ARIC Manuscript Proposal #2591

PC Reviewed: 8/11/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of ICAD with dementia and mild cognitive impairment: the ARIC-Neurocognitive Study

b. Abbreviated Title (Length 26 characters): ICAS and CI

2. Writing Group:

Writing group members: M. Fareed K. Suri, Ye Qiao, Alvaro Alonso, Haitao Chu, Adnan I Qureshi, Bruce Wasserman, Tom Mosley, Rebecca Gottesman, Lisa Wruck, Richey Sharrett

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

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3. Timeline: This study is based on qualitative image analysis of vascular magnetic resonance imaging (MRI) collected for Intracranial Atherosclerotic Disease (ICAD) and Cognitive Impairment (ICAD-CI) Study. Qualitative image analysis has been completed. We plan to complete the statistical analysis for this project by September 2015.

4. Rationale: Every year about 70,000 to 90,000 strokes are estimated to be secondary to ICAD[1,2] in U.S. and approximately 75% of them are secondary to previously

asymptomatic ICAD. ICAD, besides being a common etiology of ischemic stroke, is also suspected to be causally related to cognitive dysfunction and dementia.[3-5] Cognitive impairment secondary to ICAD can be due to deep "strategic infarcts" or multiple distal emboli[6,7] or due to reduced blood flow, even in the absence of infarcts.[3-5] There is also growing evidence to suggest that ICAD-induced brain hypoperfusion contributes to the clinical and pathological manifestations of Alzheimer's disease (AD).[8-10] This association of ICAD with cognitive impairment and AD, however, remains poorly studied. Our proposed study will help determine if ICAD is associated with cognitive impairment. We will use intracranial atherosclerotic stenosis (ICAS) as a measure of ICAD for this study.

5. Main Hypothesis/Study Questions: To determine if ICAS is associated positively with 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).

Study design: Cross-sectional

Inclusion: All subjects who have received vascular MRI for ICAD-CI Study

Exclusion:

1. Poor image quality or poor protocol adherence (n=194)
2. History of stroke

Outcome variables:

- MCI, dementia, as defined through the ARIC-NCS adjudication process
- Etiological types of MCI or dementia

Methodology:

ICAS: As a part of qualitative analysis of ICAD, ICAS was categorized into ordinal categories (0%, <50%, 50-69%, 70-99% and occlusion) for each vessel segment - supraclinoid and cavernous segments of the internal carotid artery (ICA), middle cerebral artery (MCA, M1 to M4 segments), anterior cerebral artery (ACA, A1-A3 segment), intracranial segments of the vertebral artery (VA), basilar artery (BA), and posterior cerebral artery (PCA, P1 to P3 segments). We will use maximal stenosis per-person for this analysis. We will also evaluate association of anterior (ICA, MCA, ACA) and posterior circulations (VA, BA), and right side (right ICA, MCA) vs left side (left ICA, MCA, ACA) anterior circulation with the outcome measures.

Other covariates: Analysis will be adjusted for conventional risk factors assessed at visit 5. These include — age, sex, race (or center), education, body mass index, smoking status, alcohol consumption, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, diabetes, blood pressure (or hypertension), use of cholesterol lowering medications, and use of antihypertensive medication. Additional analysis will adjust for only demographic variables and education.

We will not adjust for heart disease as it is not directly related to ICAD. All regression models will include sample weights to allow us to account for the stratified sampling by race and as well as to allow us to immediately extrapolate our results to the entire ARIC population.

Statistical analysis:
The association of ICAS (ordinal) with cognitive impairment (dichotomous) will be assessed with ordinary logistic regression models with proper consideration of the sampling weights provided by the ARIC Coordinating Center, adjusting for potential confounders as listed above.
We will perform analysis for following outcomes separately:

1. Mild cognitive impairment and dementia (any-cognitive impairment) vs no cognitive impairment
2. Dementia vs no cognitive impairment
3. Pure Alzheimer's disease MCI/Dementia vs no cognitive impairment
4. Pure Cerebrovascular disease related MCI/Dementia vs no cognitive impairment

Associations will also be examined separately by race.

Limitations:

1. This is a cross-sectional analysis and it is not possible to establish a causal relationship from this study.
2. We are using all subjects who have received ARIC-NCS MRI. Although the subject selection for MRI was based on stratified sampling, this is not a random sample and does not provide the prevalence estimate of the general population. The use of sampling weights will partially address that problem.
3. There is no standard method to determine the intracranial vasculature atherosclerosis burden. Stenosis severity is the best known prognostic indicator for risk of stroke. We are using the standard clinical stenosis severity cut-offs to report the prevalence of atherosclerosis burden. This may not be a true representation of atherosclerosis burden, as a participant may have multiple areas of intracranial atherosclerosis without any significant stenosis.
4. Motion artifact has affected the quality of MRI for some subjects. Additional analysis will be done after excluding vessel segments and subjects with image quality scores other than excellent and will be reported if results are significantly different.

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 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? ____ 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

__YES____ 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)?

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, 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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