1.a. Full Title: Ischemic stroke risk score at baseline and 20-year cognitive decline: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Stroke risk and cognitive decline

2. Writing Group: Lisa Wruck, Rebecca Gottesman (last) and (alphabetically) Karen Bandeen-Roche, David Couper, Aaron Folsom, Gerardo Heiss, Guy McKhann, Eyal Shahar, Richey Sharrett, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. LW [please confirm with your initials electronically or in writing]

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3. Timeline: Analysis work will begin immediately using preliminary Visit 5 data, to be completed within one month of Stage 1 closure.
4. Rationale:
ARIC investigators developed the 10 year stroke risk score to predict risk of ischemic stroke (Chambless et al 2004). The risk model was developed based on data collected at ARIC Visit 1 (1987 – 1989) with follow-up for incident events through 2000 (median 12.3 years). Gender-specific Cox regression models for incident ischemic stroke were fit to assess how well nontraditional risk factors improved prediction of individual risk beyond that of the traditional risk factors. Non-traditional risk factors did not provide significant incremental value so the basic model (age at Visit 1, race, systolic blood pressure, use of antihypertensive medication, current smoking, diabetes mellitus, previous coronary heart disease, and left ventricular hypertrophy diagnosed by electrocardiogram) was recommended. Area under the ROC curve (AUC) for these models was 0.813 and 0.789 for women and men, respectively. The risk prediction model was then applied to data collected at subsequent visits.

The stroke risk score provides a useful summary of stroke risk in the ARIC population. Stroke is a known cause of cognitive impairment, but it explains only a small proportion of all clinical dementias or of all impairments believed to be vascular in origin. Thus, our interest in the stroke risk score in relation to cognitive change is based on the belief that factors relating to risk of stroke are also related to the kinds of cerebral small vessel pathology (lacunes, microinfarcts, white matter changes, cerebral hemorrhages, and consequent ischemic cerebral atrophy) that comprise the primary causes of vascular cognitive impairment (White 2009). This expectation is supported by ARIC publications showing diabetes and hypertension related to small asymptomatic infarcts (Knopman et al 2011), progressive white matter hyperintensity (Gottesman et al 2010), and measures of cerebral atrophy (Knopman et al 2011, Knopman et al 2005).

The goal of the analysis is to describe the association between stroke risk score (i.e. the cerebral small vessel pathology it represents) and cognitive change. Using the risk score instead of individual risk factors allows for an increase in power and less concern about multiple comparisons.

We will focus on participants free of overt clinical stroke at baseline. However, since stroke is an important part of the continuum of cerebral vascular disease, we will also perform analyses which consider interim strokes, for example, by comparing results which include vs. exclude those with strokes occurring after baseline but before the final cognitive exam.

5. Main Hypothesis/Study Questions:
Is stroke risk at Visit 2 associated with cognitive decline?

Hypothesis: Increased stroke risk at Visit 2 is associated with a greater degree of cognitive decline from Visit 2 to Visit 5.
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
Prospective cohort study with Visit 2 as the baseline.

Inclusion/exclusion
ARIC participants with non-missing risk factors and cognitive function measures at V2 and no prevalent stroke at V2 will be included in analysis. Analysis will be restricted to black and white participants. Blacks in Minneapolis and Washington County will be excluded. Also, exclude from analysis any cognitive tests at visits when the participant was taking CNS-altering medications (neuroleptics or benzodiazepines).

Participants excluded due to missing baseline data may well have lower cognitive function and/or greater stroke risk than participants in the analysis sample. To assess the degree and likelihood of bias, we will characterize excluded participants in terms of baseline characteristics (to the extent possible) and compare them to those included in analysis.

Outcome and other variables of interest
Outcome variables will be the three measures of cognitive function (DWRT, DSST and WFT) at Visits 2, 3, 4, Brain MRI, Carotid MRI and Visit 5/NCS. Race-specific Z-scores for each test and a global Z-score will be calculated for analysis. Note that cognitive function tests at Visit 3 as well as Brain MRI and Carotid MRI were administered to a sub-sample of the cohort.

The main exposure variable will be the 10 year stroke risk score at V2. Covariates under consideration will include demographics (race, sex and age at V2), education, and possibly other indicators of cultural disadvantage, such as income or occupational class. Interactions of covariates with time will be considered as well.

Stroke risk score at subsequent visits may be considered as a time-varying covariate in secondary analyses.

Data analysis
We will examine baseline characteristics of the analysis population as well as cognitive function at Visits 2, 3, 4, Brain MRI, Carotid MRI and Visit 5/NCS.

Random effects models, which take into account within-subject correlation of scores, will be used to examine the association of baseline stroke risk score and cognitive decline. Linear and quadratic fits will be assessed, though the accelerated decline in test scores at older age may be accommodated through the use of linear splines. The models may be
stratified by race and/or gender. Cognitive test scores will be modeled separately as well as a composite score.

To test the primary hypothesis, we will focus on the interaction between time and Visit 2 stroke risk score.

Interim stroke (i.e. stokes that occur after baseline and prior to the final cognitive exam) is strongly associated with both stroke risk score and cognitive decline. As it is on the causal pathway, we will not adjust for it as a covariate. A secondary analysis will be conducted excluding participants with interim stroke, to assess impact on inference for the primary hypothesis.

We will use methods to account for attrition of the cohort, as dropout has been shown to be informative and is likely to bias results. We will consider inverse probability of attrition weighting and/or shared parameter models.

References


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?
   ____ 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.cscce.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)?


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)* __________ __________

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