

ARIC Manuscript Proposal #2673

PC Reviewed: 11/10/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Intracranial atherosclerosis and cognitive function and impairment across domains

b. Abbreviated Title (Length 26 characters):

Intracranial atherosclerosis and cognitive function

2. Writing Group:

Writing group members: Jennifer L. Dearborn, Bruce Wasserman, Ye Qiao, Rebecca F. Gottesman, Tom Mosley, Alvaro Alonso, Andrea Rawlings, A. Fareed Suri, David Knopman, Eliseo Guallar, Yiyi Zhang, Li Liu

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __JD__

First author: Jennifer Dearborn, MD MPH

Address: 15 York Street, LCI 1001
New Haven, CT
Phone (203) 737-1057
jennifer.dearborn @yale.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: Bruce Wasserman
Address: 600 N. Wolfe St., Park 367A
Baltimore, MD 21287
Phone (410) 614-6626
bwasser@jhmi.edu

3. Timeline: Analyses to begin as soon as manuscript proposal is approved.
Goal for completion within calendar year.

4. Rationale:

Dementia and cognitive decline affect millions of U.S. adults annually. The economic burden of dementia exceeds that of heart disease and cancer combined.¹ There is increasing recognition that vascular risk factors significantly contribute to dementia, and distinguishing vascular dementia and Alzheimer's disease (AD) is challenging as they often coexist.²

Furthermore, intracranial atherosclerotic disease (ICAD) and dementia share the same risk

factors, such as diabetes and hypertension.^{2,3} ICAD is highly prevalent in older U.S. adults,⁴ especially in blacks⁵⁻⁷ and is well recognized as an important cause of stroke worldwide. Increasing evidence supports its role in causing progressive dementia as well.⁸

ICAD is thought to influence the development of cognitive impairment by two potential mechanisms: 1) it may predispose to cerebral hypoperfusion and 2) it is associated with impaired blood brain barrier from endothelial dysfunction.¹² For example, the Rotterdam study found associations with calcification volume of the intracranial arteries on CT angiography with dementia and cognitive decline.¹³ Another study demonstrated that participants with ICAD causing luminal narrowing >50% had a faster decline from mild cognitive impairment to dementia.¹⁴ Several studies have demonstrated that extracranial carotid atherosclerosis is associated with cognitive decline.⁹⁻¹¹ Quantitative studies, with detailed neuroimaging such as in the proposed analysis are needed to better characterize the role of ICAD in cognitive impairment.²

ARIC is well suited for investigating the relation between ICAD and cognitive impairment. For example, the above-referenced studies used measures such as CT angiography to identify ICAD, but stenosis will often underestimate disease prevalence.¹⁵ In ARIC, up to 11.3% of participants studied at visit 5 had non-stenotic ICAD. Furthermore, investigations of ICAD and cognitive impairment have relied on patients with cerebrovascular ischemia and do not offer insight into the role of ICAD in a predominantly asymptomatic population as we have in ARIC, which is more relevant to the US population. This is an important distinction because recent stroke is a confounder, as stroke may affect cognitive function.

High-resolution black blood MRI (BBMRI) has emerged as a reliable technique for identifying an intracranial atherosclerotic lesion and characterizing its size and morphology.¹⁶ In particular, three-dimensional BBMRI, as was acquired in ARIC NCS, can achieve excellent resolution and mapping of the geometry of the vessel wall over the curved course of intracranial vessels.^{17, 18} This technique can simultaneously capture all ICAD lesions within the intracranial circulation of each participant.¹⁶

5. Main Hypothesis/Study Questions:

1. ICAD presence and size will be associated with poor cognitive function with adjustments for age, education, sex, smoking status, alcohol use and physical activity score. Domain specific cognitive function will be evaluated. Adjustments for risk factors known to influence both ICAD

and poor cognitive function, such as hypertension, diabetes, cholesterol and history of stroke or prevalent heart disease will attenuate the above associations.

2. ICAD will be associated with dementia and mild cognitive impairment after adjustments. The outcome will be the adjudicated values based on visit 5 neurocognitive testing.

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 methodological limitations or challenges if present).

Study Design: Primary analysis will be cross-sectional with intracranial vascular MRI and cognitive testing performed in Visit 5. Covariates will include visit 1 risk factors (hypertension, diabetes, etc.) to approximate midlife contribution to ICAD/dementia. We will adjust for midlife vascular risk factors in models of ICAD leading to cognitive impairment and dementia.

Inclusion: All ARIC participants with a completed vascular MRI exam and cognitive evaluation at visit 5.

Exclusion: Missing intracranial vascular MRI data; Missing covariates, outlying dementia scores

Data Analysis:

Hypothesis 1: Logistic regression;

Independent variables, predicting poor cognitive function (bottom quintile) will be:

ICAD index (ordinal scale and any/no presence of ICAD used in separate models). The index will represent a participant-specific global measure of ICAD burden and will be comprised of the following variables:

1. Plaque presence
2. Plaque size: Max thickness, Volume over fixed segment, Total volume over segment
3. Number of segments involved
4. Number of plaques per participant

Cognitive outcome will be defined by: 1) a summary “z-score” and 2) a domain specific score defined below.

Linear regression; the independent variables (ICAD ordinal scale, any/no presence) predicting cognitive test score (outcome). Weighting will account for probabilistic sampling plan in the ARIC-Neurocognitive Study. Sampling weights will be derived as the product of inverse sampling fractions and the inverse probability of completing the examination to account for

dropout and missing values. All models incorporated these probability sampling weights will represent the full ARIC visit 5 cohort.

A second model will be created for hypothesis 1 & 2 with the adjustments below. We will test for effect modification (interaction) by age, sex and race.

Hypothesis 2: Logistic regression; dementia, mild cognitive impairment, or either will be used in

| Model | Adjustments |
|-------|--|
| 1 | Unadjusted |
| 2 | Model 1 + Age, sex, alcohol use, history of smoking, education, race-center |
| 3 | Model 2 + diabetes, hypertension, total cholesterol, history of MI, history of stroke, prevalent CHD |
| 4 | Model 3 + APOE E genotype |

separate models. Predictors will be the same as in Hypothesis 1.

ICAD index definition:

Any atherosclerosis and no atherosclerosis have been categorized. We will also develop an ICAD index as described above.²⁰

Covariates of interest: Other variables that may influence ICAD will be included in the models and will include: age, race/center (combined variable), sex, education, composite physical activity variable, hypertension, diabetes, history of coronary artery disease, history of smoking, total caloric intake, and body-mass index. Statin medications is another important covariate as will APOE E genotype.

Outcome: 8 neuropsychological tests have been performed (Delayed Word Recall Test, Logical Memory Parts I and II, the Word Fluency Test, Animal Naming, the Trail Making Test Parts A and B and the Digit Symbol Substitution Test).²¹ Cognitive domains will include the following as has been previously described: memory (delayed word recall test, Logical Memory immediate and delayed recall, and incidental Learning from the Wechsler Memory Scale-III), psychomotor speed/executive function (PS/EF; digit symbol substitution test, trail making test parts A and B, and WAIS-R digit span backwards), and language (letter fluency, Boston Naming Test, and Animal Naming).²² We will also construct Z-scores for each domain by averaging the test scores within a domain, subtracting the domain mean and dividing by the domain SD. A global composite Z-score will be derived from the 3 domain scores.²²

Dementia and mild cognitive impairment (MCI) were adjudicated by committee members, and these verified outcomes will be used.

Limitations: There are several study limitations. First, this study is cross-sectional and therefore we cannot prove causality of ICAD with cognitive function and/or dementia. Second, motion artifact has affected the quality of MRI for some subjects. Finally, there is a selection bias for those who undergo an intracranial MRA since participants who survived to visit 5 are less likely to have extremes of disease burden. Multiple attempts to adjust for participant dropout will be used in this analysis as sensitivity analyses.

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? __X__ Yes ____ No
(This file ICTDER03 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? __X__ Yes ____ No
We will use ApoE genotype data and FTO genotype data

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”? ____X__ Yes ____ No

8. c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?
____ Yes ____X__ 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/search.php>

__X__ Yes ____ No

Some overlap noted with intracranial stenosis MP with primary author M. Fareed K. Suri, however he is included on this MP

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)?

Wasserman BA, Astor BC, Sharrett AR, Swingen C, Catellier D. MRI measurements of carotid plaque in the atherosclerosis risk in communities (ARIC) study: Methods, reliability and descriptive statistics. *Journal of Magnetic Resonance Imaging* 2010;31:406-415.

Gottesman RF, Rawlings AM, Sharrett AR, Albert M, Alonso A, Bandeen-Roche K, Coker LH, Coresh J, Couper DJ, Griswold ME, Heiss G, Knopman DS, Patel MD, Penman AD, Power MC, Selnes OA, Schneider AL, Wagenknecht LE, Windham BG, Wruck LM, Mosley TH. Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC neurocognitive study. *Am J Epidemiol.* 2014 Apr 15;179(8):956-66. doi: 10.1093/aje/kwu020.
Schneider ALC, Sharrett AR, Gottesman RF, et al. Normative Data for 8 Neuropsychological Tests in Older Blacks and Whites From the Atherosclerosis Risk in Communities (ARIC) Study. *Alzheimer Disease & Associated Disorders* 2015;29.

Knopman DS, Griswold ME, Lirette ST, et al. Vascular Imaging Abnormalities and Cognition: Mediation by Cortical Volume in Nondemented Individuals: Atherosclerosis Risk in Communities-Neurocognitive Study. *Stroke* 2015;46:433-440.

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* _____)**
☐ **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.csc.unc.edu/aric/forms/>

12. 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.

REFERENCES

1. Zaccai J, Ince P, Brayne C. Population-based neuropathological studies of dementia: design, methods and areas of investigation - a systematic review. *BMC Neurology* 2006;6:2.
2. Gorelick PB, Scuteri A, Black SE, et al. Vascular Contributions to Cognitive Impairment and Dementia: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2011;42:2672-2713.
3. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: A large worldwide burden but a relatively neglected frontier. *Stroke* 2008;39:2396-2399.
4. Wasserman B. MRI Measures of Intracranial Atherosclerosis in a Population-Based Study. *American Journal of Neuroradiology* 2015. (In Press)
5. Caplan LR, Gorelick PB, Hier DB. Race, sex and occlusive cerebrovascular disease: a review. *Stroke* 1986;17:648-655.
6. Qiao Y, Liu L, Zhang Y, et al. Abstract T P108: MRI Measurements of Intracranial Atherosclerosis in the ARIC Neurocognitive Study: Methods, Reliability and Descriptive Statistics. *Stroke* 2015;46:ATP108-ATP108.
7. White H, Boden-Albala B, Wang C, et al. Ischemic Stroke Subtype Incidence Among Whites, Blacks, and Hispanics: The Northern Manhattan Study. *Circulation* 2005;111:1327-1331.
8. Qureshi AI, Caplan LR. Intracranial atherosclerosis. *Lancet* 2014;383:984-998.
9. Demarin V, Zavoreo I, Kes VB. Carotid artery disease and cognitive impairment. *Journal of the neurological sciences* 2012;322:107-111.
10. Sander K, Bickel H, Forstl H, et al. Carotid- intima media thickness is independently associated with cognitive decline. The INVADE study. *International journal of geriatric psychiatry* 2010;25:389-394.
11. Komulainen P, Kivipelto M, Lakka TA, et al. Carotid intima-media thickness and cognitive function in elderly women: a population-based study. *Neuroepidemiology* 2007;28:207-213.
12. Farooq M, Gorelick P. Vascular Cognitive Impairment. *Current Atherosclerosis Reports* 2013;15:1-7.
13. Bos D, Vernooij MW, de Bruijn RFAG, et al. Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline. *Alzheimer's & Dementia* 2015;11:639-647.e631.
14. Zhu J, Wang Y, Li J, Deng J, Zhou H. Intracranial artery stenosis and progression from mild cognitive impairment to Alzheimer disease. *Neurology* 2014;82:842-849.
15. Feldmann E, Wilterdink JL, Kosinski A, et al. The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial. *Neurology* 2007;68:2099-2106.
16. Qiao Y, Zeiler SR, Mirbagheri S, et al. Intracranial plaque enhancement in patients with cerebrovascular events on high-spatial-resolution MR images. *Radiology* 2014;271:534-542.
17. Antiga L, Wasserman BA, Steinman DA. On the overestimation of early wall thickening at the carotid bulb by black blood MRI, with implications for coronary and vulnerable plaque imaging. *Magnetic Resonance in Medicine* 2008;60:1020-1028.
18. Qiao Y, Steinman DA, Qin Q, et al. Intracranial arterial wall imaging using three-dimensional high isotropic resolution black blood MRI at 3.0 Tesla. *Journal of Magnetic Resonance Imaging* 2011;34:22-30.

19. Zhao DL, Deng G, Xie B, et al. High-resolution MRI of the vessel wall in patients with symptomatic atherosclerotic stenosis of the middle cerebral artery. *J Clin Neurosci* 2015;22:700-704.
20. Flora GC, Baker AB, Loewenson RB, Klassen AC. A comparative study of cerebral atherosclerosis in males and females. *Circulation* 1968;38:859-869.
21. Schneider ALC, Sharrett AR, Gottesman RF, et al. Normative Data for 8 Neuropsychological Tests in Older Blacks and Whites From the Atherosclerosis Risk in Communities (ARIC) Study. *Alzheimer Disease & Associated Disorders* 2015;29.
22. Knopman DS, Griswold ME, Lrette ST, et al. Vascular Imaging Abnormalities and Cognition: Mediation by Cortical Volume in Nondemented Individuals: Atherosclerosis Risk in Communities-Neurocognitive Study. *Stroke* 2015;46:433-440.