ARIC Manuscript Proposal #3806

PC Reviewed: 3/9/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Midlife blood biomarkers levels and 20-year cognitive decline and incident dementia

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members: Myriam Fornage, Michael Griswold, Xiaoqian Zhu, Kunali Ghelani, Kevin, Sullivan, Rebecca Gottesman, Tom Mosley, others welcome

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]**

First author: **Myriam Fornage, PhD**
Address: 1825 Pressler Street
Houston, TX 77030

Phone: 713-500-2463 Fax: 713-500-2447
E-mail: myriam.fornage@uth.tmc.edu

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).

Name: **Thomas H. Mosley, PhD**
Address: University of Mississippi Medical center

Phone: 601-984-4467 Fax:
E-mail: tmosley@umc.edu

3. Timeline: Analyses through Spring 2021; manuscript anticipated by May 2021

4. Rationale:
Age-related cognitive impairment and dementia represent one of the greatest risks to public health both in the US and globally. Clinical trials to prevent cognitive impairment due to small vessel disease are being conducted but are hampered by the limited availability of “biomarkers”. The MarkVCID Consortium aims to analyze and optimize candidate VCID biomarkers. As part

of this consortium, we have measured multiple circulating biomarkers reflecting glial cell dysfunction as well as neuronal and axonal injury on V3 ARIC participants with a brain MRI using ultrasensitive immunoassays. These include soluble CD14 and YKL-40, biomarkers of microglial cell activation; glial-fibrillary acidic protein (GFAP), a biomarker of astrocyte reactivity, neurofilament light chain (NFL), Tau, and Ubiquitin C-terminal hydrolase L1 (UCH-L1), biomarkers of neuronal and axonal degeneration. To date, the longitudinal associations of these biomarkers with cognitive decline and incident dementia have not been assessed in a population-based cohort setting.

5. Main Hypothesis/Study Questions:
1) We aim to investigate the association of midlife levels of selected biomarkers of glial cell dysfunction and neuronal and axonal degeneration with cognitive decline over 20 years.

2) We will also investigate the association of midlife levels of selected biomarkers of glial cell dysfunction and neuronal and axonal degeneration with incident dementia over the same period.

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
At Visit 3, stroke-free participants aged 50 years or older from two field centers were invited to undergo brain MRI and a cognitive assessment. A total of 1,934 participants underwent brain MRI and were selected for biomarker assessment. A total of 1,893 have valid biomarker data and are included in the proposed analyses.

Primary Outcomes
The primary outcome is the 20-year decline in global cognition, measured with a Z-score. Z-scores for individual cognitive tests, including DWRT, DSST, and WFT were calculated at each assessment, standardized to visit 2 results (the first cognitive assessment), then averaged to create a global Z-score at each visit, as previously reported (PMID: 25090106).
Both global cognitive function and domain-specific cognitive function will be evaluated.

Incident dementia up to the end of visit 7 (December 31st, 2019) using the level 3 definition published previously (PMID: 28783817). This definition included the use of cognitive tests from visits 2 and 4, adjudicated dementia from complete evaluation at the ARIC-NCS visit (visit 5), dementia classified based on Telephone Interview for Cognitive Status–Modified (TICSm), dementia based on informant telephone interviews using a modified version of the Clinical Dementia Rating and the Functional Activities Questionnaire among a subset identified as having suspect dementia, or dementia cases identified solely by surveillance based on a prior discharge hospitalization ICD-9 or death certificate code for dementia.

Statistical Analyses

Analyses will be performed by Dr. Griswold.

Mixed effects models with random slopes and intercepts will be used to examine associations between biomarker measurements and cognitive decline. Biomarker levels will be log-transformed as appropriate. Years since the index visit will be used for the time scale and models will be adjusted for non-time varying covariates: index age, sex, race and education.

Incident dementia analyses: We will use competing risk survival analysis based on the Fine & Gray method to account for mortality. Analyses will adjust for age, sex, race and education. Significance level will be set at p-value < 0.05.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? __X__ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

___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)? None.

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* _2016.04___)
___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.