ARIC Manuscript Proposal #2081

PC Reviewed: 2/12/13   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Cerebral MRI Changes in Mid-life to Older Age and Incident Stroke: the Atherosclerosis Risk in Communities 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, Kenneth Butler, Dave Knopman, Rebecca Gottesman, Gerardo Heiss, 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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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: Data analysis: April- May 2013
                       Writing: April – Fall 2013
                       Submit first draft to publications committee: Winter 2014

4. Rationale:

White matter lesions (WML) and MRI-defined subclinical brain infarcts (SBIs) have been associated with increased risk of incident stroke and mortality in population-based studies, mainly in older people.[1-12] Some have demonstrated similar risk in middle-aged populations,[4] although studies in middle-aged African Americans (AA) are limited. In addition, not all studies adjusted for important potential confounders including known stroke risk factors.[4] The association of WMLs to incident stroke in ARIC has been reported,[12] but only for limited follow-up and with few incident strokes cases. Furthermore, the relationship of SBI in the ARIC cohort to stroke and stroke subtypes has not been reported. Most studies of the association of MRI changes to clinical incident stroke have been conducted in older populations. In addition, the relationship of WML and SBI to stroke-related and overall mortality has not been reported in ARIC or other AA populations. Thus, the significance of brain changes on risk of stroke and stroke subtypes in middle-aged community-dwelling persons, particularly in AA, remain unclear. The current proposal will extend findings regarding the association of SBI and WMH on incident stroke, and stroke-related and all-cause mortality in middle-aged and older individuals including a large cohort of AA, adjusting for traditional and non-traditional risk factors.[13]

5.   Main Hypothesis/Study Questions:
SBI will be associated with incident stroke including stroke subtypes (power permitting), and WML and SBI will be associated with increased risk of stroke-related mortality and overall mortality.

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 to 12/31/09.

Datasets:
    1. ARIC visit 3 MRI data (Jackson and Forsyth County).
    3. ARIC visit 3 derived variables.
    4. ARIC stroke and CHD incidence data through 2009

Exclusions:
Previous history of stroke, symptoms of stroke/TIA.
Missing data for MRI variables.

Outcomes:
    1. Incident stroke (all types) between date of MRI and 2009.
            1.a. If numbers are sufficient, type of stroke (hemorrhagic, ischemic (all, lacunar, non-lacunar), other) will also be examined.

2. All-cause and stroke mortality between date of MRI and 2009.

Measures:
     1. Crude and adjusted incidence and mortality rates.
     2. Kaplan-Meier survival curves for incidence and mortality.
     3. Adjusted hazard ratios (from Cox PH regression) for incidence and mortality.

Main predictor variables:
MRI variables:
     1. Cerebral infarct (any)
        1.a. Type (level) of infarct: cortical, lacunar – if numbers allow.
        1.b. Number of infarcts: 1, 2, 3 or more
     2. WMH (0-9), grade ≥ 3 versus <3

Covariates:
The following covariates will be used to examine adjusted regression models: age, sex, race, center, education, hypertension, systolic and diastolic BP, diabetes, lipids (total cholesterol, HDL, LDL), BMI, waist-hip-ratio, Lp(a), history CHD, physical activity, smoking status, drinking status, LVH, carotid IMT, von Willebrand factor (vWF), WBC. Parsimonious models will be examined and compared to models adjusted for all listed covariates.

Anticipated problems:
Insufficient events may limit ability to examine different types of stroke.

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)?

317, "Covert Neurological Symptoms associated with Silent Stroke from Mid-Life to Older Age: The Atherosclerosis Risk in Communities Study" (Windham et al)

#753: Retinal microvascular abnormalities and its relation to cerebral white matter lesions and atrophy: The Atherosclerosis Risk in Communities Study (Wong T).

#824: Ischemic Stroke Risk Prediction in the Atherosclerosis Risk in Communities Study (Chambless L)

#1090: Risk Factors for Ischemic Stroke Subtypes. The Atherosclerosis Risk in Communities (ARIC) Study (Ohira T).

1663A   Risk of intraparenchymal hemorrhage with magnetic resonance imaging-defined leukoaraiosis and brain infarcts. Folsom AR, Yatsuya H, Mosley TH Jr, Psaty BM, Longstreth WT Jr.

753 Cerebral white matter lesions, retinopathy, and incident clinical stroke. Wong T, Klein R., Sharrett A. R., Couper D. J., Klein B. E., Liao D. P., Hubbard L. D., Mosley T. H.

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

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12. Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA : the journal of the American Medical Association.* Jul 3 2002;288(1):67-74.

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