ARIC Manuscript Proposal # 924

PC Reviewed: 03/27/03	**Status: __A__**	**Priority: __2__**
SC Reviewed: 03/31/03	**Status: __A__**	**Priority: __2__**

1.a. Full Title:

Apolipoprotein E genotype, cardiovascular risk factors, and cognitive decline in a middle-aged cohort: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

APOE, CVD, & cognitive chg

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

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3. Timeline:

Data Analysis:	June / 2003
Manuscript Preparation:	September / 2003

4. Rationale:

Studies have shown that carriers of the apolipoprotein E (APOE) epsilon 4 allele have a higher risk of Alzheimer disease (AD) as well as an earlier age at onset. Other studies have shown an association between this genotype and diminished cognitive performance, especially learning and memory tests. Furthermore, associations between cardiovascular risk factors, particularly hypertension and diabetes mellitus, and cognitive decline have been observed in many longitudinal studies, including ARIC.

With the ARIC cohort, we can examine the effect of the APOE genotype on cognitive change over a 6-year time period among middle-aged individuals while accounting for cardiovascular risk factors or looking at potential interactions.

5. Main Hypothesis/Study Questions:

Decline in cognitive function will be greater among carriers of the APOE epsilon 4 (ε4) allele compared with non-carriers among a middle-aged, normal population. Furthermore, the effect of APOE- ε4 will be greater in the presence of hypertension, cholesterol (LDL & HDL), and diabetes.

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

The African American portion of the ARIC cohort has been genotyped for APOE and will be the focus of this analysis. If the genotyping of the remainder of the cohort becomes available by early summer, it will also be included in this analysis.

Exclusions: missing data for cognitive test scores or APOE genotype, history of stroke or transient ischemic attack, use of medications affecting CNS (antipsychotics, antidepressants, etc.)

Exposure: APOE genotype

Outcome: Cognitive function change, as measured by the difference in DWR, WF, and DSS test scores between visits 2 and 4

Covariates: age, ethnicity, sex, education, blood pressure, cholesterol, diabetes, smoking, physical activity, alcohol, depressive symptomatology, marital status

Analyses:

For each of the three neuropsychological tests, DWR, WF, and DSS, the following analyses will be performed:

ANCOVA will be used to compare mean change in cognitive function by APOE genotype before and after accounting for hypertension and diabetes. Each of the six APOE genotypes will be examined separately with ε3/ ε3 as the reference group. Since some of the genotypes are much less common, additional analyses will evaluate four genotype groups that will be defined as follows: 1) ε2/ ε 2, ε2/ ε3, 2) ε3/ ε3 (reference group), 3) ε2/ ε4, ε3/ ε4, and 4) ε4/ ε4. Tests for interaction between APOE and cardiovascular risk factors (diabetes, hypertension, LDL, and HDL) will be performed using ANCOVA.

Logistic regression will be used to determine the odds of having a greater decline in cognitive function for one APOE genotype versus another (see groups described above).

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 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? __X_ 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? **__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 ICTDER02 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://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)?

There are no other manuscript proposals in ARIC analyzing the APOE genotype and cognitive function.