1.a. Full Title: Replication of Mayo Clinic Risk Profile for Mild Cognitive Impairment

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
   Writing group members: Rosebud Roberts, Ron Petersen, Michelle Mielke, David Knopman, Richey Sharrett, Tom Mosley, Lisa Wruck, Rebecca Gottesman

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __DSK__ [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: TBD

4. Rationale: The Mayo Clinic Study of Aging recently reported a risk profile for prediction of mild cognitive impairment (Pankratz et al Neurology 84:1433-42, 2015). As the study was done in the ethnically and racially homogeneous locale of Rochester MN, we wish to see how well the profile performed in a multi-racial, geographically diverse population such as ARIC’s, and particularly in African Americans, who have the highest incidence and prevalence of dementia.

5. Main Hypothesis/Study Questions:
To test the hypothesis that the MCSA MCI risk score (see below for its composition) predicts MCI in the ARIC cohort in all locales and in all ethnicities (Caucasian, African American, and other).

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).

The published (Neurology 84:1433) basic risk score composite is made up of the following variables that are available in all ARIC participants: education, ever dx with alcohol problem (can be estimated in ARIC with measure of daily alcohol intake), history of stroke, history of diabetes, history of atrial fibrillation, presence of agitation, apathy, and these others that are specific to women (W) or men (M): smoking status (W), midlife dyslipidemia (W), midlife hypertension (W), BMI at any age (M), marital status (M). The only item from the MCSA risk score not available at ARIC MRI is “self-reported memory concerns.” There are two ways to address this latter item. One would be to compute the risk score without it, and the second would be to approximate it with our objective measure of memory performance by dichotomizing the ARIC MRI DWR score and \( \geq 3 \) words recalled.

We shall use ARIC MRI participants because of the more recent observations, as opposed to the entire ARIC cohort whose full examinations at ARIC V4 were over 10 years before ARIC v5. The duration of time between ARIC MRI and ARIC V5 approximates the duration of followup in the Mayo Study of Aging.

The analysis plan is as follows:

We will identify all ARIC participants who have participated in ARIC MRI and possibly ARIC V5. The former would be for the baseline characterization, and the latter for the outcomes. We will characterize participants in regard to the variables listed above. We will compute a risk score for each participant using the MCSA risk score. We will identify participants with the following outcomes as determined at v5 (or earlier in the case of dementia): incident MCI and dementia (all-cause and AD) during follow-up, and will compute duration of follow-up from ARIC MRI examination date to the incident event, last follow-up, death, or loss to follow-up. We will then use proportional hazards models to determine whether the risk score predicts risk of i) first ever MCI, 2) dementia, or 3) first event of MCI or dementia. We will assess the effects of competing risk of death on these outcomes. In these models, we will use age as a time variable, and adjust for ethnicity if we used all ARIC cohorts.

In separate models, we will perform subgroup analyses by ethnicity to determine whether the MCSA risk score predicts the study outcomes in Caucasians and in African Americans, and in other ethnicities. We will also use area under the curve methodology to determine how well the risk score predicts cognitive impairment in Caucasians, African Americans, and non-AA/non-Caucasian ethnicities with large enough numbers to provide adequate power to perform these analyses. We will also compute the sensitivity and specificity, predictive values positive and negative.
Potential challenges will include missing information on the variables needed to compute the risk score and considerable losses to follow-up (especially prior to development of MCI or dementia).

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ Yes ____ 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? _X_ 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.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)?

   There are none like this since the proposal is to use the Mayo algorithm on ARIC data.

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* 2008.06)
   ____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 1999.01 & 2008.06)

*ancillary studies are listed by number at http://www.csc.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.