Perceived Stress Is Associated with Subclinical Cerebrovascular Disease in Older Adults

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Objective: *To examine the association of perceived stress with magnetic resonance imaging (MRI) markers of subclinical cerebrovascular disease in an elderly cohort.* **Methods:** *Using a cross-sectional study of a community-based cohort in Chicago, 571 adults (57% women; 58.1% African American; 41.9% non-Hispanic white; mean [SD] age: 79.8 [5.9] years) from the Chicago Health and Aging Project, an epidemiologic study of aging, completed questionnaires on perceived stress, medical history, and demographics as part of an in-home assessment and 5 years later underwent a clinical neurologic examination and MRI of the brain. Outcome measures were volumetric MRI assessments of white matter hyperintensity volume (WMHV), total brain volume (TBV), and cerebral infarction.* **Results:** *Stress was measured with six items from the Perceived Stress Scale (PSS); item responses, ranging from never (0) to often (3), were summed to create an overall stress score (mean [SD]: 4.9 [3.3]; range: 0−18). Most participants had some evidence of vascular disease on MRI, with 153 participants (26.8%) having infarctions. In separate linear and logistic regression models adjusted for age, sex, education, race, and time between stress assessment and MRI, each one-point increase in PSS score was associated with significantly lower TBV (coefficient = −0.111, SE = 0.049, t[563] = −2.28, p = 0.023) and 7% greater odds of infarction (odds ratio: 1.07; 95% confidence interval: 1.01, 1.13; Wald χ^2[1] = 4.90; p = 0.027). PSS scores were unrelated to WMHV. Results were unchanged with further adjustment for smoking, body mass index, physical activity, history of heart disease, stroke, diabetes, hypertension, depressive symptoms, and dementia.* **Conclusions:** *Greater perceived stress was significantly and independently associated with cerebral infarction and lower brain volume assessed 5 years later in this elderly cohort.* (Am J Geriatr Psychiatry 2014; 22:53−62)

Key Words: MR measures, perceived stress, biracial population sample

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http://dx.doi.org/10.1016/j.jagp.2012.06.001

INTRODUCTION

A growing body of research shows that various indicators of stress, including job strain, chronic severe stress, and poor stress-coping capability, are associated with excess risk of incident stroke and stroke-related mortality.[1–5] These studies add to the existing literature regarding the influences of psychosocial factors on cardiovascular disease (CVD), which clearly documents the important contributions of chronic psychological stress to CVD morbidity, mortality, and other CVD-related health outcomes.[1,6–10] A number of studies have examined measures of stress in relation to prevalence and progression of subclinical atherosclerosis or other subclinical forms of CVD. However, few previous studies have investigated stress in relation to subclinical indicators of cerebrovascular disease as revealed by magnetic resonance imaging (MRI). Understanding the impact of stress earlier in the disease process may further understanding of disease progression and of the mechanisms by which chronic stress can contribute to increased stroke risk.

We used data from more than 500 participants in the Chicago Health and Aging Project (CHAP) to examine the association between perceived stress and subclinical cerebrovascular disease measured on average 5 years later. We hypothesized that higher levels of perceived stress would be associated with greater subclinical cerebrovascular disease, as measured by MRI and manifested as greater white matter hyperintensity volume (WMHV), lower total brain volume (TBV), and increased risk of cerebral infarction. We further hypothesized that these associations would be independent of known vascular risk factors and conditions.

METHODS

Study Design

CHAP is a longitudinal population-based study of common chronic health problems among older adults, with a focus on dementia and cognitive decline. CHAP study design and population characteristics have been previously reported.[11,12] Briefly, a complete census of three adjacent community areas in south Chicago was completed between 1993 and 1997. All residents identified via the census who were age 65 years or older were invited to participate; 78.9% of eligible persons (N = 6,158) agreed and provided informed consent. This is the CHAP Original Cohort. The study population reflects the race/ethnicity makeup of the community areas at the time of the census, predominantly African American and non-Hispanic white (<1% reported another race category or Hispanic ethnicity). Five data collection cycles have occurred, with data obtained, on average, every 3 years; that is, 1993–1997 (cycle 1), 1997–1999 (cycle 2), 2000–2002 (cycle 3), 2003–2005 (cycle 4), and 2006–2008 (cycle 5). Beginning with data collection cycle 3, residents from the CHAP community areas who had since turned 65 years old and who were identified through the previous community census or commercially available lists were enrolled into CHAP. These are the CHAP study Successive Cohorts, and they follow the same 3-year interview cycles and complete the same measures as the CHAP Original Cohort. For analyses, data from both cohorts are combined.

Procedures

Each CHAP data collection cycle has 1) an in-home population interview, with brief tests of physical function, psychosocial variables, and cognitive function, and 2) a clinical evaluation of a stratified random sample (about one-sixth) of subjects at each cycle that includes neuropsychological testing, a neurologic examination, medical history, laboratory testing, and expert clinical assessment for dementia. Starting with cycle 3 and continuing with subsequent cycles, those completing the clinical evaluation were invited to complete a neurologic imaging evaluation (MRI). Clinical evaluations usually take place in the subjects' homes and are conducted by a team of examiners led by a senior neurologist (NTA). Structured neurologic examinations and medical histories are performed by specially trained nurse clinicians. The diagnosis of dementia required the senior neurologist's assessment of loss of cognitive function and impairment in two or more areas during cognitive performance testing. The diagnosis of Alzheimer disease used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association,[13] except that subjects who met these criteria and had another condition that impaired cognition were retained (i.e., enrolled in the present study). Vascular dementia diagnosis followed

the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement criteria.[14]

Study Sample

As previously reported,[15] of the 1,260 persons who completed the clinical evaluation as part of cycle 3 and cycle 4, 663 (52.6%) participated in the MRI evaluation and thus were eligible for inclusion in the present analysis. Persons without MRI data (N = 597) were older (mean age: 81.5 ± 6.5 versus 80.1 ± 5.9 years; t [1211] = 4.1; p <0.001), less educated (mean years of education: 12.4 ± 3.5 versus 12.9 ± 3.7; t [1258] = −2.3; p = 0.02), and more likely to be women (396 of 775 women versus 201 of 485 men, $\chi^2[1] = 11.15$, p = 0.008) compared with those who had complete MRI data. The final study sample was limited to 571 subjects who had complete data on the Perceived Stress Scale (PSS), which was obtained at the CHAP study visit at cycle 2, as well as complete data on the MRI measures, which were obtained at either cycle 3 or 4. Due to missing values on covariates, the total number of participants for analyses ranged from 557 to 571. The mean (SD) for time between stress assessment and MRI was 5.2 (1.8) years. Signed informed consent was obtained from each subject, and the Institutional Review Board of Rush University Medical Center approved the study.

MRI Evaluation

The methods for MR image acquisition and assessment of TBV, WHMV, and degree of cerebral infarction have been previously described.[15–17] The same MRI methods were used for this study. WMHV was calculated as a proportion of total cranial volume (to account for variations in head size) and log-transformed (natural log) to achieve a normal distribution (skew, −0.21). TBV was computed as the ratio of total parenchymal volume to total cranial volume and had an approximately normal distribution (skew, −0.10). The presence or absence of cerebral infarction was determined manually by the operator, based on the lesion's size and imaging characteristics. The image analysis system allowed for superimposition of the fluid-attenuation inversion recovery image, proton density image, and T2-weighted image at three times magnified view to assist in interpreting lesion characteristics. Signal void seen on T2-weighted images was interpreted as being indicative of a vessel. Lesions 3 mm or larger were considered to be cerebral infarctions. Inter-rater reliability for the MRI measures was previously published,[18,19] and intra- and inter-rater reliabilities for this study were consistently above 0.90. The frequency of cerebral infarction had a skewed distribution; therefore, for analyses we created a dichotomous variable ("yes" or "no") to indicate the presence of an infarction. MRI scoring was completed by a neurologist (CD) who was blind to the data on reported levels of stress from CHAP participants.

Assessment of Stress

Stress was assessed by the PSS as part of the in-home CHAP interview. The PSS assesses the degree to which the respondent appraises situations in the previous month to be stressful and is considered an indicator of the global level of stress experienced by a person.[20,21] The most frequently used version of the PSS includes 10 items; due to considerations regarding participant burden and the wide range of assessments completed as part of the CHAP in-home interview, 6 of the 10 PSS items were used, as follows: 1) In the last month, how often have you been upset because of something that happened unexpectedly? 2) In the last month, how often have you felt that you were unable to control the important things in your life? 3) In the last month, how often have you felt that confident about your ability to handle your personal problems? 4) In the last month, how often have you felt that things weren't going your way? 5) In the last month, how often have you felt that you were on top of things? and 6) In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

PSS item responses typically are on a five-point scale ranging from never (0) to very often (4). However, to streamline responses to a number of questionnaire items in the CHAP in-home interview, we modified the response options slightly, creating a four-point scale, with categories that ranged from never (0) to often (3). Scores for positively worded items were reverse-coded and responses to all items were summed (range: 0–18) to create an overall score, where higher scores indicate greater stress. These scores had an approximately normal distribution and required no transformation. The PSS is well validated and has been used widely in epidemiologic studies.[20,21] The six PSS

items show good reliability (Cronbach coefficient alpha: 0.75) in CHAP. A four-item version of the PSS, which includes items 2, 3, 4, and 6 above, also has been published[21]; the correlation between the six items used in CHAP and the four-item scale is >0.95.

Assessment of Covariates

Several questions assessing self-reporting of vascular risk factors were asked during the CHAP in-home interviews, including a history of smoking, heart disease, stroke, diabetes, and use of antihypertensive medications. Smoking status was classified on the basis of questions about whether the patient currently smoked, smoked in the past, or had never smoked and was coded according to these questions as "ever smoked" or "never smoked." Heart disease was ascertained by the question, "Have you ever been told by a nurse or physician that you have had an MI, or experienced angina?" and coded as "yes" or "no." Diabetes was identified by 1) self-reported history of diagnosis of diabetes or 2) medication to treat diabetes, as determined by direct inspection of prescriptions and of prescription medication containers. History of hypertension was identified by 1) self-reported history of diagnosis of hypertension, 2) measured blood pressure at the CHAP visit $\geq$ 140/90 mm Hg based on the average of two seating measurements after at least a 5-minute rest, or 3) use of antihypertensive medications ascertained by direct inspection of prescription medication containers. Body mass index was calculated as weight in kilograms divided by meters squared; height and weight were measured using standard protocols appropriate for elderly adults.[22] Physical activity was assessed via self-report using questions from the Established Populations for Epidemiologic Studies of the Elderly project.[23] Self-reported history for the diagnosis of stroke was obtained with the question, "Have you ever been told by a doctor or nurse that you had a stroke?" and was rated as "yes" or "no." Depressive symptoms were assessed with a 10-item form of the Center for Epidemiologic Studies Depression Scale (CES-D), which was developed for use with older cohorts.[24] The items inquire about depressive symptoms during the past week, and the dichotomous ("yes" or "no") responses are coded in a manner in which higher scores indicate greater depressive symptomatology (range: 0−10). The CES-D is widely used in epidemiologic studies of older persons, and the reliability of this version of the CES-D has been established.[24] For all participants, data on vascular risk factors and the CES-D were obtained coincident with the data collection cycle when perceived stress was measured.

Data Analysis

Descriptive statistics were calculated for the demographic characteristics of our sample. Correlations (r) and t tests (t) were used to examine the relationship between perceived stress and sociodemographic characteristics of the sample. The association of the perceived stress measure with each MRI measure was examined in a series of separate linear (for TBV and WMHV) and logistic (for cerebral infarctions) regression models. Model 1 included covariates for age, sex, education, race, and time from the ascertainment of perceived stress to MRI (years). Model 2 additionally adjusted for five vascular risk factors: history of diabetes, heart disease, stroke, hypertension, and smoking. Model 3 further adjusted for depressive symptoms and a dementia diagnosis. Analyses were first conducted with perceived stress modeled continuously; subsequently, analyses were repeated to evaluate whether a threshold effect for stress existed by modeling the PSS scores in approximate tertiles from low (reference) to high levels of stress. Interactions were tested between perceived stress and age, sex, education, and race. In addition, sensitivity analyses were conducted that excluded persons with a self-reported history of stroke at any CHAP assessment before the MRI. Model assumptions about linearity, normality, independence, and homoscedasticity of errors were assessed graphically and analytically and were adequately met. Analyses were performed using SAS/STAT software version 9.2 (SAS Institute, Cary, NC). Results with a $p < 0.05$ are reported as significant unless otherwise specified.

RESULTS

Participant Characteristics

Table 1 presents the demographic and neurologic imaging characteristics for the sample overall and also by each categorical level of perceived stress. The mean PSS score in our sample was 4.9 (SD: 3.3). Perceived stress was unrelated to age (r[569] = 0.017,

p = 0.68), educational attainment (r[569] = −0.078, p = 0.061), or sex (t[569] = 0.77, p = 0.44). African Americans reported higher perceived stress levels than did non-Hispanic whites [mean: 5.4 for African Americans versus 4.1 for non-Hispanic whites; t[569] = −4.59, p <0.0001].

Stress and MRI Outcomes

Table 2 presents findings from our primary analyses that evaluated the association of perceived stress with TBV, with results from the models with PSS modeled continuously shown in the upper half of the table and results from the models with PSS modeled categorically shown in the lower half of the table. Controlling for age, sex, race, education, and time from stress ascertainment to MRI (Model 1), each one-point higher PSS score was associated with significantly lower TBV, assessed, on average, 5 years later. This association was unchanged with further adjustment for vascular risk factors (Model 2) and depressive symptoms and dementia (Model 3). Subsequent categorical analysis using approximate tertiles of stress revealed a graded association between stress level and subsequent TBV. In the fully adjusted model (Model 3), participants who had the highest levels of stress had nearly 1.2% lower TBV relative to those with low stress. Although persons with medium stress levels had approximately 0.5% lower TBV than those with low stress, this difference was not significant.

Table 3 shows the results for the stress analyses in relation to infarctions as shown on MR images, with the findings from the logistic regression models with PSS modeled continuously shown in the upper half of the table and findings with PSS modeled in approximate tertiles shown in the lower half of the table. Controlling for age, sex, education, and time from stress ascertainment to MRI (Model 1), each one-point higher PSS score was associated with a 7% greater odds of having an infarction. The inclusion of vascular risk factors (Model 2), dementia, and depression (Model 3) did not modify any observed associations. With PSS modeled categorically, we observed a graded association between stress and odds of occurrence of a cerebral infarction. As shown in the bottom half of Table 3, compared with those with low stress levels, participants who experienced high levels of stress had more than twice the odds of cerebral infarction, which was significant in all models. For the moderate stress group, the odds ratio for infarcts was approximately 1.5, but this did not differ significantly from the low stress group.

Stress scores were unrelated to WMHV (coefficient = 0.019; SE = 0.013; t[563] = 1.46; p = 0.14), which was unchanged after additional covariate adjustment (not shown). Because little is known about the relationship of stress to outcomes as shown on MR images, we also examined whether the observed associations varied in demographically defined subgroups. No interactions between PSS score and age, sex, education, or race (each tested as a two-way interaction in separate models) were noted (data not shown).

Sensitivity Analyses

In subsequent analyses that excluded 65 persons with a history of stroke and 6 additional persons whose stroke history was unknown, we observed similar though somewhat weaker associations for both TBV and infarcts. In a risk factor–adjusted model, perceived stress modeled continuously was associated with lower brain volume, but the association was marginally significant (coefficient = −0.091; SE = 0.052; t[479] = −1.76; p = 0.079). However, the most stressed group (top tertile) still showed significantly lower brain volume relative to the least stressed group (coefficient = −0.897; SE = 0.45; t[478] = −2.0; p = 0.047). For infarcts, a graded association with stress levels was evident. The odds ratios were 1.31 (95% confidence interval: 0.75, 2.26; Wald χ^2[1] = 0.93; p = 0.33) for the moderate stress group and 1.82 (95% confidence interval: 1.01, 3.27; Wald χ^2[1] = 3.93; p <0.05) for the high stress group, adjusting for demographic characteristics and vascular risk factors.

DISCUSSION

In this study of more than 500 elderly individuals from a population sample of African Americans and non-Hispanic whites, we found that greater perceived stress was significantly and independently associated with TBV and MRI infarcts, but not with WMHV, measured 5 years later. The association with TBV and infarcts measures remained robust after controlling for vascular risk factors, depressive

TABLE 1. Clinical and Neuroimaging Characteristics: CHAP

	All Participants (N = 571)		Low Stress (N = 159)		Moderate Stress (N = 238)		High Stress (N = 174)	
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)
Age, years		79.8 (5.9)		79.8 (5.9)		79.0 (5.8)		80.4 (6.1)
Sex								
Male	245 (42.9)		73 (46.0)		100 (42.0)		72 (41.4)	
Female	326 (57.1)		86 (54.1)		138 (58.0)		102 (58.6)	
Race								
Black	332 (58.1)		78 (49.1)		127 (53.4)		127 (73)	
White	239 (41.9)		81 (50.9)		111 (46.6)		47 (27)	
Education, years		12.9 (3.7)		13.4 (3.6)		13.1 (3.7)		12.4 (3.7)
Smoking								
Ever	286 (50.1)		79 (50.3)		118 (49.8)		86 (50.3)	
Never	285 (49.9)		78 (49.7)		119 (50.2)		85 (49.7)	
Body mass index, kg/m^2		27.0 (5.1)		27.2 (4.7)		26.9 (5.4)		26.8 (5.1)
Physical activity[a]		2.5 (4.2)		2.6 (3.9)		2.9 (4.7)		2.0 (3.4)
Chronic conditions[b]								
Diabetes	51 (9.0)		10 (6.4)			25 (10.6)	16 (9.4)	
Heart disease	100 (17.7)		33 (21.0)			42 (17.7)	25 (14.6)	
Stroke	65 (11.5)		15 (9.6)			27 (11.4)	23 (13.5)	
Hypertension	461 (81.6)		117 (74.5)			173 (73)	129 (75.4)	
Dementia	81 (14.2)		21 (13.2)			29 (12.3)	31 (17.8)	
Depressive symptoms[c]		1.3 (1.8)		0.8 (1.3)		1.1 (1.6)		2.1 (2.1)
Perceived stress[d]		4.9 (3.3)		1.1 (0.9)		4.4 (1.1)		9.1 (1.9)
MRI measures[e]								
TBV, %		74.3 (4.6)		74.6 (4.5)		74.6 (4.8)		73.7 (4.4)
WMHV, %		−5.13 (1.09)		−5.18 (1.04)		−5.18 (1.08)		−5.0 (1.12)
Infarcts (yes/no)	153 (26.8)		32 (20.1)		64 (26.9)		57 (32.8)	

Notes: Due to small numbers of missing values on smoking, blood pressure, chronic conditions, and depressive symptoms, Ns for these variables ranged from 558 to 565.

[a]Physical activity measured by self-report using questions from the Established Populations for Epidemiologic Studies of the Elderly.

[b]Chronic conditions (except dementia) defined by self-report of a physician diagnosis of each condition; diabetes further defined by use of insulin or other medications for diabetes; hypertension also included measured blood pressure of 140/90 mm Hg or higher and/or use of antihypertensive medications; dementia defined by the loss of cognitive function and impairment in two or more areas during cognitive performance testing.

[c]Depressive symptoms measured by 10-item Center for Epidemiologic Studies Depression Scale; scores ranged from 0 to 10.

[d]Stress categories based on approximate tertiles of the distribution of perceived stress scores.

[e]TBV calculated as (total parenchymal volume/total cranial volume), and WMHV calculated as natural log(white matter hyperintensity volume/total cranial volume). Infarcts defined as presence/absence of an infarction at least 3 mm in size.

symptoms, or dementia status. Furthermore, no differences were noted in the association of stress with cerebral infarction as shown on MRI and with TBV by sociodemographic subgroup. This suggests that perceived stress may contribute to subclinical vascular findings on MR images in a diverse population of older adults.

We are not aware of any previous population-based studies that directly examined the relationship of perceived stress measures to multiple subclinical MRI markers. Our results, however, are consistent with smaller clinical studies that have examined the association of MRI markers to other psychosocial factors. Indeed, a number of studies have linked decreased hippocampal volume to depressive episodes[25–27] and psychiatric conditions.[28–30] Other studies examining late-life depression, bipolar disorder, anxiety, and post-traumatic stress disorder have demonstrated an association between these conditions and smaller amygdala volumes.[31–34] Depression also is recognized as an important risk factor for stroke[35] and is related to subclinical cerebrovascular disease,[30] yet the effects of stress on TBV and infarcts were independent of depressive symptoms in our analyses. Our findings suggest that perceived stress may reflect additional important psychological characteristics that are negatively and independently associated with subclinical MRI markers in old age.

The present study could not evaluate whether reported stress contributed to changes in brain

TABLE 2. Relationship of Perceived Stress With TBV[a]: CHAP

	Model 1 (N = 571)					Model 2 (N = 559)					Model 3 (N = 557)				
	Regression Coefficient	SE	t[563]	p	Adjusted R^2	Regression Coefficient	SE	t[544]	p	Adjusted R^2	Regression Coefficient	SE	t[540]	p	Adjusted R^2
Results of linear regression models with perceived stress modeled continuously															
Perceived stress	−0.111	0.049	−2.28	0.023	0.317	−0.105	0.049	−2.14	0.032	0.329	−0.134	0.05	−2.69	0.0074	0.354
	Model 1 (N = 571)					Model 2 (N = 559)					Model 3 (N = 557)				
	Regression Coefficient	SE	t[562]	p	Adjusted R^2	Regression Coefficient	SE	t[543]	p	Adjusted R^2	Regression Coefficient	SE	t[539]	p	Adjusted R^2
Results of linear regression models with perceived stress modeled categorically															
Low stress	—	—	—	—		—	—	—	—		—	—	—	—	
Moderate stress	−0.449	0.392	−1.15	0.252		−0.438	0.389	−1.13	0.261		−0.532	0.383	−1.39	0.165	
High stress	−0.965	0.429	−2.25	0.025	0.316	−0.920	0.427	−2.15	0.032	0.328	−1.178	0.432	−2.73	0.0066	0.353

Notes: Values shown are from regression models adjusted for covariates, as follows: Model 1 included age, sex, race, education, time between stress assessment, and MRI. Model 2 included Model 1 covariates and vascular risk factors (risk factors included history of smoking, heart disease, stroke, diabetes, and history of hypertension). Model 3 included Model 2 covariates and depressive symptoms and diagnosis of dementia. In each model shown, df were calculated as N: number of parameters in the model. SE: standard error.
[a]Total brain volume calculated as total parenchymal volume/total cranial volume.

volume, greater white matter hyperintensities, or increased infarctions over time. However, our data on stress were collected on average over 5 years earlier than the MRI data and at least 3 years earlier for 90% of participants. Our findings thus show that perceptions of stress at an earlier point in time are related to future MRI markers of subclinical disease in this elderly cohort. It is possible that MRI abnormalities can influence perceptions of stress, and to the extent that any abnormalities were present at the earlier cycles of data collection when PSS scores were obtained could be also be affecting our results. A small subset of CHAP participants have completed more than one MRI, and as additional data become available, we will be able to assess whether stress relates to progression of subclinical cerebrovascular disease.

Although the relationship between stress and MRI markers in the general population remains poorly understood, the association between stress and health and disease has been well characterized. Some studies have shown that stress is related to outcomes that involve the cardiovascular and metabolic systems[9,36] and the immunologic and inflammatory systems[31] and that these contribute to morbidity and mortality from stroke.[1–5] One possible mechanism suggests that stress can cause a surge in blood pressure that, in turn, may cause a cardiac event. Alternatively, sustained stress may accelerate atherosclerosis, increasing the risk of myocardial infarction or stroke. Another mechanism is related to the hypothalamo-pituitary-adrenal axis[37] and the effects of glucocorticoids on the brain. Stress is thought to increase the activity of the hypothalamo-pituitary-adrenal axis and the levels of these hormones, thereby causing structural and functional damage to the brain (i.e., reduction in hippocampus volumes).[34] Some studies have implicated inflammatory and immunologic processes as potential mediators between stress and health;[33] others have examined genetic factors (e.g., allelic frequencies or polymorphisms) that may interact with chronic stress exposures to influence health;[38–40] and still others have focused on pathways related to socioeconomic, behavioral, and life style variables that may provide links between psychosocial factors and health.[41,42] Stress has also been postulated to influence the appearance of subclinical MRI markers on neuroimaging through its association with underlying CVD.[43,44] In this community-based sample, however, adjusting for cardiovascular

TABLE 3. Relationship of Perceived Stress With Infarcts: CHAP

	Model 1				Model 2				Model 3			
	Odds Ratio	95% CI	Wald χ^2	p	Odds Ratio	95% CI	Wald χ^2	p	Odds Ratio	95% CI	Wald χ^2	p
Results of logistic regression models with perceived stress modeled continuously												
Perceived stress	1.07	1.01–1.13	4.90	0.027	1.07	1.00–1.13	4.17	0.041	1.06	0.99–1.12	3.16	0.076
Results of logistic regression models with perceived stress modeled categorically												
Low stress	—	—	—	—	—	—	—	—	—	—	—	—
Moderate stress	1.52	0.93–2.49	2.82	0.093	1.50	0.90–2.49	2.41	0.120	1.49	0.90–2.48	2.38	0.123
High stress	2.07	1.23–3.50	7.49	0.006	3.51	1.17–3.82	6.42	0.011	1.94	1.11–3.40	5.41	0.020

Notes: N = 571 in Model 1; due to missing data on covariates, N = 559 in Model 2 and N = 557 in Model 3. Infarcts modeled as presence/absence of lesions at least 3 mm in size. Model 1 included covariates for age, sex, race, education, time between stress assessment, and MRI. Model 2 included the covariates from Model 1 and vascular risk factors (history of smoking, heart disease, stroke, diabetes, and history of hypertension). Model 3 included all covariates from Model 2 and depressive symptoms and diagnosis of dementia. In each model shown, df = 1 for each variable in the model.

risk factors did not affect the association between stress and MRI infarcts and TBV, suggesting that these risk factors may not be an important mediator of this relationship.

In the present study, stress was associated with TBV and infarcts but not with WMHV. Our findings are somewhat consistent with two prior studies that examined stress or distress and brain volumes, including white matter hyperintensities. In a small study of 48 healthy postmenopausal women, Gianaros et al.[45] reported that women with higher perceived stress scores over a 20-year period had decreased gray matter volume in both the right orbitofrontal cortex and right hippocampus, relative to women with low stress levels, although stress was not associated with total gray matter volume. No associations were noted between stress and white matter hyperintensities (graded by severity) in that study. A second study showed that psychological distress measured in midlife was related to atrophy in specific gray matter regions later in life in a population-based cohort of women.[46] However, we were unable to ascertain regional brain volumes in the present study so we cannot specify whether hippocampal volumes or volumes of other brain regions were specifically related to stress levels in our older community-based cohort. Future research should address this issue.

Both our study and that of Gianaros et al.[45] failed to find an association between stress and WMHV, which is in contrast to the findings of Johansson et al.,[46] who identified a link between distress at midlife and later odds of white matter lesions. Although replication is needed in future studies, that two studies found no relation is interesting to the extent that WMHV has been thought to be a robust marker for clinical vascular disease, with prominent manifestations in the brain.[39,40] The correlation between stress and WMHV in our study may not have reached statistical significance because a significant proportion of our sample was obtaining medical treatment with respect to cardiovascular risk factors (i.e., 74.1% of the sample was taking antihypertensive medications, whereas 25.9% of the sample had no history of hypertension, and less than 10% of the sample had a history of diabetes). Whether this or other factors play a role in the relation of stress to MRI markers remains to be determined in other studies, which would need to replicate and expand on the findings reported here. Data on biomarkers for stress may help clarify these findings.

The strengths of our study are the inclusion of both African American and non-Hispanic white participants, the use of volumetric brain MRI techniques, and the availability of both medical and psychosocial data. This study also has important limitations. These analyses utilized a single self-reported measure of perceived stress, which may have weakened our ability to detect levels of perceived stress. We also did not include laboratory stress biomarker data, which would have provided us with a better understanding of the potential mechanisms linking stress to subclinical cerebrovascular disease. Despite this, however, we did find associations of stress with two of our MRI measures. Our MRI data do not distinguish volumes for brain regions so we could not analyze the association of stress with hippocampal volume, for example, which other research suggests may be particularly influenced by stress.[47,48] Finally,

although our measure of stress was obtained earlier in time than the measures of subclinical cerebrovascular disease, a lack of baseline MRI data precludes our ability to examine stress in relation to change in MRI indicators of subclinical cerebrovascular disease and does not allow us to rule out whether subclinical vascular disease was present at baseline. Longitudinal analyses will provide increased insight into the relationship of stress to subclinical MRI markers of cerebral infarction. Overall, our findings suggest that perceived stress may have a separate and distinct role in the brain, affecting the occurrence of subsequent MRI markers in an apparently healthy population.

The authors are indebted to the hundreds of participants in the CHAP study. The authors also thank the study coordinators, Jennifer Tarpey and Colleen Plunkett, data and analytic programmers, George Dombrowski, M.S., and the faculty and staff of the Rush Institute for Healthy Aging. This study was supported by the National Institutes of Health (NIH) grants HL084209, AG11101, and ES010902. Dr. Clark was supported by grant 1UL1RR033183 from the National Center for Research Resources (NCRR) of the NIH to the University of Minnesota Clinical and Translational Science Institute (CTSI). The University of Minnesota CTSI is part of a national Clinical and Translational Science Award consortium created to accelerate laboratory discoveries into treatments for patients. Contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the CTSI or the NIH.

Dr. Clark received research support from NIH grants R01 HL084209 and 1UL1RR033183. Mr. Beck received research support from NIH grants R01 AG11101 and R01 HL084209. Dr. Aggarwal has received honoraria for serving as a consultant for Pfizer from 2009—2010, and is funded by grants from NIH: R01 AG022018, P30 AG010161 [Clinical Core Co -Leader] , R01 AG011101, R01 AG009966, R01 HL084209, R01 AG032247; U01 AG010483 [Site Principal Investigator] and the Alzheimer's Association: IIRG-06—27429. Dr. DeCarli serves as a Editor in Chief for Alzheimer's Disease and Associated Dementias–An International Journal and is a Consultant to Advanir, Takeda, and Bayer Corporations. Dr. Everson-Rose was Principal Investigator and received research support from NIH grant R01 HL084209 and is an Associate Editor and on the Editorial Board of Psychosomatic Medicine. Dr. Mendes de Leon served as Associate Editor of the Journals of Gerontology Social Sciences and serves on the editorial boards of Psychosomatic Medicine, the Journal of Aging & Health, the International Journal of Behavioral Medicine, and the Archives of Internal Medicine and receives/has received research support from the NIH [Principal Investigator or Co —Investigator] grants R01 AG021972, R01 HL084209, R01 AG11101, R01 ES010902, R01 AG032247 and R01 AG022018. Dr. Evans received honoraria for serving on the Data Monitoring Committee of a trial for Eli Lily and Company from 2007 to 2008. He is funded [Principal Investigator or Co-Investigator] by NIH grants AG11101, AG036650, AG09966, AG030146, AG10161, AG021972, ES10902, NR009543, HL084209, and AG12505l.

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