

# Association of Cardiac Structure and Function With Neurocognition in Hispanics/Latinos: The Echocardiographic Study of Latinos

Mohamed Faher Almahmoud, MD, MS; Hector M. Gonzalez, PhD; Katrina Swett, MS; Wassim Tarraf, PhD; Neil Schneideman, PhD; Mayank M. Kansal, MD; Melissa Lamar, PhD; Gregory A. Talavera, MD, MPH; and Carlos J. Rodriguez, MD, MPH

## Abstract

**Objective:** To study the associations of comprehensive measures of cardiac structure and function with multidimensional neurocognitive measures.

**Patients and Methods:** The Echocardiographic Study of Latinos is a population-based cohort of Hispanic/Latino adults older than 45 years enrolled from October 1, 2011, through June 30, 2014. Neurocognitive measures included Word Fluency (WF), Brief-Spanish English Verbal Learning Test (B-SEVLT), and Digit Symbol Substitution Test. The B-SEVLT included B-SEVLT-recall and B-SEVLT-sum. Echocardiographic measures included cardiac structure, systolic and diastolic function, and myocardial strain. Multivariable regression models were fit using survey statistics and sampling probabilities.

**Results:** A total of 1794 participants (mean age,  $56 \pm 0.5$  years; 56% women) were included in the analysis. In the adjusted model, higher left ventricular mass index was associated with lower B-SEVLT-sum and Digit Symbol Substitution Test scores. Left ventricular systolic dysfunction was associated with lower WF scores. Abnormal left ventricular geometry was associated with lower B-SEVLT-sum scores. Higher relative wall thickness was associated with B-SEVLT-recall and B-SEVLT-sum scores. Mitral annular relaxation velocities were associated with lower B-SEVLT-recall, B-SEVLT-sum, and WF scores. Higher mitral inflow to annular early diastolic velocity ratio was associated with lower B-SEVLT-recall and B-SEVLT-sum scores. Diastolic dysfunction was associated with lower B-SEVLT-sum scores. Finally, lower global longitudinal strain was associated with lower WF scores.

**Conclusion:** Alterations in cardiac structure, systolic and diastolic function, and myocardial strain were associated with worse neurocognitive function. Further study is needed to determine the mechanisms (ie, impairment of cerebral flow and silent brain infarctions) mediating these heart-brain associations.

© 2018 THE AUTHORS. Published by Elsevier Inc on behalf of Mayo Foundation for Medical Education and Research. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) ■ *Mayo Clin Proc Inn Qual Out* 2018;2(2):165-175

Neurocognitive impairment, an important challenge facing the growing elderly population, is characterized by a decline in cognitive function domains such as memory, verbal learning, processing speed, and executive function.<sup>1</sup> This decline ranges from a mild cognitive impairment, an at-risk state for dementia in which subjective and objective cognition difficulties do not impair daily functioning,<sup>2</sup> to a more form progressive deterioration of cognition and loss of basic functional abilities known as dementia.

Studies have linked coronary artery disease, heart failure, and atrial fibrillation to cases of nongenetic dementia.<sup>3</sup> Similarly, neurocognitive impairment is correlated with self-reported history of coronary artery disease,<sup>4,5</sup> heart failure,<sup>6</sup> and atrial fibrillation.<sup>7</sup> Interestingly, abnormalities of left ventricular (LV) systolic and diastolic indices,<sup>6,8</sup> left atrial (LA) indices,<sup>9</sup> cardiac output,<sup>10</sup> LV mass,<sup>11,12</sup> aortic root diameter,<sup>13</sup> and epicardial fat thickness<sup>14</sup> have also been associated with neurocognitive impairment. However, these studies did not involve comprehensive assessments of cardiac structure



From the Department of Internal Medicine, Division of Cardiology, University of Texas Medical Branch, Galveston (M.F.A.); Department of Neurosciences, University of San Diego, San Diego, CA, and Shiley-Marcos Alzheimer's Disease Research Center, La Jolla, CA (H.M.G.); Institute of Gerontology,

*Affiliations continued at the end of this article.*

and function as well as myocardial strain. Many of these studies were small (some with a sample size of <30 participants) and were carried out in selected populations such as the chronically ill or hypertensive, the elderly (age, >70 years), or individuals with known cerebrovascular disease, with known prevalent cardiovascular disease, or undergoing cardiac rehabilitation.<sup>8,13,15,16</sup> Furthermore, many of these studies involved only a single measure of neurocognition. Lastly, to our knowledge, only the Sacramento Area Latino Study on Aging has examined neurocognitive function in Hispanics/Latinos, but focusing on heart rate variability measures as opposed to cardiac structure and function.<sup>17</sup>

Thus, we examined the association of neurocognition across several dimensions (learning and memory, fluency, and processing speed) known to be associated with risk of dementia, with comprehensive echocardiographic parameters in a population-based community cohort of Hispanics/Latinos. We hypothesized that alterations in cardiac structure, systolic and diastolic function, and LV strain would be associated with neurocognitive impairment.

## PATIENTS AND METHODS

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a prospective, multi-site, population-based cohort study with baseline examination conducted from October 1, 2011, through June 30, 2014. Data were collected from 4 field centers—Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California—with each center recruiting approximately 4000 eligible, self-identified Hispanic/Latino adults (age, 18-74 years; n=16,415). Of the original sample, after excluding individuals younger than 45 years and individuals with incomplete Latino heritage information (individuals specifying either “more than one” or “other” as Hispanic/Latino background), 9652 middle-aged and older Hispanics/Latinos (age, 45-74 years) were eligible for neurocognitive testing. The HCHS/SOL also excluded individuals who had plans to move from the region within 6 months, were unable to travel to the field center, and/or were unable to complete the study questionnaires in English or Spanish. Pregnant women were rescheduled for a study visit 3 months postpartum. Detailed HCHS/SOL sampling methods have been published elsewhere.<sup>18</sup>

The Echocardiographic Study of Latinos (ECHO-SOL) ancillary study enrolled 1818 participants through a random stratified sampling process representative of the HCHS/SOL's Hispanic background group distribution across the 4 field centers (1794 had neurocognitive data available and are included in this analysis). The ECHO-SOL characterized a comprehensive list of echocardiographic parameters to determine the prevalence and correlates of abnormal cardiac structure and function (systolic and diastolic) in a Hispanic/Latino community-based cohort. The Data Coordinating Center at the University of North Carolina at Chapel Hill identified participants who met ECHO-SOL eligibility criteria and directly forwarded the participant identification number to the respective HCHS/SOL site to initiate contact. After conducting the echocardiographic study, digital image files were electronically transferred from the field centers to the Wake Forest School of Medicine Echo Core Lab using a password-protected, fully encrypted, regularly compliant image transport application. The Wake Forest University School of Medicine institutional review board provided approval and oversight of all study materials and activities. All ECHO-SOL participants gave informed consent. Further details regarding the design of the ECHO-SOL have been published.<sup>19,20</sup>

Information pertaining to demographic characteristics and medical history was obtained using interviewer-administered questionnaires by trained staff. *Diabetes* was defined on the basis of American Diabetes Association definition<sup>21</sup> using 1 or more of the following criteria: (1) fasting serum glucose level of 126 mg/dL or greater (to convert to mmol/L, multiply by 0.0259); (2) oral glucose tolerance test glucose level of 200 mg/dL or greater; (3) self-reported diabetes; (4) hemoglobin A<sub>1c</sub> level of 6.5% or greater; or (5) taking antidiabetic medication or insulin. Trained and certified clinic staff obtained blood samples and anthropometric and blood pressure measurements from all HCHS/SOL participants. Height was measured to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg with the use of a balance scale. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. *Obesity* was defined as a

BMI of 30 kg/m<sup>2</sup> or greater. After a 5-minute rest, blood pressure was measured 3 times at 1-minute intervals using an automated oscillometric device with the participant in a seated position. The average of the second and third blood pressure measurements was used for this analysis. *Hypertension* was defined as a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher, or taking antihypertensive medications.

### Primary Echocardiographic Outcome Measurements

Echocardiographic measures were classified into 4 categories as previously described<sup>19,20</sup>:

1. *Variables of LV structure*: LV end-systolic volume (LVESV) (mL), LV end-diastolic volume (mL), relative wall thickness (RWT) (mm), LV geometry (normal vs abnormal), LV mass (g), and LV mass index (LVMI) (g/m<sup>2</sup>).  
LV geometry was classified as normal or abnormal (consisting of patterns of eccentric hypertrophy, concentric hypertrophy, or concentric remodeling).<sup>19</sup>
2. *Variables of LV systolic function*: LV ejection fraction (EF) (%), LV stroke volume (mL), cardiac output (L/min), and peak systolic annular velocity (S') (cm/s).
3. *Variables of LV diastolic function*: LA volumes indexed to body surface area (mL/m<sup>2</sup>), mitral annular velocities (cm/s), E/e' ratio (defined as the ratio of the early mitral inflow velocity [cm/s] to the mitral annular early diastolic velocity [cm/s]), and e' (defined as the mitral annular early diastolic velocity [cm/s]). Left ventricular diastolic dysfunction (grades 0-III) determined following an algorithm using 3 parameters: transmitral inflow velocities (E/A ratio), E/e' ratio, and LA volume index (LAVI) (mL/m<sup>2</sup>).
4. *Variables of LV myocardial strain*: Average global longitudinal strain (GLS) (%) and average global circumferential strain.

### Neurocognitive Function

The neurocognitive tests were administered in the participants' preferred language during face-to-face interviews by study staff who were trained and supervised by doctorate-level,

licensed clinical neuropsychologists. The details of neurocognitive measures performed in the HCHS/SOL have been published.<sup>22</sup> The 4 neurocognitive tests administered were as follows:

1. *Word Fluency (WF)*<sup>23</sup> is a measure of verbal fluency that assesses sustained attention and mental processing speed. In this task, participants were asked to produce as many words as possible that begin with the letters F and A within a time limit of 60 seconds for each letter.
2. *Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale-Revised*<sup>24</sup> is a measure of psychomotor speed and sustained attention. Participants were asked to rapidly copy symbols encoded to numbers (ie, 1-9) onto blank spaces below numbers printed on scoring sheets within 90 seconds.
3. *Brief-Spanish English Verbal Learning Test (B-SEVLT)*<sup>22,25</sup> is a measure of verbal episodic learning and verbal memory that entails participants learning a 15-word list that is repeated over 3 learning trials (B-SEVLT-sum) and is later recalled after a delay with distracting tasks (B-SEVLT-recall). This test is highly sensitive to mild cognitive impairment and related dementias.
4. *Six-Item Screener (SIS)* is a brief mental status screening test derived from the Mini-Mental Status Examination.<sup>26</sup> The SIS scores were dichotomized to 4 or less, or more than 4 or (out of a total possible score of 6) on the basis of previous studies of neurocognitive impairment.<sup>22</sup>

### Statistical Analyses

We applied survey methods using sampling weights to adjust for sampling probability and nonresponse, thus providing weighted frequencies of descriptive variables. Descriptive statistics were generated for the overall analytical sample as well as stratified by an SIS score of 4 or less, or more than 4. Socio-demographic characteristics, clinical characteristics, and echocardiographic measures were summarized using means  $\pm$  SEs for continuous variables and proportions for categorical variables. We performed bivariate descriptive statistical analyses using the Student *t* test to

TABLE 1. Echocardiographic Measures by Neurocognitive Impairment Status<sup>a,b</sup>

Characteristic	Individuals with SIS score ≤4	Individuals with SIS score >4	P value
LAVI (mL/m <sup>2</sup> )	23.3±0.6	23±0.3	.69
LVESV (mL)	34.6±1.0	33.5±0.3	.28
LVEDV (mL)	83.5±1.8	83.1±0.7	.80
EF (%)	59.2±0.5	59.9±0.2	.13
LVM (g)	158.7±4.2	152.5±1.7	.16
LVMl (g/m <sup>2</sup> )	43.1±1.1	41.2±0.4	.10
LV geometry (%)			.67
Normal	53.3±4.5	55.3±1.8	
Abnormal	46.6±4.5	44.6±1.8	
LV diastolic dysfunction (%)			.01
Grade 0	37.9±4.1	49±1.8	
Grade I-III	62.1±4.1	51±1.8	
RWT (mm)	0.4±0.0	0.4±0.1	.60
E/e' ratio	10.1±0.3	9.9±0.1	.40
e' (cm/s)	7.6±0.2	8.1±0.1	.03
Lateral S' (cm/s)	8.3±0.2	8.3±0.1	.80
SVLVOT (mL)	73±1.7	70±0.6	.20
Cardiac output (L/min)	4769±114	4535±46	.05
Average GLS (%)	-17.1±0.3	-17.6±0.1	.04
Average GCS (%)	-24.1±0.6	-24.3±0.2	.80

<sup>a</sup>e' = mitral annular early diastolic velocity; E/e' ratio = ratio of the early mitral inflow velocity to the mitral annular early diastolic velocity; EF = ejection fraction; GCS = global circumferential strain; GLS = global longitudinal strain; LAVI = left atrial volume index; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVM = left ventricular mass; LVMl = left ventricular mass index; RWT = relative wall index; S' = peak systolic annular velocity; SIS = Six-Item Screener; SVLVOT = stroke volume left ventricular outflow tract diameter.

<sup>b</sup>Data are presented as mean ± SE for echocardiographic measures presented by neurocognitive impairment status defined by an SIS score of ≤4 and as proportions of participants with normal vs abnormal by SIS score for LV geometry and LV diastolic dysfunction.

compare means of echocardiographic measures by neurocognitive impairment status as defined by an SIS score of 4 or less. The  $\chi^2$  test was used to compare the proportions of normal vs abnormal LV geometry and LV diastolic dysfunction by SIS score. We used linear regression models to separately examine the associations between each of our echocardiographic measures and each of the neurocognitive measures of interest regardless of SIS status. For the continuous standardized neurocognitive measures, we started with unadjusted models and then we adjusted for age, sex, diabetes status, hypertension status, and BMI. To examine the association between SIS scores and echocardiographic measures, we used multivariable logistic regression models. All analyses were performed using SAS version 9.3 (SAS Institute Inc). A P value

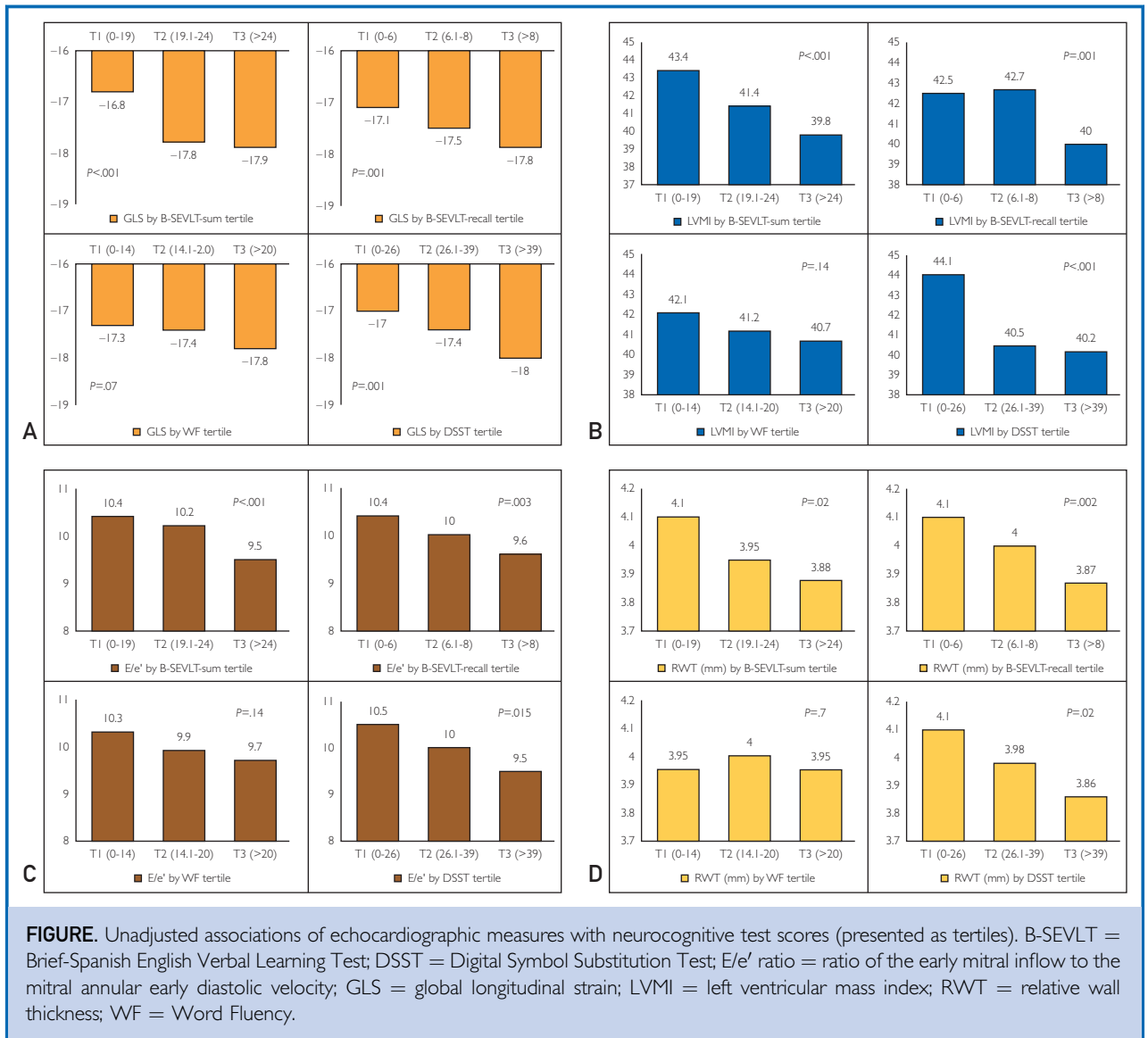
less than .05 was used to denote statistical significance.

## RESULTS

The age range for participants was 42 to 74 years. Overall, 16.5% of participants had an SIS score of 4 or less; of these, 34.3% were older than 65 years. Compared with participants with an SIS score of more than 4, those with an SIS score of 4 or less were more likely older (age, >65 years), were less educated, had lower income, and were diabetic, hypertensive, current smokers, and more likely to have a history of coronary artery disease. We also observed statistically significant differences ( $P<.001$ ) in neurocognitive impairment status based on the Hispanic/Latino heritage group (Supplemental Table 1, available online at <http://www.mayoclinicproceedings.org>).

No significant differences were found in LA or LV structure. However, 51% of participants with an SIS score of more than 4 vs 62.1% of those with a score of 4 or less had LV diastolic dysfunction ( $P=.01$ ). Compared with participants with an SIS score of more than 4, those with a score of 4 or less had lower e'. There was no significant difference in cardiac output by SIS score ( $P=.05$ ). Lower average GLS values were observed in those with an SIS score of 4 or less than in those with an SIS score of more than 4 ( $P=.04$ ) (Table 1).

Older age was associated with lower B-SEVLT-recall, B-SEVLT-sum, DSST, and SIS scores. Lower income was associated with lower B-SEVLT-recall, B-SEVLT-sum, WF, and DSST scores. In addition, compared with nondiabetic participants, those with diabetes performed worse on all the tests; prediabetic participants performed worse on B-SEVLT-recall, B-SEVLT-sum, and DSST. Hypertensive participants had lower scores on all the tests. Obesity was associated with lower WF scores. Compared with participants with moderate physical activity, those with low physical activity had lower B-SEVLT-recall, B-SEVLT-sum, and DSST scores. Compared with nonsmokers, former smokers had lower B-SEVLT-recall scores, although current smokers had lower B-SEVLT-recall, B-SEVLT-sum, and WF scores and were more likely to have neurocognitive impairment as defined by an SIS score of 4 or less. Participants with a history of coronary



artery disease had lower B-SEVLT-recall, B-SEVLT-sum, and DSST scores and were more likely to have neurocognitive impairment as defined by an SIS score of 4 or less. Women performed better on B-SEVLT-recall, B-SEVLT-sum, and DSST. Higher education was associated with better performance on all neurocognitive measures. Participants with higher education were less likely to have neurocognitive impairment as defined by an SIS score of 4 or less. We noted Hispanic/Latino heritage variation in neurocognitive performances. Compared with the reference group (Mexicans), Hispanics of Dominican, Cuban, and

Puerto Rican backgrounds had lower scores on all tests (Supplemental Table 2, available online at <http://www.mayoclinicproceedings.org>).

Compared with participants in the higher tertiles of B-SEVLT-recall, B-SEVLT-sum, and DSST scores, those in the lower tertiles had lower average GLS scores, increased LVMI, increased RWT (smaller, thicker hearts), and higher E/e' ratio (increased LV filling pressures). Although we found no significant difference per tertiles of WF scores (Figure). In the multivariable regression model adjusted for common cardiovascular risk factors including age, sex, diabetes status, and BMI

TABLE 2. Multivariable Analyses of Cardiac Structure and Function Associated With Neurocognitive Tests<sup>a,b,c</sup>

Variable	B-SEVLT-recall		B-SEVLT-sum		WF		DSST <sup>d</sup>		SIS (score ≤4)	
	M1 <sup>d</sup>	M2 <sup>d</sup>	M1 <sup>d</sup>	M2 <sup>d</sup>	M1 <sup>d</sup>	M2 <sup>d</sup>	M1 <sup>d</sup>	M2 <sup>d</sup>	M1 <sup>d</sup>	M2 <sup>d</sup>
LAVI (mL/m <sup>2</sup> )	0.017 (0.01)	0.02 <sup>c</sup> (0.01) <sup>c</sup>	0.02 (0.02)	0.04 (0.02)	0.04 (0.03)	0.04 (0.03)	0.005 (0.06)	0.03 (0.05)	1.0 (0.98-1.0)	1.0 (0.98-1.0)
LVESV (mL)	-0.01 <sup>c</sup> (0.01) <sup>c</sup>	0.006 (0.01)	-0.03 <sup>c</sup> (0.01) <sup>c</sup>	0.006 (0.02)	-0.03 (0.02)	-0.02 (0.02)	-0.01 (0.03)	0.001 (0.04)	1.0 (0.99-1.0)	1.0 (0.99-1.0)
LVEDV (mL)	-0.01 (0.004)	0.01 (0.005)	-0.01 (0.01)	0.01 (0.01)	-0.01 (0.01)	0.001 (0.01)	0.01 (0.02)	0.02 (0.02)	1.0 (0.99-1.0)	1.0 (0.98-1.0)
EF (%)	0.03 <sup>c</sup> (0.01) <sup>c</sup>	0.02 (0.01)	0.1 <sup>c</sup> (0.02) <sup>c</sup>	0.05 (0.03)	0.1 <sup>c</sup> (0.04) <sup>c</sup>	0.1 <sup>c</sup> (0.04) <sup>c</sup>	0.1 (0.10)	0.1 (0.10)	1.0 (0.94-1.0)	1.0 (0.95-1.0)
LVM (g)	-0.01 <sup>c</sup> (0.001) <sup>c</sup>	-0.001 (0.002)	-0.02 <sup>c</sup> (0.003) <sup>c</sup>	-0.005 (0.004)	-0.005 (0.005)	0.004 (0.01)	-0.02 <sup>c</sup> (0.01) <sup>c</sup>	0.003 (0.01)	1.0 (0.99-1.0)	1.0 (0.99-1.0)
LVMl (g/m <sup>2</sup> )	-0.04 <sup>c</sup> (0.01) <sup>c</sup>	-0.2 (0.01)	-0.1 <sup>c</sup> (0.02) <sup>c</sup>	-0.05 <sup>c</sup> (0.02) <sup>c</sup>	-0.05 <sup>c</sup> (0.02) <sup>c</sup>	-0.02 (0.02)	-0.2 <sup>c</sup> (0.04) <sup>c</sup>	-0.1 <sup>c</sup> (0.04) <sup>c</sup>	1.0 (0.99-1.0)	1.0 (0.99-1.0)
Abnormal LV geometry	-0.6 <sup>c</sup> (0.20) <sup>c</sup>	-0.3 (0.20)	-1.1 <sup>c</sup> (0.40) <sup>c</sup>	-0.7 <sup>c</sup> (0.30) <sup>c</sup>	-0.5 (0.50)	-0.04 (0.50)	-3.1 <sup>c</sup> (0.90) <sup>c</sup>	-1.7 (1.0)	1.1 (0.8-1.6)	1.0 (0.7-1.4)
LV diastolic dysfunction (grades I-III)	-0.3 (0.20)	-0.1 (0.20)	-0.9 <sup>c</sup> (0.30) <sup>c</sup>	-0.6 <sup>c</sup> (0.30) <sup>c</sup>	-1.0 <sup>c</sup> (0.40) <sup>c</sup>	-0.5 (0.40)	-1.2 (0.10)	-0.3 (0.90)	1.6 (1.1-2.2)	1.2 (0.8-1.6)
RWT (mm)	-2.4 <sup>c</sup> (0.8) <sup>c</sup>	-1.7 <sup>c</sup> (0.80) <sup>c</sup>	-4.1 <sup>c</sup> (1.50) <sup>c</sup>	-3.2 <sup>c</sup> (1.50) <sup>c</sup>	-0.5 (2.70)	1.2 (2.60)	-8.9 (5.10)	-5.8 (5.40)	1.0 (0.1-7.2)	0.7 (0.1-5.4)
E/e' ratio	-0.1 <sup>c</sup> (0.03) <sup>c</sup>	-0.06 <sup>c</sup> (0.03) <sup>c</sup>	-0.2 <sup>c</sup> (0.05) <sup>c</sup>	-0.15 <sup>c</sup> (0.06) <sup>c</sup>	-0.2 <sup>c</sup> (0.10) <sup>c</sup>	-0.1 (0.10)	-0.3 (0.20)	-0.1 (0.20)	1.0 (0.9-1.1)	1.0 (0.9-1.1)
e' (cm/s)	0.2 <sup>c</sup> (0.05) <sup>c</sup>	0.1 <sup>c</sup> (0.05) <sup>c</sup>	0.4 <sup>c</sup> (0.01) <sup>c</sup>	0.3 <sup>c</sup> (0.10) <sup>c</sup>	0.5 <sup>c</sup> (0.10) <sup>c</sup>	0.4 <sup>c</sup> (0.10) <sup>c</sup>	0.6 <sup>c</sup> (0.20) <sup>c</sup>	0.4 (0.20)	1.0 (0.9-1.1)	1.0 (0.9-1.1)
S' (cm/s)	0.06 (0.04)	0.05 (0.04)	0.2 <sup>c</sup> (0.07) <sup>c</sup>	0.1 <sup>c</sup> (0.07) <sup>c</sup>	0.3 <sup>c</sup> (0.01) <sup>c</sup>	0.3 <sup>c</sup> (0.10) <sup>c</sup>	0.5 <sup>c</sup> (0.20) <sup>c</sup>	0.4 (0.2)	1.0 (0.9-1.1)	1.0 (0.9-1.1)
SVLVOT (mL)	0.002 (0.005)	0.004 (0.005)	-0.003 (0.01)	-0.001 (0.01)	0.01 <sup>c</sup> (0.01) <sup>c</sup>	0.02 (0.01)	0.01 (0.02)	0.02 (0.02)	1.0 (0.99-1.0)	1.0 (0.99-1.0)
Cardiac output (L/min)	0.00003 (0.0001)	0.0001 (0.0001)	0.00003 (0.0001)	0.0001 (0.0001)	0.0003 (0.0002)	0.0003 (0.0002)	0.0001 (0.0003)	0.0004 (0.0003)	1.0 (0.99-1.0)	1.0 (0.99-1.0)
Average GLS (%)	-0.12 <sup>c</sup> (0.03) <sup>c</sup>	-0.01 (0.03)	-0.26 <sup>c</sup> (0.05) <sup>c</sup>	-0.07 (0.05)	-0.24 <sup>c</sup> (0.08) <sup>c</sup>	-0.2 <sup>c</sup> (0.08) <sup>c</sup>	-0.62 <sup>c</sup> (0.15) <sup>c</sup>	-0.3 (0.18)	1.06 <sup>c</sup> (1.05-1.12) <sup>c</sup>	1.02 (0.96-1.01)
Average GCS (%)	-0.02 (0.01)	-0.01 (0.01)	-0.06 <sup>c</sup> (0.03) <sup>c</sup>	-0.04 (0.02)	-0.02 (0.04)	-0.01 (0.04)	-0.02 (0.08)	-0.01 (0.07)	1.0 (0.97-1.04)	1.0 (0.97-1.03)

<sup>a</sup>B-SEVLT = Brief-Spanish English Verbal Learning Test; DSST = Digital Symbol Substitution Test; e' = mitral annular early diastolic velocity; E/e' ratio = ratio of the early mitral inflow velocity to the mitral annular early diastolic velocity; EF = ejection fraction; GCS = global circumferential strain; GLS = global longitudinal strain; LAVI = left atrial volume index; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVM = left ventricular mass; LVMl = left ventricular mass index; RWT = relative wall index; S' = peak systolic annular velocity; SIS = Six-Item Screener; SVLVOT = stroke volume left ventricular outflow tract diameter; WF = Word Frequency.

<sup>b</sup>Data are presented as β (SE) or odds ratio (95% CI).

<sup>c</sup>Indicates significant values (P<.05).

<sup>d</sup>Multivariate assessment of echocardiographic variables and neurocognitive test scores. Model 1 (M1) was unadjusted, and model 2 (M2) was adjusted for age (<55 y vs 55-64 y vs >65 y), sex, diabetes mellitus status (nondiabetic vs prediabetic vs diabetic), hypertension (yes or no), and body mass index (<25 kg/m<sup>2</sup> vs 25-29.9 kg/m<sup>2</sup> vs >30 kg/m<sup>2</sup>).



(Table 2), lower EF was associated with lower WF scores. Higher LVMI was associated with lower B-SEVLT-sum and DSST scores. Abnormal LV geometry was associated with lower B-SEVLT-sum scores. Left ventricular diastolic dysfunction was associated with lower B-SEVLT-sum scores. Higher RWT was associated with lower B-SEVLT-recall and B-SEVLT-sum scores. Higher  $E/e'$  ratio was associated with lower B-SEVLT-recall and B-SEVLT-sum scores. Lower  $e'$  was associated with lower B-SEVLT-recall, B-SEVLT-sum, and WF scores. Lower lateral  $S'$  was associated with lower B-SEVLT-sum and WF scores. Finally, lower GLS was associated with lower WF scores.

The percentage of words with F letters out of the overall number of words among those who took the test in Spanish is 50% vs 54.3% among English takers. The overwhelming majority of participants (86%) took the tests in Spanish, and participants were equally likely to use A and F letters. In addition, we ran a sensitivity analysis for WF including language preference as an additional control and it did not quantitatively change the results.

## DISCUSSION

In a community-dwelling cohort of middle-aged and older Hispanics/Latinos, we found that abnormalities of cardiac structure and systolic and diastolic function were associated with worse neurocognitive performance across several domains (global, language, memory, and executive function) of neurocognitive function. To our knowledge, this is the first study to examine this relationship using comprehensive myocardial echocardiographic measures of structure and function including GLS. Given the known high cardiovascular disease risk burden in Hispanics/Latinos,<sup>27,28</sup> our findings highlight related cardiac and neurocognitive functional problems in middle-aged and older Latinos.

We observed significant differences in neurocognitive performance among participants from different Hispanic/Latino backgrounds. These findings are consistent with the study by González et al,<sup>29</sup> in which Hispanics/Latinos of Caribbean (Cubans, Dominicans, and Puerto Ricans) background had lower neurocognitive test scores than did other

Hispanic/Latino groups. Although models were adjusted for major socioeconomic factors (income, education, and home ownership), other cultural and demographic factors may still play a role in explaining some of these neurocognitive differences between Hispanic/Latino groups, such as acculturation, marital status, employment status, and living in rural vs urban communities.

Furthermore, significant differences in echocardiographic measures of cardiac structure and chamber measures were noted between participants from different Hispanic/Latino backgrounds. Qureshi et al<sup>30</sup> found that compared with Mexican individuals, participants of Cuban heritage had highest values of LVMI, left ventricular posterior wall thickness at end diastole, left ventricular internal diameter at end diastole, left ventricular end systolic volume, and LV end-diastolic volume ( $P < .001$ ) whereas Central American individuals had the lowest 95th percentile cutoffs of these measures. In that study, Qureshi et al found gross differences in reference limits for Hispanics/Latinos compared to American Society of Echocardiography chamber quantification guidelines. In addition, previous studies reported racial differences in cardiac structure and function, which support using ethnic-based reference limits and encourage further ethnic-based studies.<sup>31,32</sup>

We observed significant associations of diabetes, hypertension, obesity, smoking, and sedentary lifestyle with lower performance on neurocognitive tests, highlighting the importance of ideal cardiovascular health (CVH) for neurocognitive function.<sup>33</sup> In the Coronary Artery and Risk Development in Young Adults study, those with ideal CVH factors as young adults had better performance on neurocognitive tests in midlife.<sup>34</sup> The Reasons for Geographic and Racial Differences in Stroke study found that adherence to ideal CVH metrics was associated with a reduced incidence of neurocognitive impairment.<sup>35</sup> Lastly, the multiethnic Northern Manhattan Study found an increasing number of ideal CVH metrics associated with less decline in neurocognitive domains. These findings were similar for whites, blacks, and Hispanics.

We observed a significant inverse relationship between higher LVMI and poor

neurocognitive performance. Previous studies have found consistent associations between higher LVMI with lower Mini-Mental Status Examination scores and cognitive decline.<sup>11,12</sup> Others have also linked LV hypertrophy to the development of stroke<sup>36</sup> and asymptomatic cerebral ischemia.<sup>37</sup> A similar observation was noted by Elias et al<sup>38</sup> in the Framingham Offspring Study, which found a significant relationship of higher LVMI with neurocognitive impairment in the basic model that was attenuated after adjusting for cardiovascular risk factors.

An association between EF and poor neurocognitive performance is consistent with previous studies that linked lower LV systolic function with poorer neurocognitive performance.<sup>6,39</sup> Jerskey et al<sup>39</sup> found that lower EF was associated with decrements in sustained attention and vigilance. In a previous longitudinal population-based study, van den Hurk et al<sup>6</sup> reported that lower EF was associated with worse performance on attention and executive functioning measures at follow-up. However, we extend these previous findings to other more comprehensive measures of LV systolic function, such as LVESV, cardiac output, and LV  $S'$ , which were all also associated with poorer neurocognitive performance. Furthermore, we found a significant association between neurocognitive performance and average LV GLS (a relatively new measure of LV function). This finding is important because no previous study has investigated the association between myocardial strain and cognitive functions.

Furthermore, our finding of an association of LV diastolic dysfunction with neurocognitive impairment is consistent with previous observations; however, the present study used comprehensive measures of LV diastolic dysfunction. van den Hurk et al<sup>6</sup> found the association of selected echocardiographic markers of LV diastolic dysfunction with lower scores on attention and executive functioning measures. Shimizu et al<sup>40</sup> found that LV diastolic dysfunction was associated with cerebral white matter lesions in elderly patients free of ischemic heart disease and stroke.

The pathophysiological mechanisms underlying the associations of abnormal LV systolic function, diastolic function, and LV strain with neurocognitive impairment are not yet fully

understood. The presence of cardiac structural and function abnormalities predict future clinical heart failure.<sup>41</sup> Others have found an association between worse GLS and subclinical brain disease, specifically silent brain infarcts.<sup>42</sup> Further potential mechanisms of the association of lower LV function with poor neurocognitive performance is impaired cerebral autoregulation along with poor cerebral flow observed in individuals with congestive heart failure.<sup>15</sup> Additional hypothesized mechanisms include reduced cerebrovascular reactivity,<sup>43</sup> hypercoagulable state, higher prevalence of atrial fibrillation, or abnormal vascular endothelial function<sup>44</sup> in those with clinical heart failure. Further studies are needed to explore and confirm these etiological mechanisms in those with abnormalities in cardiac structure and function.

Our study has several implications. First, it extends previous observations of the relationship between alterations in cardiac structure and function and alterations in neurocognitive function to Hispanics/Latinos. Second, identifying these echocardiographic measures even before the development of clinical heart failure may help identify those at risk of neurocognitive impairment and help us possibly prevent or delay the progression to dementia. We also establish a relationship of neurocognitive performance with LV strain. Finally, our study determines the most useful echocardiographic measures associated with neurocognitive impairment that can be studied further in future risk models, such as LVMI, diastolic dysfunction, and GLS.

The strengths of this study include its large prospective, multicenter, community-based cohort of middle-aged and older Hispanics/Latinos. This study included comprehensive neurocognitive measures targeting several domains of psychomotor speed, verbal episodic learning, and memory function. In addition, our use of comprehensive echocardiographic measures of cardiac structure, systolic and diastolic function, and LV strain measures simultaneously in a single visit makes this one of the most extensive reports on the relationship between cardiac abnormalities and cognitive function. Some limitations should also be considered. First of all, the HCHS/SOL was limited to 4 US communities precluding generalization outside these



communities; however, the use of a probability sampling design within preselected diverse regions is superior to convenience sampling used in many previous neuropsychological cohort studies. Echocardiographic studies were not performed simultaneously with the other HCH/SOL data; however, all efforts were made to make the time gap as small as possible. In addition, because of the cross-sectional nature of our analysis, we could not determine directionality in the relationship between echocardiographic cardiac measures and neurocognitive function. We found a positive relationship between increasing LAVI and better performance on B-SEVLT. Previous studies found that greater LA size was associated with cognitive impairment<sup>9</sup> using a 2-dimensional construct of LA size, which may not be directly relatable to our 3-dimensional volumetric construct. Both previous study populations were 10 and 20 years older, respectively, than our ECHO-SOL population. Because LAVI is a barometer of time exposure to LV filling pressures, the relationship may be different in our relatively young population. Finally, although we adjusted for potential confounders, we cannot rule out additional residual confounding.

## CONCLUSION

This is the first study comparing the relationship of cardiac structure, systolic and diastolic function, and myocardial strain to multiple dimensions of neurocognitive performance in Hispanics/Latinos. Our findings implicate abnormalities of LVMI, LV systolic function, LV diastolic function, and LV myocardial strain in cognitive impairment and poor neurocognitive performance. Further studies are needed to explore the pathways potentially responsible for these associations. Given that the presence of cardiac structural and function abnormalities predict future clinical heart failure,<sup>41</sup> our findings further highlight the heart-brain intersection of both epidemics of heart failure and cognitive decline.

## ACKNOWLEDGMENTS

We thank the staff and participants of the Hispanic Community Health Study/Study of Latinos and Echocardiographic Study of Latinos for their important contributions. For

details about the study and its investigators, visit <http://www.csc.unc.edu/hchs/>.

## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** BMI = body mass index; B-SEVLT = Brief-Spanish English Verbal Learning Test; CVH = cardiovascular health; DSST = Digit Symbol Substitution Test; ECHO-SOL = Echocardiographic Study of Latinos;  $e'$  = mitral annular early diastolic velocity;  $E/e'$  ratio = ratio of the early mitral inflow velocity to the mitral annular early diastolic velocity; EF = ejection fraction; GLS = global longitudinal strain; HCHS/SOL = Hispanic Community Health Study/Study of Latinos; LA = left atrial; LAVI = left atrial volume index; LV = left ventricular; LVESV = left ventricular end-systolic volume; LVMI = left ventricular mass index; RWT = relative wall thickness;  $S'$  = peak systolic annular velocity; SIS = Six-Item Screener; WF = Word Fluency

**Affiliations (Continued from the first page of this article.):** and Department of Health Care Sciences, Wayne State University, Detroit, MI (W.T.); Department of Psychology, University of Miami, Coral Gables, FL (N.S.); Division of Cardiology, University of Illinois at Chicago, Chicago (M.M.K.); University of Illinois at Chicago, Chicago (M.L.); Graduate School of Public Health, San Diego State University, San Diego, CA (G.A.T.); and Department of Medicine and Department of Epidemiology, Wake Forest School of Medicine, Winston-Salem, NC (K.S., C.J.R.).

**Grant Support:** The Hispanic Community Health Study/Study of Latinos was carried out as a collaborative study supported by contract N01-HC65233 from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina; contract N01-HC65234 from the University of Miami; contract N01-HC65235 from the Albert Einstein College of Medicine; contract N01-HC65236 from the Northwestern University; and contract N01-HC65237 from the San Diego State University. The following institutes/centers/offices contribute to the Hispanic Community Health Study/Study of Latinos through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, and Office of Dietary Supplements of the National Institutes of Health. The Echocardiographic Study of Latinos was supported by grant R01-HL104199 (Principal Investigator: C.J.R.) from the NHLBI.

**Potential Competing Interests:** Dr Lamar gave a continuing education course at a local hospital system and received payment for her time and travel from Advocate Health. She also received an award as well as payment for

her travel to a conference from The International Neuropsychological Society (both outside the submitted work). The rest of the authors report no competing interests.

**Correspondence:** Address to Carlos J. Rodriguez, MD, MPH, Division of Public Health Sciences, Wake Forest University, Medical Center Blvd, Winston-Salem, NC 27152 ([crodrigu@wakehealth.edu](mailto:crodrigu@wakehealth.edu)).

## REFERENCES

- Ferri CP, Prince M, Brayne C, et al; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366(9503):2112-2117.
- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome [published correction appears in *Arch Neurol*. 1999;56(6):760]. *Arch Neurol*. 1999;56(3):303-308.
- de Toledo Ferraz Alves TC, Ferreira LK, Wajngarten M, Busatto GF. Cardiac disorders as risk factors for Alzheimer's disease. *J Alzheimers Dis*. 2010;20(3):749-763.
- Roberts RO, Knopman DS, Geda YE, Cha RH, Roger VL, Petersen RC. Coronary heart disease is associated with non-amnesic mild cognitive impairment. *Neurobiol Aging*. 2010; 31(11):1894-1902.
- Singh-Manoux A, Sabia S, Lajnef M, et al. History of coronary heart disease and cognitive performance in midlife: the Whitehall II study. *Eur Heart J*. 2008;29(17):2100-2107.
- van den Hurk K, Reijmer YD, van den Berg E, et al. Heart failure and cognitive function in the general population: the Hoom Study. *Eur J Heart Fail*. 2011;13(12):1362-1369.
- Knecht S, Oelschläger C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J*. 2008;29(17):2125-2132.
- Moser DJ, Cohen RA, Clark MM, et al. Neuropsychological functioning among cardiac rehabilitation patients. *J Cardiopulm Rehabil*. 1999;19(2):91-97.
- Karadag B, Ozyigit T, Ozben B, Kayaoglu S, Altuntas Y. Relationship between left atrial volume index and cognitive decline in elderly patients with sinus rhythm. *J Clin Neurosci*. 2013;20(8):1074-1078.
- Jefferson AL. Cardiac output as a potential risk factor for abnormal brain aging. *J Alzheimers Dis*. 2010;20(3):813-821.
- Scuteri A, Coluccia R, Castello L, Nevola E, Brancati AM, Volpe M. Left ventricular mass increase is associated with cognitive decline and dementia in the elderly independently of blood pressure. *Eur Heart J*. 2009;30(12):1525-1529.
- Hayakawa M, Yano Y, Kuroki K, et al. Independent association of cognitive dysfunction with cardiac hypertrophy irrespective of 24-h or sleep blood pressure in older hypertensives. *Am J Hypertens*. 2012;25(6):657-663.
- Paul RH, Gunstad J, Poppas A, et al. Neuroimaging and cardiac correlates of cognitive function among patients with cardiac disease. *Cerebrovasc Dis*. 2005;20(2):129-133.
- Mazzocchi G, Dagostino MP, Vinciguerra M, et al. An association study between epicardial fat thickness and cognitive impairment in the elderly. *Am J Physiol Heart Circ Physiol*. 2014;307(9): H1269-H1276.
- Choi BR, Kim JS, Yang YJ, et al. Factors associated with decreased cerebral blood flow in congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2006;97(9):1365-1369.
- Bossola M, Laudisio A, Antocicco M, et al. Cognitive performance is associated with left ventricular function in older chronic hemodialysis patients: result of a pilot study. *Aging Clin Exp Res*. 2014;26(4):445-451.
- Zeki Al Hazzouri A, Haan MN, Deng Y, Neuhaus J, Yaffe K. Reduced heart rate variability is associated with worse cognitive performance in elderly Mexican Americans. *Hypertension*. 2014; 63(1):181-187.
- Lavange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol*. 2010;20(8):642-649.
- Rodríguez CJ, Dharod A, Allison MA, et al. Rationale and design of the Echocardiographic Study of Hispanics/Latinos (ECHO-SOL). *Ethn Dis*. 2015;25(2):180-186.
- Mehta H, Armstrong A, Swett K, et al. Burden of systolic and diastolic left ventricular dysfunction among Hispanics in the United States: insights from the Echocardiographic Study of Latinos. *Circ Heart Fail*. 2016;9(4):e002733.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010;33(suppl 1):S62-S69.
- González HM, Tarraf W, Gouskova N, et al. Neurocognitive function among middle-aged and older Hispanic/Latinos: results from the Hispanic Community Health Study/Study of Latinos. *Arch Clin Neuropsychol*. 2015;30(1):68-77.
- Lezak MD, Lezak MD. *Neuropsychological Assessment*. Oxford, NY: Oxford University Press; 2004.
- Wechsler D. *WAIS-R Manual*. San Antonio, TX: Psychological Corporation; 1989.
- González HM, Mungas D, Reed BR, Marshall S, Haan MN. A new verbal learning and memory test for English- and Spanish-speaking older people. *J Int Neuropsychol Soc*. 2001; 7(5):544-555.
- Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-Item Screener to identify cognitive impairment among potential subjects for clinical research. *Med Care*. 2002;40(9): 771-781.
- Daviglus ML, Talavera GA, Avilés-Santa ML, et al. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *JAMA*. 2012;308(17):1775-1784.
- Rodríguez CJ, Allison M, Daviglus ML, et al; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular and Stroke Nursing. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. *Circulation*. 2014;130(7):593-625.
- González HM, Tarraf W, Gouskova N, et al. Life's Simple 7's cardiovascular health metrics are associated with Hispanic/Latino neurocognitive function: HCHS/SOL results. *J Alzheimers Dis*. 2016;53(3):955-965.
- Qureshi WT, Leigh JA, Swett K, et al. Comparison of echocardiographic measures in a Hispanic/Latino population with the 2005 and 2015 American Society of Echocardiography reference limits (the Echocardiographic Study of Latinos). *Circ Cardiovasc Imaging*. 2016;9(1):e003597.
- Mayet J, Shahi M, Foale RA, Poulter NR, Sever PS, Thom SAM. Racial differences in cardiac structure and function in essential hypertension. *BMJ*. 1994;308(6935):1011-1014.
- Poppe KK, Doughty RN, Whalley GA. Redefining normal reference ranges for echocardiography: a major new individual person data meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2013; 14(4):347-348.
- González HM, Tarraf W, Rodríguez CJ, et al. Cardiovascular health among diverse Hispanics/Latinos: Hispanic Community Health Study/Study of Latinos (HCHS/SOL) results. *Am Heart J*. 2016;176:134-144.
- Reis JP, Loria CM, Launer LJ, et al. Cardiovascular health through young adulthood and cognitive functioning in midlife. *Ann Neurol*. 2013;73(2):170-179.
- Thacker EL, Gillett SR, Wadley VG, et al. The American Heart Association Life's Simple 7 and incident cognitive impairment: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc*. 2014;3(3):e000635.
- O'Neal WT, Almahmoud MF, Qureshi WT, Soliman EZ. Electrocardiographic and echocardiographic left ventricular hypertrophy in the prediction of stroke in the elderly. *J Stroke Cerebrovasc Dis*. 2015;24(9):1991-1997.

37. Selvetella G, Notte A, Maffei A, et al. Left ventricular hypertrophy is associated with asymptomatic cerebral damage in hypertensive patients. *Stroke*. 2003;34(7):1766-1770.
38. Elias MF, Sullivan LM, Elias PK, et al. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. *Hypertension*. 2007;49(3):439-445.
39. Jerskey BA, Cohen RA, Jefferson AL, et al. Sustained attention is associated with left ventricular ejection fraction in older adults with heart disease. *J Int Neuropsychol Soc*. 2009;15(1):137-141.
40. Shimizu A, Sakurai T, Mitsui T, et al. Left ventricular diastolic dysfunction is associated with cerebral white matter lesions (leukoaraiosis) in elderly patients without ischemic heart disease and stroke. *Geriatr Gerontol Int*. 2014;14(suppl 2):71-76.
41. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation [published correction appears in *Circulation*. 2010;121(12):e258]. *Circulation*. 2009;119(14):e391-e479.
42. Russo C, Jin Z, Homma S, et al. Subclinical left ventricular dysfunction and silent cerebrovascular disease: the Cardiovascular Abnormalities and Brain Lesions (CABL) study. *Circulation*. 2013;128(10):1105-1111.
43. Georgiadis D, Sievert M, Cencetti S, et al. Cerebrovascular reactivity is impaired in patients with cardiac failure. *Eur Heart J*. 2000;21(5):407-413.
44. Taylor J, Stott DJ. Chronic heart failure and cognitive impairment: co-existence of conditions or true association? *Eur J Heart Fail*. 2002;4(1):7-9.