ARIC Manuscript Proposal #3547

PC Reviewed: 1/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Carotid Intima-Media Thickness with Brain MRI Markers in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

b. Abbreviated Title (Length 26 characters): **cIMT and brain MRI markers**

2. Writing Group: Wendy Wang; Faye L. Norby; Alvaro Alonso; Rebecca F. Gottesman; Michelle L. Meyer; David S. Knopman; Kevin Sullivan; Pamela L. Lutsey

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

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3. Timeline:
Data analysis to begin immediately; pen draft expected spring/summer 2020.

4. Rationale:
Elevated carotid intima-media thickness (cIMT) is a marker for carotid atherosclerosis and can be quantified through a noninvasive ultrasound procedure.[1] Carotid atherosclerosis may

reduce cerebral blood flow[2] and be a source of microemboli, which could contribute to white matter hyperintensities (WMH) and silent brain infarcts, and ultimately lead to brain atrophy.[3] Thus, elevated cIMT levels may be associated with various brain MRI markers of dementia, such as silent brain infarcts, increased WMH, decreased gray matter volume, and cerebral microhemorrhages, but its prospective association is not well known.

Silent brain infarcts and white matter lesions have been found to be associated with an increased risk of stroke[4,5] and dementia.[6] In the Framingham Offspring study, elevated IMT of the common carotid artery was associated with a higher prevalence of silent brain infarcts and lower brain volume, though these associations were no longer significant in the fully adjusted model.[7] A study in Japan reported no significant association between increased cIMT (defined as $\geq$ 1.0mm) and silent brain infarcts.[8] In ARIC, elevated cIMT was cross-sectionally associated with silent brain infarcts in African Americans but not in whites.[9] WMH in the brain is also associated with an increased risk of stroke[5] and are prevalent among those with cognitive impairment[10] and dementia.[6,11] In the Northern Manhattan study, a significant association between cIMT and brain WMH, particularly in the elderly (>70 years old), was noted independent of hypertension and other vascular factors.[12] However, in the CARDIA study, no association between cIMT and either gray matter or WMH was found, though greater cIMT was cross-sectionally associated with lower cerebral blood flow in gray matter, but this association attenuated after adjusting for cardiovascular risk factors.[13] The presence of cerebral microbleeds has also been associated with an increased risk of stroke,[14,15] mortality,[15,16] cognitive impairment,[15,17,18] and dementia.[15,18] A study in Taiwan found that increased cIMT is cross-sectionally associated with cerebral microbleeds independent of demographics and cardiovascular risk factors among community-dwelling adults over 50 years old,[19] while the Framingham Offspring study found no significant association between cIMT and cerebral microbleeds.[20]

Prior studies have shown that the association between cIMT and brain MRI markers for dementia may potentially exist. However, as these studies have often been cross-sectional and produced varying results, we propose to investigate the prospective relationship between cIMT and brain MRI markers.

5. Main Hypothesis/Study Questions:

Aim: to determine the association between cIMT and brain MRI markers of vascular dementia (white matter hyperintensities volume, number of infarcts, cerebral microhemorrhages) and Alzheimer's disease (gray matter volume, Alzheimer's signature region).

We hypothesize that those with an increased cIMT thickness or carotid plaque present will have more infarcts and cerebral microhemorrhages, greater white matter hyperintensities volume, lower gray matter volume, and lower Alzheimer's signature region volume.

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:
Visit 2 will serve as the baseline. Prospective cohort from V2 to V5.

Inclusion/Exclusion:
Participants with missing cIMT data or prevalent dementia, stroke, heart failure, or coronary heart disease at visit 2 will be excluded. Those whose race was other than black or white will be excluded, as well as blacks from the MN and MD centers. We will also exclude those with missing covariates.

Variables

Exposures:

1. cIMT will be measured using the 6-site imputed IMT variable and will be represented in several ways: as a continuous variable, in quintiles, and according to the ESC/ESH cut point for abnormal (cIMT>0.9mm)[21]
2. Carotid plaque (present or absent)
3. Interadventitial diameter as a continuous variable and in quintiles

Primary outcome: We will look at the following brain MRI measures at visit 5

1. White matter hyperintensities volume
2. Number of lacunar infarcts
3. Cerebral microhemorrhages
4. Gray matter volume
5. AD signature region volume

Possible effect modifiers or mediators: age, sex, race, APOE ε4

Other confounders/covariates: age, sex, race/center, education, APOE ε4, BMI, systolic blood pressure, antihypertensive medication, smoking status, pack-years, diabetes, total intracranial volume

Statistical analysis

- Baseline characteristics will be described using mean ± SD for continuous variables and proportions for categorical variables, stratified by cIMT quintiles.
- Logistic regression will be used to model infarcts and cerebral microhemorrhages.
- Linear regression will be used to model white matter hyperintensities, gray matter, and Alzheimer's signature region volumes.
- For all analyses, the following models will be used:
    - Model 1 will be adjusted for age, sex, race/center, education, APOE ε4, total intracranial volume (for volume measurements)
    - Model 2 will be adjusted for model 1 plus BMI, systolic blood pressure, smoking status, pack-years of smoking, antihypertensive medications, and diabetes

- Interactions by age, sex, race, and APOE ε4 will be analyzed by including a cross-product term in the model.
- Inverse probability weighting will be used to account for attrition due to death, visit non-attendance, and selection into brain MRI study.

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.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)?

#2816: carotid IMT and SBI (Caughey)

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* __2008.06 (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.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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