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Research Article

The Association of Stress, Metabolic Syndrome, and Systemic Inflammation With Neurocognitive Function in the Hispanic Community Health Study/Study of Latinos and Its Sociocultural Ancillary Study

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Abstract

Objectives: Identifying sociocultural correlates of neurocognitive dysfunction among Hispanics/Latinos, and their underlying biological pathways, is crucial for understanding disparities in Alzheimer's disease and related dementias. We examined cross-sectional associations between stress and neurocognition, and the role that metabolic syndrome (MetS) and systemic inflammation might play in these associations.

Method: Participants included 3,045 adults aged 45–75 (56% female, education 0–20+ years, 86% Spanish-speaking, 23% U.S.-born), enrolled in the Hispanic Community Health Study/Study of Latinos and its Sociocultural Ancillary Study. Global neurocognition was the primary outcome and operationalized as the average of the *z* scores of measures of learning and memory, word fluency, and processing speed. Stress measures included self-report assessments of stress appraisal (perceived and acculturative stress) and exposure to chronic and traumatic stressors. MetS was defined via established criteria including waist circumference, high blood pressure, elevated triglycerides, fasting plasma glucose, and high levels of high-density lipoprotein cholesterol. Systemic inflammation was represented by high-sensitivity C-reactive protein (hs-CRP).

Results: Separate survey multivariable linear regression models adjusting for covariates showed that higher perceived ($b = -0.004$, $SE = 0.002$, $p < .05$) and acculturative stress ($b = -0.004$, $SE = 0.001$, $p < .0001$) were significantly associated

with worse global neurocognition, while lifetime exposure to traumatic stressors was associated with better global neurocognition (b = 0.034, SE = 0.009, p < .001). Neither MetS nor hs-CRP were notable pathways in the association between stress and neurocognition; rather, they were both independently associated with worse neurocognition in models including stress measures (ps < .05).

Discussion: These cross-sectional analyses suggest that stress appraisal, MetS, and systemic inflammation may be targets to reduce neurocognitive dysfunction among Hispanics/Latinos.

Keywords: Cardiovascular disease, Cognition, Minority and diverse populations

Alzheimer's disease and related dementias (ADRDs) are a major public health issue, particularly among Hispanics/Latinos, who may be at increased risk for mild cognitive impairment and ADRDs (González et al., 2015; Gurland et al., 1999; Tang et al., 2001). With the growing population of Hispanics/Latinos reaching older age, the number of Hispanics/Latinos with Alzheimer's disease is expected to increase to 3.5 million by 2060—a growth of 832% relative to 2012—representing the largest increase in ADRDs of any racial/ethnic group in the United States (USC Edward R. Roybal Institute on Aging and the LatinosAgainstAlzheimer's Network, 2016). While the factors underlying these Hispanic/Latino disparities in ADRDs are not well understood, they do not appear to include known genetic risks for ADRD (Farrer et al., 1997). Better understanding of key sociocultural factors underlying neurocognitive function among older Hispanics/Latinos, and the biological pathways contributing to these associations, may facilitate targeted culturally relevant interventions aimed at preventing neurocognitive disorders in this group.

Among the many potential sociocultural factors impacting neurocognitive function in older Hispanics/Latinos, stress may be an important one to consider. Some Hispanics/Latinos face stressors related to socioeconomic disadvantages, limited English language use, place of birth, and experiences with discrimination. Notably, stress has been linked to increased risk for ADRDs and poor neurocognitive function among older persons (Lupien et al., 2009; Machado et al., 2014). Most of the research in this area has been in primarily non-Hispanic samples, and the scant research among Hispanics/Latinos has yielded mixed findings, possibly due to varying methodological approaches across studies, including different stress assessments (Muñoz et al., 2021; Nguyen et al., 2012; Zahodne, Sol, et al., 2019). Stress is a complex multidimensional construct, with measures differing in whether they capture the experience of challenging environmental events (e.g., trauma, life events), or the appraisal of these events (e.g., perceived stress), as well as dimensions of time and severity (Gallo, Roesch, et al., 2014; Monroe, 2008). In the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Muñoz and colleagues (2021) examined whether measures of chronic stress exposure and acculturative stress (i.e., the psychosocial strain experienced as a result of the process of adapting to cultural norms that differ from one's own) were associated with individual neurocognitive tests among middle- to older-aged Hispanics/Latinos (Muñoz et al., 2021). Chronic stress was associated with worse verbal learning, though this association was no longer significant after adjusting for a range of mental (depression and anxiety) and physical health symptoms (i.e., presence of hypertension, coronary heart disease/angina, stroke/transient ischemic attack, diabetes, and heart failure; and body mass index classification). Acculturative stress was linked with worse performance on several neurocognitive tests, with most associations remaining significant after similar adjustments. While not directly examined, some of these findings support the notion that a marker of cardiovascular disease (CVD) risk, such as metabolic syndrome (MetS), might play an important role in the association between stress and neurocognition among Hispanics/Latinos. The increased prevalence of MetS and its components in this group (Heiss et al., 2014) further highlights its relevance to understanding disparities in neurocognitive outcomes among Hispanics/Latinos.

Several lines of research indicate that stress may influence neurocognition through both direct and indirect pathways. Stress has been linked to CVD (Dimsdale, 2008; Steptoe & Kivimäki, 2013) and chronic inflammation (Hänsel et al., 2010; Shivpuri et al., 2012), which in turn have been associated with poor neurocognitive outcomes (Heppner et al., 2015; Siervo et al., 2014), underscoring the role of these factors as potentially important underlying mechanisms in the link between stress and ADRD risk (Bisht et al., 2018; Justice, 2018). A small number of studies have directly examined the mediating role of metabolic and inflammation markers in the association of stress and cognition (Vitaliano et al., 2005; Zahodne, Kraal, et al., 2019). For example, Zhadone and colleagues (2019) found that systemic inflammation (as assessed by high-sensitivity C-reactive protein [hs-CRP]) partially mediated the association between discrimination and memory cross-sectionally in a diverse group of persons aged 51+, but did not mediate longitudinal association between discrimination and cognitive decline, while Vitalino and colleagues (2005) showed that an index of metabolic risk partially mediated differences in longitudinal neurocognitive decline between caregivers and noncaregivers of persons with Alzheimer's disease.

Within Hispanics/Latinos, stress has been linked to increased presence of CVD risk factors and inflammation (Gallo, Roesch, et al., 2014; Isasi et al., 2015; McCurley et al., 2015), as well as with adverse health behaviors linked to CVD

such as poor diet, sedentary behaviors, and smoking (Gallo, Roesch, et al., 2014; Isasi et al., 2015). In turn, CVD risk, including composite measures such as MetS, has been associated with worse neurocognitive function (González et al., 2018; Lamar et al., 2019; Tarraf et al., 2020; Yaffe et al., 2007). Yet, investigation of biological pathways, including MetS and systemic inflammation, linking stress and neurocognition among Hispanics/Latinos is scant.

Building upon previous work in HCHS/SOL (González et al., 2018; Muñoz et al., 2021), the main purpose of the current study was to examine the roles that MetS and systemic inflammation may play in associations between stress (appraisal and exposure) and neurocognition among middle- and older-aged Hispanics/Latinos. In order to do so, we first examined associations between several key stress constructs relevant to Hispanic/Latino health (i.e., perceived stress, acculturative stress, and exposure to ongoing chronic stressors and traumatic events) with neurocognitive function (global and domain specific) in a large and well-characterized cohort of middle- and older-aged Hispanics/Latinos from the HCHS/SOL study. The stress measures that were the focus of this study represent both measures of stress appraisal (perceived and acculturative stress) and exposure to experiences that are typically considered challenging (life events/trauma), and have been linked to worse neurocognition and/or MetS indicators within Hispanics/Latinos (Gallo, Roesch, et al., 2014; Muñoz et al., 2021). For those stress measures that were significantly associated with neurocognition, we investigated whether MetS and systemic inflammation (assessed via serum hs-CRP) helped explain the association between stress and neurocognition via pathway analyses. We hypothesized that higher stress, particularly the appraisal of stress, would be associated with worse neurocognitive function, and with increased MetS and inflammation. Furthermore, accounting for MetS and inflammation would significantly attenuate the association between increased stress and decreased neurocognition among middle- and older-aged Hispanics/Latinos. We also investigated whether the experience of stress might interact with the presence of MetS and inflammation to impact neurocognition. Given the biological importance of age and sex (Farrer et al., 1997) in the development of neurocognitive disorders, a secondary aim of the study was to examine whether age and sex might modify the associations between stress and neurocognition. As we strive to improve our understanding of risk factors for neurocognitive problems in Hispanics/Latinos, it is important to consider whether such factors differ by sex or with increasing age.

Method

Participants

The HCHS/SOL is a multisite (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA), prospective cohort study (Visit 1 [V1]; 2008–2011 total unweighted n = 16,415) of CVD among diverse Hispanics/Latinos aged 18–74 years at V1 (Sorlie et al., 2010). Current analyses included HCHS/SOL participants 45–74 years old, who participated in its Sociocultural Ancillary Study (SCAS) and had neurocognitive data available. Study details are available in previously published reports (Gallo, Penedo, et al., 2014; González et al., 2015; Sorlie et al., 2010). Briefly, all HCHS/SOL participants who consented to being contacted for future research and were willing and able to attend a separate visit within 9 months of HCHS/SOL V1 were eligible for SCAS. During the SCAS visit, which for most participants occurred within 4 months of HCHS/SOL V1, participants completed multiple measures of stress and other sociocultural factors (Gallo, Penedo, et al., 2014). SCAS enrolled 5,313 eligible HCHS/SOL participants, of which 3,282 completed neurocognitive testing during HCHS/SOL V1. For this analysis, we excluded 15 participants in HCHS/SOL younger than 45 years old and 120 participants who self-reported histories of stroke or transient ischemic attack. We also excluded 102 participants who were missing data on covariates of interest (see section below). The unweighted analytical sample size was n = 3,045.

Materials and Procedures

Neurocognition was assessed via the Brief-Spanish English Verbal Learning Test (B-SEVLT (González et al., 2002), the Controlled Oral Word Association Test (COWAT)-Letters F and A (Benton & Hamsher, 1989), and Digit Symbol Substitution test (Wechsler, 1981). Participants completed the neurocognitive assessment battery in their preferred language (Spanish or English). Individual continuous neurocognitive tests scores were transformed into z scores derived from the entire sample of participants who completed neurocognitive testing during HCHS/SOL V1. Global neurocognition was the primary outcome and operationalized as the average of the z scores using four neurocognitive measures, including learning (sum of three learning trials on the B-SEVLT), memory (recall trial of the B-SEVLT), word fluency (sum of scores on letters F and A on the COWAT), and processing speed (Digit Symbol Substitution test total score).

Participants completed various self-reported measures of *stress*. *Perceived stress* was assessed via the Perceived Stress Scale (Cohen et al., 1983), a 10-item Likert-type measure of the degree to which situations in one's life over the past month are appraised as stressful (range 0–40), and higher scores indicate higher perceived stress. *Acculturative stress* was assessed using the Hispanic Stress Inventory (Cervantes et al., 1990), which measures stress associated with the process of living and integrating in a new culture. This 17-item scale asks about specific events over the last 3 months (e.g., "Because I am Latino I have had difficulty finding the type of work I want"), and degree of worry/tension associated with each event using a

5-point scale (from [1] "Not at all worried/tense" to [5] "Extremely worried/tense"). Higher total scores (range 0–85) indicate more acculturative stress. Current *chronic stress* was measured via the Chronic Stress Burden Scale (Bromberger & Matthews, 1996), an eight-item measure which captures the ongoing presence of life stressors (e.g., Have you had a serious ongoing health problem?) in several domains (e.g., health, work, finances, personal relationships). Total scores (range: 0–8) represent the total number of current stressors lasting at least 6 months. Exposure to *traumatic events* (e.g., robberies, natural disasters, sexual and physical assault) was assessed via the Traumatic Stress Schedule (Norris, 1990), a 10-item measure that asks about exposure to traumatic life events (e.g., "Did anyone ever beat you up or attack you?"). Scores range from 0 to 10 and reflect lifetime and past-year exposure to these events.

MetS was operationalized using International Diabetes Federation (2006). Accordingly, MetS was defined by the presence of abdominal obesity (waist circumference >94 cm in men and >80 cm in women) and the presence of two or more of the following: (a) triglycerides ≥150 mg/dL or treatment for lipid abnormality, (b) high-density lipoprotein (HDL)-cholesterol <40 mg/dL in men and <50 mg/dL in women or specified treatment for lipid abnormality, (c) blood pressure ≥130/85 mmHg or use of antihypertension medications, and (d) fasting glucose ≥100 mg/dL, or previous diagnosis of diabetes or use of antidiabetic medications. In secondary analyses, we investigated individual components of MetS and incorporated pulse pressure. *Inflammation* was assessed via hs-CRP, which was measured continuously and categorically using standard clinical thresholds, that is, ≤3 mg/L as normal and >3 mg/L as high (Pearson et al., 2003).

Covariates included the following demographic characteristics: age in years, years of education, sex, place of birth (U.S. or U.S. territory vs foreign-born), Hispanic/Latino heritage background, and language preference. In sensitivity models, we also controlled for study site and two mental health measures assessing symptoms of depression and anxiety. Depression was measured via the 10-item Center for Epidemiological Studies Depression Scale (Andresen et al., 1994), which assesses the frequency of depressive symptoms in the past week, with higher scores indicating higher depression (range 0–30). Anxiety was measured via the 10-item Trait Anxiety Subscale of the State–Trait Anxiety Inventory (Spielberger et al., 1983), with scores ranging from 10 to 40, and higher scores indicating greater anxiety.

Statistical Analyses

We generated descriptive statistics to characterize our target population overall, and by MetS (yes/no) and inflammation status (normal and high). Survey adjusted *t* tests were used to test differences in continuous measures and survey adjusted chi-squared tests for categorical variables. In order to investigate the roles that MetS and systemic inflammation may play in explaining associations between stress and neurocognition among Hispanics/Latinos, we first fit survey linear models to independently examine the associations between each of the stress exposures and global neurocognition (measured in *z* score units), following a four-step approach: (a) adjustment for demographics (age, sex, years of education, Hispanic/Latino background, place of birth, and language preference); (b) adjustment for demographics and MetS only; (c) adjustment for demographics and hs-CRP only; and (d) adjustment for demographics, MetS, and hs-CRP simultaneously. Unstandardized regression coefficients and standard errors were generated and presented in tables. Standardized beta coefficients can be obtained by multiplying the reported coefficients by the standard deviation of the stress measures of interest as presented in Table 1. Sensitivity analyses included adjustments for study site and symptoms of depression and anxiety. This process was repeated for all secondary outcomes to examine neurocognitive domain-specific associations between the stress measures and neurocognition and the degree of attenuation through MetS and inflammation adjustments. All outcomes were modeled using survey linear regression. Additionally, we modeled the primary outcome (global neurocognition) as a function of the individual MetS factors, as well as pulse pressure to investigate the independent impact of individual components. For stress measures that were significantly associated with global neurocognition and biomarkers (MetS and hs-CRP), we then fit structural equation models (SEMs) to estimate direct, indirect (through hs-CRP and MetS status), and total effects for the associations between stress measures and global neurocognition. We followed standard recommendations for fitting the models, and derived direct, indirect, and total effects and their SEs within an SEM framework. We used Robust Maximum Likelihood estimators to account for potential deviation from normality assumptions in the outcomes. SEM modeling was conducted using MPLUS version 8.3 (Muthén & Muthén, 1998–2017), which allows testing of complex indirect effects models using noncontinuous mediators (binary measures in our case) and could accommodate the complex design features of the data (Muthén et al., 2017). Theoretical and applied treatments of these methods have been published elsewhere (Hayes, 2017). To investigate whether MetS and hs-CRP modified the association between stress and cognition, we refit fully adjusted survey linear regression models on global neurocognition, including interaction terms of stress by MetS (yes/no) and hs-CRP (high/normal). Lastly, to investigate whether age or sex modified the association between stress and neurocognition, we refit fully adjusted survey linear regression models on global neurocognition, including interaction terms of stress by age (younger: 45–64 and older: 65+) and sex (male and female).

Table 1. Descriptive Statistics of the Hispanic Community Health Study/Study of Latinos Target Population Overall, and by Metabolic Syndrome (MetS) and High-Sensitivity C-Reactive Protein (hs-CRP)

	Overall sample[a]	MetS[a]			hs-CRP[a,b]		
		No	Yes	*p* value	Normal	High	*p* value
Demographics							
Age	56.60 (9.86)	54.70 (9.09)	58.30 (10.05)	<.001	56.40 (9.65)	56.89 (10.16)	.299
Years of education	11.27 (5.50)	11.79 (5.48)	10.81 (5.45)	<.001	11.34 (5.58)	11.16 (5.37)	.418
Female sex, % (*SE*)	56.33 (1.30)	55.01 (1.96)	57.51 (1.72)	.335	48.96 (1.77)	67.20 (1.83)	<.001
Language preference (% [*SE*] Spanish)	85.62 (1.58)	83.56 (2.52)	87.45 (1.42)	.104	84.83 (1.88)	86.78 (2.26)	.468
U.S.-born, % (*SE*)	22.61 (1.72)	22.22 (2.58)	22.96 (1.84)	.794	20.80 (1.98)	25.27 (2.45)	.103
Latino background, % (*SE*)				.354			.010
Mexican	29.30 (2.24)	30.30 (2.90)	28.41 (2.33)		32.77 (2.59)	24.21 (2.33)	
Cuban	28.42 (2.60)	26.76 (2.91)	29.91 (2.83)		26.43 (2.66)	31.37 (3.30)	
Puerto Rican	18.38 (1.61)	17.74 (2.46)	18.96 (1.66)		16.70 (1.83)	20.86 (2.43)	
Dominican	10.21 (0.99)	11.58 (1.34)	9.00 (1.09)		10.08 (1.12)	10.42 (1.29)	
Central American	6.34 (0.67)	5.66 (0.74)	6.95 (0.90)		6.21 (0.82)	6.53 (0.83)	
South American	6.15 (0.56)	6.70 (0.85)	5.67 (0.72)		6.59 (0.74)	5.51 (0.75)	
More than one heritage	1.18 (0.21)	1.27 (0.32)	1.10 (0.27)		1.22 (0.31)	1.11 (0.27)	
Cognition, *z* scores							
Global neurocognition	0.00 (0.77)	0.12 (0.74)	−0.11 (0.77)	<.001	0.04 (0.76)	−0.06 (0.78)	.004
B-SEVLT sum	−0.00 (1.00)	0.12 (0.99)	−0.11 (0.99)	<.001	0.02 (1.01)	−0.04 (0.98)	.155
B-SEVLT recall	0.00 (1.00)	0.11 (0.96)	−0.09 (1.02)	<.001	0.05 (0.97)	−0.07 (1.03)	.011
Word fluency	0.01 (1.01)	0.11 (1.02)	−0.09 (0.99)	<.001	0.06 (0.99)	−0.08 (1.03)	.002
Digit Symbol Substitution	0.02 (0.97)	0.16 (0.96)	−0.10 (0.95)	<.001	0.05 (0.95)	−0.02 (0.98)	.111
Stress measures							
Total perceived stress	14.42 (8.61)	14.32 (8.40)	14.51 (8.80)	.611	14.09 (8.46)	14.90 (8.81)	.026
Total acculturative stress	12.88 (16.14)	13.25 (16.44)	12.55 (15.86)	.321	12.64 (16.41)	13.23 (15.72)	.391
Chronic stress total	2.03 (2.02)	1.99 (1.96)	2.07 (2.06)	.387	1.95 (2.00)	2.16 (2.03)	.018
Traumatic stress	—	—	—	—	—	—	—
Lifetime total	2.15 (2.14)	2.31 (2.19)	2.00 (2.07)	.013	2.22 (2.12)	2.04 (2.14)	.100
Past year	0.14 (0.55)	0.15 (0.59)	0.13 (0.50)	.537	0.13 (0.52)	0.14 (0.58)	.742
MetS, % (*SE*)	52.83 (1.36)	—	—	—	44.50 (1.86)	65.09 (1.96)	<.001
Abdominal obesity	86.06 (0.84)	—	—	—	80.47 (1.27)	94.30 (0.86)	<.001
Hypertension	58.38 (1.33)	—	—	—	54.91 (1.83)	63.49 (1.86)	.001
High fasting glucose	43.87 (1.53)	—	—	—	40.63 (1.89)	48.65 (2.08)	.002
Low HDL-cholesterol	38.95 (1.24)	—	—	—	32.23 (1.62)	48.83 (2.06)	<.001
High triglycerides	37.07 (1.25)	—	—	—	35.05 (1.65)	40.05 (1.89)	.047
Inflammation	—	—	—	—	—	—	—
hs-CRP (continuous)	4.54 (9.37)	3.79 (9.97)	5.21 (8.72)	<.001	1.41 (0.94)	12.72 (9.04)	<.001
hs-CRP, % (*SE*) high	40.45 (1.38)	29.93 (2.08)	49.83 (1.68)	<.001	—	—	—

Notes: B-SEVLT = Brief-Spanish English Verbal Learning Test; HDL-cholesterol = high-density lipoprotein cholesterol. Sum: sum of three learning trials. *p* Values are derived from chi-squared tests for categorical variables and *t* tests for continuous variables.
[a]Values represent means (*SD*s) unless otherwise noted. [b]Normal: ≤3 mg/L and high: >3 mg/L.

Results

Characteristics of the Study Sample

Table 1 shows descriptive characteristics of the study sample overall and by MetS and hs-CRP status. Age ranged from 45 to 74 years, and years of education from 0 to 20+. A little over half of the target population was female and most (86%) completed testing in Spanish. Regarding Hispanic/Latino background, over half of the target population was of Caribbean heritage (i.e., Cuban, Puerto Rican or Dominican), a third of Mexican heritage, and the remaining were of other or more than one heritage. Individuals meeting MetS criteria were older and less educated than those who did not meet criteria. Women were more likely than men to have elevated hs-CRP, and there were differences in hs-CRP based on Hispanic/Latino background. Global neurocognition was lower among participants with MetS and elevated hs-CRP. Perceived and chronic stress were higher among those with elevated hs-CRP, and lifetime traumatic stress was lower in those meeting MetS criteria, with no other significant associations of the stress measures with MetS and hs-CRP. Over

half of the sample met criteria for MetS, with over three quarters of participants meeting criteria for abdominal obesity, and approximately 40% showed elevated hs-CRP. All MetS components were significantly associated with elevated hs-CRP. Descriptive characteristics comparing the target population (HCHS/SOL sample age 45+) with SCAS participation status are provided in Supplementary Table 1. Demographic characteristics, neurocognitive scores, and metabolic and inflammatory markers of participants in the HCHS/SOL parent study were not substantially different from those in the SCAS, except that participants in SCAS were significantly less likely to have high fasting glucose than participants in the parent study. Comparisons between the overall HCHS/SOL and SCAS samples have been reported previously (Gallo, Penedo, et al., 2014).

Associations of Stress Measures and Global Neurocognition

Separate analyses by stress measures (Table 2) showed that increased perceived stress and acculturative stress were each significantly associated with worse global neurocognition, and higher lifetime traumatic stress exposure was associated with better global neurocognition. The size of the effects of these associations was fairly small. Based on the standardized beta coefficients (obtained by multiplying the reported coefficients in Table 2 [M1] by the standard deviation of the stress measures of interest presented in Table 1), for every 1 *SD* increase in perceived stress and acculturative stress, global cognition decreased by 0.04 and 0.08 *SD*s, respectively, while for every 1 *SD* increase in lifetime traumatic stress, global cognition increased by 0.08 *SD*. These associations were statistically significant in both the model adjusting for demographics only (M1) and models adjusted also for MetS and/or hs-CRP (M1 + MetS, M1 + hs-CRP, M1 + MetS + hs-CRP), with both MetS and hs-CRP being significantly and independently associated with global neurocognition in these latter models. Traumatic stress over the past year and chronic stress were not significantly associated with global neurocognition, and thus were not considered further in analyses on global neurocognition.

Sensitivity analyses (Supplementary Table 2), adjusting for study site, depression, and anxiety (in addition to other previously considered demographics), yielded largely comparable findings, except perceived stress was no longer significantly associated with worse neurocognition. A series of models (Supplementary Table 3A and B) adjusting for individual MetS components separately (waist circumference, high blood pressure, fasting glucose, triglycerides, HDL-cholesterol) and pulse pressure, in addition to demographics (age, education, sex, Hispanic heritage, place of birth and language preference) showed comparable findings to similar models adjusting for the MetS composite (yes/no; Table 2, M1 + MetS).

Association of Stress Measures and Individual Neurocognitive Measures

Findings from models on individual neurocognitive measures (Supplementary Table 4) showed that higher perceived

Table 2. Associations Between the Primary Stress Measures and Global Neurocognition, Considering Metabolic Syndrome (MetS) and High-Sensitivity C-Reactive Protein (hs-CRP) in These Associations, Among Participants in the Hispanic Community Health Study/Study of Latinos

	Global neurocognition (*B* [*SE*])			
	M1	M1 + MetS	M1 + hs-CRP	M1 + MetS + hs-CRP
Perceived stress	−0.005* (0.002)	−0.004* (0.002)	−0.004* (0.002)	−0.004* (0.002)
MetS (yes)	—	−0.098*** (0.028)	—	−0.088** (0.028)
hs-CRP (high)	—	—	−0.070** (0.026)	−0.053* (0.025)
Acculturative stress (total)	−0.005*** (0.001)	−0.004*** (0.001)	−0.004*** (0.001)	−0.004*** (0.001)
MetS (yes)	—	−0.095*** (0.028)	—	−0.086** (0.027)
hs-CRP (high)	—	—	−0.068** (0.025)	−0.051* (0.024)
Chronic stress (total)	0.000 (0.008)	0.002 (0.008)	0.001 (0.008)	0.002 (0.008)
MetS (yes)	—	−0.103*** (0.028)	—	−0.094*** (0.028)
hs-CRP (high)	—	—	−0.068** (0.026)	−0.050 (0.025)
Traumatic stress (lifetime)	0.036*** (0.009)	0.035*** (0.009)	0.036*** (0.009)	0.034*** (0.009)
MetS (yes)	—	−0.092*** (0.027)	—	−0.082** (0.027)
hs-CRP (high)	—	—	−0.070** (0.024)	−0.054* (0.024)
Traumatic stress (past year)	0.033 (0.035)	0.034 (0.036)	0.036 (0.035)	0.036 (0.036)
MetS (yes)	—	−0.101*** (0.028)	—	−0.091** (0.028)
hs-CRP (high)	—	—	−0.072** (0.025)	−0.054* (0.025)

Notes: Model 1 (M1): age, sex, education, and Hispanic/Latino background, language preference (Spanish/English), and place of birth; M1 + MetS: variables in M1 and MetS (reference: no); M1 + hs-CRP: variables in M1 and hs-CRP (reference: low); and M1 + MetS + hs-CRP: variables in M1, MetS, and hs-CRP.
*$p < .05$. **$p < .01$. ***$p < .001$. *

stress was associated with worse learning and memory, and higher acculturative stress was associated with worse neurocognition across domains. In contrast, higher chronic stress was significantly associated with better word fluency, and higher lifetime traumatic stress was associated with better word fluency and processing speed (assessed by the Digit Symbol Substitution test). There were no significant associations with exposure to traumatic stressors over the past year. Estimates of the effects of each stress measure on individual neurocognitive measures were comparable in models adjusted for demographics only and those adjusted for MetS and hs-CRP (in addition to demographics).

Indirect Effects of Stress Measures on Global Neurocognition via MetS and hs-CRP

Results from fully adjusted SEM analyses investigating the role of hs-CRP (Table 3) in explaining the negative association of perceived stress with global neurocognition (and adjusting for demographics) showed no substantive evidence of indirect effects for perceived stress via hs-CRP. While there was a statistically significant indirect effect, the size of this effect was very small (indirect effect: $b < 0.000$, $SE < 0.000$). Because acculturative stress was not significantly associated with MetS or hs-CRP (Table 1), comparable SEM analyses were not performed on this stress measure despite its significant association with worse global neurocognition (Table 2).

Interactions of Stress Measures With MetS and hs-CRP on Neurocognition

Findings (Figure 1a–c) from analyses investigating whether the presence of MetS modified the association between stress and global neurocognition, adjusting for demographics (age, sex, education, background, place of birth, and language preference), were not significant. Similar models investigating interactions with hs-CRP (Figure 1d and e) showed a significant interaction with acculturative stress ($p = .01$), such that its association with global neurocognition was stronger among those with normal hs-CRP ($B = -0.006$, $SE = 0.001$, $p < .01$) than those with high hs-CRP ($B = -0.002$, $SE = 0.001$, $p = .28$). Follow-up comparable analyses on individual neurocognitive measures (Supplementary Figure 1) with terms for the hs-CRP and acculturative stress interaction showed a significant interaction on learning ($p = .04$), indicating that the association between increased acculturative stress and worse learning was stronger among those with normal hs-CRP ($B = -0.006$, $SE = 0.002$, $p < .01$) than those with high hs-CRP ($B = -0.001$, $SE = 0.002$, $p = .44$).

Interactions of Stress Measures With Age and Sex on Neurocognition

Results (Figure 2) from analyses investigating modifications in the associations between stress and global neurocognition by age (45–64 vs 65–74) and sex, adjusting for age (in sex modification), sex (in age modification), education, background, place of birth, language preference, and MetS and hs-CRP, showed no evidence for modifications (nonsignificant interactions). Similarly, interaction tests for individual neurocognitive measures showed no consistent evidence for modifications between the stress measures and neurocognition by age or sex (results not shown).

Table 3. Model Examining the Association Between Perceived Stress and Global Neurocognition (*z* Score Units), Including Estimates of the Indirect Effects Testing Whether High-Sensitivity C-Reactive Protein (hs-CRP) Might Account for This Association in the Hispanic Community Health Study/Study of Latinos

	Perceived stress	
	B (*SE*)	*p* value
Global neurocognition		
hs-CRP	−0.077 (0.025)	.003
Stress indicator	−0.004 (0.002)	.032
hs-CRP		
Stress indicator	0.017 (0.007)	.018
Intercepts		
Global neurocognition	0.152 (0.124)	.22
OR scale		
	OR (*SE*)	*p* value
hs-CRP		
Stress indicator	1.017 (0.007)	.019
	B (*SE*)	*p* value
Indirect effect	<0.000 (<0.000)	.033
Direct effect	−0.004 (0.002)	.032
Total effect	−0.005 (0.002)	.023

Notes: OR = odds ratio. Model is adjusted for age, sex, education in years, Hispanic/Latino background, language preference (Spanish/English), and place of birth.

Discussion

Prior studies have linked increased stress with worse neurocognitive outcomes, including increased risk for ADRDs (Bisht et al., 2018; Justice, 2018; Machado et al., 2014). The biological pathways underlying this association are likely varied, with CVD risk and systemic inflammation being two of the proposed mechanisms. The present study adds to the current literature by showing significant associations between several stress measures and neurocognition among Hispanics/Latinos living in the United States, and indicating that these associations do not differ significantly by sex or age in this group. Specifically, we found that increased perceived and acculturative stress were significantly associated with worse global neurocognition, while traumatic stress was associated with better global

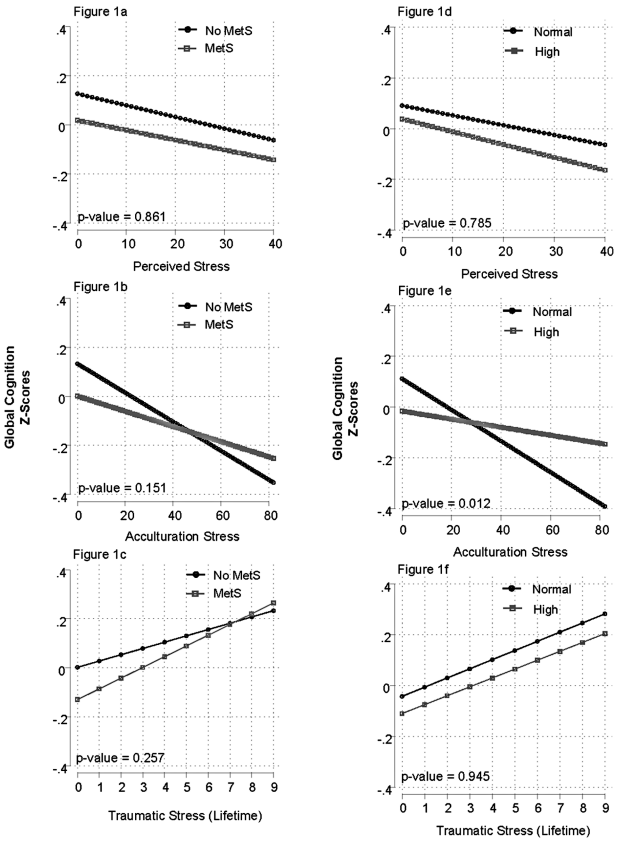

Figure 1. Results from survey linear models examining modifications in associations between stress and global neurocognition by metabolic syndrome (MetS: yes/no) and high-sensitivity C-reactive protein (hs-CRP: high/normal), adjusting for age, sex, education, background, language, and place of birth. Results from interaction terms for each of the models were as follows: (**a**) MetS × Perceived stress: $B = 0.001$, $SE = 0.004$, $p = .86$. (**b**) MetS × Acculturative stress: $B = 0.003$, $SE = 0.002$, $p = .15$. (**c**) MetS × Lifetime traumatic stress: $B = 0.018$, $SE = 0.016$, $p = .26$. (**d**) hs-CRP × Perceived stress: $B = –0.001$, $SE = 0.004$, $p = .79$. (**e**) hs-CRP × Acculturative stress: $B = 0.005$, $SE = 0.002$, $p = .01$. (**f**) hs-CRP × Lifetime traumatic stress: $B = –0.001$, $SE = 0.016$, $p = .95$.

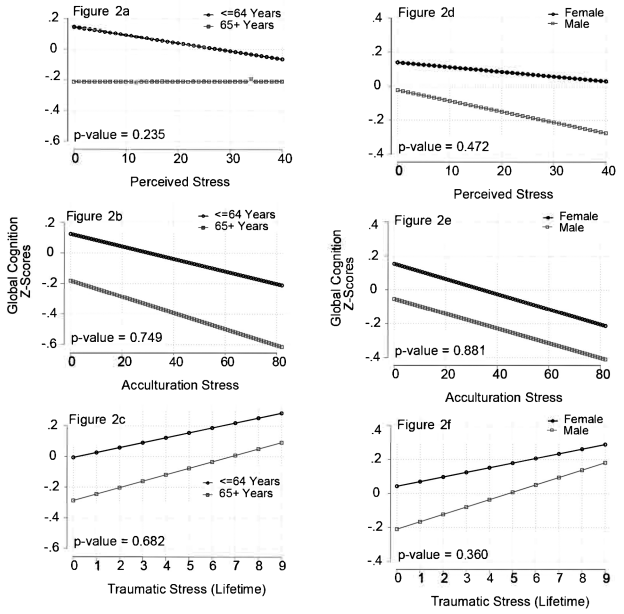

Figure 2. Results from survey linear models examining modifications in associations between stress and global neurocognition by age (45–64 vs 65–74) and sex, adjusting for age (in sex modifications), sex (in age modification), education, background, language, place of birth, and metabolic syndrome and high-sensitivity C-reactive protein Results from interaction terms for each of the models were as follows: (**a**) Age × Perceived stress: $B = 0.01$, $SE = 0.01$, $p = .24$. (**b**) Age × Acculturation stress: $B = –0.001$, $SE = 0.00$, $p = .75$. (**c**) Age × Lifetime traumatic stress: $B = 0.01$, $SE = 0.03$, $p = .68$. (**d**) Sex × Perceived stress: $B = –0.00$, $SE = 0.01$, $p = .47$. (**e**) Sex × Acculturation stress: $B = 0.00$, $SE = 0.00$, $p = .88$. (**f**) Sex × Lifetime traumatic stress: $B = 0.02$, $SE = 0.02$, $p = .36$.

neurocognition. Inconsistent with our hypothesis, neither markers of CVD risk (MetS) or systemic inflammation (hs-CRP) were notable pathways in the association of stress and neurocognition. They were, however, both independently associated with worse neurocognition in models including the stress measures. Furthermore, the impact of stress on neurocognition was not significantly modified by MetS or hs-CRP, except that higher acculturative stress was associated with worse neurocognition among participants with normal hs-CRP, but not among those with elevated hs-CRP.

The present study builds on prior findings (Nguyen et al., 2012), including some based on the HCHS/SOL cohort (González et al., 2018; Muñoz et al., 2021), and shows that two measures of stress appraisal (acculturative and perceived stress) show a negative association with global neurocognition, that is independent of the effect of MetS and inflammation on neurocognition. Analyses of findings within individual neurocognitive tests showed that acculturative stress was associated with all neurocognitive measures assessed. The association of perceived stress with global neurocognition, however, appeared to be primarily driven by the domains of learning and memory, underscoring the relevance of stress to neurocognitive domains typically impacted early on in neurodegenerative processes, such as Alzheimer's disease. Of note, the effect sizes of these negative associations between measures of perceived and acculturative stress with neurocognition were fairly small. This might be explained by the presence of other related "protective" factors that might buffer the deleterious impact of stress on neurocognition in this sample of Hispanics/Latinos. Recent findings showed positive psychosocial factors (e.g., purpose in life, social support) were associated with better neurocognition in HCHS/SOL (Estrella et al., 2021), and underscore the need to examine potentially interactive effects of stress with "protective" psychosocial factors on neurocognition in future studies.

In contrast to findings on stress appraisal measures (i.e., perceived and acculturative stress), lifetime exposure to traumatic stress was linked to better global neurocognitive function, and exposure to ongoing chronic stressors showed no significant associations with global neurocognition. Both of these latter stress measures were significantly linked to better performance on tests of word fluency, with lifetime traumatic stress also being linked to

faster psychomotor speed. The seemingly disparate findings across measures of stress in their association with neurocognition might be partly explained by the fact that while perceived and acculturative stress instruments assessed participants' self-appraisals of their experience of stress, the chronic stress and traumatic stress measures capture events that are typically considered challenging (e.g., trauma). It has long been posited that appraisal of events plays an important role in the impact of such events on health outcomes (Somerfield & McCrae, 2000), and it is the felt experience that accompanies such neurocognitive processes that drives the deleterious effect of stress on health (Monroe, 2008). This conceptualization helps explain why measures of perceived and acculturative stress would be linked to worse neurocognition, while measures of report of challenging events might not. Yet, it does not fully explain why self-report of exposure to traumatic events would be linked to better neurocognition. Considering the cross-sectional nature of our findings, the possibility that better neurocognitive function might lead to better recall of life events should be considered. However, present results suggesting that individuals with greater traumatic stress exposure are also less likely to meet MetS criteria concur with those from a prior study in this cohort showing an association of traumatic stress with decreased CVD risk factors (Gallo, Roesch, et al., 2014). Thus, these counterintuitive effects do not appear to be specific to neurocognitive processes.

Considering our findings regarding traumatic stress in the context of posttraumatic growth theory (Linley & Joseph, 2004) might help shed some light into their interpretation. Posttraumatic growth theory posits that individuals might rise to a higher level of functioning through the process of struggling with adversity and refers to these "positive changes" as "adversarial growth." While this construct was not assessed in the present study, future longitudinal studies incorporating assessments of adversarial growth might better discern whether the experience of traumatic life events results in positive behavioral changes in some individuals in this cohort, which might lead to better health. This interpretation is in line with observed resilience within the Hispanic/Latino population living in the United States, which has been posited to contribute to the Hispanic health paradox.

Prior findings in HCHS/SOL have linked stress with CVD/metabolic risk factors (Gallo, Roesch, et al., 2014), and MetS with worse neurocognition (González et al., 2018), and showed that there was not a significant interaction between MetS and hs-CRP on neurocognition (González et al., 2018). Inconsistent with our hypothesis and with prior findings (Vitaliano et al., 2005; Zahodne, Kraal, et al., 2019), we found that MetS and hs-CRP did not notably explain the link between increased stress and worse neurocognition in the HCHS/SOL population. Instead, stress appraisal (perceived and acculturative stress), MetS, and hs-CRP were all independently associated with worse neurocognition. If supported by longitudinal research, these results indicate that interventions targeting stress appraisal might have added benefits to neurocognition among Hispanics/Latinos over and above the effect of interventions targeting MetS and hs-CRP. This notion is further supported by findings indicating that the association between stress and neurocognition was largely comparable among participants with and without MetS and high and normal hs-CRP. The single exception was that acculturative stress was associated with worse global neurocognition (and learning) among participants with normal hs-CRP, but not those with high hs-CRP. While these results need to be interpreted with caution, they might indicate that in the presence of high systemic inflammation, the impact of acculturative stress on neurocognition is reduced, as high systemic inflammation overrides the biological mechanisms driving the association of acculturative stress with neurocognition.

Future studies examining other markers of inflammation and other posited mechanisms may further elucidate the underlying biological pathways linking stress and neurocognition among Hispanics/Latinos. Some of these mechanisms include the role of microglia (Bisht et al., 2018), multisystemic physiological dysregulation, as captured by the concept of allostatic load (Juster et al., 2010), activation of the hypothalamic–pituitary–adrenal axis, which increases production of glucocorticoids (Justice, 2018; Lupien et al., 2009), and dysregulated sleep (Lucey, 2020), as well as mechanisms by which advancing neurological disease disrupts neural and endocrine circuits that mediate the stress response (Justice, 2018). Present findings showing that the association of stress and neurocognition was not significantly different by age or sex indicate that interventions aimed at reducing stress appraisal are likely to be beneficial across age and for both men and women in middle-aged and older Hispanics/Latinos.

Limitations of the present study include its cross-sectional design, which restricts our ability to ascribe directionality to our findings. Collection of SCAS stress data occurred up to 9 months after collection of neurocognitive and biological data, possibly explaining the generally small effects of stress on neurocognition, though most participants' data were collected within 4 months of the HCHS/SOL baseline. While our cohort was quite diverse in its Hispanic/Latino heritage, a large proportion of participants were born outside the United States and although we account for place of birth in our analyses, caution is warranted in generalizing to U.S.-born Hispanics/Latinos. Future studies might explore whether our findings differ based on sociodemographic characteristics that vary among Hispanics/Latinos. While the neurocognitive battery used in the present study assessed a number of neurocognitive domains, it did so with a limited number of tests, and does not include measures of other neurocognitive domains which are impacted by aging and ADRDs (e.g., visuospatial abilities, executive function), and may be incorporated in future studies. Our assessment

of MetS included a widely used composite based on established criteria. Yet, other markers of CVD risk burden, such as the Framingham Cardiovascular Risk Score and Global Vascular Risk Score(Lamar et al., 2019; Tarraf et al., 2020), have been linked to neurocognition in HCHS/SOL and their consideration in future studies might shed further light on the role of CVD risk in the association of stress and neurocognition.

The estimated large numbers of Hispanics/Latinos reaching older age and projected to develop ADRDs underscores the dire need for research into mechanisms driving neurocognitive impairment in this population. The appraisal of stress (rather than exposure to challenging events), MetS, and systemic inflammation had additive (independent) associations with neurocognition in this diverse cohort of Hispanics/Latinos. This highlights the potential importance of considering them all as potential targets in the development of prevention and intervention efforts to ameliorate neurocognitive dysfunction among Hispanics/Latinos.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

None declared.

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