc.unc.edu/aric/forms/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.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.