1.a. Full Title:

The associations of psychosocial stress and discrimination with brain MRI and cognitive function: the shared cohort of the Atherosclerosis Risk in Communities Study and the Jackson Heart Study

b. Abbreviated Title (Length 26 characters): Stress & Brain MRI

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. [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 data analysis and manuscript completion will optimistically be by the end of October and December, 2010, respectively.
4. **Rationale:**

The brain is a target organ of stress. It is an essential organ in the adaptation to psychosocial stress and regulates the physiological and behavioral coping processes that maintain homeostasis in the brain and the body\(^1\). Responses to major stressors involve two-way communications between the brain and biological systems via neural and endocrine signaling\(^2\). Two key biological systems that are thought to be implicated in the association between stress and the maintenance of homeostasis in the brain and the body\(^3\) are the sympathetic nervous system (SAM) and the hypothalamic-pituitary adrenocortical (HPA) axis. The SAM is the faster acting response system (i.e., fight-or-flight) with direct effects on cardiovascular and metabolic functions, including vasoconstriction and increased blood flow to skeletal muscles. The slower acting activation of the HPA has direct effects on metabolic, immune, and reproductive functions. These HPA effects include additional effects for lipolysis and gluconeogenesis mediated through cortisol.

The adaptation of multiple systems in the human body in response to psychosocial stress ("allostasis") is a critical component in maintaining internal viability and functioning\(^3\). It has been hypothesized that failure of an individual’s biological systems to adapt is associated with an over or inadequate production of biological mediators ("allostatic state"). Sterling and Ever (1998) defined allostatic load (AL) as the process by which wear and tear accumulates in the brain (and the body) due to repeated activation and dysregulation of physiological systems that respond to change, particularly from external stressors. Population studies have found that the cumulative physiologic dysregulation of multiple systems (i.e., AL) is predictive of stroke\(^4\) and cardiovascular mortality\(^5-6\). Moreover, AL has been shown to be associated with atrophy of nerve cells in brain\(^7\). Taken together, acute and chronic stressor can exert adverse health outcomes on the brain via AL.

Stress has been shown to be a biologically significant and pervasive factor that negatively impacts memory, cognitive function, and brain structure and function in laboratory animals and humans\(^8-13\). Neurological changes mirror the pattern seen in the cardiovascular, metabolic, and immune systems, that is, in the maintenance of allostasis or the cumulative long-term damage of AL\(^14\). For example, the hippocampus and amygdala undergo atrophy in several psychiatric disorders and respond to repeated stressors through the shrinkage in dendritic branching and reduction in the number of neurons in the dentate gyrus\(^15\). A number of studies in humans have shown stress-induced physiological changes in the hippocampus including alterations in synaptic plasticity, neuronal morphology, neurotoxicity, and neurogenesis in adults\(^16\). These studies suggest that psychosocial stressors are important risk factors for cerebrovascular risk.

Previous work indicates that African Americans are more likely than their White counterparts to experience greater cumulative exposures to stress and other adverse conditions, including major negative life events and discrimination\(^17\). Discrimination, a psychosocial stressor, refers to the unjust behavior of an individual or group against a different individual or group\(^18\) and can be based on characteristics such as age, sex, race/ethnicity, and weight/height. Research has shown significant mental and physical health consequences associated with exposure to racial discrimination\(^19\). Documenting...
the contribution of acute and chronic stress and discrimination to brain structure and function (i.e., cognitive functioning) will enhance our understanding of the mechanisms through which stress may influence cerebrovascular health and other health outcomes.

We propose to examine the associations of four psychosocial stressors, including perceived discrimination, with magnetic resonance imaging (MRI) measurements and neurocognitive assessments in the shared cohort of the Atherosclerosis Risk in Communities (ARIC) and the Jackson Heart Study (JHS).

Reference List


5. Main Hypothesis/Study Questions:

The central hypotheses that guide this research are:

1. Perceived psychosocial stress and discrimination will be associated with cerebral MRI abnormalities, such as visual pattern (MRI-defined infarcts, white matter hyperintensities volume, ventricular size, and sulcal size), brain volume and brain atrophy (total intracranial volume – brain volume/intracranial volume).
2. Perceived psychosocial stress and discrimination will be associated with cognitive functioning, such as global mental status, delayed word recall, word fluency, processing speed, and executive functioning.

**Secondary to each hypothesis:** The associations of perceived measures of stress and discrimination with brain structure (Hypothesis 1) and cognitive function (Hypothesis 2) will differ by sex.

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.

**Inclusion:** JHS participants who completed the JHS baseline examination (2000-2004) who also underwent ARIC MRI follow-up exam (2004-2006).

**Exclusion:** Participants missing stress and discrimination measures (at JHS baseline exam) and Brain MRI measures and neurocognitive assessments. Prevalent stroke.

**MRI assessment (from the ARIC MRI follow-up study):** MRI-defined infarcts (> 3 mm), white matter hyperintensities volume, ventricular size, sulcal size, brain volume and brain atrophy (total intracranial volume - brain volume / intracranial volume).

**Neurocognitive Assessment (from the ARIC MRI follow-up study):** cognitive functioning, defined as global mental status, verbal memory (including delayed word recall), word fluency, processing speed, and executive functioning.

**Psychosocial stress:**
GPSS measured the perception of the severity of stress experienced over a prior period of twelve months in eight domains including employment, relationships, related to one’s neighborhood, caring for others, legal problems, medical problems, racism and discrimination, and meeting basic needs. Participants rated stress severity for each domain on a 4-point scale ranging from “not stressful” to “very stressful.” Responses will be scored from 0 to 4 and summed to compute an overall GPSS score.

The WSI consisted of an 87-item questionnaire that assessed minor discrete experiences of stress across a broad range of life domains (over the past week) including, work tasks, relationships, finances, transportation, household tasks and responsibilities, leisure time activities, and others. Participants were asked to assess the severity of the stressors during the past week on a 7-point scale with levels defined as follows: did not happen; not stressful; slightly stressful; mildly stressful; moderately stressful; stressful; very stressful; extremely stressful. The WSI was given to study participants at the baseline exam with instructions to complete at home and mail back to the JHS Coordinating Center.
The survey of MLE included 11 items for which participants were asked if they had occurred in the last 12 months by answering “yes” or “no.” The items included: (1) experiencing serious personal illness; (2) being a victim of physical assault; (3) being a victim of a robbery or home burglary; (4) losing a loved one due to violence; (5) experiencing gunfire at home/neighborhood; (6) having a close friend/relative die; (7) having a close friend/relative experience major illness/injury; (8) moving to a worse residence/neighborhood; (9) losing a job; (10) being forced to retire when didn’t want to; (11) experiencing divorce/separation from spouse.

Risk factors:  
CVD/stroke risk factors: systolic blood pressure, anti-hypertensive medication use, type 2 diabetes, left ventricular hypertrophy  
Health behaviors: cigarette smoking, alcohol intake, dietary intake, and physical activity  
Adiposity: Body mass index and waist circumference

Confounders: age, sex, education, income.

Data analysis:  
All analyses will be stratified by sex because prior work has suggested differential associations of psychosocial stress with structural plasticity and remodeling in the adult brain by sex. Descriptive statistics and the appropriate statistical tests will be used to describe (and compare) the brain structure and function measures with stress and discrimination measures, and socio-demographic characteristics by sex.

To examine the independent relationships between the three psychosocial stress measures and brain structure and function (separately), a sequence of linear multivariable regression models will be fit: Model 1 adjusts for age and sex (except in sex-specific models), and socio-economic status; Model 2 adjusts for the variables in Model 1 plus health behaviors; Model 3 adjusts for the variables in Model 2 plus standard adiposity measures (e.g., BMI); and, Model 4 adjusts for the variables in Model 3 plus CVD/stroke risk factors. Because many of the adiposity and psychosocial measures are highly correlated, collinearity will be assessed by examining the variance inflation factor; values greater than 3 suggest collinearity between covariates and the strongest predictor (based on the standard error) will be retained. In addition, effect modification/interactions by sex will be tested in Model 1. With respect to cognition, we will examine effect modification with Apolipoprotein E (APOE).

We will also consider developing a chronic stress measure by either (1) standardizing subscales or (2) ‘high-risk’ (i.e., upper 25th percentile) quartiles and summing across the three stress measures.

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
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 at:  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)?


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

_____ 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.