ARIC Manuscript Proposal # 1553

PC Reviewed: 9/8/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Associations between vascular risk factors and longitudinal changes in ventricular size: a 14 year longitudinal study**

b. Abbreviated Title (Length 26 characters): Vascular risk factors and ventricular enlargement

2. Writing Group:
Writing group members: Knopman, Mosley, Catellier, Coker, Penman, Shibata

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: The plan is to have sufficient preliminary results to submit an abstract by Dec 1, 2009. Completed manuscript by May 2010

4. Rationale:

Several cross-sectional studies including a prior one from ARIC have shown that vascular risk factors such as diabetes and hypertension are associated with smaller brain volumes.

While cross-sectional analyses of vascular risk factors and brain volume loss exist including our own 2005 paper, there are no studies that we are aware of that have

examined the trajectory of brain volume loss over time with respect to vascular risk factors. Question such as: Is the longitudinal brain volume loss what would be expected based on the cross-sectional data, taking attrition into account, or is it more or less than expected?

If the consequences of vascular risk factors were already manifest at the time of an initial scan in midlife, and there were no subsequent accumulation of brain injury, then one would expect that the brain volume losses would be of the same magnitude later (in our case 14 years). However, although the vascular risk factors are likely to have been treated over the time interval, it would be plausible to believe that treatment would not be fully protective, and therefore, additional injury to the brain from the vascular risk factors would occur over time. Therefore, a followup imaging study in someone with vascular risk factors at baseline should show more atrophy at followup (as measured by a larger separation between those without versus those with the vascular risk factors.)

Understanding the relationship between vascular risk factors and brain volume loss is a critical element to understanding the broader question of how cerebrovascular disease contributes to late-life dementia. Brain volume loss is clearly a critical element in the development of symptomatic cognitive impairment, and may be the common pathophysiological pathway shared by Alzheimer pathology and cerebrovascular disease. If it could be demonstrated that the additivity of these two pathologies occurs at the level of brain volume loss (which in turn represents neuronal and synaptic loss in isocortex), a major puzzle in late life dementia could be addressed in a focussed way. On the other hand, if brain volume loss is not the place where additivity of the two pathologies occur, then other upstream (eg in relationships between ischemia and amyloid production or alteration of tau) would seem more likely.

As a result of the work of the ARIC study, we have a unique opportunity to examine MR scans performed 14 years after an initial scan and 16 years after a thorough evaluation of vascular risk factors were assessed.

5. Main Hypothesis/Study Questions:

Loss of brain volume over a 14 year period will be related to vascular risk factors measured at ARIC v2, incident stroke and APOE e4 genotype.
The rate of brain volume loss associated with vascular risk factors from ARIC v3 to ARIC yr 14 will accelerate because of the cumulative effects of those risk factors on brain structural integrity.

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).

Subjects: The 1031 participants of ARIC MR study who had scans in 2004-2006 and in 1994-5
Cognitive assessments: baseline cognitive status, already described in Knopman 2009 will be used. The three ARIC cognitive measures - DWR, DSS and WF – will be used.
Risk Factors: Assessed at ARIC visit 2 in 1990-1992

Diabetes mellitus was defined as a fasting glucose of > 126 mg/dl, non-fasting glucose of > 200mg/dl, a self-reported history of diabetes, or treatment for diabetes in the past 2 weeks. Serum glucose was assessed by the hexokinase method.

Hypertension was defined as systolic blood pressure > 140 mm Hg, diastolic BP > 90 mm Hg, or use of antihypertensive medications in the past 2 weeks.

Plasma lipids and lipoproteins were determined by enzymatic methods in a laboratory standardized by the Centers for Disease Control.

We constructed a variable that represented the metabolic syndrome, using the National Cholesterol Education Program (NCEP) criteria[, 2001 #2772], i.e., any 3 of the following: fasting blood sugar > 110 mg/dL or use of antidiabetic agent; triglycerides >150 mg/dL; HDL cholesterol < 40 mg/dL in men, < 50 mg/dL in women; hypertension defined as systolic >130 or diastolic >85 mm Hg or current use of an antihypertensive agent; or waist circumference > 88 cm in women, 102 cm in men.

Adiposity measures: BMI, waist circumference

Urinary albumin or creatinine

APOE genotype

Prevalent stroke at visit 2

Incident stroke between visit 2 and last ARIC update

Treatment considerations: We will create a set of indicator variables for treatment of diabetes, hypertension and cholesterol at ARIC visit 2-4. We will consider treating these indicator variables as time-dependent covariates in the analysis, and will construct a variable that characterizes the cumulative pattern of medication use (e.g., proportion of follow-up in which the participant was treated for diabetes/hypertension/hypercholesterolemia)

Imaging: (A) Longitudinal change: Scans analyzed qualitatively at ARIC visit 3 and at ARIC yr 14. Change in ventricular volume (vent vol) will be the principal imaging variable.

(B) Lagged cross-sectional: Ventricular volume at yr 14 assessed semi-quantitatively (based on 0-9 point scaling).

(C) Baseline white matter hyperintensity (WMH) and change in WMH will be used as covariates in these analyses

Analyses:

1. Descriptive: We have already characterized the cohort (see Knopman 2009) in terms of demographics, vascular risk factors and cognitive change. This also included characterization of nonparticipants (Table 1 in Knopman 2009).

2. We will provide summary statistics for change in vent vol for the group as a whole and by groupings according to age (55-59, 60-64, 65+), sex, race, risk factor (present or absent), baseline vent vol (≤ 2 or >2: median split at baseline scan), baseline WMH (median split).

3. Models for Longitudinal change: Change in vent vol grade will be categorized into 2 groups combining a negative, 0 or 1 grade-point change as "no change", and ≥ 2 grade-point change as evidence of ventricular volume loss. Based on prior experience analyzing change in MRI parameters we expect model result to be similar if the outcome variable is categorized into 3 groups (≤ 0 grade change, 1 grade, ≥ 2 grade). Thus, preliminary analyses will assess the association between risk factors and change in risk of

dichotomous vent vol loss using logistic regression models adjusting for age, sex and race. Initially, we will examine each risk factor separately. We will also fit models with baseline vent vol and it's interaction with the risk factor to determines whether change in vent vol differs as a function of baseline vent vol and whether it modifies the effect of the risk factor on risk of vent vol loss.

4. Subsequent models will include all risk factors (but not APOE) that met a $p<0.1$ threshold in univariate analyses.

5. For vascular risk factors, we will stratify by APOE e4 +/- genotype since that is a fixed characteristic.

Expected Results

From preliminary analyses, 245 subjects had no change in vent vol grade or a lower grade at the follow-up MRI (38/245, 15.5%, or 3.8% of total group); 424 had 1 grade enlargement, 297 had a 2 grade enlargement, and 65 had 3-5 grades of enlargement. The proportion of subjects with $\geq$2 grades of vent vol enlargement consistently increased by age (27.3% for 55-59 36.9% for 60-64 and 42.5% for 65+), but not sex or race. Persons with diabetes, hypertension, and prevalent stroke at visit 2 were also more likely to have 2 grade or larger change in vent vol (49.5% vs 33.7%, 36.7% vs 34.4%, 41.7% vs 35%, respectively). These observations will need to be examined in multivariate models as described above.

Conclusions

Based on our prior work and examination of raw data from serial imaging, our results (will) show that certain vascular risk factors present in middle age were associated with ventricular enlargement over a 14 year period. Diabetes is likely to be the most important risk factor associated with brain volume loss. Hypertension may or may not prove to be important. APOE e4 carriage (which I believe we can take as a surrogate for increased risk for AD and not vascular disease) may not be a risk factor for ventricular vol loss because in the age range of the ARIC cohort, the only brain changes associated with APOE are likely to be in the hippocampus.

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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?

_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.cscc.unc.edu/ARIC/search.php

__XXX____ 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 DS, Mosley TH, Catellier DJ, Coker LH. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimers Dement 2009;5:207-14.

Knopman DS, Mosley TH, Catellier DJ, Sharrett AR. Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. Neurology 2005;65:876-81

Gottesman RF, Coresh J, Catellier DJ et al. Blood Pressure and White Matter Disease Progression in a Biethnic Cohort: The Atherosclerosis Risk in Communities (ARIC) Study. Submitted July 2009

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __XX__ Yes ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* = ARIC Brain MRI study; 1999.01**)**

___ 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/

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.