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Journal

Journal of Alzheimer's Disease, 97(3)

ISSN

1387-2877

Authors

Márquez, Freddie

Tarraf, Wassim

Stickel, Ariana M

et al.

Publication Date

2024

DOI

10.3233/jad-230424

Journal of Alzheimer's Disease 97 (2024) 1449–1461
DOI 10.3233/JAD-230424
IOS Press

Hypertension, Cognitive Decline, and Mild Cognitive Impairment Among Diverse Hispanics/Latinos: Study of Latinos-Investigation of Neurocognitive Aging Results (SOL-INCA)

Freddie Márquez[a], Wassim Tarraf[b], Ariana M. Stickel[a,c], Kevin A. González[a], Fernando D. Testai[d], Jianwen Cai[e], Linda C. Gallo[c], Gregory A. Talavera[c], Martha L. Daviglus[f], Sylvia Wassertheil-Smoller[g], Charles DeCarli[h], Neil Schneiderman[i] and Hector M. González[a,*]
[a]*Department of Neurosciences and the Shiley-Marcos Alzheimer's Disease Research Center, UC San Diego, San Diego, CA, USA*
[b]*Institute of Gerontology & Department of Healthcare Sciences, Wayne State University, Detroit, MI, USA*
[c]*Department of Psychology, San Diego State University, San Diego, CA, USA*
[d]*Department of Neurology and Rehabilitation, University of Illinois at Chicago, College of Medicine, Chicago, IL, USA*
[e]*Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA*
[f]*Institute for Minority Health Research, University of Illinois at Chicago, College of Medicine, Chicago, IL, USA*
[g]*Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York, NY, USA*
[h]*Department of Neurology and Alzheimer's Disease Center, UC Davis, Sacramento, CA, USA*
[i]*Department of Psychology, University of Miami, Miami, FL, USA*

Accepted 29 November 2023
Pre-press 16 January 2024

Abstract.
Background: Hypertension can have deleterious effects on cognitive function; however, few studies have examined its effects on cognition among Hispanics/Latinos.
Objective: To assess associations between hypertension status with 1) change in cognitive performance, and 2) having mild cognitive impairment (MCI) among diverse Hispanics/Latinos.
Methods: This population-based, prospective cohort, multisite study included Hispanic/Latino adults aged 45 to 72 years in enrolled in the *Hispanic Community Health Study/Study of Latinos* at Visit 1 (2008–2011; mean age of 63.40 ± 8.24 years), and the *Study of Latinos-Investigation of Neurocognitive Aging* at Visit 2 (2016–2018), with a mean follow-up duration of 7 years ($n = 6{,}173$). Hypertension status was assessed at both visits: normotension (no hypertension), incident hypertension (only at Visit 2), and persistent hypertension (at both visits). We examined change in cognitive performance and having MCI (only assessed at Visit 2) relative to hypertension status and adjusted for demographics and cardiovascular disease risk factors.

*Correspondence to: Hector M. González, PhD, UC San Diego, Department of Neurosciences and the Shiley-Marcos Alzheimer's Disease Research Center, 9500 Gilman Drive #0949, La Jolla, CA 92093-0949, USA. Tel.: +1 858 534 5361; E-mail: hectorgonzalez@ucsd.edu.

ISSN 1387-2877/$35.00

Results: Compared to normotension, persistent hypertension was associated with significantly increased decline in verbal fluency ($\beta = -0.08$; CI = [–0.16;–0.01]; $p < 0.05$), and processing speed ($\beta = -0.11$; CI = [–0.20;–0.02]; $p < 0.05$). Incident hypertension was not associated with significant change in cognitive performance. Both incident (OR = 1.70; CI = [1.16;2.50]; $p < 0.01$) and persistent hypertension (OR = 2.13; CI = [1.57;2.88]; $p < 0.001$) were associated with significantly higher odds ratios of having MCI.

Conclusions: These findings indicate that persistent hypertension is associated with clinical impairment and domain-specific cognitive decline in middle-aged and older Hispanics/Latinos. It underscores the importance of monitoring blood pressure in routine healthcare visits beginning at midlife in this population to reduce the burden of cognitive decline.

Keywords: Alzheimer's disease, blood pressure, cognitive decline, cognitive function, dementia, epidemiology, Hispanics, hypertension, Latinos, mild cognitive impairment, neuroepidemiology, neuropsychology, population neuroscience

INTRODUCTION

Modifying risk factors can potentially reduce or prevent around 40% of Alzheimer's disease and related dementias (ADRD) [1]. Hypertension is particularly prevalent [2], especially as people age. In the United States (US), around 33% of individuals aged 40–59 have hypertension and this prevalence increases to 63% for those aged 60 and older [3]. Since there are numerous approved treatments for hypertension, addressing it could be a key strategy for maintaining cognitive health as people get older. Hypertension has been linked with reduced abstract reasoning (executive dysfunction), slowing of mental processing speed, and memory deficits [4]. Moreover, a history of hypertension is associated with higher risk of mild cognitive impairment (MCI), which is a state that increases risk for developing dementia [5, 6].

In coming decades, the Hispanic/Latino older adult population is projected to quadruple and have the largest increase in ADRD prevalence of any ethnic or racial group in the US [7, 8]. Hispanics/Latinos individuals have diverse backgrounds in regards to genetic ancestry, culture, and environmental exposures [9, 10]. When it comes to hypertension, Hispanics/Latinos have a high proportion of poorly controlled blood pressure, possibly due to facing healthcare disparities [11]. Additionally, differences in the prevalence of hypertension by Hispanic/Latino background exist [12]. Despite the high prevalence of hypertension in this population, limited research has investigated its impact on cognitive aging [13]. One study in Hispanics/Latinos older adults found that history of hypertension has been associated with poorer executive function [14]. We have also observed that higher mean arterial pressure is negatively associated on various cognitive functions among middle-aged and older Hispanics/Latinos, including executive function, psychomotor speed and sustained attention, verbal episodic learning and memory, speech fluency, and mental status measures [15]. However, further longitudinal studies are required to establish the long-term relationships between hypertension with cognitive change and having MCI in this population.

In this study, we evaluated the association between hypertension and 1) change in cognitive performance, and 2) prevalence of MCI among diverse Hispanic/Latino middle-aged and older adults in the US. We hypothesized that persistence of hypertension would be associated with 1) increased decline in cognitive performance over 7 years relative to normotension, and 2) increased odds ratio of having MCI.

METHODS

Study design

The *Study of Latinos–Investigation of Neurocognitive Aging* (SOL-INCA) is a *Hispanic Community Health Study/Study of Latinos* (HCHS/SOL) ancillary study. Descriptions of HCHS/SOL and SOL-INCA study designs and rationales have been previously published and are available on the HCHS/SOL website: https://sites.cscc.unc.edu/hchs/ [16–18]. Briefly, HCHS/SOL is a prospective cohort study of diverse Hispanics/Latinos conducted across multiple sites. It employs a complex sampling design, which includes stratification and clustering, for its probability-based sample (Visit 1; 2008–2011) [17]. The complex survey sampling procedures used in HCHS/SOL were designed to yield representative data for Hispanics/Latinos in four targeted US metropolitan areas: Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA. Each Field Center enrolled about 4,000 eligible, self-identified Hispanics/Latinos from diverse backgrounds (ages 18–74 years; N = 16,415) [10]. SOL-INCA leveraged the HCHS/SOL cohort for a follow-up examination (Visit

2; 2016–2018) to obtain a second time point of cognitive testing.

The HCHS/SOL and the SOL-INCA studies were reviewed and approved by the Institutional Review Boards of the University of California San Diego and all participating sites.

Baseline cognitive testing at HCHS/SOL Visit 1 involved only middle-aged and older (ages 45–74 years) participants ($n = 9{,}714$). The Neurocognitive Reading Center trained and the Field Centers directly supervised bicultural/bilingual technicians who administered the brief cognitive battery, which included 3 tests: 1) Brief-Spanish English Verbal Learning Test (B-SEVLT Sum and Recall; verbal episodic learning and memory) [19]; 2) Word Fluency (WF; verbal fluency); and 3) Digit Symbol Subtest (DSS; processing speed, executive function) [20]. The B-SEVLT is an episodic verbal learning and memory test with 2 scores for: (1) learning (the summed total of correctly learned items across 3 trials [B-SEVLT-sum; range, 0–45]), which is followed by an interference trial, and (2) memory (total correctly recalled items; range, 0–15). The WF is a phonemic verbal fluency test (sum of correctly generated words within 1 minute for the letters F and A; range, 0–50). The DSS is a mental processing speed and executive functioning examination (range, 0–90 s). A global cognitive composite score (global cognition) was derived by averaging the z-scores across the domain-specific tests, as described herein. Of all eligible participants, only 59 (<1%) did not participate due to health limitations and/or refusals. Additional information about the cognitive tests used at Visit 1 and the cohort have been previously published [21]. Baseline cognitive measures were standardized (z-scored) relative to the baseline target population to facilitate comparison across estimates.

SOL-INCA cognitive tests were administered to eligible HCHS/SOL participants who returned for Visit 2 with a mean follow up of about 7 years. The cognitive battery was expanded to derive a MCI research diagnosis based on National Institute on Aging-Alzheimer's Association (NIA-AA) criteria [22]. In addition to Visit 1 tests, the assessment included the Trail Making Test (TMT, parts A and B, processing speed and executive function). More detailed information about the battery of tests has been published [16, 23]. SOL-INCA cognitive measures were standardized (z-scored) relative to the SOL-INCA target population to facilitate comparison across estimates. A global cognition (GC) score for SOL-INCA was operationalized using the average z-scores of the individual tests of the repeated battery. The PVT was used to assess premorbid cognitive function since these scores remain stable with age and into later neurodegenerative stages, and to control for potential educational quality test biases [24]. At HCHS/SOL Visit 2, the Coordinating Center identified 7,420 potentially eligible participants for SOL-INCA. Inclusion criteria were: 1) Visit 2 completion, 2) Visit 1 neurocognitive testing completion, and 3) age 50 years and older at Visit 2. Of this group 222 were determined to be ineligible (e.g., missing Visit 1 data), 569 were eligible but refused, and 6,377 were eligible and agreed to participate. Eligible participants returning for SOL-INCA had largely similar Visit 1 characteristics compared to those in the overall Visit 1 eligible participant pool. Furthermore, to guard against possible biases by sample attrition, the HCHS/SOL Coordinating Center generated study-specific calibrated probability weights that adjust for non-response (e.g., deaths) and allow generalization of estimates to the HCHS/SOL metropolitan area target populations aged 50 years and older. For this study, we exclude $n = 87$ observations with missing data on any of the model covariates as specified below, we also excluded $n = 117$ participants who did not report a specific Hispanic/Latino background. The final unweighted analytical sample was $n = 6{,}173$.

Cognitive change scores for repeated cognitive tests were calculated using regression-based methods. Weighted linear regression models were used to predict cognitive performance at Visit 2 (SOL-INCA) as a function of Visit 1 cognitive performance, adjusting for elapsed time (in days) between cognitive assessments. Regression-based change score methods and their application to neurocognitive measures have been detailed elsewhere [25]. Briefly, test specific standardized measures of change were subsequently calculated using $(T2 - T2_{pred})/RMSE$ where $T2$ was the respondent cognitive score at Visit 2, $T2_{pred}$ their predicted score at Visit 2 and the regression derived root mean squared error (RMSE). Using a similar methodology, global cognitive change was assessed based on the z-score averages of the repeated cognitive domains [16].

MCI criteria were operationalized to generate four core NIA-AA criteria: 1) any cognitive score in the mildly impaired range, that is, from –1 to –2 standard deviations (SD) compared to the SOL-INCA internal robust norms (age, education, and sex adjusted scores); 2) significant cognitive decline ($\leq$–0.055 SD/year) from Visit 1; 3) self-reported cognitive

decline; and 4) no or minimum IADL impairment [22]. Cognitive impairment and significant cognitive decline criteria were used to reduce false positive bias. Individuals with severe cognitive impairment (below –2 SD relative to SOL-INCA robust norms and with significant functional impairment) were not included in these MCI prevalence estimates ($n = 86$) [23].

Hypertension at HCHS/SOL Visit 1 and Visit 2 was defined using National Health and Nutrition Examination Survey (NHANES) criteria: individuals were considered meeting criteria for hypertension if systolic or diastolic blood pressure was greater than or equal to 140/90 mmHg or if they self-reported currently taking antihypertensive mediations; individuals declining a blood pressure measurement and not reporting medication use were assumed to be not meeting criteria [15]. We generated three groups: 1) normotension (no hypertension; $n = 2{,}763$), 2) incident hypertension (hypertension only at Visit 2; $n = 988$), and 3) persistent hypertension (hypertension at both visits; $n = 2{,}422$) to capture associations between hypertension exposure with cognitive outcomes. Normotension was set as the reference group.

In sensitivity models, the persistent hypertension group was further split into two subgroups: persistent with anti-hypertensive medication treatment, and persistent without anti-hypertensive treatment at Visit 1 to generate a four-category measure: 1) normotension, 2) incident hypertension (only at Visit 2), 3) persistent hypertension without medication (hypertension at both visits without anti-hypertensive treatment; $n = 1{,}089$), and 4) persistent hypertension with medication (hypertension at both visits with anti-hypertensive treatment; $n = 1{,}333$). Normotension was set as the reference group.

Covariables included age at Visit 2 (50–59, 60–69, and 70+ years), sex (male, female), education (less than high school, high school or equivalent and more than high school), Hispanic/Latino background (Dominicans, Cubans, Central Americans, Mexicans, Puerto-Ricans, and South Americans), and language preference (English/Spanish). Given the extensive literature linking cardiovascular disease (CVD) risk factors to cognitive decline in Hispanics/Latinos [26–29], we also adjusted for CVD risk factors including body mass index (BMI; in kg/m^2), current smoking status, dyslipidemia status, stroke/transient ischemic attack, and diabetes status. Diabetes status was determined using the American Diabetes Association criteria [30]. Dyslipidemia was a binary variable constructed using HDL, LDL, and triglyceride values to determine presence/absence of dyslipidemia as follows: if LDL-cholesterol ≥ 160 mg/dL, HDL-cholesterol < 40, or Triglycerides ≥ 200 mg/dL. Except for age, all covariables used were from the baseline assessment.

Analytic approach

First, we generated descriptive statistics to characterize our target population across different hypertension groups (Table 1). Second, we fit a series of survey regression models (linear for continuous measures of performance and change, and logit for the binary MCI outcome) to test the associations between hypertension status and cognitive outcomes. For each outcome, we tested (1) unadjusted (2) age, sex, education, Hispanic/Latino background, and language preference adjusted and (3) fully adjusted (including all covariables as described above) models. Regression estimates (β/ORs) and their 95% confidence intervals (95% CI) are presented in Tables 2–4 for cognitive performance at Visit 2, cognitive change, and having MCI (precise *p*-values are additionally presented in Supplementary Tables 1-3). Third, *post-hoc* ANOVA methods were used to estimate average marginal means and probabilities and their 95% confidence intervals and plots of these marginal estimates are visualized in Fig. 1 and Supplementary Figures 1 and 2. To examine modifications by age and Hispanic/Latino background we refit the fully adjusted regression models above including interactions between categorial age (<60; 60+) and Hispanic/Latino background variables and hypertension and tested for the significance of these interactions using F-tests (Supplementary Table 4). In additional models and to ensure that we are appropriately powered for testing Hispanic/Latino background interactions, a three-category indicator, reflecting risk stratification [12], was generated to include (1) Mexicans, Central Americans, and South Americans, (2) Puerto Ricans and Dominicans, and (3) Cubans (results, available from authors, were not qualitatively different). All regression analyses were repeated by using the four-category hypertension with treatment indicator. These results are shown in Supplementary Tables 5 through 7 (precise *p*-values are additionally presented in Supplementary Tables 8–10). In sensitivity models, we adjusted for field center as a potential confounder. For models where cognitive performance and MCI are included as outcomes, we also adjusted for time lapse between the baseline and SOL-INCA visits. Results were not

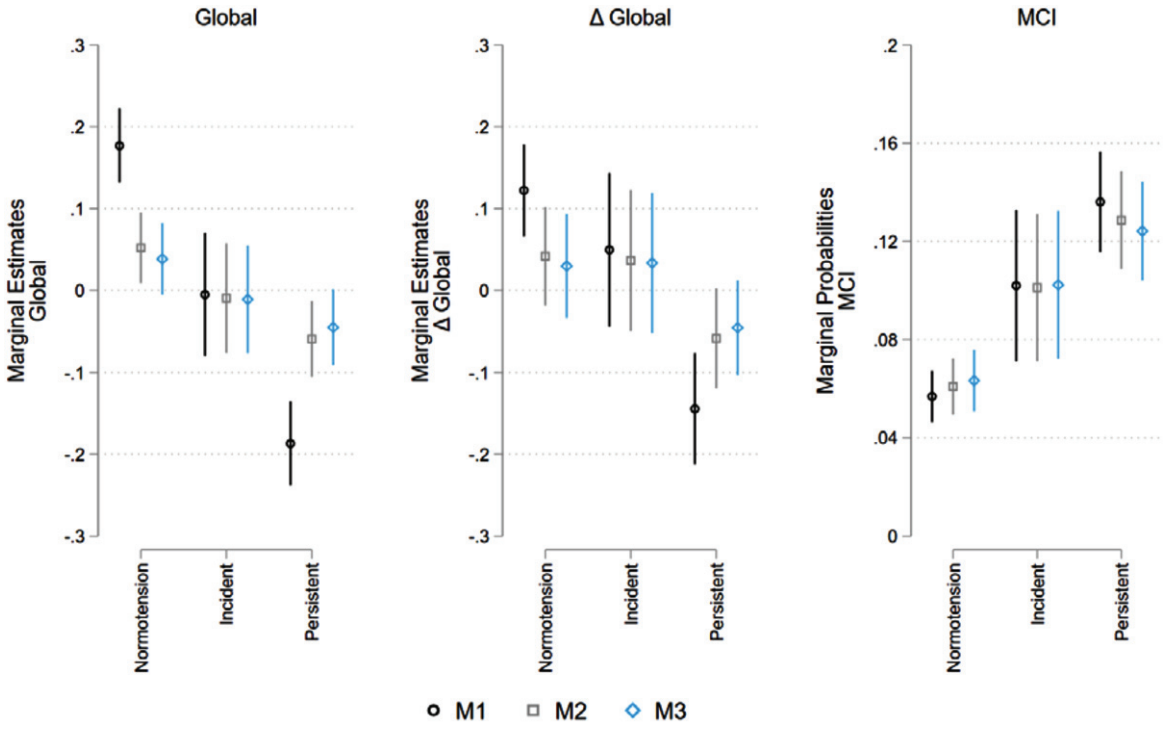

Fig. 1. Estimates of unadjusted and adjusted marginal means and probabilities (and their 95% CIs) for cognitive function, cognitive change, and mild cognitive impairment (MCI). Model 1: Unadjusted, Model 2: Adjusts for age, sex, education, Hispanic/Latino background, and language preference, Model 3: Model 2 + body mass index, stroke/transient ischemic attack, dyslipidemia, diabetes, and smoking status. Note: Global cognition based on repeated tests only (B-SEVLT Sum, B-SEVLT-Recall, Word Fluency, and Digit Symbol Subtest).

quantitatively or qualitatively distinct from the primary findings (available from authors).

All analyses were conducted in Stata 17 using the survey functionalities to appropriately account for the complex sampling design of HCHS/SOL and SOL-INCA and allow generalizability to the SOL-INCA target population.

RESULTS

Descriptives

The target population characteristics and covariables of interest are shown in Table 1 for both the overall sample and by hypertension status. Briefly, close to two-thirds of individuals in the target population had a high school degree or more (61.18%), slightly more than half were female (54.62%), nearly 9 in 10 preferred testing in Spanish over English (87.98%). Regarding Hispanic/Latino background, 34.40% identified as Mexican, 26.82% Cuban, 16.01% Puerto-Rican, 9.85% Dominican, 7.51% Central American, and 5.40% South American. The average age was 63.40 years $\pm$ 8.24 (SD) and mean BMI was 29.73 $\pm$ 5.49 kg/m^2.

Those with persistent hypertension (42.1%) were significantly older, more likely to be female, less likely to report more than high school education, and had higher BMI compared to those meeting criteria for incident hypertension (15.5%) followed by the normotensive group (42.4%). Differences in language preference were not significant between groups (Table 1).

Standardized cognitive scores at visit 2

At Visit 2, persistent hypertension was associated with lower global (β_{GC} = –0.08; CI = [–0.13; –0.03]; $p < 0.001$) and domain specific performance in verbal fluency (β_{WF} = –0.10; CI = [–0.17; –0.02]; $p < 0.05$) and processing speed (β_{DSS} = –0.10; CI = [–0.16; –0.03]; $p < 0.01$) compared to normotension after adjustment for covariates (Table 2 and Supplementary Table 1). Incident hypertension was associated with significantly slower processing speed (β_{DSS} = –0.12; CI = [–0.20; –0.04]; $p < 0.01$)

Table 1
Descriptive statistics at Visit 1 to characterize the population of SOL-INCA overall and across different hypertension groups

		Normotension	Incident	Persistent	Total	
N (%)						
	Unweighted N	2,763	988	2,422	6,173	
	%	42.4	15.5	42.1	100	
		% (SE)				
Education						
	Less than High School (HS)	34.73 (1.47)	41.87 (2.47)	41.83 (1.46)	38.83 (1.09)	$p = 0.003$
	HS or Equivalent	22.96 (1.24)	19.89 (1.84)	20.73 (1.08)	21.55 (0.76)	
	More than HS	42.31 (1.53)	38.24 (2.18)	37.44 (1.40)	39.63 (0.99)	
Sex						
	Female	52.06 (1.36)	53.95 (2.19)	57.44 (1.36)	54.62 (0.85)	$p = 0.021$
	Male	47.94 (1.36)	46.05 (2.19)	42.56 (1.36)	45.38 (0.85)	
Age						
	<60 y	53.95 (1.56)	40.52 (2.33)	22.38 (1.09)	38.58 (0.99)	$p < 0.001$
	60–70 y	32.97 (1.27)	37.02 (2.17)	38.06 (1.46)	35.74 (0.95)	
	70+ y	13.07 (1.30)	22.45 (2.20)	39.57 (1.72)	25.68 (1.03)	
Hispanic/Latino background						
	Dominican	7.98 (0.88)	9.07 (1.32)	12.03 (1.11)	9.85 (0.79)	$p < 0.001$
	Central American	8.07 (0.80)	7.88 (1.19)	6.81 (0.63)	7.51 (0.58)	
	Cuban	21.59 (1.92)	25.96 (2.63)	32.41 (2.53)	26.82 (1.95)	
	Mexican	42.30 (2.09)	34.56 (2.46)	26.39 (1.95)	34.40 (1.73)	
	Puerto-Rican	13.75 (0.99)	15.98 (1.73)	18.30 (1.24)	16.01 (0.86)	
	South American	6.31 (0.62)	6.55 (1.14)	4.07 (0.51)	5.40 (0.40)	
Field Center						
	Bronx	24.05 (1.67)	27.46 (2.53)	29.49 (1.94)	26.87 (1.51)	$p < 0.001$
	Chicago	15.16 (1.09)	13.73 (1.45)	9.86 (0.80)	12.71 (0.84)	
	Miami	32.05 (2.36)	37.45 (2.73)	40.01 (2.82)	36.24 (2.31)	
	San Diego	28.74 (2.10)	21.36 (1.95)	20.64 (1.90)	24.19 (1.68)	
Language preference						
	Spanish	86.78 (1.04)	87.75 (1.47)	89.28 (0.95)	87.98 (0.74)	$p = 0.12$
	English	13.22 (1.04)	12.25 (1.47)	10.72 (0.95)	12.02 (0.74)	
Stroke/TIA						
	No	98.19 (0.39)	97.48 (0.78)	94.58 (0.76)	96.56 (0.38)	$p < 0.001$
	Yes	1.81 (0.39)	2.52 (0.78)	5.42 (0.76)	3.44 (0.38)	
Dyslipidemia						
	No	58.73 (1.45)	54.70 (2.35)	53.69 (1.56)	55.99 (1.01)	$p = 0.04$
	Yes	41.27 (1.45)	45.30 (2.35)	46.31 (1.56)	44.01 (1.01)	
Diabetes						
	No	33.70 (1.24)	25.85 (1.92)	15.09 (0.88)	24.65 (0.70)	$p < 0.001$
	Pre	49.98 (1.40)	48.13 (2.19)	42.92 (1.39)	46.72 (0.89)	
	Yes	16.32 (1.11)	26.03 (1.98)	41.99 (1.41)	28.63 (0.92)	
Current Smoker						
	No	79.16 (1.19)	78.31 (1.89)	85.01 (1.04)	81.49 (0.79)	$p < 0.001$
	Yes	20.84 (1.19)	21.69 (1.89)	14.99 (1.04)	18.51 (0.79)	
				Mean (SD)		
Age		60.38 (7.51)	62.92 (7.97)	66.63 (7.77)	63.40 (8.24)	$p < 0.001$
BMI		28.51 (5.09)	29.55 (5.7)	31.02 (5.46)	29.73 (5.49)	$p < 0.001$

compared to normotension following covariates adjustment.

Cognitive change

Persistent hypertension was also linked to more pronounced decline in verbal fluency ($\beta\Delta_{WF} = -0.08$; CI = [–0.16; –0.01]; $p < 0.05$) and processing speed ($\beta\Delta_{DSS} = -0.11$; CI = [–0.20; –0.02]; $p < 0.05$) compared to normotension after adjusting for covariates (Table 3 and Supplementary Table 2). Incident hypertension was only associated with decline in processing speed ($\beta_{DSS} = -0.13$; CI = [–0.23; –0.04]; $p < 0.01$), but the effect was completely attenuated by covariate adjustment.

Prevalent MCI

Consistent with the findings above, persistent hypertension was associated with an increased odds ratio of having MCI (OR = 2.61; CI = [2.01; 3.40]; $p < 0.001$). Incident hypertension was also

Table 2
Associations of hypertension status with z-scored values of cognitive performance at Visit 2

	Model 1 B [95% CI]	Model 2 B [95% CI]	Model 3 B [95% CI]
		Global Cognition	
Normotension	ref	ref	ref
Incident	–0.18*** [–0.27;–0.10]	–0.06 [–0.13;0.01]	–0.05 [–0.12;0.02]
Persistent	–0.36*** [–0.42;–0.31]	–0.11*** [–0.16;–0.06]	–0.08*** [–0.13;–0.03]
		B-SEVLT Sum	
Normotension	ref	ref	ref
Incident	–0.18** [–0.29;–0.06]	–0.06 [–0.17;0.05]	–0.05 [–0.16;0.05]
Persistent	–0.34*** [–0.42;–0.27]	–0.09* [–0.16;–0.01]	–0.07 [–0.15;0.01]
		B-SEVLT Recall	
Normotension	ref	ref	ref
Incident	–0.13* [–0.23;–0.02]	–0.02 [–0.12;0.08]	–0.02 [–0.11;0.08]
Persistent	–0.33*** [–0.41;–0.25]	–0.08 [–0.15;0.00]	–0.07 [–0.15;0.01]
		WF	
Normotension	ref	ref	ref
Incident	–0.11* [–0.22;–0.01]	–0.03 [–0.13;0.07]	–0.01 [–0.11;0.09]
Persistent	–0.29*** [–0.37;–0.22]	–0.15*** [–0.22;–0.07]	–0.10* [–0.17;–0.02]
		DSS	
Normotension	ref	ref	ref
Incident	–0.31*** [–0.42;–0.20]	–0.14*** [–0.22;–0.06]	–0.12** [–0.20;–0.04]
Persistent	–0.49*** [–0.56;–0.41]	–0.14*** [–0.20;–0.07]	–0.10** [–0.16;–0.03]
		TMT A (Reverse Coded)	
Normotension	ref	ref	ref
Incident	–0.24*** [–0.38;–0.10]	–0.11 [–0.23;0.01]	–0.10 [–0.22;0.02]
Persistent	–0.37*** [–0.44;–0.29]	–0.09** [–0.16;–0.03]	–0.06 [–0.13;0.01]
		TMT B (Reverse Coded)	
Normotension	ref	ref	ref
Incident	–0.21*** [–0.31;–0.10]	–0.08 [–0.17;0.02]	–0.06 [–0.16;0.03]
Persistent	–0.36*** [–0.44;–0.27]	–0.10* [–0.17;–0.02]	–0.07 [–0.14;0.01]

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. Model 1: Unadjusted, Model 2: Adjusts for age, sex, education, Hispanic/Latino background, and language preference, Model 3: Model 2 + body mass index, stroke/transient ischemic attack, dyslipidemia, diabetes, and smoking status. Note 1: B-SEVLT, Brief Spanish English Verbal Learning Test; WF, Word Fluency; DSS, Digit Symbol Subtest; TMT, Trails Making Test. Note 2: B, Beta Coefficient; CI, confidence interval. Note 3: Global cognition based on repeated tests only (B-SEVLT Sum, B-SEVLT-Recall, Word Fluency, and Digit Symbol Subtest).

associated with an increased odds ratio of having MCI (OR = 1.88; CI = [1.28; 2.77]; $p < 0.01$). The odds ratios for both persistent (OR = 2.13; CI = [1.57; 2.88]; $p < 0.001$) and incident hypertension (OR = 1.70; CI = [1.16; 2.50]; $p < 0.01$) were only slightly attenuated by adjustment to covariates (Table 4 and Supplementary Table 3).

Interactions with age and Hispanic/Latino background

We found no evidence to indicate modifications in associations between hypertension grouping with cognitive performance at Visit 2, change, or having MCI by either age or Hispanic/Latino background. The F-tests for the tested interaction effects and their associated *p*-values are presented in Supplementary Table 4 (all $p \geq 0.1$).

Hypertension treatment analysis

We found that persistent hypertension with medication had significantly lower performance in global cognition ($\beta_{GC} = –0.08$; CI = [–0.14; –0.02]; $p < 0.05$), verbal fluency ($\beta_{WF} = –0.10$; CI = [–0.18; –0.01]; $p < 0.05$), processing speed ($\beta_{DSS} = –0.08$; CI = [–0.16; –0.00]; $p < 0.05$), and executive function ($\beta_{TrailsB} = –0.09$; CI = [–0.18; –0.01]; $p < 0.05$) relative to the normotensive group after full covariate adjustment (Supplementary Tables 5 and 8). Persistent hypertension without medication at Visit 1 also had significant lower performance in global cognition ($\beta_{GC} = –0.09$; CI = [–0.15; –0.02]; $p < 0.01$), verbal fluency ($\beta_{WF} = –0.10$; CI = [–0.19; –0.00]; $p < 0.05$), and processing speed ($\beta_{DSS} = –0.12$; CI = [–0.20; –0.04]; $p < 0.01$) relative to the normotensive group after full covariate adjustment.

Table 3
Associations of hypertension status with cognitive change

	Model 1 B [95% CI]	Model 2 B [95% CI]	Model 3 B [95% CI]
		Global Cognition	
Normotension	ref	ref	ref
Incident	–0.07 [–0.18;0.04]	–0.01 [–0.11;0.10]	0.00 [–0.10;0.11]
Persistent	–0.27*** [–0.35;–0.18]	–0.10* [–0.18;–0.02]	–0.08 [–0.16;0.01]
		B-SEVLT Sum	
Normotension	ref	ref	ref
Incident	–0.11 [–0.23;0.01]	–0.04 [–0.16;0.07]	–0.04 [–0.15;0.07]
Persistent	–0.23*** [–0.32;–0.15]	–0.07 [–0.15;0.02]	–0.06 [–0.15;0.03]
		B-SEVLT Recall	
Normotension	ref	ref	ref
Incident	–0.04 [–0.15;0.08]	0.03 [–0.08;0.14]	0.03 [–0.08;0.14]
Persistent	–0.20*** [–0.28;–0.12]	–0.04 [–0.12;0.05]	–0.03 [–0.12;0.05]
		WF	
Normotension	ref	ref	ref
Incident	–0.03 [–0.14;0.08]	0.01 [–0.10;0.12]	0.02 [–0.09;0.13]
Persistent	–0.20*** [–0.27;–0.12]	–0.11** [–0.19;–0.03]	–0.08* [–0.16;–0.01]
		DSS	
Normotension	ref	ref	ref
Incident	–0.13** [–0.23;–0.04]	–0.07 [–0.16;0.03]	–0.05 [–0.15;0.04]
Persistent	–0.31*** [–0.39;–0.22]	–0.15** [–0.24;–0.06]	–0.11* [–0.20;–0.02]

***$p<0.001$; **$p<0.01$; *$p<0.05$. Model 1: Unadjusted, Model 2: Adjusts for age, sex, education, Hispanic/Latino background, and language preference, Model 3: Model 2 + body mass index, stroke/transient ischemic attack, dyslipidemia, diabetes, and smoking status. Note 1: B-SEVLT, Brief Spanish English Verbal Learning Test; WF, Word Fluency; DSS, Digit Symbol Subtest. Note 2: B, Beta Coefficient; CI, confidence interval. Note 3: Global cognition based on repeated tests only (B-SEVLT Sum, B-SEVLT-Recall, Word Fluency, and Digit Symbol Subtest).

Table 4
Associations of hypertension status with having MCI at Visit 2

	Model 1	Model 2	Model 3
	OR [95% CI]	OR [95% CI]	OR [95% CI]
		MCI	
Normotension	ref	ref	ref
Incident	1.88** [1.28;2.77]	1.75** [1.20;2.55]	1.70** [1.16;2.50]
Persistent	2.61*** [2.01;3.40]	2.30*** [1.74;3.05]	2.13*** [1.57;2.88]

***$p<0.001$; **$p<0.01$; *$p<0.05$. Model 1: Unadjusted, Model 2: Adjusts for age, sex, education, Hispanic/Latino background, and language preference, Model 3: Model 2 + body mass index, stroke/transient ischemic attack, dyslipidemia, diabetes, and smoking status. Note: OR, odds ratio; CI, confidence interval.

Persistent hypertension with medication at Visit 1 had significant declines in verbal fluency ($\beta\Delta_{WF} = -0.10$; CI = [–0.19; –0.00]; $p<0.05$), processing speed ($\beta\Delta_{DSS} = -0.12$; CI = [–0.24; –0.01]; $p<0.05$), and was associated with an increased odds ratio of having MCI (OR = 2.35; CI = [1.66; 3.32]; $p<0.001$) relative to the normotensive group after full covariate adjustment (Supplementary Tables 6, 7, 9, and 10). We also found that persistent hypertension without medication at Visit 1 did not differ in cognitive decline but was associated with an increased odds ratio of having MCI (OR = 1.92; CI = [1.35; 2.73]; $p<0.001$) relative to normotension.

DISCUSSION

Identifying risk factors for ADRDs can improve prevention and interventions. Moreover, the U.S. population is increasingly more diverse, and older. In a large representative cohort of middle-aged and older Hispanics/Latinos from diverse backgrounds, both incident and persistent hypertension were associated with lower cognitive scores, the former only for processing speed. Only persistent hypertension was associated with decline in cognitive scores over time. Having hypertension (incident or persistent) was associated with a significantly greater odds ratio of having MCI. These findings did not differ across

age or Hispanic/Latino background. Our findings underscore the importance of managing and monitoring hypertension, not only for cardiovascular health but also for healthy cognitive aging. They emphasize the potential benefits of early intervention to help preserve cognitive function and reduce the risk of cognitive decline in the long term. This has substantial implications for public health strategies and clinical practice in addressing cognitive health in individuals with hypertension. Our findings also suggest that treatment of hypertension may warrant further investigation.

In this study, we expanded upon previous work examining hypertension, a CVD risk factor, and cognition in middle-aged and older Hispanics/Latinos. Here we show that incident hypertension was only associated with significantly lower performance in processing speed. A possible explanation is that in newly diagnosed individuals, decline evolves gradually, and processing speed may be impaired earlier than other domains in those with hypertension. This would suggest a possible window for early intervention. The mechanisms by which hypertension affects the risk of cognitive impairment remains unclear. However, previous studies have suggested that chronic blood pressure dysregulation, including through hypertension, increases risk for atherosclerosis, weakens arterial integrity, damages blood flow regulation, compromises the cerebral energy supply and waste clearance, and this affects brain structure and function [31]. Previous studies have also reported that those with hypertension had a smaller prefrontal cortex, and increased frontal white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) [32]. This would suggest regional vulnerability of prefrontal regions, which are important for executive functions such as processing speed. Alternatively, dietary habits such as a salt-rich diet, a precursor of hypertension, has also been proposed to promote AD and cognitive impairment. In AD, accumulation of hyperphosphorylated tau, a hallmark of AD pathology, is also linked to vascular cognitive impairment [33, 34]. Salt intake alters nitric oxide production in cerebral endothelial cells, reducing cerebral perfusion, and inducing tau hyperphosphorylation [35]. Here we also find that persistent hypertension was associated with lower performance in global cognition, verbal fluency, and processing speed, which is consistent with previous findings reporting that hypertension was negatively associated with worse performance on several cognitive domains [15, 36, 37]. Furthermore, we found that persistent hypertension was linked to more pronounced declines verbal fluency and processing speed. This could suggest that prolonged exposure to hypertension may lead to widespread changes across cognitive domains. Hypertension has also been associated with increased risk of stroke [38], and has been linked to small vessel damage, and increases in WMH on MRI [32, 39]. In contrast to our study, one recent longitudinal study among Brazilian participants found that hypertension at baseline was associated with reduction in memory, and global cognitive scores, but not executive function over a 4 year follow up [40]. However, one thing to note in that study is that among participants that had hypertension, 92.7 percent used anti-hypertensive medication. In our study, only 55.0 percent of the participants that had hypertension used anti-hypertensive medication.

Several studies have previously examined the relation of hypertension with MCI. In the Cardiovascular Health Study, significantly higher percentages of the participants with MCI had hypertension [41]. Studies focused on risk factors for MCI have found that hypertension diagnosed in midlife increased the risk of developing MCI [42]. A study among older adults also found that hypertension was related to a higher risk of MCI [43]. Here we find that persistent hypertension was associated with a higher odds ratio of MCI. Despite minimal links to cognitive performance and change, incident hypertension was associated with a higher odds ratio of MCI compared to normotensive individuals.

The association between hypertension at middle-age and cognitive decline is well documented, but this relationship is inconsistent in the literature among older adults. Our study did not show a significant interaction with hypertension status and cognitive change or odds ratio for MCI for different age groups (middle-aged and older adults). Additionally, Hispanics/Latinos in the US can trace their origins to different countries or backgrounds. A previous study has reported differences in hypertension prevalence among Hispanics/Latinos background [12]. In our study, there were no differences in cognitive decline or odds ratio for MCI with hypertension status across Hispanic/Latino background.

Recent evidence suggests that intensive blood pressure therapy in a randomized clinical trial was shown to reduce cognitive decline and risk for cognitive impairment [44]. As such, managing blood pressure would offer an effective means of reducing cognitive impairment and dementia at the population level. However, those with medicated hypertension

have also been reported to be more likely to convert to MCI than those without medicated hypertension [43]. In this study, those with persistent hypertension that were on medication and not on medication had significantly lower performance in verbal fluency, and processing speed relative to those without hypertension, and the odds ratio of having MCI was significantly higher for those with persistent hypertension regardless of treatment. However, those that were on medication also had significantly lower performance in executive function and significantly more pronounced declines in verbal fluency and processing speed. There are some aspects to consider in interpreting these results. Our analysis does not account for adherence to medication, hypertension severity, or control. This may partially explain the differences observed in the group with persistent hypertension receiving treatment. The readings are isolated and may be influenced by other factors such as ambulatory blood pressure that does not necessitate treatment, limited access to healthcare, or potential bias due to specific medical conditions (confounding by indication). Prevalence of hypertension has been reported to be lower among Hispanics/Latinos than other racial or ethnic groups, yet treatment and control of hypertension is much lower [12]. There are also differences in medications used to treat hypertension, which we did not account for. In a cross-sectional study among Hispanics/Latinos, individuals with controlled systolic blood pressure outperformed those with uncontrolled systolic blood pressure on information processing speed [45]. Future work should examine how hypertension control may help reduce the burden of cognitive decline and dementia.

There are some limitations and strengths to consider in evaluating the current study. The effect sizes of our associations were modest, but given the representativeness of our cohort, the public health benefits would likely be large. Given our study design, we were unable to accurately estimate the duration of hypertension since the onset. Therefore, we are unable to precisely characterize the effects of total disease duration from onset. One other caveat in our study is that there could be factors related to how hypertension is identified and categorized that affect the findings. For example, the definition of hypertension has changed over time. Thus, someone on hypertension treatment at Visit 2 (therefore meeting the NHANES definition of hypertension) could have been categorized as not hypertensive at Visit 1, which could dilute the "no-hypertension" category. However, our study reports significant domain specific cognitive changes, which speaks about the robustness of the results. Additionally, where multiple analyses are conducted, the risk of multiplicity is possible. However, to overcome this potential limitation, we have presented all analysis tables in either text or supplementary materials. Despite the limitations, the current study has some notable strengths to consider. Since hypertension is a chronic condition, one major strength is that our follow up is over a 7-year period. If hypertension changes the trajectory of cognitive decline, then the effect of hypertension may increase over time. To our knowledge, this is the largest study to look at relationships between hypertension, cognitive decline, and significantly greater odds of having MCI in a diverse Hispanic/Latino cohort. Our findings provide new insights into the effects of hypertension on cognitive aging and impairment among Hispanics/Latinos from diverse backgrounds.

Conclusion

Overall, in a population-representative study of middle-aged and older Hispanics/Latinos of diverse backgrounds, persistent hypertension was related to 7-year decline in verbal fluency and processing speed. Furthermore, both persistent and incident hypertension were associated with increased odds of having MCI relative to normotension. The results remained after adjusting for demographics and CVD risk factors and show no differences across age or Hispanic/Latino background. These findings suggest that hypertension may have a negative impact to cognitive aging in Hispanics/Latinos, which may have implications for understanding ADRDs.

ACKNOWLEDGMENTS

The authors thank the staff and participants of HCHS/SOL and SOL-INCA staff for their important contributions. Investigators website - http://www.cscc.unc.edu/hchs/.

FUNDING

This work is support by National Institute on Aging (R01AG048642, RF1AG054548, RF1AG061022, and R21AG056952). Dr. González also receives additional support from P30AG062429 and P30AG059299. Dr. Stickel receives additional support from K08 AG075351 and L30 AG074401.

The Hispanic Community Health Study/Study of Latinos was carried out as a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (N01-HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01-HC65236), and San Diego State University (N01-HC65237). The following Institutes/Centers/Offices contribute to the HCHS/SOL 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, NIH Institution-Office of Dietary Supplements.

This work was supported by the National Institute on Aging and National Heart Lung Blood Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the HCHS/SOL website: https://sites.cscc.unc.edu/hchs/.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-230424.

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