

ARIC Manuscript Proposal #3363

PC Reviewed: 5/14/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Association of Carotid Intima-Media Thickness, Plaque, and Distensibility with Incident Dementia in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

b. Abbreviated Title (Length 26 characters): cIMT and plaque with dementia

2. Writing Group: Wendy Wang, Faye Norby, Kristen George, Alvaro Alonso, Tom Mosley, Rebecca Gottesman, Michelle L Meyer, Pamela Lutsey, others welcome

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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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).

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3. Timeline:

Data analysis to begin immediately; pen draft expected summer 2019.

4. Rationale:

Dementia is a neurocognitive disorder that is characterized by difficulties with memory, language, and other cognitive skills that can affect a person's activities of daily living. This decline in cognitive function occurs when neurons in parts of the brain are damaged or destroyed. Dementia generally occurs in late-life, but changes in the brain can begin years before the onset of symptoms. With people generally living longer, the prevalence of dementia cases will continue to rise.¹ Therefore, identifying markers for dementia, particularly in midlife, continues to be of importance.

Carotid intima-media thickness (cIMT), plaque, and carotid distensibility are markers for carotid atherosclerosis and can be quantified through a noninvasive ultrasound procedure.² Elevated cIMT, plaque, and carotid distensibility have all been established as predictors for cardiovascular disease.^{3,4} However, there is evidence of plaque being present even when cIMT is not elevated, and evidence suggests that a combination of cIMT and presence of plaque may provide a better assessment of cardiovascular disease.^{3,5} Carotid atherosclerosis can often be asymptomatic,⁶ and may be useful as a screening tool.

Studies analyzing the relationship between carotid stiffness and dementia are scarce.⁷ Carotid distensibility, a stiffness parameter, has previously been shown to have no association with dementia risk.⁸ However, more recently, the Maastricht study found a link between carotid distension and cognitive performance.⁷ Alternatively, there have been more studies linking plaque and elevated cIMT with risk of dementia. Prior studies have suggested that cIMT must reach a specific thickness before an association with dementia is evident.⁹ In the Baltimore Longitudinal Study of Aging and the Rotterdam study, the highest quintile of cIMT was associated with dementia,^{9,10} while the highest quartile of cIMT showed this association in the Cardiovascular Health Study.¹¹ Additionally, a French multi-site study, which aimed to differentiate plaque and cIMT measurements, found an association between plaque and incident dementia. However, no association was noted with cIMT measured in plaque-free sites.¹²

There are several pathways through which plaques and cIMT may lead to dementia. First, plaque or elevated cIMT can disrupt or reduce cerebral blood flow, which may lead to silent brain infarctions,⁶ a precursor to cognitive decline¹³ and/or could rupture.¹⁴ Secondly, if part of an unstable carotid plaque embolizes, it can cause a stroke and may ultimately lead to dementia.^{15,16} Elevated cIMT levels have also been associated with silent brain infarctions in African Americans,¹⁷ suggesting this link with dementia may also exist with cIMT. Lastly, several risk factors for carotid atherosclerosis, such as hypertension, smoking, and diabetes have also been associated with both an increased level of brain amyloid¹⁸ and incident dementia.¹⁹

5. Main Hypothesis/Study Questions:

Aim: to determine the association of cIMT, carotid plaque, and carotid distensibility with incident dementia.

We hypothesize that participants with higher cIMT thickness, presence of carotid plaque, and lower carotid distensibility will be at an increased risk for dementia.

We will also evaluate whether cIMT and carotid plaque are jointly associated with dementia risk.

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 served as the baseline. Prospective cohort from V2 to V6.

Inclusion/Exclusion:

We will exclude participants who at baseline had prevalent dementia, heart failure, CHD, or stroke. Additionally, those with missing cIMT or carotid plaque data will be excluded. Those whose race was other than black or white will be excluded, as well blacks from the MN and MD centers. We will also exclude those missing covariates.

Variables

Exposures:

1. Two variables for carotid artery measurements will be used:
 - a. cIMT thickness 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)²⁰
 - b. Interadventitial diameter (IAD) as a continuous variable and in quintiles
2. Carotid plaque (present or absent)
3. We will also evaluate cIMT and carotid plaque jointly, using the ESC/ESH cut point for abnormal (yes/no) and carotid plaque (present or absent).
4. Carotid distensibility will be modeled as a continuous variable and in quintiles.

Primary outcomes: Dementia and mild cognitive impairment (MCI) outcomes will be defined using the three-level definition as previously identified in ARIC.²¹

- Level 1 includes adjudicated outcomes from visits 5 and 6 NCS evaluations including evidence of cognitive decline based on assessments from earlier visits.
- Level 2 includes cases identified in level 1, as well as participants who did not attend NCS visits, but had their cognitive status evaluated through a validated phone-based cognitive assessment interview.
- Level 3 includes cases identified in level 1 and 2, as well as participants only identified through surveillance for hospitalization discharge codes (ICD-9) or death certificate codes related to dementia.

Separate analyses will be run using two definitions of dementia and MCI outcomes:

1. All incident dementia cases available in ARIC (level 3 cases)
2. From visit 5 only, adjudicated etiologic events: dementia or MCI due to Alzheimer's disease (AD) (as primary diagnosis) or cerebrovascular disease (as primary or secondary diagnosis) (level 1 cases)

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

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

Statistical analysis

- Baseline characteristics will be described using mean ± SD for continuous variables and proportions for categorical variables, stratified by cIMT thickness.
- Dementia incidence will be calculated, stratified by cIMT thickness, presence of plaque, and carotid distensibility.
- Cox proportional hazards will be used to assess the relationships of cIMT thickness, carotid plaque, and carotid distensibility with incident dementia (level 3 cases).
- Relative risk regression will be used to assess the association between cIMT thickness, plaque, and carotid distensibility with adjudicated dementia and MCI cases due to AD (as primary diagnosis) or cerebrovascular disease (as primary or secondary diagnosis) (level 1 cases; visit 5 only). Inverse probability weighting to account for censoring caused by death or failure to attend visit 5.
- Interactions by race, sex, hypertension, diabetes, and APOE ε4 will be analyzed.
- For all analyses, the following models will be used:
 - Model 1 will be adjusted for age, sex, race/center, education, APOE ε4
 - Model 2 will be adjusted for model 1 plus BMI, systolic blood pressure, antihypertensive medications, smoking status, pack-years of smoking, diabetes
- Restricted cubic splines will also be used to evaluate the associations with dementia.
- Secondary analysis will be run looking at the associations with and without those who developed a stroke.

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.csc.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)?

#2103: carotid plaque and cognition (Wendell)

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 (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 shows you which journals automatically upload articles to PubMed central.

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