ARIC Manuscript Proposal # 953

PC Reviewed: 08/07/03 **Status: __A__** **Priority: __2__**
SC Reviewed: 08/07/03 **Status: __A___** **Priority: __2__**

1.a. Full Title: Risk Factors for Brain Atrophy in a Population-Based Middle-Aged Cohort

b. Abbreviated Title (Length 26 characters): Risk Factors and Atrophy

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

Manuscript proposal to Publication's Committee:	July / 2003
Data analysis completed:	October / 2003
Completed manuscript to Publication's Committee:	December / 2003

4. Rationale:

Brain atrophy is associated with a number of neurodegenerative diseases. Recent epidemiologic studies have found that atrophic changes are also common in relatively healthy elderly samples. The clinical significance of brain atrophy in otherwise asymptomatic individuals remains unclear. Two large population-based studies of the elderly, the Rotterdam Scan Study and the Cardiovascular Health Study (CHS), found that brain atrophy was associated with decreased cognitive functioning. We have recently completed a manuscript examining cognitive correlates of atrophy in the ARIC cohort, and found that high grade atrophy was associated with significantly increased risk of impaired performance on measures of cognitive functioning (MS # 314; Mosley et al.).

To the extent that atrophy is a marker of cognitive decline, the identification and control of risk factors for atrophy may reduce the risk of cognitive decline and dementia in late-life. Risk factors for brain atrophy are currently poorly defined. Age is the most frequent correlate. Some studies also have shown a relationship with vascular risk factors, primarily hypertension and stroke. Longitudinal studies based on data from the NHLBI Twin Study also support a relationship with vascular factors. DeCarli et al. (1999), for example, found that systolic and diastolic blood pressure assessed at midlife were inversely associated with brain atrophy 25 years later. In a sample of 74 monozygotic twins, Carmelli et al. (1999) found that with-in pair

differences in history of coronary heart disease, systolic blood pressure, alcohol consumption, and level of physical activity were associated with cerebral atrophy. In the elderly CHS cohort, atrophy (defined as ventricular and sulcal size) was associated with age, sex (greater in men), and ethnicity (greater in non-blacks; Yue et al. 1997). In a separate analysis of CHS data, atrophy was related to several vascular risk factors, but few common factors were observed for men and women (Longstreth et al., 2000). Surprisingly, hypertension and silent infarction were not independently associated with atrophy in multivariate models of these data. The advanced age of the CHS cohort and potential survival bias may have hampered the ability to identify independent associations with prevalent risk factors, particularly hypertension.

In ARIC, ventricular and sulcal size have been shown to be independently associated with retinal microvascular abnormalities (specifically retinopathy; MS # 753a; Wong et al., in press) and alcohol intake (MS # 404; Ding et al., under review). A comprehensive examination of potential risk factors for brain atrophy in ARIC has not been performed. In the current study, we propose to utilize ARIC's extensive vascular risk factor data to identify risk factors for brain atrophy in middle-aged adults.

5. Main Hypothesis/Study Questions:

To characterize the relationship between vascular risk factors and brain atrophy.

6. Data (variables, time window, source, inclusions/exclusions):

Demographic variables: age, race, gender, education
Risk factor variables: diastolic and systolic blood pressure, total cholesterol, HDL, LDL, BMI, fibrinogen, prevalent disease (HTN, diabetes), fasting blood sugar, stroke/TIA status, smoking status, physical activity, ETOH intake, antihypertensive use, HRT use (women), FEV_1, carotid IMT.
MRI variables: ventricular size and sulcal size are the primary dependent variables. White matter lesions and infarct-like lesions will be tested as covariates

Due to the small number of individuals with high grade abnormalities on the atrophy variables, grades 4 and higher will be combined for ventricular size and grades 3 and higher will be combined for sulcal size. Because of the potential for age, ethnicity, and sex to confound the relationship between brain atrophy and potential risk factors, all analyses will control for these factors.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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 ICTDER02 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.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)?

Brain atrophy has been related to retinal microvascular abnormalities and alcohol intake in two ARIC manuscripts (MS# 753a, in press; and MS# 404, under review).

11. 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.