ARIC Manuscript Proposal # 3006

PC Reviewed: 7/11/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Metabolomics Studies of Incident Stroke and Vascular Brain Aging

b. Abbreviated Title (Length 26 characters): **Metabolomics of stroke**

2. Writing Group:

Writing group members: Bing Yu, Tom Mosley, Rebecca Gottesman, Yuichiro Yano, Eric Boerwinkle

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MF___ **[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: Summer 2017

4. Rationale: Ischemic stroke is a heterogeneous disease and despite decades of research, few treatments are available. Management of stroke risk factors remain the first line strategy to decrease the burden of ischemic stroke. In addition, stroke classification and diagnosis are not straightforward and mostly rely on neuroimaging techniques that are costly, time-consuming,

and not universally available. Thus, the discovery of novel blood-based biomarkers that aid in the early identification of high-risk patients and in the classification and diagnosis of stroke has the potential to facilitate the management of patients with cerebral ischemia and improve the understanding of stroke etiology.

5. Main Hypothesis/Study Questions:

1) We will examine the association of metabolites measured on stored serum collected at the baseline examination with incident stroke and its subtypes.
2) We will examine the association of metabolites measured on stored serum collected at the baseline examination with brain MRI endophenotypes of vascular brain aging. These include white matter hyperintensities, brain infarcts, microbleeds (NCS only).
3) To shed light on possible molecular pathways that may underlie identified associations of metabolites with disease outcomes, we may integrate genetic and epigenetic information through identification of possible genetic and DNA methylation correlates of the selected metabolites identified in the association analyses. These will then be examined for their association with incident stroke or brain MRI endophenotypes.

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).

For analyses of incident stroke, we will exclude participants with self-report of a stroke or TIA at baseline.
We will use Cox proportional hazards to examine the association of incident stroke (and subtypes) with standardized levels of each metabolites, adjusting for relevant covariates, including age, sex, field center, diabetes, hypertension, current smoking, BMI, and estimated glomerular filtration rate.
We will use linear (logistic) regression to examine the association of WMH volume (or presence of brain infarct/ microbleed on MRI) with each serum metabolite adjusting for relevant covariates, including intracranial volume.
Correction for multiple testing will be applied using Bonferroni or False Discovery Rates as appropriate.
GWAS or EWAS of selected metabolites identified in the above analyses may be conducted to identify genetic and DNA methylation correlates. Formal Mendelian Randomization techniques may be applied to examine the causal relationship of identified metabolites with brain outcomes.

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)?
Other metabolomics papers by Bing Yu and Eric Boerwinkle who are co-authors in this research.

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* _____)
___ 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, approved manuscripts using 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.