ARIC Manuscript Proposal #3809

PC Reviewed: 4/13/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

The Vascular Contribution to Volume Loss and Cognitive Decline

b. Abbreviated Title (Length 26 characters):

Vascular risk to Dementia

2. Writing Group:
Writing group members:

Bruce Wasserman, Ye Qiao, Eliseo Guallar, Li Liu, Di Zhao, Rebecca Gottesman, Dave Knopman, Tom Mosley. Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. B.W. **[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:
The manuscript will be complete within 12 months upon the approval of this proposal.

4. Rationale:

Dementia is highly prevalent in the US and is responsible for an economic burden exceeding that of heart disease and cancer combined[1]. Alzheimer's Disease (AD) is the most common type of dementia diagnosed clinically and there is increasing evidence that intracranial atherosclerotic disease (ICAD) may be an important contributor to its pathobiologic origin[2], supported by proteome-wide associations[3]. Mechanisms linking these pathologies are complex and continue to be studied. For example, the accumulation of amyloid β (Aβ) peptide, which is characteristic of AD, can occur as a byproduct of foam cell formation[4] or cerebral hypoperfusion[5, 6], and conversely, Aβ may cause endothelial toxicity and ICAD formation[7]. Rates of hippocampal atrophy have been shown to relate to cognitive decline[8, 9] and there is evidence suggesting ICAD may promote this volume loss in cognitively impaired individuals[10, 11]. Cerebral small vessel diseases (SVD) such as arteriolosclerosis and cerebral amyloid angiopathy also cause impaired flow associated with cognitive decline and must be considered to isolate the contribution of ICAD especially given their shared risk factors [12, 13]. Cross-sectional associations of ICAD with MCI and dementia have been reported in ARIC at V5[14], but whether ICAD is causal or a consequence of cognitive decline continues to be debated due to a relative lack of longitudinal data.

The present lack of an effective treatment for AD as well as potential toxicities of those treatments under investigation highlights the importance of identifying biomarkers that can predict those at risk. The longitudinal cognitive evaluations and brain MRI/MRA studies in ARIC offer unique insight into the neurovascular contribution to AD. We propose this investigation of the relation between vascular risk factors, ICAD and its progression, and SVD, with measures of cognitive change between V5 and V6/7. Large infarcts are uncommon causes of dementia and not our primary analytic focus.

5. Main Hypothesis/Study Questions:

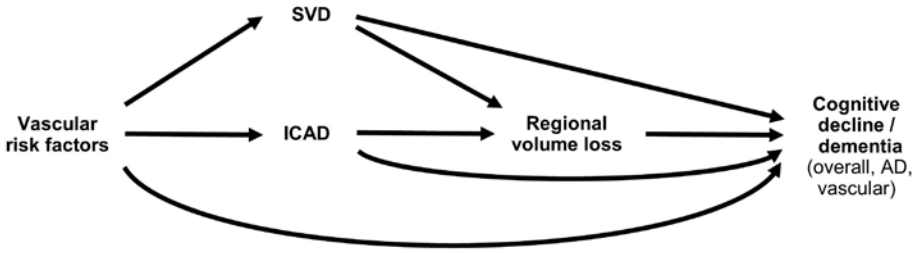
1. Establish if ICAD measures are independently associated with the development of cognitive outcomes. We will determine the contribution of three classes of predictors: ICAD measures, vascular risk factors, and SVD. For ICAD measures, we will (a) establish a risk index based on ICAD measures at baseline (Visit 5), and (b) analyze the incremental value of ICAD progression from Visit 5 to 6/7 adjusting for baseline ICAD size. We will assess the relative contribution of SVD to cognitive outcomes by considering WMH lacunes and microhemorrhages. Sub-aim: To identify which ICAD features, based on geographic distribution, global plaque burden, and global stenosis score, best predict cognitive outcomes.

   Hypothesis: We hypothesize that cognitive impairment will be identified more frequently in participants with baseline ICAD and the effect will be potentiated by ICAD progression even after adjusting for vascular risk factors and SVD burden.

2. To determine the importance of baseline (Visit 5) ICAD in accelerating regional volume loss and its relation with subsequent cognitive impairment (by Visit 6/7). Specifically, we will determine if regional volume loss from the baseline to the follow up scan is predicted by ICAD presence at the corresponding vascular territory at baseline accounting for change in SVD. We will test whether ICAD influences the associations between regional brain volume loss and cognitive outcomes, addressing whether ICAD with corresponding brain volume loss more strongly predicts accelerated cognitive impairment compared to volume loss alone.

Subaim: We will test whether regional volume loss, known to predict accelerated cognitive impairment, relates to ICAD. We will also explore the relative impact of global measures of SVD (i.e., total WMH, microhemorrhage, and lacunes) versus local ICAD on accelerated volume loss.

Hypothesis: We hypothesize that interval regional volume loss partially mediates the association of ICAD with accelerated cognitive impairment. This association will be independent from SVD.



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).

We will use MRI exams from 2,000 ARIC participants acquired at Visit 5 for baseline measures of ICAD, regional brain volumes, and SVD (WMH, lacunes and microhemorrhage burden). ICAD measures will be derived from both imaging of the lumen (time-of-flight MRA) and of the vessel wall (3D high-resolution vessel wall imaging [VWI]) and will include both qualitative (plaque presence, stenosis category, etc) and quantitative (wall thickness and volume per standard segments and of plaques) assessments. ICAD progression is available on 705 participants who had a follow up MRI exam at Visits 6 and 7.

Brain measures will include volumes, cortical thickness, WMH, lacunes, and microhemorrhages. We will analyze both global and regional measures, in particular the 'temporal lobe volume/thickness meta ROI' which includes the entorhinal cortex, fusiform gyri, inferior temporal lobe, middle temporal lobe, hippocampus, and amygdala. Volume measurements will be adjusted for head size. To compare WMH measured at V5 using 2D FLAIR with WMH measured at V6/7 using 3D FLAIR, a subset of participants (approximately 160) had both sequences acquired in their MRI exams. A linear regression model of this subset will be used to convert 3D WMH to 2D WMH for total brain and temporal lobe measurements and account for differences in sensitivity between methods.

Cognitive outcomes will include V6 dementia, V6 dementia+MCI, V6 MCI separately, and V6 global cognition factor scores for global cognitive change over time. From these measures we will construct a V6 minus V5 global cognitive factor score difference. We will also test derived factor scores for the cognitive domains. We will also perform a subanalysis stratified by dementia etiology subtypes, specifically AD and VAD considering the larger sample sizes for these categories.

In a subanalysis we will stratify by apoE4 allele carrier status and test interactions between groups.

Exposure of interest will be traditional cardiovascular risk factors measured over 20 years including age, sex, race, BMI, smoking, alcohol consumption, physical activity, total cholesterol, LDL and HDL cholesterol, triglycerides, metabolic syndrome, fasting glucose/diabetes, blood pressure/hypertension, history of cardiovascular event, use of antiplatelet drugs, use of statin and use of antihypertensive medications.

Statistical analysis
We will follow the statistical recommendations detailed in Manual 30_200207.

Aim 1: Since identification of incident MCI and dementia will be interval-censored, we will use survival analyses with a parametric proportional hazards model[15, 16] that accounts for interval censoring to estimate hazard ratios (with 95% confidence intervals) for incident MCI and dementia associated with baseline exposures (e.g., ICAD, SVD). Furthermore, since participants will be subject to substantial competing risks by mortality, we will apply a parametric version of the model of Fine and Gray to account for competing risks[17-19]. In these analyses, the primary endpoint will be the combined incidence of MCI or dementia. We will also perform additional analyses with MCI and dementia as separate secondary endpoints. In addition to the survival analyses, we will assess the association between ICAD progression (from Visit 5 to Visit 6/7) and the risk of MCI or dementia at Visit 6/7 using ordered logistic regression. In this analysis, we will also asses the incremental value of ICAD progression beyond ICAD at visit 5 for predicting these outcomes. Finally, in addition to evaluating MCI and dementia as clinical outcomes, we will also analyze the association of ICAD with quantitative measures of cognitive decline (e.g., global cognitive factor scores) using linear mixed models with random intercepts.

For the primary analysis in this aim we will establish a ***risk index*** based on Visit 5 ICAD measures that were associated with MCI or dementia in cross-sectional analyses (see Preliminary Studies, C.8) and test its ability to predict future cognitive outcomes. In order to investigate the relative contribution of location, burden and hemodynamic impact of ICAD to cognitive outcomes, we will analyze ICAD features separately, including a global (per participant) measure of (1) ICAD distribution (plaque segment location, territories involved weighted to number of plaques per territory), (2) size (mean wall thickness, mean and total volumes, NWI) and total plaque number, and (3) stenosis (%stenosis, presence of plaques >50% or >70% stenosis). Combinations of these features (e.g., territory and stenosis scores) will also be explored. For each analysis, we will build 4 models with covariates added sequentially (**Table 1**), first adjusting for socio-demographic factors, then vascular risk factors, and finally SVD measures (WMH, microhemorrhages, and lacunes). In all analyses, we will systematically evaluate interactions of ICAD measures with age, sex, race, and SVD groups using product terms in the regression models.

Table 1: Adjustment models

Model	Adjustments
1	Unadjusted
2	Model 1 + Age, sex, race-center, education
3	Model 2 + systolic blood pressure, total cholesterol, diabetes, use of antihypertensive medication, use of lipid-lowering medication, prevalent CHD, prevalent stroke, cortical infracts, and APOE ε4 allele genotype
4	Model 3 + WMH volume, lacunar infarct frequency

We will use multiple imputation by chained equations (MICE) to impute missing data in order to avoid underestimating cognitive decline over time.

Aim 2: We will determine the association between the presence of ICAD at Visit 5 and brain volume loss from Visit 5 to Visits 6/7, overall and by segmented brain region. Based on the MRA, intracranial plaques will be assigned primary and secondary locations that indicate proximity to each brain region (i.e., immediate contact versus further upstream from the brain region, respectively). We will estimate the average difference in volume loss (total and for each brain region) comparing participants with and without ICAD (anywhere and at locations corresponding to each brain region) at Visit 5 using linear mixed models with random intercepts. For regional analyses, the primary plaque locations will be used, but we will determine the incremental value of combining primary with secondary plaque locations. The strategy of adjustment and subgroup analyses will be similar to those in Aim 1, although regional WMH and lacunes will be used. As part of this aim, we will also test whether ICAD influences the associations between volume loss (i.e., hippocampus) and cognitive outcomes, addressing whether interval volume loss mediates the association of ICAD with accelerated cognitive impairment.

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/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)?

No prior manuscript proposals have characterized vessels on brain MRI exams or assessed structural changes on brain MRI related to cognitive change in ARIC.

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* 2015.32, 2009.27**)**

___ 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/

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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