ARIC Manuscript Proposal # 3054

PC Reviewed: 10/3/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Brain Structural MRI Abnormalities Predict Dementia, MCI and Cognitive Decline in an Older Population

b. Abbreviated Title (Length 26 characters): Brain lesions and Dementia

2. Writing Group:

Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. A.W. **[please confirm with your initials electronically or in writing][1]**

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3. Timeline:

Most of the data to be used in this proposal are already available. Analyses and manuscript preparation will be performed with available data in the next few months and completed shortly after MCI/dementia diagnoses from Visit 6 become available (approximately March 2018).

4. Rationale:

The development of cognitive impairment or dementia involves many factors, including brain lesion accumulation and the level of a person's cognitive reserve (the ability to maintain normal cognitive function in the presence of brain changes). The relevant pathological damage is hypothesized to happen long before the cognitive impairment.[2] The most prevalent vascular pathologies detectable by MRI are markers of brain small vessel disease, including white matter lesions, *e.g.* white matter hyperintensity (WMH), infarcts (primarily lacunes), and micro-hemorrhages. Previous studies showed associations of white matter lesions[3-5] and infarcts[4-6] with cognitive decline, while inconsistent evidence supports the association of microbleeds with cognitive impairment [7-10]. On the other hand, brain atrophy, as a measure of total neuron loss in the brain, relates to cognitive decline. Atrophy in certain brain region, like hippocampus, may indicate pathological damages related to specific neurodegenerative diseases, like Alzheimer's disease (AD).[5] While, white matter lesions, lacunes, and microbleeds can also be seen in cognitively "normal" older adults,[1, 11, 12] where they may be associated with relatively lower cognitive performance. Persons with high cognitive reserve may have high tolerance of the pathologies.

Vascular lesions in different brain regions contribute to impairments in different cognitive domains. For example, lesions in the hippocampus are associated with memory impairment, while damage in frontal cortical regions are more likely to affect executive function.[5, 13] Comprehensive exploration of the roles, global and local, that brain vascular pathologies, play on cognitive decline and dementia development in older adults is needed.

In ARIC, a cross-sectional study conducted by Dr. Knopman[5] found a significant association of WMH volume and visible infarcts with brain cortical volume and cognitive function at Visit 5. Our study will evaluate the prospective associations of the same MRI signs with cognitive decline and incident dementia at older ages (after the imaging performed at Visit 5).

Compared to the previous studies, this study has following unique features:

1) We have longitudinal cognitive function measurements at participants' older age (a mean age of 70) after brain lesion measurements.
2) This community-dwelling population has a large sample of "cognitively normal" participants at study baseline, which represents the entire normal ARIC cohort population.
3) ARIC visit 5 and visit 6 examinations had comprehensive assessment for mild cognitive impairment (MCI). With this unique data on home (rather than clinic) based MCI, we are able to assess the role vascular pathologies play for MCI incidence and the subsequent cognitive decline and the development of dementia in those with MCI at visit 5.
4) With comprehensive longitudinal evaluation of cognitive function at the study baseline and follow up, we will be able to untangle the brain lesion-dementia association from cognitive reserve.
5) We can study the patterns of cognitive impairment separately in persons with MCI and normal cognition at baseline (visit 5).

5. Main Hypothesis/Study Questions:

Study Aims:

Assess whether measures of cerebral small vessel disease, including visible infarcts, white matter hyperintensity volume, and micro-hemorrhages, as well as a measure of overall neurodegeneration, *i.e.*

brain atrophy (measured as reduced cortical volumes of the entire brain or regions of interest (ROI)), especially in AD signature regions, at Visit 5 are associated with post-Visit 5 cognitive outcomes, including incident dementia, development of MCI and cognitive decline.

Hypotheses:

1. Higher levels of cerebral small vessel disease, including visible infarcts, white matter hyperintensity volume, and brain micro-hemorrhages, are associated with higher risks of incident dementia, development of MCI, and steeper cognitive decline.
2. Smaller brain/ROI cortical volumes, especially in AD signature regions, are associated with higher risks of incident dementia, development of MCI, and more cognitive decline.
3. The association of brain-lesions with cognitive decline is stronger in cognitively normal participants at the study baseline than in those with MCI; the hazard ratio of brain-lesions with dementia is less in cognitively normal participants at study baseline than in those with MCI.
4. Cognitive decline and dementia incidence will be greater in amnestic than in persons with non-amnestic MCI (defined by memory impairment).
5. These associations are similar in African Americans and whites.

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

We will utilize a longitudinal study design with Visit 5 as study baseline. We will assess the association of brain structure abnormalities measured at Visit 5 using MRI with incident dementia and MCI after Visit 5 and cognitive decline from Visit 5 to Visit 6.

Study population

Inclusion Criteria:

1,864 non-demented ARIC participants who had a brain structure MRI scan at Visit 5 NCS with valid cognitive outcomes measured from Visit 5 to 6 (718 of them determined to be cognitively normal)

Exclusion Criteria:

We will exclude participants:

- Neither white nor African-American and non-white in Washington Co. and Minnesota.
- Missing key covariate information (e.g. education).
- With prevalent stroke at Visit 5.
- Dementia at or before visit 5

We will also exclude cognitive tests in the evaluation of cognitive change if the participant was on CNS-altering medications (neuroleptics or benzodiazepines) at the corresponding study visit, to minimize the impact of prevalent disease status/medications on cognitive scores.

In the analysis on the development of MCI, we will restrict our analytical population to those without MCI or dementia at the Visit 5 (study baseline) and who had a cognitive evaluation at Visit 6.

Cognitive Outcomes

1) Incident dementia:
   Diagnosed dementia cases post-Visit 5 were identified via comprehensive dementia assessment at Visit 6 and dementia surveillance system (hospital discharge code/death code). In addition, we will

include probable cases identified through Annual Follow-Up interviews using ARIC's dementia screening instruments, the Six Item Screener (SIS) and AD8.

2) Newly diagnosed MCI:
   MCI were evaluated using comprehensive cognition assessment at Visit 6. Previously identified MCI cases at Visit 5 will be excluded from the analysis.
3) Cognitive decline:
   Cognitive decline from Visit 5 to Visit 6 will be measured as the change of global and domain specific cognitive function scores, constructed using global and 3 domain-specific factors based on the entire cognitive battery performed at both visits.

Exposures

The exposures are brain structure abnormalities measured on MRI imagining, including:

1) Subclinical infarcts:
   a. Existence of cortical, subcortical, and lacunar infarcts. (Binary variable)
   b. Frequency of cortical, subcortical, and lacunar infarcts. (Categorical variable)
2) White matter hyperintensity volume: total volume of the area with WMH, adjusted for intracranial volume, analyzed as a continuous variable.
3) Total gray-matter volume: total gray-matter volume adjusted for intracranial volume, analyzed as a continuous variable.
4) ROI volumes: total gray-matter volume for AD signature regions (lateral temporal, lateral parietal, medial parietal, hippocampus and olfactory region), medial temporal lobe, and parts of frontal lobe (lateral frontal and medial frontal), analyzed as continuous variables.
5) Micro-hemorrhages:
   a. Existence of micro-hemorrhages. (Binary variable)
   b. Frequency of micro-hemorrhages. (Categorical variable)

Covariates

We will use variables measured at study baseline (Visit 5), including: age, gender, race-center, smoking status (current, former, never), alcohol consumption (current, former, and never), body mass index (BMI), apolipoprotein E ε4 genotype, total cholesterol, hypertension (yes or no, defined as use of blood pressure–lowering medication, systolic blood pressure greater than 140 mm Hg, or diastolic blood pressure greater than 90 mm Hg), diabetes status (yes or no, defined as self-reported diabetes diagnosis by physicians, use diabetes medication, or having HbA1c level of 6.5% or greater), and prevalent coronary heart disease prior to Visit 5. One exception is for the covariates measured only at visit 1: education level (< high school, high school or equivalent, or > high school).

Statistical Analysis

Primary Analyses:

<u>Incident Dementia</u>

The Cox proportional hazard model will be used to model the risk of incident dementia associated with specific brain structure abnormalities. The study baseline is Visit 5.

<u>Development of MCI</u>

The logistic model will be used to model the odds ratio of newly incident MCI at Visit 6 with specific brain structure abnormalities at Visit 5.

<u>Cognitive Decline</u>

Linear regression will be used to model the association of the scale of specific brain structure abnormalities with the magnitude of cognitive decline.

For all outcomes, three models will be constructed:
Model 1: Demographical variables at Visit 5, and education level, and Apolipoprotein E ε4 genotype.
Model 2: Model 1 + CVD risk factors (smoking/drinking status, BMI, hypertension, diabetes, total cholesterol, history of coronary heart disease)
Model 3: Modeling ROI volumes and markers of small vessel diseases that are significant when considered alone together.

The study population was sampled from the entire ARIC cohort at Visit 5 based on pre-defined sampling fraction. For all analyses on incident dementia and cognitive decline, we will apply the sampling weight in the model to mimic the results in the original cohort population.

Sensitivity Analysis:

a) *Subgroup analysis*
   Subgroup analysis will be conducted with the following covariates: age categories, gender, race, apolipoprotein E ε4 genotype, baseline cognition/MCI status. Subgroup analyses will use the same methods as in the primary analyses.
b) *Account for Cohort Attrition*
   People lost to follow-up are generally sicker and have relatively poor cognitive function and therefore differential cohort attrition is likely. We will control for the potential bias due to cohort attrition using inverse propensity score for attrition weighting. The propensity scores for attrition will be the probability of an individual been lost-to-follow-up or dead during follow-up time from Visit 4 to 6, given the relevant covariates. In addition to the covariates listed above, the propensity scores will also include activity index, quality of life, health insurance, marital status, sleeping problem, hormone use, and social economic status at Visit 4 and 5 (or at a prior Visit if only measured at a prior Visit) for propensity score construction.
c) *Generalizability*
   Brain MRI scan were conducted on a pre-selected population. To evaluate whether the study population differs from the overall Visit 5 cohort, we will compare the incidence of dementia and the magnitude of cognitive decline among non-imaged non-demented visit 5 participants based on their SIS and AD8 screening results.

Advantages & Limitations

ARIC has more complete dementia surveillance after Visit 5 (with high completion rates for the SIS and AD8 instruments) than it had earlier and more complete data with which to adjust for potential attrition bias. Also cognitive outcomes are measured using a more complete battery at both visits 5 and 6. Of notes, participants in this study have old age (a mean age of 75). By excluding prevalent dementia cases (and MCI for one of the sub-study), we naturally select on participants with relatively healthier condition or more cognitive reserve. There are limitations to the proposed analysis. Firstly, since Visit 5 (2011-2013), we only have 4-5 years of follow-up by the end of Visit 6 (2016-2017). Due to the relatively short follow-up, our statistical power may be limited by the number of new dementia and MCI cases and the magnitude of the cognitive decline observed. Secondly, brain structure images were measured at Visit 5. With one-time measurement, we cannot really assess brain atrophy. Instead, we will use the relative size of brain cortical volume among the study population as a surrogate measurement for atrophy. Lastly, cognitive impairment may begin before the brain structure measurement at Visit 5, especially among cognitively "normal" participants. The temporal relationship between the exposure and the outcome we are evaluating may be weakened by this fact.

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?
__X__ Yes ____ 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"? __X__ 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)?
We are the first study to evaluate Visit 5 brain MRI measurements with cognitive outcome after Visit 5. Previous study proposed on brain MRI measurement and cognitive outcome include: MP #2288, #2266, #2586, and #1119. Key authors of these proposals contributed to the current proposal and appropriate coordination will be made.
In addition, proposals related to cognitive impairment/dementia include: MP #1211, #1973, #969, #672, #1703, #2002, #1365, #1871, #2264, #2211, #2262, #2628, #1739, #2545, and #2201r; proposals related to small vessel diseases/brain atrophy include: # 2866, # 2822, # 1894, #2244, #2606, #2145, #2551, #2865, and #953.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No ARIC NCS and ARIC-PET

11.b. If yes, is the proposal
_X__ A. primarily the result of an ancillary study (list number* _2008.06_and 2009.29__)
___ 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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

Reference

1. Tsushima Y, Tanizaki Y, Aoki J and Endo K. MR detection of microhemorrhages in neurologically healthy adults. *Neuroradiology*. 2002;44:31-6.
2. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC and Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet neurology*. 2010;9:119.
3. Schmidt R, Ropele S, Enzinger C, Petrovic K, Smith S, Schmidt H, Matthews PM and Fazekas F. White matter lesion progression, brain atrophy, and cognitive decline: The Austrian stroke prevention study. *Annals of Neurology*. 2005;58:610-616.
4. Jokinen H, Lipsanen J, Schmidt R, Fazekas F, Gouw AA, van der Flier WM, Barkhof F, Madureira S, Verdelho A, Ferro JM, Wallin A, Pantoni L, Inzitari D and Erkinjuntti T. Brain atrophy accelerates cognitive decline in cerebral small vessel disease: The LADIS study. *Neurology*. 2012;78:1785-1792.
5. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR, Jr., Graff-Radford J, Schneider AL, Windham BG, Coker LH, Albert MS and Mosley TH, Jr. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. *Stroke*. 2015;46:433-40.
6. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ and Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *The New England journal of medicine*. 2003;348:1215-22.
7. van Norden AGW, van den Berg HAC, de Laat KF, Gons RAR, van Dijk EJ and de Leeuw F-E. Frontal and Temporal Microbleeds Are Related to Cognitive Function. *The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study*. 2011;42:3382-3386.

8. Lei C, Lin S, Tao W, Hao Z, Liu M and Wu B. Association between cerebral microbleeds and cognitive function: a systematic review. *Journal of Neurology, Neurosurgery & Psychiatry*. 2013;84:693-697.
9. Werring DJ, Gregoire SM and Cipolotti L. Cerebral microbleeds and vascular cognitive impairment. *Journal of the neurological sciences*. 2010;299:131-5.
10. Qiu C, Cotch MF, Sigurdsson S, Jonsson PV, Jonsdottir MK, Sveinbjrnsdottir S, Eiriksdottir G, Klein R, Harris TB, van Buchem MA, Gudnason V and Launer LJ. Cerebral microbleeds, retinopathy, and dementia: the AGES-Reykjavik Study. *Neurology*. 2010;75:2221-8.
11. Ylikoski A, Erkinjuntti T, Raininko R, Sarna S, Sulkava R and Tilvis R. White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. *Stroke*. 1995;26:1171-7.
12. Roob G, Schmidt R, Kapeller P, Lechner A, Hartung HP and Fazekas F. MRI evidence of past cerebral microbleeds in a healthy elderly population. *Neurology*. 1999;52:991-4.
13. Mungas D, Harvey D, Reed BR, Jagust WJ, DeCarli C, Beckett L, Mack WJ, Kramer JH, Weiner MW, Schuff N and Chui HC. Longitudinal volumetric MRI change and rate of cognitive decline. *Neurology*. 2005;65:565-71.