ARIC Manuscript Proposal # 1066

PC Reviewed: _02/11/05	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Metabolic Syndrome, Diabetes and Decline in Cognitive Function

b. Abbreviated Title (Length 26 characters):
MetS, DM & Cog Function

2. Writing Group:
Writing group members: Annie McNeill, Diane Catellier, Tom Mosley, Molly Bray, Kari North, Sherita Hill Golden, Wayne Rosamond

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3. Timeline:

Data Analysis:	To begin upon approval of Manuscript Proposal
Manuscript preparation:	October 2005

4. Rationale:

Decline in cognitive function in middle and older age can occur as part of the natural aging process. However, research suggests that several cardiovascular risk factors can heighten or accelerate this decline prematurely. Diabetes is one such disease that has been associated with an array of affective, neurological, and vascular disorders, such as diminished cognitive function, vascular dementia, depression, and Alzheimer's Disease.[1-3] Diabetes is a multi-faceted disease characterized by both decreased insulin sensitivity and hyperglycemia. At present, there is no clear consensus about whether chronic hyperglycemia is mainly responsible for the increased incidence of these conditions associated with diabetes or whether insulin resistance and compensatory hyperinsulinemia or other metabolic abnormalities associated with insulin resistance also directly contribute to the disease processes.[4]

Recent genetic studies[5] have provided evidence that the presence of the *APOE* epsilon4 allele is one of the strongest determinants of the risk and mean age of onset of Alzheimer's Disease. A recent analysis by Blair and colleagues[6] investigated the association between *APOE* genotype and change in cognitive function and found that middle-aged Caucasian participants with the *APOE 4* had the greatest cognitive decline and participants with the *APOE2* allele had the smallest cognitive decline, when compared to APOE3 carriers.. Further, investigators found that this association was significantly larger among subjects with diabetes or hypercholesterolemia.

Several other disorders, including obesity[7, 8] and hypercholesterolemia[9] have been prospectively associated with cognitive functional decline. Identification of individuals at risk for accelerated decline in cognitive functioning before the manifestation of overt diabetes would allow for early intervention to either prevent or ameliorate this condition. The metabolic syndrome, also known as the insulin resistance syndrome, is the co-occurrence of conditions, including central obesity, impaired glucose metabolism, dyslipidemia, and elevated blood pressure.[10] Individuals with the ATP III-defined metabolic syndrome[10] are 4-5 more likely to develop diabetes than those without this syndrome.[11, 12] If the metabolic syndrome characterizes a population at much greater risk for diabetes, it may also be useful to identify a population at increased risk of cognitive impairment who may benefit from early recognition of this predisposition.

We propose to estimate the association between diabetes and metabolic syndrome and longitudinal changes in cognitive functioning over 6 years (Visits 2-4).

5. Main Hypothesis/Study Questions:

- A dose effect will be observed between the degree of impaired glucose metabolism at baseline and decline in cognitive function. That is, compared to subjects with normal glucose metabolism (fasting plasma glucose <100 mg/dl), the decline in cognitive function will be greater among participants with impaired glucose tolerance (FPG 100-125mg/dl) and greatest among participants with frank diabetes (>=126 mg/dl or self-reported physician diagnosis or use of diabetes medications).

- Among participants without diabetes at baseline, the decline in cognitive function will be greater among participants with the metabolic syndrome than among participants without the syndrome.

    - The association between the metabolic syndrome and cognitive functional decline will be greater among carriers of the APOE epsilon 4 (ε4) allele compared with non-carriers.

    - Measures of insulin resistance at visit 1(fasting insulin, HOMA) and baseline presence of the metabolic syndrome will be independently associated with cognitive decline

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

Main Exposures:

- Diabetes and impaired fasting glucose according to current ADA criteria.
- Metabolic syndrome and individual components according to the definition recommended by ATP III.

Outcomes: The primary outcome is change in cognitive function derived from 3 semi-continuous variables (delayed recall, information processing speed, and word fluency) measured at ARIC visits 2 and 4. In addition, a composite summary measure of cognitive function will be also be derived by standardizing the 3 measures of cognition (mean=0, SD=1) and taking the mean of the 3 standardized measures. Thus, we will also look at change in the composite measure of cognition from V2 to V4.

A series of linear models will be fit adjusted for age, race/gender and other potential confounders.

Potential Effect Modifiers: *APOE* genotype

Population /Exclusions: ARIC cohort members with the following exclusions:

1. Race not black or white, or blacks from Minn. or Washington
2. Missing data on cognitive function variables obtained at V2 or V4.
3. Visit 1 bloodwork obtained after less than 8 hours fasting
4. Missing Visit 1 data for variables required to determine metabolic syndrome status or insulin resistance.
5. History of stroke or TIA at baseline
6. Incident stroke prior to V4

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes

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?
(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

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

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

Yes

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 D et al. *Cardiovascular risk factors and cognitive decline in middle-aged adults.* Neurology 2005 56(1):42-48.

- Authors estimated the association between several CVD risk factors including diabetes and 6-yr change in cognitive function from visits 2 and 4 but did not estimate associations between "prediabetic" states such as IFG and metabolic syndrome and cognitive decline.

Blair CK et al. *APOE genotype and cognitive decline in a middle-aged cohort*. Neurology. 64(2):268-76, 2005.
Authors reported that the association between the APOE genotype and cognitive decline was greater among subjects with diabetes or hypercholesterolemia.

- The proposed study will investigate whether the association between the metabolic syndrome and cognitive decline is modified by the presence of the APOE genotype.

Tom Mosley and Molly Bray, co-authors from the two proposals cited above, have been invited to collaborate on this proposed study.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? **Yes**

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* _____)

Yes **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)***

1995.07

*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.

The authors agree to these conditions.

References

1. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol.* May 2004;61(5):661-666.

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3. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med.* Jan 24 2000;160(2):174-180.

4. Kumari M, Brunner E, Fuhrer R. Minireview: mechanisms by which the metabolic syndrome and diabetes impair memory. *J Gerontol A Biol Sci Med Sci.* May 2000;55(5):B228-232.

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8. Stewart R, Masaki K, Xue QL, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol.* Jan 2005;62(1):55-60.

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10. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486-2497.

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12. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM. The metabolic syndrome as predictor of type 2 diabetes: the san antonio heart study. *Diabetes Care.* Nov 2003;26(11):3153-3159.