1.a. Full Title:

Cerebral MRI Findings and CT-Defined Abdominal Adiposity: the Shared Cohort of the Atherosclerosis Risk in Communities Study and the Jackson Heart Study

b. Abbreviated Title (Length 26 characters): Cerebral MRI and CT-defined abdominal adiposity

2. Writing Group:

Writing group members: Liu J, Mosley T, Taylor HA, Sims M, Hickson D, Penman A, Butler K, Knopman D and Shibata D.

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

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3. Timeline:

- Analysis will begin as soon as manuscript is approved.
- Timeline for the reports to the ARIC and JHS committees from the preliminary data analysis and data completion will optimistically be by the end of October and December, 2010, respectively.
4. **Rationale:**

White matter hyperintensities and brain atrophy are important prognostic factors for cognitive impairment, dementia\(^1\-^3\) and even stroke\(^4,^5\). Recent studies indicate that obesity is linked to the development of Alzheimer’s disease and alterations in brain structure\(^6\-^8\). Such an association between obesity and Alzheimer’s disease may be mediated by several potential obesity-related risk factors including diabetes\(^9\), hypertension\(^10\), and vascular disease\(^11\). Based on associations among obesity, metabolic and vascular disease, and dementia, it is important to further investigate changes in brain structure in relation to abdominal adiposity, defined by computed tomography. More importantly, abdominal visceral adipose tissue is a metabolically active fat depot and is a major driving risk factor for insulin resistance, dyslipidemia, diabetes and coronary heart disease in both men and women across different ethnic groups\(^12\-^17\).

Although body mass index (BMI) is widely accepted as a simple marker of adiposity in population studies, it should be more properly viewed as an index of weight excess, rather than body fatness. The disadvantage of BMI measurement is that it does not provide information on body composition or distinguish between fat and fat-free mass, or between abdominal visceral fat (VAT) and abdominal subcutaneous fat (SAT)\(^12\). Along with this, the neurochemical, hormonal, inflammatory and vascular factors implicated in cognitive impairment, dementia and stroke are more likely related to adipose tissue distribution (in particular VAT) rather than to general measures of overweight/adiposity (BMI).

Cardiometabolic risk factors, including obesity, dyslipidemia, metabolic syndrome, diabetes and hypertension suggested to cardiovascular disease (CVD)\(^12,^13,^15\), were also proposed to explain individuals having the higher cognitive impairment, dementia and stroke\(^18,^19\). Quantitative measurement of abdominal fat depot by CT examination, in uncomplicated obesity, appears to take in account the fat depot in abdomen more than BMI for the circulating levels of these hormones and cytokines\(^18,^19\). Furthermore, abdominal VAT exerts the metabolic and inflammatory actions both at its regional site (paracrine action)\(^20\) and also systemically\(^12\), which will contribute to the relationship between VAT and an increase of CVD risk\(^12\-^16\). The evidence above suggests that VAT is the main contributor for CVD risk. Thus, the role of abdominal VAT and the systemic action of VAT has been proposed as factors affecting brain health and subsequent cognitive impairment, dementia and stroke, and deserves further investigation.

We will evaluate how VAT/SAT, considered as a predictor of CVD and a component of the metabolic syndrome, may be associated with changes seen on brain MRI in this shared cohort of the Atherosclerosis Risk in Communities (ARIC) and the Jackson Heart Study (JHS).

**Reference List**


5. Main Hypothesis/Study Questions:

The central hypothesis of this study is that cerebral MRI abnormalities will be independently associated with abdominal VAT and SAT measured by computed tomography. We anticipate that the strongest associations with VAT/SAT will be observed for white matter hyperintensity (WMH) volume and infarct-like lesions (ILL).

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).

Study design: A cross-sectional study.


Exclusion: Participants with stroke or missing brain MRI and abdominal CT.

MRI assessment (from the ARIC MRI follow-up study)\textsuperscript{21-23}:

- White matter hyper-intensity (WMH) volume: graded 0-9, and categorized into normal, mild, moderate and severe.
- Incident infarct-like lesions (ILL): defined as $\geq$3mm in diameter.
- Ventricular volume.
- Total brain volume and atrophy: defined as difference between total intracranial volume and brain volume.
- Sulcal grade (SG): graded 0 – 9.
CT assessment: VAT and SAT measured by computed tomography.

Risk factors: CVD risk factors, hypertension, diabetes, metabolic syndrome (defined by ATP III criteria) and medication use recorded at the JHS Exam 2.

Covariates: age, gender, smoking and alcohol use status, education and family income.

Data analysis: Comparison between participants with cerebral MRI lesions and those without will be evaluated using $\chi^2$ for categorical variables and $t$ test for continuous variables. A multivariable regression analysis will be used to test the independent associations between VAT/SAT (separately) and WMH volume, ventricular volume, total brain volume and atrophy, SG and incident ILL, adjusted for covariates including CVD risk factors, age, gender, presence of medical illness, alcohol and smoking status, and medication use.

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 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  _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 ICTDER03 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: http://www.cscc.unc.edu/ARIC/search.php
   ____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)?
   n/a
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  __X__ Yes  _____ No
11.b. If yes, is the proposal
X ___ A. primarily the result of an ancillary study (list number* AS#: 1999.01 – ARIC MRI Study)
___ 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.