1.a. Full Title: Mid-life Cerebral Infarct Burden Relationships with MCI and Dementia: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Cerebral MRI Changes and Incident Stroke

2. Writing Group:
   Writing group members: B. Gwen Windham, Michael E. Griswold, Wanmei Wang, Dave Knopman, Rebecca Gottesman, Dean Shibata, Tom Mosley

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

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3. Timeline:
4. **Rationale:**

Cerebral small vessel disease, including white matter hyperintensities (WMH) and clinical and subclinical brain infarcts (SBIs) have been associated with increased risk of incident stroke, dementia, cognitive decline and mortality in population-based studies.\(^{(1-12)}\) Many of these studies were conducted in older adults, when such changes may be less amenable to treatment and preventive interventions to preserve brain health. Existing cerebral small vessel disease appears to represent later stages of a chronic disease process that results in end organ damage in the brain over extended periods of time when one is exposed to risk factors. Earlier markers of vascular disease are needed to identify at-risk persons in whom preventive interventions could be developed.

Our work in ARIC has shown that very small changes in the brain during midlife – changes that are ignored in clinical and research settings - are associated with stroke, stroke mortality and cognitive decline. Specifically, the presence of infarcts less than 3 millimeters in size in stroke-free ARIC participants during midlife was associated with a 3 fold greater risk of stroke and stroke-mortality;\(^{(13)}\) we observed relationships of infarcts <3mm with cognitive decline over twenty years of follow-up that was similar to relationships of typical-sized infarcts with cognitive decline. (Windham et al, under review) Having both sizes of infarcts (infarcts 3-20mm and infarcts <3mm) was associated with a seven to eight fold higher risk of stroke or stroke-mortality\(^{(13)}\) and more than a full standard deviation lower cognitive score after twenty years of follow-up compared to having no infarcts. (Windham et al, under review) In addition, the smaller infarcts were three times more prevalent in African Americans than whites in ARIC. These findings represent a growing clinical evidence base for the importance of early changes in the cerebral vascular system on brain health, cerebrovascular outcomes and mortality. However, the relationship of smaller infarcts (that is, less than 3mm) with clinical cognitive outcomes, e.g., mild cognitive impairment (MCI) and dementia remain uncertain.

The Alzheimer’s Disease-Related Dementia (ADRD) Summit 2016, sponsored by the National Institutes of Health, National Institute of Neurological Disorders and Stroke (NIH-NINDS), highlighted the need to “Improve tools for assessment of disparities in risks, preclinical disease characteristics, and costs of ADRD among disparities populations by leveraging existing data and cohorts.” The Summit also recommended developing “…longitudinally tracked noninvasive markers of key vascular processes related to vascular cognitive impairment dementia.” Our work in ARIC suggests that smaller infarcts (<3mm) may represent early, preclinical vascular changes that begin in mid-life, are more common in African Americans, and potentially contribute to health inequities among African Americans. This proposal leverages existing cohort data in ARIC to assess the role of pre-clinical, mid-life vascular changes in the brain with dementia risk in a biracial cohort. These findings could improve knowledge regarding the epidemiology and mechanisms of disparities with respect to MCI and dementia.

5. **Main Hypothesis/Study Questions:**

We will examine the hypothesis that smaller infarcts (<3mm) during midlife and larger,
typical sized infarcts (3-20mm) will be associated with increased risk for late life MCI and dementia and these relationships will be similar for smaller and larger infarct size.

We will also examine associations of smaller and larger infarcts with progression in cognitive status from visit 5 to visit 6, from normal to MCI and/or dementia, and from MCI to dementia.

We hypothesize that associations will be similar in African Americans and whites, acknowledging limited power to truly describe relationships by race.

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).

Design:
Longitudinal (follow-up) study design with follow-up through visit 6.

- V3 MRI infarct-burden associations with:
  - Time to dementia (survival model approach)
  - V5 Normal/MCI/Dementia (3-level cross-temporal multinomial approach)
  - V5 Normal/MCI/Dementia/Death (4-level cross-temporal approach)
  - V5->V6 progression (when data become available)

- V5 MRI infarct-burden associations with:
  - V6 3-level and 4-level outcome variables (when data become available)
  - V5->V6 progression (when data become available)

Datasets:
1. ARIC visit 3 MRI data (Jackson and Forsyth County).
2. ARIC visit 3 derived variables.
3. ARIC visit 5 derived variables.
4. ARIC visit 5 and visit 6 cognitive status (normal, MCI, dementia)
5. ARIC incident dementia variable
6. ARIC death status variable
7. APOE

Exclusions:
Previous history of stroke at visit 3
Missing data for MRI variables

Outcomes:
1. Incident dementia
2. MCI and/or dementia at visit 5
3. Progression from visit 5 to visit 6 in cognitive state (normal to MCI and/or dementia; MCI to dementia).

Main predictor variables:
MRI variables:
Cerebral infarct burden (0=no infarcts (reference);
  0=smaller <3mm only;
  1=larger infarcts only (3-20mm);
We will also consider the category (n=50) with both sizes,
  2=both sizes

We will consider influences of other cerebral small vessel disease, e.g. white matter hyperintensities.

Covariates:
Primary models will adjust for visit 3 age, race-center, education, APOE e4 and sex. The following additional visit 3 covariates may be considered in adjusted regression models, although concern for these operating as potential mediators leads us to propose omitting these in our primary analyses: systolic and diastolic BP, diabetes, lipids, BMI, hypertension medications, heart failure, CHD, smoking status, and drinking status.

Analyses:
Analyses of incident dementia outcomes (time to dementia), will be performed using survival model techniques (e.g. Cox, Weibull, similar). Dementia status (3-level and 4-level outcomes) and progression will use multinomial and ordinal (where supported) logistic regression models. Attrition effects of death and loss to follow up (LTFU) will be examined using inverse proportional weighting (IPW) and joint-modelling approaches. V5 MRI subpopulations will be unweighted using coordinating center defined v5 stage 3 sampling weights.

Anticipated problems:
Small numbers of participants with small only infarcts or both sizes limit analyses. Interpretations of results will take this into account. Progression from V5 to V6 may further contribute to limitations due to small sample sizes attribute to further attrition. Participants with infarct burden measures at visit 3 who did not return to visit 5 were more likely to be older, African American, and have a greater infarct burden. The influence of missing data at follow-up will be investigated using shared parameter models. This method was previously used in ARIC papers examining relations of infarct burden with cognitive decline.

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/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)?  

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  
____ Yes  ____X__ 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.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.  

References


