1.a. Full Title: COGNITIVE, VASCULAR RISK FACTOR AND APOE GENOTYPE PREDICTORS OF HIPPOCAMPAL VOLUME

b. Abbreviated Title (Length 26 characters): Hippocampal Volume Predictors

2. Writing Group:
   Writing group members: Knopman, Mosley, Jack, Sharrett, Gottesman, Coker, Shibata, Catellier (tentative, not confirmed), Penman

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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3. Timeline: Initial analyses completed within 2 months of Pubs Committee approval; final version 4 months later.

4. Rationale: The hippocampus is one of the sites of the earliest atrophic processes in Alzheimer’s disease. Hippocampal atrophy is a plausible surrogate marker of preclinical (asymptomatic) Alzheimer pathology. The ARIC MRI study obtained ~1100 MR scans in 2004-06 that included volumetric measurement of the hippocampus. There are few, if any, other studies that have the capability of asking the question of whether measures of cognition and vascular risk factors assessed 14 years earlier predicted volume loss in the hippocampus.
Main Hypothesis/Study Questions:

H1. Low hippocampal volume at one point in time might reflect, at least at group level data, subtle declines in cognition a decade earlier. Therefore, cognitive function as measured at ARIC visit 2 will be associated with hippocampal volume measured at the ARIC MRI visit
   H1.1. Only the memory test score, and not the tests of psychomotor speed or verbal fluency, will show significant associations with hippocampal volume
   H1.2. A measure of change (slope) on the DWR (the ARIC memory test) but not DSS or WF, over ARIC visits will be associated with hippocampal volume
   Alternative: Even with the sample size of ARIC MR cohort, we may lack power to detect a very subtle association between earlier cognition and MR, in keeping with the notion that the changes in hippocampus are truly “preclinical.”

H2. Vascular risk factors might act synergistically with Alzheimer pathophysiology. Therefore, vascular risk factors as measured at ARIC visit 2, in particular diabetes mellitus and hypertension, will be associated with low hippocampal volume
   H2.1. Variables reflecting the cumulative exposure to vascular risk factors over ARIC visits will also be associated with low hippocampal volume
   Alternative: If the changes in the hippocampus are truly specific for Alzheimer pathophysiology, then it is possible that vascular risk factors will have no association with hippocampal atrophy.

H3. APOE e4 genotype may be specifically linked to Alzheimer pathophysiology. Therefore, APOE e4 genotype will be associated with hippocampal volume in the young elderly cohort of ARIC MRI.

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).

All subjects who had a successful measurement of hippocampal volume on the MR scan in the ARIC MR study are eligible. Within that subject group, no one else will be excluded.

The analyses would follow the study hypotheses.
1. Vascular risk factors assessed at ARIC V2 would be used: based on our prior work, the main ones are diabetes (defined by the composites of history of DM, use of a medication to treat DM, or an elevated fasting blood sugar >125 mg/dl) and hypertension (defined in analogous way).
   1a. We have also created a variable that reflects the presence of the vascular risk factor at each visit. This “cumulative” vascular risk factor will also be treated as a predictor. We will also examine hyperlipidemia (defined as SBP >140, DBP>90 or on medications for hypertension), and hs-C reactive protein.
2. Cognition at ARIC V2 will be based on scores on the 3 cognitive tests administered at that visit.
   2a. We will also generate a change score over ARIC visits subsequent to V2, probably using a slope or another regression technique, in order to create a cognitive change score for each test. Each cognitive test will be evaluated separately.
3. APOE genotype has been measured and carriage of one or more e4 alleles will be used in analyses.
4. The outcome measure is hippocampal volume, as measured in Cliff Jack’s laboratory from the ARIC MR scans.

Two types of analyses are planned. In one set, using hippocampal volume as a continuous measure, linear regression models will be used to relate visit 2 cognition, vascular risk factor status and APOE genotype to hippocampal volume. Analyses will be conducted first with no covariates, second, covarying by age, sex and education and then third, covarying for the demographic variables plus ventricular size. In a second set of analyses, a level of hippocampal volume will be defined as “atrophic,” and logistic regression analyses will be used to assess associations of the predictor variables with hippocampal atrophy.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ___ Yes  _XX_ 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 ICTDER03 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?  _XX_ 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”?  _XX_ 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.csecc.unc.edu/ARIC/search.php  ___XX_ 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)?
    Knopman et al. Neurology in press. ARIC ms #1553. Vascular Risk Factors and longitudinal changes in brain MRI – the ARIC Study

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  (yes: the ARIC MRI study)  _XX_ Yes  ____ No

b. If yes, is the proposal
    ___ A. primarily the result of an ancillary study (list number* __________)
    _XX  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/](http://www.cscc.unc.edu/aric/forms/)

12. 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.