

ARIC Manuscript Proposal # 1902

PC Reviewed: 2/14/12
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

The Metabolic Syndrome, MRI Volumetrics and Cognitive Outcomes: Brain Structure and Function in the ARIC cohort

b. Abbreviated Title (Length 26 characters):

Metabolic Syndrome Cognition

2. Writing Group:

Writing group members: Jennifer Dearborn, Rebecca Gottesman, Thomas Mosley, David Knopman, A. Richey Sharrett, Andrea Schneider, Cliff Jack, Laura Coker, others welcome

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Analyses to begin as soon as manuscript proposal is approved.

Goal for abstract submission for International Stroke Conference 2013 (submission deadline August 2012)

4. Rationale:

Over one third of US adults and 17% of US children are obese (1). Obesity is a major risk factor for the metabolic syndrome (Ms), which has various consequences for cardiovascular health and overall morbidity. The Ms is defined by at least 3 of the following: increased waist circumference, elevated triglycerides, low HDL cholesterol, elevated systolic blood pressure, and elevated fasting glucose (2). Dementia, including Alzheimer's dementia (AD), vascular and mixed type dementias, and mild cognitive impairment (MCI), had a global economic impact of

604 billion dollars in 2010 (3). Recently, a link between dementia and Ms has emerged. This proposal seeks to further explore this connection.

The Ms has a role in several inflammatory cytokines which influence the nervous system. Leptin is a molecule involved in appetite regulation, and leptin treated mice had increased brain weights and expression of synaptic and glial proteins (4). In an epidemiological study, log-leptin levels were inversely associated with all cause dementia, and subjects with higher baseline concentrations had larger brain volumes (5). Adiponectin is another adipokine, which improves insulin sensitivity, has shown an inverse relationship with Ms (6). Small study results of plasma adiponectin levels in MCI have been conflicting (7,8). A study published recently showed that increased plasma adiponectin levels in women are associated with an increased risk of dementia (9). TNF alpha, interleukin 6, and monocyte chemoattractant protein 1 (MCP-1) are other potentially interesting adipokines that have not been well studied in association with cognitive decline. Insulin, a defining molecule in the Ms, has receptors in the amygdala and hippocampus, and in AD there are reduced insulin signaling molecules (10).

Epidemiologic associations have described a U-shaped curve in the relationship between lifetime obesity and dementia. Being underweight, overweight and obese during midlife are positively associated with dementia (10,11,12). An imaging study suggested that a high midlife BMI was associated with reduced concentrations of markers of neuronal viability, especially in the frontal lobes (13). One small study showed an increase in BMI was related to some of the variance of decreases in gray matter volume between pre and post menopausal women (14). The clinical significance of these studies is unclear, as is whether these imaging findings relate to a later life risk of developing dementia. Some studies also suggest that late life obesity may be protective against cognitive decline (10,11,12). In the ARIC cohort, it was also shown that diabetes, hypertension, stroke and APOE E genotype were associated with cognitive decline (15). It is unclear to what degree the metabolic syndrome is an independent contributor to outcome measurements, rather than the sum of its parts (i.e. hypertension, diabetes, hyperlipidemia, BMI). This proposal will also sort to parse out the independent contributors to outcomes thought to be influenced by the metabolic syndrome, to better understand the effect garnered by variables related to a spectrum of endocrinologic change (such as insulin resistance).

5. Main Hypothesis/Study Questions:

1. The Ms (presence or absence upon study entry) and each of its individual components will be positively associated with cognitive dysfunction, as measured by neuropsychological testing. It will also be associated with a change in cognitive performance, as determined by examining change in neuropsychological testing at two time points (visit 2 (1990-92) and visit 4 (1996-99) in the whole cohort). Presence of Ms at baseline (visit 1) will be most predictive of change in cognitive functioning. We will also look at each of the anthropomorphic measurements collected at visit 1, as well as each of the individual components of the Ms collected at both visit 1 and visit 2 (lipids, hemoglobin A1C, triglycerides, hypertension) to test this hypothesis. For the subset of individuals who have cognitive assessment as part of the ARIC BRAIN MRI ancillary study, we will evaluate change in cognitive performance across these three visits, from visit 2 (1990-2) through the BRAIN 2004-6 and Carotid MRI visit in the same time period. We expect the relationship between Ms and cognition to be strongest for this group, since the likelihood of decline in cognitive performance is greatest in this group. Using techniques previously used in ARIC in which cognitive data from either the Brain or Carotid MRI visit is used (whichever is done earlier in individuals with testing at both time points), we will be able to include more individuals who were in either of these two ancillary studies.

2. Presence of the Ms and each of its components will be associated with increased subclinical white matter disease and decreased gray matter volumes. In 1993 to 1995 (visit 3), 1,929 subjects had MRI brain performed. In 2004 to 2006, as part of the Brain MRI ancillary study, 1,134 subjects had a 2nd MRI scan. MRI markers including subclinical infarcts, extent of white matter hyperintensity (WMH) (qualitative measurements at visit 3 and both qualitative and semi quantitative volumetric measurements at the Brain MRI visit), and gray matter volumes have all been measured. The primary outcomes of interest will be incident subclinical infarcts (with a particular focus on lacunes/ smaller infarcts), change in WMH volume (using the previously published methods to calculate estimated volume of progression) (16), WMH volumes at visit 3 and Brain MRI visit, qualitative sulcal width and ventricular size measurements from visit 3, and gray matter volumes from the Brain MRI visit.

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 methodological limitations or challenges if present).

Study Design: prospective data collection on risk factors with cross-sectional definition of the outcome based on the neuropsychological assessment performed 1990-92 and 1996-99, and 2004 to 2006 and the ARIC Brain MRI in 1993 to 1995 and 2004-2006.

Inclusion: All individuals in the ARIC cohort with at least one cognitive assessment

Exclusion: Missing Brain MRI data (for structural brain volume hypotheses); Missing anthropometric data, Missing neuropsychological testing, pre-existing neurologic condition that might impact cognition, use of medications felt to impact cognition at the time of testing (exclude only those testing dates when these medications are in use).

Data Analysis:

Hypothesis 1: Linear regression with metabolic syndrome (composite variable, presence/absence) or waist circumference, triceps measurement, hip and calf measurement, fasting glucose, BMI, diabetes, triglycerides, systolic blood pressure and HDL cholesterol (categorical variables) as independent variables, predicting cognitive outcome, as measured by either change in neuropsychological testing scores between visit 2 and visit 4, or scores at visit 4. Depending on the available sample size, for individuals in the Brain MRI or Carotid MRI study, we will use random-effects linear regression models to account for the intra-individual correlation of cognitive scores. The primary exposure of interest will be the Ms X time term in these random-effects models, or just Ms in the linear regression looking at change for people with scores at 2 time points. The measures for the independent variables will be taken from visit 1 or visit 2. The delayed word recall, digit symbol substitution task and word fluency tests will each be analyzed independently. We will also consider a “global” z-score from the 3 neuropsychological tests as a composite variable. Covariates will include age, gender, prevalent CHD, ApoE status, and diabetes in addition to those already listed above.

Hypothesis 2: Linear regression; Ms Presence/ absence (independent variable), WM volume (using variables/ calculated progression as described above), gray matter volume (dependent variable). Same covariates. Also logistic regression using top quintile of WMH progression or incident subclinical infarcts/ lacunar infarcts as dependent variable with same independent variables will be used.

Outcome: Delayed word recall, digit symbol substitution task and word fluency scores and a global score (mean of z for each test). White matter lesions: Volume (measured volumetrically) and white matter grade. Gray matter volume.

Variables of interest: Metabolic syndrome (composite variable), waist circumference, triceps measurement, hip and calf measurement, fasting glucose, BMI, diabetes, triglyceride, systolic blood pressure and HDL cholesterol from visit 1.

Brain MRI data from visit #3 (1993 to 1995) and Brain MRI study visits (2004-2006).
Other potential confounders: Weight loss (from visit 1 to ARIC Brain MRI visit), diabetes, age, APOE E genotype.

Limitations:

The presence or absence of the metabolic syndrome at different points in life can affect cognitive outcomes. It may be that obesity in late life, but not early life is protective. Measuring factors related to the Ms at visit 1 may not represent a lifetime of exposure, for example a subject who meets criteria for Ms at visit 1 could lose significant weight by follow up visits, and whether they are at the same risk for the predicted outcomes as someone who has the Ms throughout life is difficult to separate out. Also, in this subset, neuropsychological testing and brain MRIs were performed fairly early, perhaps before the subjects exhibited cognitive decline. Therefore the absence of an association in this study will not negate the presence of an association in later life.

7. a. Will the data be used for non-CVD analysis in this manuscript? 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? 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? Yes No (We will use ApoE genotype data)

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

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? 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.csc.unc.edu/ARIC/search.php>

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)?

1999.01-BrainMRI 1553 Knopman DS, Penman AD, Catellier DJ, Coker LH, Shibata DK, Sharrett AR, Mosley TH Jr. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. Neurology. 2011 May 31;76(22):1879-85.

2003.05-HbA1cV2, 2006.15C-HbA1cDM 1418. Christman AL, Matsushita K, Gottesman RF, Mosley T, Alonso A, Coresh J, Hill-Briggs F, Sharrett AR, Selvin E. Glycated haemoglobin and

cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*. 2011 Jul; 54(7):1645-52. Epub 2011 Mar 1. PubMed PMID: 21360189

2008.09-AFIBinARIC 1389. Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 2010 May; 159(5):850-6
2009.11 1121. Knopman DS, Mosley TH, Catellier DJ, Coker LH; Atherosclerosis Risk in Communities Study Brain MRI Study. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimer's Dement*. 2009 May;5(3):207-14. Epub 2009 Apr 11.

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* ARIC Brain MRI: 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.csc.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.

1. <http://www.cdc.gov/obesity/data/trends.html>. Accessed 8/22/2011
2. Alberti KG, Eckel RH, Grundy SM, et al. International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009 Oct 20;120(16):1640-5.
3. Abbott A. Dementia: a problem for our age. *Nature*. 2011 Jul 13;475(7355):S2-4.
4. Ahima RS, Bjorbaek C, Osei S, Flier JS. Regulation of neuronal and glial proteins by leptin: implications for brain development. *Endocrinology*. 1999 Jun;140(6):2755-62.
5. Lieb W, Beiser AS, Vasan RS, et al. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. *JAMA*. 2009 Dec 16;302(23):2565-72.
6. Espinola-Klein C, Gori T, Blankenberg S, Munzel T. Inflammatory markers and cardiovascular risk in the metabolic syndrome. *Front Biosci*. 2011 Jan 1;16:1663-74.
7. Une K, Takei YA, Tomita N, et al. Adiponectin in plasma Kamogawa K, Kohara K, Tabara Y, Uetani E, Nagai T, Yamamoto M, Igase M, Miki T. Abdominal fat, adipose-derived hormones and mild cognitive impairment: the J-SHIPP study. *Dement Geriatr Cogn Disord*. 2010;30(5):432-9.
8. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch Neurol*. 2009 Mar;66(3):300-5.

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9. van Himbergen TM, Beiser AS, Ai M, Seshadri S, Otokozawa S, Au R, Thongtang N, Wolf PA, Schaefer EJ. Biomarkers for Insulin Resistance and Inflammation and the Risk for All-Cause Dementia and Alzheimer Disease: Results From the Framingham Heart Study. *Arch Neurol.* 2012;0(2012).
10. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev.* 2011 May;12(5):e426-37.
11. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, Luchsinger JA. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol.* 2009 Mar;66(3):336-42.
12. Forti P, Pisacane N, Riatti E, et al. Metabolic syndrome and risk of dementia in older adults. *J Am Geriatr Soc.* 2010 Mar;58(3):487-92.
13. Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ. Body mass index and magnetic resonance markers of brain integrity in adults. *Ann Neurol.* 2008 May;63(5):652-7.
14. Soreca I, Rosano C, Jennings JR, et al. Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. *Psychosom Med.* 2009 Jun;71(5):485-90.
15. Knopman DS, Mosley TH, Catellier DJ, Coker LH; Atherosclerosis Risk in Communities Study Brain MRI Study. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimer's Dement.* 2009 May;5(3):207-14. Epub 2009 Apr 11.
16. Gottesman RF, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH Jr. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke.* 2010 Jan;41(1):3-8.