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Authors

Levine, Deborah A
Gross, Alden L
Briceño, Emily M
et al.

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Blood Pressure and Later-Life Cognition in Hispanic and White Adults (BP-COG): A Pooled Cohort Analysis of ARIC, CARDIA, CHS, FOS, MESA, and NOMAS[1]

Deborah A. Levine[a,b,c], Alden L. Gross[d], Emily M. Briceño[a,e], Nicholas Tilton[a], Rachael Whitney[a], Dehua Han[a], Bruno J. Giordani[f], Jeremy B. Sussman[a,c,g], Rodney A. Hayward[a,c,g], James F. Burke[b,c,g], Mitchell S.V. Elkind[h,i], Andrew E. Moran[j], Sarah Tom[i], Rebecca F. Gottesman[k], Darrell J. Gaskin[l], Stephen Sidney[m], Kristine Yaffe[n], Ralph L. Sacco[o], Susan R. Heckbert[p], Timothy M. Hughes[q], Oscar L. Lopez[r], Norrina Bai Allen[s] and Andrzej T. Galecki[a,t]

[a]*Department of Internal Medicine and Cognitive Health Services Research Program, University of Michigan, Ann Arbor, MI, USA*
[b]*Department of Neurology and Stroke Program, University of Michigan, Ann Arbor, MI, USA*
[c]*Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA*
[d]*Department of Epidemiology, Johns Hopkins Bloomberg School Public Health, Baltimore, MD, USA*
[e]*Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI, USA*
[f]*Department of Psychiatry & Michigan Alzheimer's Disease Center, University of Michigan, Ann Arbor, MI, USA*
[g]*VA Ann Arbor Healthcare System, Ann Arbor, MI, USA*
[h]*Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA*
[i]*Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA*
[j]*Department of Medicine, Division of General Medicine, Columbia University, New York, NY, USA*
[k]*Stroke Branch, National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, MD, USA*
[l]*Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*
[m]*Kaiser Permanente Northern California Division of Research, Oakland, CA, USA*
[n]*Departments of Psychiatry, Neurology and Epidemiology, University of California, San Francisco, San Francisco, CA, USA*
[o]*Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA*
[p]*Department of Epidemiology, University of Washington, Seattle, WA, USA*
[q]*Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA*
[r]*University of Pittsburgh, Pittsburgh, PA, USA*
[s]*Department of Internal Medicine, Northwestern University, Chicago, IL, USA*
[t]*Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA*

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*Correspondence to: Deborah A. Levine, MD, MPH, University of Michigan Division of General Medicine, NCRC 16-430W, 2800 Plymouth Road, Ann Arbor, MI 48109-2800, USA. Tel.: +1 734 936 5216; E-mail: deblevin@umich.edu.

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Abstract.
Background: Ethnic differences in cognitive decline have been reported. Whether they can be explained by differences in systolic blood pressure (SBP) is uncertain.
Objective: Determine whether cumulative mean SBP levels explain differences in cognitive decline between Hispanic and White individuals.
Methods: Pooled cohort study of individual participant data from six cohorts (1971–2017). The present study reports results on SBP and cognition among Hispanic and White individuals. Outcomes were changes in global cognition (GC) (primary), executive function (EF) (secondary), and memory standardized as t-scores (mean [SD], 50 [10]); a 1-point difference represents a 0.1 SD difference in cognition. Median follow-up was 7.7 (Q1–Q3, 5.2–20.1) years.
Results: We included 24,570 participants free of stroke and dementia: 2,475 Hispanic individuals (median age, cumulative mean SBP at first cognitive assessment, 67 years, 132.5 mmHg; 40.8% men) and 22,095 White individuals (60 years,134 mmHg; 47.3% men). Hispanic individuals had slower declines in GC, EF, and memory than White individuals when all six cohorts were examined. Two cohorts recruited Hispanic individuals by design. In a sensitivity analysis, Hispanic individuals in these cohorts had faster decline in GC, similar decline in EF, and slower decline in memory than White individuals. Higher time-varying cumulative mean SBP was associated with faster declines in GC, EF, and memory in all analyses. After adjusting for time-varying cumulative mean SBP, differences in cognitive slopes between Hispanic and White individuals did not change.
Conclusion: We found no evidence that cumulative mean SBP differences explained differences in cognitive decline between Hispanic and White individuals.

Keywords: Blood pressure, cognition, dementia, ethnic groups, Hispanic Americans

INTRODUCTION

Between 2014 and 2060, the U.S. older Hispanic population will grow from 8% to 22%, so understanding and reducing their AD/ADRD risk is a public health priority [1]. Some studies suggest older Hispanic individuals are 1.5 times more likely than older non-Hispanic White (White) individuals to develop Alzheimer's disease and related dementias (AD/ADRD) [2–5], though this varies by population [6, 7]. Similarly, some studies suggest Hispanic adults have faster cognitive decline related to AD/ADRD [8, 9], although this varies by population or cohort [10, 11]. Preventing or delaying AD/ADRD can lead to longer survival, less disability and nursing home use, lower health care costs, and better quality of life. Hispanic individuals with AD/ADRD have total costs that are up to 35% higher than White individuals with AD/ADRD [12]. Experts recommend identifying the biological and medical care mediators of sociodemographic differences in older adults' AD/ADRD risk [13, 14], but these remain incompletely understood. Vascular risk factors likely play a major role in Hispanic adults' excess AD/ADRD risk [2, 15]. Identifying the vascular risk factors for AD/ADRD disparities is critical to reduce risk and improve health equity.

High blood pressure (BP), particularly in mid-life, is a common risk factor for cognitive decline and AD/ADRD and a promising target for interventions to reduce AD/ADRD inequities [16, 17]. Hispanic individuals are more likely to have undiagnosed, untreated, and uncontrolled high BP than White individuals [18–20]. Hispanic individuals are also more likely than White individuals to have detrimental brain effects associated with high BP, including stroke, cerebrovascular disease, and increased white matter hyperintensity volume [21–23]. Some evidence suggests that high BP has a more detrimental effect on cognitive test performance in Hispanic individuals than non-Hispanic individuals [24]. We found that Black individuals' higher cumulative BP levels partially explain differences in later-life cognitive decline due to AD/ADRD between Black and White individuals [25]. The extent to which Hispanic individuals' higher cumulative BP levels contribute to differences in cognitive decline between Hispanic and White individuals is uncertain.

Leveraging six population-based cohorts of individuals with repeated objective measures of BP and cognition, we conducted a pooled cohort study to determine the extent to which differences between Hispanic and White individuals in cognitive decline after adjusting for covariates are explained by ethnic differences in cumulative BP levels. We hypothesized that Hispanic individuals have faster cognitive decline than White individuals, and higher cumulative BP levels in Hispanic individuals contribute to ethnic disparities in cognitive decline.

METHODS

Study design, participants, and measurements

The report follows the STROBE reporting guideline for cohort studies [26]. This pooled cohort analysis examined individual participant data from six well-characterized American prospective cohort studies with repeated measures of BP and cognition: Atherosclerosis Risk in Communities Study (ARIC) [27], Coronary Artery Risk Development in Young Adults Study (CARDIA) [28], Cardiovascular Health Study (CHS) [29], Framingham Offspring Study (FOS) [30], Multi-Ethnic Study of Atherosclerosis (MESA) [31], and Northern Manhattan Study (NOMAS) [32] for years 1971 to 2017 (Supplementary Methods). This study is part of a larger pooled cohort study assessing the research question: Do Black and Hispanic individuals' higher BP levels contribute to their greater cognitive decline compared to White individuals? We have published the results of the pooled cohort analysis of the association between BP and later-life cognition among Black and White individuals already [25]. The current study represents the second study on the association between BP and later-life cognition among Hispanic and White individuals.

We included participants who had $\geq$1 measurement of cognition and $\geq$1 measurement of BP at or before the first cognition measurement. We included participants with no history of cohort-defined dementia or stroke at each cohort's baseline (because stroke can alter cognitive trajectory [33]) and no incidence of cohort-defined dementia or stroke before first cognitive assessment.

The University of Michigan Institutional Review Board approved the study. Participating institutions approved the cohort studies. Participants provided written informed consent.

Cognitive function assessments

As part of the larger pooled cohort study, we harmonized the cognitive measures across the six cohorts [34]. Trained cohort staff administered cognitive tests consistent with the Vascular Cognitive Impairment Harmonization Standards [35] to participants in-person. In three cohorts (ARIC, NOMAS, CHS), trained staff also administered tests of global cognition by telephone for participants unable to attend some exam visits in-person. Global cognition tests can be measured reliably and precisely over the telephone in adults [36].

To make inferences about cognitive domains instead of individual cognitive test items, and to resolve the challenge of different cognitive tests administered across the cohorts, we co-calibrated available cognitive test items into factors representing global cognition (global cognitive performance), memory (learning and delayed recall/recognition), and executive function (complex and/or speeded cognitive functions) using item response theory methods (a graded response model) that leverage all available cognitive information [10, 37]. The pre-statistical harmonization methods have been published previously [34]. Cognitive factor scores, estimated using the regression-based method in Mplus [38, 39], were set to a t-score metric (mean 50, standard deviation [SD] 10) at a participant's first cognitive assessment; a 1-point difference represents a 0.1 SD difference in the distribution of cognition across the six cohorts. Higher cognitive scores indicate better performance (Supplementary Methods). The primary outcome was change in global cognition. Secondary outcomes were change in memory and executive function.

Measurement of race/ethnicity

We included participants who self-reported White race or Hispanic ethnicity (any race). We use the term "Hispanic" as the term is consistently preferred and acknowledge other terms that describe this population (e.g., Latinx/e) [40]. CHS, MESA, and NOMAS collected data on race and ethnicity and contributed participants to both groups. ARIC, CARDIA, and FOS did not collect data on ethnicity and contributed White participants. These participants were included because they provide: 1) Geographic and/or age diversity; 2) Information and precision for the estimates of cognitive decline in White individuals and the estimates of cognitive decline associated

with SBP; and 3) Overlapping cognitive test items enabling cross-cohort cognitive harmonization. We did not examine subgroups of Hispanic participants because the subgroups sizes were small, but most Hispanic participants in MESA and NOMAS tend to be Latin American immigrants [41, 42]. A small number of participants in CARDIA ($n = 14$) and FOS ($n = 13$) reported White race at baseline and Hispanic ethnicity during follow-up. We analyzed these participants as White for the primary analysis and removed them, along with the 45 CHS participants who reported White race and Hispanic ethnicity, for a sensitivity analysis.

Measurement of blood pressure

Each cohort study measured BP at in-person visits using standard protocols and equipment. We summarized systolic BP (SBP) as the time-dependent cumulative mean (i.e., running average) of all SBP measurements before each cognitive assessment because SBP tends to be a stronger predictor of BP-related outcomes than diastolic BP [17, 43, 44]; long-term cumulative mean SBP has improved prediction of clinical outcomes compared with single measurements [45] or means over discrete intervals (e.g., $\leq$1 year, 1 to 5 years) before outcome measurement [43]; and time-dependent cumulative mean SBP is associated with cognitive trajectories [25].

Covariates

We followed a pre-specified conceptual model based on the Andersen Behavioral Model [46], the National Institutes on Aging health disparities research framework [13], a vascular contributions to cognitive impairment and dementia framework [15], and a model of the potential confounders of the race and cognitive decline relationship [47]. By study design, we examined the independent effect of cumulative SBP on differences in cognitive decline between Hispanic and White individuals after adjusting for demographics, socioeconomic status, and other vascular risk factors. We used covariate values measured closest to, but not after, the first cognitive assessment. Demographics included age, sex, years of education, and cohort study. Vascular risk factors included cigarette smoking, body mass index, waist circumference, physical activity, fasting glucose, low-density lipoprotein cholesterol, and history of atrial fibrillation [48]. Hypertension medication use was measured at or before the first cognitive assessment based on evidence of medication bottles and self-report from exams.

Statistical analysis

We followed a pre-specified analysis plan to test the hypothesis, "There is a significant effect of Hispanic ethnicity on the rate [slope] of cognitive decline after adjusting for time-varying cumulative mean SBP levels and other covariates." We compared participant characteristics by ethnicity using Wilcoxon Rank Sum tests or χ^2 tests as appropriate. We used linear mixed-effects models to estimate changes in each continuous cognitive outcome over time by ethnicity. Because the pooled data involved a small number of cohorts ($n = 6$), we associated a fixed effect with cohorts when pooling the data [49, 50]. The models included subject-specific random effects for intercepts and slopes, covariates listed in Table 1, and two-way interaction terms involving follow-up time crossed with sex and age at the time of first cognitive assessment. Follow-up time was treated as a continuous measure defined as years since the first measurement of each cognitive outcome.

For each outcome, all available cognitive observations were used in the primary analysis except observations after the time of first cohort-adjudicated incident stroke during follow-up [26]. We evaluated model assumptions by inspecting residual plots. There was no evidence of non-linear effects of covariates or a significant ethnicity*SBP*follow-up time interaction or time on cognitive trajectories ($p > 0.05$).

To estimate differences in cognitive decline between Hispanic and White individuals, Model A included an ethnicity*follow-up time interaction term to estimate the effect of Hispanic ethnicity on cognitive decline after controlling for all covariates except for BP levels. To examine whether time-dependent cumulative mean SBP explained differences in cognitive decline between Hispanic and White individuals, Model B added cumulative mean SBP and a cumulative mean SBP*follow-up time interaction term to Model A. To investigate whether hypertension treatment explained differences in cognitive decline between Hispanic and White individuals, Model C added hypertension treatment and a hypertension treatment*follow-up time interaction term to Model B.

We performed a complete case analysis excluding a small number of participants ($n = 501/19{,}879$; 2.52%) due to missing covariate data. Figure 1 shows the

Table 1
Characteristics of participants at first cognitive assessment by ethnicity

Variable*	Hispanic individuals ($n = 2,475$)	White individuals ($n = 22,095$)
Age at first SBP measurement, full range, y	40–98	5–95
Age at first SBP measurement, y	62 (56, 69)	54 (46, 64)
Age at first cognitive assessment, full range, y	42–100	25–100
Age at first cognitive assessment, y	67 (61, 75)	60 (52, 68)
Women, No. (%)	1465 (59.2%)	11655 (52.7%)
Cohort, No. (%)		
ARIC	0	10099 (45.7%)
CARDIA	0	1835 (8.3%)
CHS	54 (2.2%)	4350 (19.7%)
FOS	0	3475 (15.7%)
MESA	951 (38.4%)	1860 (8.4%)
NOMAS	1470 (59.4%)	476 (2.2%)
Education, No. (%)		
Eighth grade or less	1161 (46.9%)	1169 (5.3%)
Grades 9–11	328 (13.3%)	1905 (8.6%)
Completed high school	400 (16.2%)	6794 (30.8%)
Some college but no degree	380 (15.4%)	3848 (17.4%)
College graduate or more	206 (8.3%)	8379 (37.9%)
Current cigarette smoking, No. (%)	276 (11.2%)	3770 (17.1%)
Any physical activity, No. (%)	1711 (69.1%)	18375 (83.2%)
Body mass index	28.2 (25.5, 31.7)	26.5 (23.7, 29.7)
Waist circumference, cm	96.5 (88.9, 104.1)	95 (85.7, 104)
History of atrial fibrillation, No. (%)	71 (2.9%)	370 (1.7%)
Fasting glucose, mg/dL	95 (85, 110)	97.5 (91, 105.9)
LDL cholesterol, mg/dL	119 (95, 143)	125.2 (103, 149.2)
Anti-hypertensive medication use, No. (%)	1388 (56.1%)	6253 (28.3%)
Follow-up time from first cognitive assessment, y	6.3 (0, 11.8)	7.9 (5.5, 20.4)
SBP cumulative mean (SD) at first cognitive assessment, mmHg	132.5 (120, 149)	134 (123, 147)
Total number of SBP measurements	3 (1, 4)	5 (3, 7)
Number of SBP measurements before first cognitive assessment	1 (1, 4)	1 (1, 4)
Time from first SBP measurement to first cognitive assessment, y	5.2 (2.3, 9.3)	3 (2.8, 10.3)
Cognitive testing performed in Spanish	504 (20.4%)	0
Self-reported use of a language other than English	1942 (78.5%)	1219 (5.5%)
Cognitive scores at first assessment		
General cognitive performance	44.6 (38.9, 50.4)	53.3 (48.5, 58.7)
Executive function	45.1 (39.6, 50.6)	54.5 (49.5, 59.3)
Memory	49.7 (43.1, 56.5)	52.4 (48.9, 55.9)
Number of cognitive assessments per individual		
Global cognitive performance	3 (Q1–Q3,1–8)	3 (Q1–Q3, 2–5)
Executive function	2 (Q1–Q3, 1–2)	2 (Q1–Q3, 2–4)
Memory	2 (Q1–Q3, 1–2)	2 (Q1–Q3, 2–3)

p-values for median were obtained using the Wilcoxon Rank Sum test and for means using a *t*-test. Chi-square test was used for N (%). NA, not applicable; SBP, systolic blood pressure. *Unless stated otherwise, univariate statistics for continuous variables are expressed as median and interquartile range (Q1–Q3), where Q1–Q3 is represented by (25th %ile, 75th %ile) interval. Only MESA and NOMAS offered cognitive testing in Spanish. Only FOS, MESA and NOMAS provide information relating to self-reported use of a language other than English.

derivation of the cohort. Statistical significance for all analyses was set as $p < 0.05$ (2-sided). All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Sensitivity analyses

We performed several sensitivity analyses. We included participants' cognitive observations after the time of incident stroke. We added kidney function (estimated glomerular filtration rate, eGFR [51]) and history of myocardial infarction because they may be on the causal pathway. We restricted the sample to participants with two or more cognitive assessments. Because some Hispanic individuals might have a greater practice effect on repeated cognitive assessments than White individuals [52], we included a time-varying practice effect variable. In separate analyses, we added a language of cognitive testing variable because 504 (20.4%) of the 2,475 Hispanic participants took their tests in Spanish (MESA and NOMAS only); included a variable for self-reported

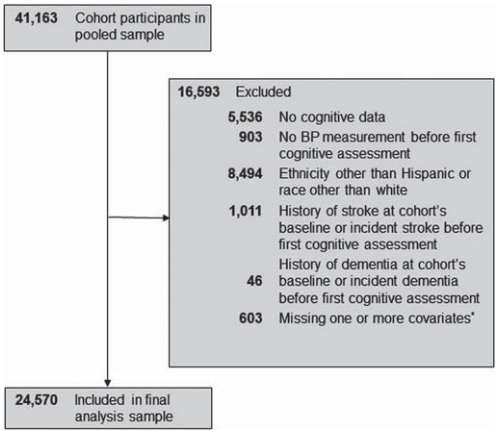

Fig. 1. Participant cohort. BP, blood pressure. Categories for missing data on covariates are not mutually exclusive. Missing data for covariates included glucose ($n = 204$), body mass index ($n = 30$), waist circumference ($n = 106$), smoking ($n = 5$), physical activity ($n = 39$), low-density lipoprotein cholesterol ($n = 267$), antihypertensive medication use ($n = 10$), and education ($n = 170$). No participants were missing history of atrial fibrillation.

use of a language other than English (FOS, MESA, and NOMAS only); and added alcohol use as a covariate. We performed an analyses in the combined MESA and NOMAS cohorts since they recruited Hispanic participants by study design.

RESULTS

The study sample included 24,570 participants (11,450 [46.6%] men and 2,475 [10.1%] Hispanic individuals). Table 1 presents characteristics of participants by ethnicity. Most patients had 2+ cognitive assessments ($n = 20,512$; 83.5%). Median follow-up was 7.7 (Q1–Q3, 5.3–20.1) years. Supplementary Table 1 shows characteristics of study participants by cohort. Because the secondary outcome measures were performed less frequently, the executive function analysis included 22,533 participants, and the memory analysis included 15,943 participants. During follow-up, 2,604 patients out of 24,570 (10.6%) died. Supplementary Table 2 has information on missing data and attrition.

Change in global cognition

Hispanic individuals had significantly lower initial scores than White individuals in global cognition (adjusted difference in intercept, –5.28 points [95% CI, –5.67 to –4.90]; $p < 0.001$) (intercept in Model A, Table 2). Hispanic individuals, compared with White individuals, had significantly slower declines in global cognition (slope in Model A, Table 2). White men at a median age of 58 years experienced decline in global cognition of –0.23 points per year (95% CI, –0.24 to –0.22; $p < 0.001$). Hispanic men of similar age experienced decline in global cognition of –0.11 points per year (95% CI, –0.14 to –0.09) (adjusted difference in slope was 0.12 points/year slower in Hispanic [95% CI, 0.09 to 0.14]; $p < 0.001$).

After adjusting for the association between time-dependent cumulative mean SBP and cognitive slope, differences between Hispanic and White individuals in cognitive slopes did not change substantially (slope in Model B, Table 2). Higher cumulative mean SBP was associated with faster cognitive decline (adjusted difference in slope was –0.021 points/year faster per 10 mmHg in cumulative mean SBP [95% CI, –0.025 to –0.016]; $p < 0.001$). Further adjustment for the association between antihypertensive medication use and cognitive slopes did not alter the difference in cognitive slopes between Hispanic and White individuals (slope in Model C, Table 2). Antihypertensive medication use was associated with slower cognitive decline (adjusted difference in slope was 0.02 points/year slower [95% CI, 0.01 to 0.04]; $p = 0.011$).

Changes in executive function and memory

Hispanic individuals had significantly lower baseline performance than White individuals in executive function (–5.62 points [95% CI, –6.06 to –5.19]; $p < 0.001$) but not memory (–0.22 points [95% CI, –1.16 to 0.72]; $p = 0.64$) (intercepts in Model A, Tables 3 and 4). Hispanic individuals, compared with White individuals, had significantly slower declines in executive function (0.10 points/year [95% CI, 0.04 to 0.15]; $p < 0.001$) and memory (0.26 points/year [95% CI, 0.17 to 0.36]; $p < 0.001$) (slopes in Model A, Tables 3 and 4). After adjusting for the association between time-dependent cumulative mean SBP and cognitive slopes, differences in cognitive slopes between Hispanic and White individuals did not change substantially (slopes in Model B, Tables 3 and 4). Further adjustment for the association between antihypertensive medication and cognitive slopes did not alter cognitive slope differences between Hispanic and White individuals (slopes in Model C, Tables 3 and 4).

Table 2
Association of global cognition decline with ethnicity and systolic blood pressure over time

Coefficient	Model A: Basic (n = 24,570)		Model B: Cumulative mean SBP added as a time-varying covariate to Model A (n = 24,570)		Model C: Hypertension treatment added as a covariate to Model B (n = 24,570)	
	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p
Change in intercept per 10 y increase in age at first cognitive assessment	–2.34 (–2.45, –2.24)	<0.001	–2.13 (–2.24, –2.02)	<0.001	–2.13 (–2.24, –2.02)	<0.001
Difference in intercept between Hispanic and White individuals at first cognitive assessment	–5.28 (–5.67, –4.90)	<0.001	–5.17 (–5.56, –4.79)	<0.001	–5.16 (–5.54, –4.77)	<0.001
Change in slope per 10 y increase in age at first cognitive assessment, per y	–0.12 (–0.13, –0.11)	<0.001	–0.12 (–0.13, –0.11)	<0.001	–0.12 (–0.13, –0.12)	<0.001
Slope in White men at median age, per y	–0.23 (–0.24, –0.22)	<0.001	–0.21 (–0.22, –0.19)	<0.001	–0.21 (–0.22, –0.20)	<0.001
Difference in slope between Hispanic and White individuals, per y	0.12 (0.09, 0.14)	<0.001	0.12 (0.09, 0.14)	<0.001	0.11 (0.08, 0.14)	<0.001
Change in slope per 10 mmHg in cumulative mean SBP, per y	N/A	N/A	–0.019 (–0.024, –0.015)	<0.001	–0.021 (–0.025, –0.016)	<0.001
Change in slope associated with hypertension treatment, per y	N/A	N/A	N/A	N/A	0.02 (0.01, 0.04)	0.011

SBP, systolic blood pressure; N/A, not applicable; y, year. Interpretative Key: Global cognition measures global cognitive performance. All cognitive measures are set to a T-score metric (mean 50, SD 10) at a participant's first cognitive assessment; a 1-point difference represents a 0.1 SD difference in the distribution of cognition across the 6 cohorts. Higher cognitive scores indicate better performance.
Linear mixed-effects models included time since first cognitive assessment and baseline values (measured before or at time of first cognitive assessment) of ethnicity (Hispanic vs White), age, sex, cohort study, years of school, cigarette smoking, body mass index, waist circumference, physical activity, fasting glucose, low density lipoprotein (LDL) cholesterol, history of atrial fibrillation, age*follow-up time, sex* follow-up time, and ethnicity* follow-up time interaction terms. To take into account correlation between longitudinal cognitive measures, we included random intercept and slope effects associated with subjects. All continuous variables were centered at the overall median, except cumulative mean SBP, which was centered at 120 mmHg. Glucose, LDL cholesterol, and SBP values were divided by 10 so that the parameter estimates refer to a 10-unit change in the variables. SBP was the time-dependent mean of all SBPs before the measurement of cognition. To estimate Hispanic-White differences in cognitive decline, Model A included an ethnicity*follow-up time interaction term. To examine whether cumulative mean SBP, a time-varying covariate, explained the Hispanic-White differences in cognitive decline, Model B added cumulative mean SBP and a cumulative mean SBP*follow-up time interaction term to Model A. To examine whether cumulative mean SBP, a time-varying covariate, explained the Hispanic-White differences in cognitive decline, Model B added cumulative mean SBP and a cumulative mean SBP*follow-up time interaction term to Model A. To investigate whether hypertension treatment explained the Hispanic-White differences in cognitive decline, Model C added a hypertension treatment and hypertension treatment at first cognitive assessment*follow-up time interaction term to Model B.

Sensitivity analyses

Results were similar in analyses, including participants' cognitive observations after the time of incident stroke, adding eGFR and history of myocardial infarction as covariates, restricting the sample to participants with two or more cognitive assessments, accounting for practice effects, removing participants with White race and possible Hispanic ethnicity, and adding language of cognitive testing, English proficiency and alcohol consumption (except Hispanic-White differences in executive function declines) were no longer significant after accounting for practice effects (Supplementary Tables 3–10). In analyses restricted to the two cohorts that recruited Hispanic individuals by study design (MESA and NOMAS), Hispanic individuals had faster declines in global cognitive performance, similar declines in executive function performance, and slower declines in memory performance than White individuals (Supplementary Table 11). Higher SBP was associated with faster cognitive declines, but some associations were no longer statistically significant. After adjusting for cumulative mean SBP, the differences in

Table 3
Association of executive function decline with ethnicity and systolic blood pressure over time

Coefficient	Model A: Basic ($n = 22,533$)		Model B: Cumulative mean SBP added as a time-varying covariate to Model A ($n = 22,533$)		Model C: Hypertension treatment added as a covariate to Model B ($n = 22,533$)	
	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p
Change in intercept per 10 y increase in age at first cognitive assessment	–3.10 (–3.22, –2.98)	<0.001	–2.96 (–3.08, –2.84)	<0.001	–2.94 (–3.06, –2.82)	<0.001
Difference in intercept between Hispanic and White individuals at first cognitive assessment	–5.62 (–6.06, –5.19)	<0.001	–5.56 (–6.00, –5.13)	<0.001	–5.57 (–6.00, –5.13)	<0.001
Change in slope per 10 y increase in age at first cognitive assessment, per y	–0.13 (–0.14, –0.12)	<0.001	–0.13 (–0.14, –0.125)	<0.001	–0.13 (–0.14, –0.12)	<0.001
Slope in White men at median age, per y	–0.31 (–0.32, –0.30)	<0.001	–0.29 (–0.30, –0.28)	<0.001	–0.29 (–0.30, –0.28)	<0.001
Difference in slope between Hispanic and White individuals, per y	0.10 (0.04, 0.15)	<0.001	0.09 (0.04, 0.14)	0.001	0.09 (0.04, 0.14)	0.001
Change in slope per 10 mmHg in cumulative mean SBP, per y	N/A	N/A	–0.012 (–0.016, –0.007)	<0.001	–0.012 (–0.016, –0.007)	<0.001
Change in slope associated with hypertension treatment, per y	N/A	N/A	N/A	N/A	–0.003 (–0.020, 0.014)	0.70

Interpretative Key: Executive function measures complex and/or speeded cognitive functions. All cognitive measures are set to a T-score metric (mean 50, SD 10) at a participant's first cognitive assessment; a 1-point difference represents a 0.1 SD difference in the distribution of cognition across the 6 cohorts. Higher cognitive scores indicate better performance. NA, not applicable.
Linear mixed-effects models included time since first cognitive assessment and baseline values (measured before or at time of first cognitive assessment) of ethnicity (Hispanic vs White), age, sex, cohort study, years of school, cigarette smoking, body mass index, waist circumference, physical activity, fasting glucose, LDL cholesterol, history of atrial fibrillation, age*time, sex*time, and ethnicity*time. To take into account correlation between longitudinal cognitive measures, we included random intercept and slope effects associated with subjects. All continuous variables were centered at the overall median, except cumulative mean SBP, which was centered at 120 mmHg. Glucose, LDL cholesterol, and SBP values were divided by 10 so that the parameter estimates refer to a 10-unit change in the variables. SBP was the time-dependent mean of all SBPs before the measurement of cognition. To estimate Hispanic-White differences in cognitive decline, Model A included a Hispanic ethnicity*follow-up time interaction term. To examine whether cumulative mean SBP, a time-varying covariate, explained the Hispanic-White differences in cognitive decline, Model B added SBP and an SBP*follow-up time interaction term to Model A. To investigate whether hypertension treatment explained the Hispanic-White differences in cognitive decline, Model C added a hypertension treatment and hypertension treatment at first cognitive assessment*follow-up time interaction term to Model B.

cognitive decline between Hispanic and White individuals did not change, consistent with the main results (Supplementary Table 11).

DISCUSSION

Among 24,570 individuals pooled from six prospective cohort studies, higher cumulative mean SBP levels were associated with faster cognitive decline in a linear fashion. Ethnic differences in SBP levels and antihypertensive medication use did not explain differences in cognitive decline between Hispanic and White individuals. We found no evidence that the magnitude of the effect of SBP on cognitive decline differed between Hispanic and White individuals.

Contrary to our hypothesis, we found little evidence that Hispanic individuals have faster cognitive decline than White individuals. Some studies [2–5], but not all studies [6, 7], suggest that older Hispanic individuals have greater AD/ADRD risk than older White individuals. So, we expected to find that Hispanic individuals had faster cognitive decline than White individuals, consistent with prior research [8, 9, 11]. We found that, compared with White indi-

Table 4
Association of memory decline with ethnicity and systolic blood pressure over time

Coefficient	Model A: Basic (n = 15,943)		Model B: Cumulative mean SBP added as a time-varying covariate to Model A (n = 15,943)		Model C: Hypertension treatment added as a covariate to Model B (n = 15,943)	
	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p
Change in intercept per 10 y increase in age at first cognitive assessment	–1.71 (–1.85, –1.57)	<0.001	–1.71 (–1.86, –1.57)	<0.001	–1.71 (–1.85, –1.56)	<0.001
Difference in intercept between Hispanic and White individuals at first cognitive assessment	–0.22 (–1.16, 0.72)	0.64	–0.18 (–1.12, 0.76)	0.71	–0.17 (–1.11, 0.77)	0.72
Change in slope per 10 y increase in age at first cognitive assessment, per y	–0.18 (–0.20, –0.16)	<0.001	–0.16 (–0.18, –0.15)	<0.001	–0.16 (–0.18, –0.14)	<0.001
Slope in White men at median age, per y	–0.29 (–0.30, –0.27)	<0.001	–0.24 (–0.26, –0.22)	<0.001	–0.24 (–0.26, –0.21)	<0.001
Difference in slope between Hispanic and White individuals, per y	0.26 (0.17, 0.36)	<0.001	0.25 (0.15, 0.34)	<0.001	0.25 (0.15, 0.34)	<0.001
Change in slope per 10 mmHg in cumulative mean SBP, per y	N/A	N/A	–0.02 (–0.03, –0.01)	<0.001	–0.02 (–0.03, –0.01)	<0.001
Change in slope associated with hypertension treatment, per y	N/A	N/A	N/A	N/A	–0.01 (–0.04, 0.02)	0.62

Interpretative Key: Memory measures learning and delayed recall/recognition. All cognitive measures are set to a T-score metric (mean 50, SD 10) at a participant's first cognitive assessment; a 1-point difference represents a 0.1 SD difference in the distribution of cognition across the 6 cohorts. Higher cognitive scores indicate better performance. SBP, systolic blood pressure; NA, not applicable.
Linear mixed-effects models included time since first cognitive assessment and baseline values (measured before or at time of first cognitive assessment) of ethnicity (Hispanic vs White), age, sex, cohort study, years of school, cigarette smoking, body mass index, waist circumference, physical activity, fasting glucose, LDL cholesterol, history of atrial fibrillation, age*time, sex*time, and ethnicity*time. To take into account correlation between longitudinal cognitive measures, we included random intercept and slope effects associated with subjects. All continuous variables were centered at the overall median, except cumulative mean SBP, which was centered at 120 mmHg. Glucose, LDL cholesterol, and SBP values were divided by 10 so that the parameter estimates refer to a 10-unit change in the variables. SBP was the time-dependent mean of all SBPs before the measurement of cognition. To estimate Hispanic-White differences in cognitive decline, Model A included a Hispanic ethnicity*follow-up time interaction term. To examine whether cumulative mean SBP, a time-varying covariate, explained the Hispanic-White differences in cognitive decline, Model B added SBP and an SBP*follow-up time interaction term to Model A. To investigate whether hypertension treatment explained the Hispanic-White differences in cognitive decline, Model C added a hypertension treatment and hypertension treatment at first cognitive assessment*follow-up time interaction term to Model B.

viduals, Hispanic individuals had slower decline in global cognitive performance, executive function performance, and memory performance in the analysis of the six cohorts, but they had faster decline in global cognitive performance, similar decline in executive function performance, and slower decline in memory performance in the sensitivity analysis of the two cohorts (MESA and NOMAS) that recruited Hispanic individuals by study design. These results suggest that White individuals' cognitive slopes in MESA and NOMAS might differ from those in the other four cohorts, and cohort variation rather than true ethnic differences could explain the differences in cognitive decline between Hispanic and White individuals we observed. Differences in sampling strategy, study population, cognitive tests, follow-up time, and methods also likely contribute to variation in the strength and magnitude of ethnic differences in cognitive decline across cohorts and cognitive domains [11, 53].

White individuals might have had a greater likelihood of regressing to a lower value than Hispanic individuals at follow-up because they had higher baseline cognitive function than Hispanic individuals. Although age at first cognitive assessment differed between Hispanic and White participants, it

is unlikely that these age differences influenced ethnic differences in cognitive slopes because we adjusted for age and an age*follow-up time interaction in all models. Despite evidence for differences in cross-sectional cognitive performance between Hispanic and White individuals, our findings add to growing evidence that Hispanic ethnicity is not strongly associated with accelerated cognitive decline after accounting for confounding factors. Prior studies have found that Hispanic individuals have slower cognitive decline [10, 54] or similar cognitive decline [55, 56] compared to White individuals, consistent with our results.

Although our results show that higher cumulative SBP levels are associated with faster cognitive decline in Hispanic and White individuals, we found no evidence that ethnic differences in cumulative SBP levels contribute to differences in cognitive decline. We hypothesized that Hispanic individuals would have higher cumulative SBP levels than White individuals, which would contribute to ethnic disparities in cognitive decline. This hypothesis is based on data showing that Hispanic individuals are more likely to have undiagnosed, untreated, and uncontrolled high BP than White individuals [18–20]. However, in our study, Hispanic individuals had lower SBP levels and greater use of anti-hypertensive medication than White individuals, suggesting reduced cerebrovascular burden. Our results might differ because study populations and sampling are different, and individuals who volunteer to participate in longitudinal research studies might differ from the general population (e.g., study volunteers might be healthier than those in the general population). A key finding of our study is that the relationship between higher SBP and faster cognitive decline did not differ between Hispanic and White groups. We also found that anti-hypertensive medication use is associated with slower cognitive decline.

Experts have classified clinically meaningful cognitive decline as a decrease in cognitive function of $\geq$0.5 standard deviations (SD) from initial cognitive scores [57–59]. If the observed ethnic differences in cognitive decline are confirmed and causal, Hispanic individuals will reach the threshold of clinically meaningful cognitive decline 20.5 years slower than White individuals for global cognition and 6.2 years slower for executive function (Supplementary Table 12). Global cognition and executive function declines are associated with increased death, dementia, and functional disability risks [60–62].

Several studies have found lower baseline cognitive performance in Hispanic individuals compared to White individuals [10, 52, 54]. Reasons for these ethnic differences are complicated and likely influenced by educational attainment, educational quality, socioeconomic disparities, and linguistic and cultural factors [56, 63, 64]. Differences in decline are more likely to be related to aging-related diseases. Hispanic individuals might have slower cognitive decline than White individuals because of differences in biological, genetic, psychosocial, and lifestyle factors. Evidence suggests a weaker association of APOE polymorphisms with AD risk in Caribbean Hispanic individuals compared to White individuals [65]. Neuropathological studies have suggested a lower prevalence of AD pathology in Hispanic compared to White deceased older adults diagnosed with dementia [23]. Our results align with the "Hispanic Paradox" phenomenon, suggesting relatively better health outcomes in some immigrant Hispanic populations than would be expected given the systemic socioeconomic and other disparities that often adversely impact health. This phenomenon may be attributable to factors such as selective immigration of healthier individuals and/or selective return migration of less healthy individuals [66]. This phenomenon may also suggest social and cultural strengths that buffer against the harmful effects of these disparities [67]. Our findings suggest a scientific need to better understand differences between Hispanic and White individuals in dementia risk and the determinants of any differences.

Our study has several strengths. We had longitudinal BP and cognitive assessments in many young, middle-aged, and older adults to estimate the effects of cumulative BP levels on cognitive decline in Hispanic and White individuals during up to 20 years of follow-up. The cohort studies systematically measured cognitive domains commonly affected by vascular factors like hypertension: global cognition, memory, and executive function [35]. Our results of differences in cognitive decline between Hispanic and White individuals were consistent across cognitive domains.

Our study has potential limitations. Only two of the six cohort studies (MESA and NOMAS) recruited Hispanic individuals by design. We included cohort studies that did not recruit or register Hispanic individuals by study design. However, a sensitivity analysis in the two cohorts that recruited Hispanic individuals by study design (MESA and

NOMAS) found that differences in SBP levels between Hispanic and White individuals did not attenuate differences in cognitive decline between the two groups, consistent with the main results. It is plausible that the differences in cognitive decline between Hispanic and White individuals we observed could be due to cohort variation rather than true ethnic differences, and that White individuals' cognitive slopes in MESA and NOMAS differ from those in the other four cohorts. It is possible that individuals who have Hispanic ethnicity and self-identified as Black or Other race in ARIC and CARDIA were excluded from the analysis because the cohorts collected race but not Hispanic ethnicity. Results were similar in results that excluded FOS individuals with possible Hispanic ethnicity. We classified Hispanic individuals (any race) based on the individual cohort procedures. Confounding by race in the Hispanic group is possible, although most Hispanic immigrants in MESA and NOMAS are from Latin America [41, 42]. We adjusted for educational years but not for educational quality, other socioeconomic factors, or depressive symptoms because they were unavailable for all cohorts at or before the first cognitive assessment. Studies suggest that socioeconomic factors tend to influence baseline cognition (intercept) rather than the change in cognition over time (slopes) [68, 69]. Although selective attrition of cognitively impaired participants could underestimate the rate of cognitive decline [70], results were similar when we required more cognitive observations per person consistent with previous research [71]. Measurement bias in cognitive instruments associated with insufficient validation in diverse samples could contribute to cognitive differences between Hispanic and White individuals [72, 73].

Hispanic individuals were more likely to be excluded for dementia before the first cognitive assessment, which could reduce cognitive differences between Hispanic and White individuals. Conversely, White individuals were more likely to be excluded for stroke before first cognitive assessment, which could increase differences between the two ethnic groups. We did not study incident dementia because some cohort studies lacked these data. By study design, we did not adjust for baseline cognition. Heterogeneity of the effect between cohorts might affect the statistical validity of the summary estimate of the effect in the pooled cohort. We had insufficient sample size to examine sub-groups and country of origin in Hispanic individuals and lacked information on factors such as nativity/immigration status/number of years in the US, bilingualism, and childhood socioeconomic status. While the assumption that participants' post-mortem cognitive data are missing at random might lead to immortal cohort bias and underestimate memory declines, it is valid to answer the research question quantifying ethnic differences in cognitive trajectories through study follow-up. Using a fixed effect for cohorts might produce conservative estimates of ethnic differences in cognitive slopes. Most individuals who self-identify as Hispanic came from only two cohorts by study design, potentially leading to cross-cohort comparisons with a risk of sample selection bias. We did not examine BP variability [74]. We did not have information on diabetes prevalence.

Conclusion

We found no evidence that differences in cumulative mean SBP levels contribute to differences in later-life cognitive decline between Hispanic and White individuals.

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SUPPLEMENTARY MATERIAL

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REFERENCES

[1] Administration for Community Living, Administration on Aging (2015) A statistical profile of older Hispanic Americans. *Department of Health and Human Services*. https://acl.gov/sites/default/files/news%202017-03/A_Statistical_Profile_of_Older_Hispanics.pdf. Accessed May 15, 2020.

[2] Alzheimer's Association (2021) 2021 Alzheimer's disease facts and figures. *Alzheimers Dement* **17**, 327-406.

[3] Gurland BJ, Wilder DE, Lantigua R, Stern Y, Chen J, Killeffer EHP, Mayeux R (1999) Rates of dementia in three ethnoracial groups. *Int J Geriatr Psychiatry* **14**, 481-493.

[4] Wright CB, DeRosa JT, Moon MP, Strobino K, DeCarli C, Cheung YK, Assuras S, Levin B, Stern Y, Sun X, Rundek T, Elkind MSV, Sacco RL (2021) Race/ethnic disparities in mild cognitive impairment and dementia: The Northern Manhattan Study. *J Alzheimers Dis* **80**, 1129-1138.

[5] Tang MX, Cross P, Andrews H, Jacobs DM, Small S, Bell K, Merchant C, Lantigua R, Costa R, Stern Y, Mayeux R (2001) Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology* **56**, 49.

[6] González HM, Tarraf W, Schneiderman N, Fornage M, Vásquez PM, Zeng D, Youngblood M, Gallo LC, Daviglus ML, Lipton RB, Kaplan R, Ramos AR, Lamar M, Thomas S, Chai A, DeCarli C (2019) Prevalence and correlates of mild cognitive impairment among diverse Hispanics/Latinos: Study of Latinos-Investigation of Neurocognitive Aging results. *Alzheimers Dement* **15**, 1507-1515.

[7] Mehta KM, Yeo GW (2017) Systematic review of dementia prevalence and incidence in United States race/ethnic populations. *Alzheimers Dement* **13**, 72-83.

[8] Alley D, Suthers K, Crimmins E (2007) Education and cognitive decline in older americans: Results from the AHEAD Sample. *Res Aging* **29**, 73-94.

[9] Sol K, Zaheed AB, Kraal AZ, Sharifian N, Arce Rentería M, Zahodne LB (2020) Psychological predictors of memory decline in a racially and ethnically diverse longitudinal sample of older adults in the United States. *Int J Geriatr Psychiatry* **35**, 204-212.

[10] Gross AL, Crane PK, Gibbons LE, Manly JJ, Romero H, Thomas M, Mungas DM, MacKay-Brandt A, Mukherjee S, Sachs B, Potter GG, Jones RN (2015) Effects of education and race on cognitive decline: An integrative study of generalizability versus study-specific results. *Psychol Aging* **30**, 863-880.

[11] Vonk JMJ, Arce Rentería M, Avila JF, Schupf N, Noble JM, Mayeux R, Brickman AM, Manly JJ (2019) Secular trends in cognitive trajectories of diverse older adults. *Alzheimers Dement* **15**, 1576-1587.

[12] US Department of Health and Human Services (2014) Racial and ethnic disparities in Alzheimer's disease: A literature review. https://aspe.hhs.gov/report/racial-and-ethnic-disparities-alzheimers-disease-literature-review. February 16, 2021.

[13] Hill CV, Perez-Stable EJ, Anderson NA, Bernard MA (2015) The national institute on aging health disparities research framework. *Ethn Dis* **25**, 245-254.

[14] Schneider J, Jeon S, Gladman JT, Corriveau RA (2019) *ADRD Summit 2019 Report to the National Advisory Neurological Disorders and Stroke Council*. National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/sites/default/files/2019_adrd_summit_recommendations_508c.pdf

[15] Corriveau RA, Bosetti F, Emr M, Gladman JT, Koenig JI, Moy CS, Pahigiannis K, Waddy SP, Koroshetz W (2016) The science of vascular contributions to cognitive impairment and dementia (VCID): A framework for advancing research priorities in the cerebrovascular biology of cognitive decline. *Cell Mol Neurobiol* **36**, 281-288.

[16] Gottesman RF, Schneider ALC, Albert M, Alonso A, Bandeen-Roche K, Coker L, Coresh J, Knopman D, Power MC, Rawlings A, Sharrett AR, Wruck LM, Mosley TH (2014) Midlife hypertension and 20-year cognitive change: The Atherosclerosis Risk in Communities Neurocognitive Study. *JAMA Neurol* **71**, 1218-1227.

[17] Levine DA, Gałecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, Cushman M, McClure LA, Safford MM, Wadley VG (2019) Blood pressure and cognitive decline over 8 years in middle-aged and older Black and White Americans. *Hypertension* **73**, 310-318.

[18] Yoon SS, Carroll MD, Fryar CD (2015) Hypertension prevalence and control among adults: United States, 2011-2014. *NCHS Data Brief* **220**, 1-8.

[19] Zhao B, Jose PO, Pu J, Chung S, Ancheta IB, Fortmann SP, Palaniappan LP (2015) Racial/ethnic differences in hypertension prevalence, treatment, and control for outpatients in northern California 2010-2012. *Am J Hypertens* **28**, 631-639.

[20] Campos CL, Rodriguez CJ (2019) High blood pressure in Hispanics in the United States: A review. *Curr Opin Cardiol* **34**.

[21] Birns J, Morris R, Jarosz J, Markus H, Kalra L (2008) Ethnic differences in the cerebrovascular impact of hypertension. *Cerebrovasc Dis* **25**, 408-416.

[22] Brickman AM, Schupf N, Manly JJ, Luchsinger JA, Andrews H, Tang MX, Reitz C, Small SA, Mayeux R, DeCarli C, Brown TR (2008) Brain morphology in older African Americans, Caribbean Hispanics, and Whites from Northern Manhattan. *Arch Neurol* **65**, 1053-1061.

[23] Filshtein TJ, Dugger BN, Jin L-W, Olichney JM, Farias ST, Carvajal-Carmona L, Lott P, Mungas D, Reed B, Beckett LA, DeCarli C (2019) Neuropathological diagnoses of demented Hispanic, Black, and Non-Hispanic White decedents seen at an Alzheimer's disease center. *J Alzheimers Dis* **68**, 145-158.

[24] Stickel A, McKinnon A, Ruiz J, Grilli MD, Ryan L (2019) The impact of cardiovascular risk factors on cognition in Hispanics and non-Hispanic whites. *Learn Mem* **26**, 235-244.

[25] Levine DA, Gross AL, Briceno EM, Tilton N, Kabeto MU, Hingtgen SM, Giordani BJ, Sussman JB, Hayward RA, Burke JF, Elkind MSV, Manly JJ, Moran AE, Kulick ER, Gottesman RF, Walker KA, Yano Y, Gaskin DJ, Sidney S, Yaffe K, Sacco RL, Wright CB, Roger VL, Allen NB, Gałecki AT (2020) Association between blood pressure and later-life cognition among Black and White individuals. *JAMA Neurol* **77**, 810-819.

[26] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J Clin Epidemiol* **61**, 344-349.

[27] Wright JD, Folsom AR, Coresh J, Sharrett AR, Couper D, Wagenknecht LE, Mosley TH Jr, Ballantyne CM, Boerwinkle EA, Rosamond WD, Heiss G (2021) The ARIC (Atherosclerosis Risk In Communities) Study: JACC Focus Seminar 3/8. *J Am Coll Cardiol* **77**, 2939-2959.

[28] Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ (1988) CARDIA: Study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* **41**, 1105-1116.

[29] Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A (1991) The Cardiovascular Health Study: Design and rationale. *Ann Epidemiol* **1**, 263-276.

[30] Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP (1975) The Framingham Offspring Study: Design and preliminary data. *Prev Med* **4**, 518-525.

[31] Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, JacobsJr DR, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP (2002) Multi-ethnic study of atherosclerosis: Objectives and design. *Am J Epidemiol* **156**, 871-881.

[32] Sacco RL, Anand K, Lee HS, Boden-Albala B, Stabler S, Allen R, Paik MC (2004) Homocysteine and the risk of ischemic stroke in a triethnic cohort: The NOrthern MAnhattan Study. *Stroke* **35**, 2263-2269.

[33] Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, Wadley VG (2015) Trajectory of cognitive decline after incident stroke. *JAMA* **314**, 41-51.

[34] Briceño EM, Gross AL, Giordani BJ, Manly JJ, Gottesman RF, Elkind MSV, Sidney S, Hingtgen S, Sacco RL, Wright CB, Fitzpatrick A, Fohner AE, Mosley TH, Yaffe K, Levine

DA (2021) Pre-statistical considerations for harmonization of cognitive instruments: Harmonization of ARIC, CARDIA, CHS, FHS, MESA, and NOMAS. *J Alzheimers Dis* **83**, 1803-1813.

[35] Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalaria RN, Vinters HV, Holtzman DM, Rosenberg GA, Wallin A, Dichgans M, Marler JR, Leblanc GG (2006) National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* **37**, 2220-2241.

[36] Manly JJ, Schupf N, Stern Y, Brickman AM, Tang M-X, Mayeux R (2011) Telephone-based identification of mild cognitive impairment and dementia in a multicultural cohort. *Arch Neurol* **68**, 607-614.

[37] Samejima F (1969) Estimation of latent ability using a response pattern of graded scores. *Psychometrika Monogr Supp* **34**, 100-100.

[38] Asparouhov T, Muthén B, Plausible Values for Latent Variables Using Mplus: Technical Report, http://www.statmodel.com/download/Plausible.pdf, Accessed April 29, 2022.

[39] Muthén LK, Muthén BO (2017) *Mplus User's Guide, 8th Edition*. Muthén & Muthén, Los Angeles, CA. https://www.statmodel.com/download/usersguide/MplusUserGuideVer_8.pdf.

[40] Noe-Bustamante L, Mora L, Lopez MH (2020) *About one-in-four U.S. Hispanics have heard of Latinx, but just 3% use it*. Pew Research Center, https://www.pewresearch.org/hispanic/wp-content/uploads/sites/5/2020/08/PHGMD_2020.08.11_Latinx_FINAL.pdf

[41] Gardener H, Sacco RL, Rundek T, Battistella V, Cheung YK, Elkind MSV (2020) Race and ethnic disparities in stroke incidence in the Northern Manhattan Study. *Stroke* **51**, 1064-1069.

[42] Manichaikul A, Palmas W, Rodriguez CJ, Peralta CA, Divers J, Guo X, Chen W-M, Wong Q, Williams K, Kerr KF, Taylor KD, Tsai MY, Goodarzi MO, Sale MM, Diez-Roux AV, Rich SS, Rotter JI, Mychaleckyj JC (2012) Population structure of Hispanics in the United States: The multi-ethnic study of atherosclerosis. *PLoS Genet* **8**, e1002640.

[43] Lau KK, Li L, Simoni M, Mehta Z, Kuker W, Rothwell PM (2018) Long-term premorbid blood pressure and cerebral small vessel disease burden on imaging in transient ischemic attack and ischemic stroke. *Stroke* **49**, 2053-2060.

[44] Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P (2001) Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: Analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension* **37**, 869-874.

[45] Pool LR, Ning H, Wilkins J, Lloyd-Jones DM, Allen NB (2018) Use of long-term cumulative blood pressure in cardiovascular risk prediction models. *JAMA Cardiol* **3**, 1096-1100.

[46] Gelberg L, Andersen RM, Leake BD (2000) The behavioral model for vulnerable populations: Application to medical care use and outcomes for homeless people. *Health Serv Res* **34**, 1273-1302.

[47] Glymour MM, Manly JJ (2008) Lifecourse social conditions and racial and ethnic patterns of cognitive aging. *Neuropsychol Rev* **18**, 223-254.

[48] Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, Haneuse S, Craft S, Montine TJ, Kahn SE, McCormick W, McCurry SM, Bowen JD, Larson EB (2013) Glucose levels and risk of dementia. *N Engl J Med* **369**, 540-548.

[49] Maas CJM, Hox JJ (2005) Sufficient sample sizes for multilevel modeling. *Methodology* **1**, 86-92.

[50] Kreft I, de Leeuw J (1998) *Introducing Multilevel Modeling*, SAGE Publications, London.

[51] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Lente FV, Greene T, Coresh J (2009) A new equation to estimate glomerular filtration rate. *Ann Intern Med* **150**, 604-612.

[52] Early DR, Widaman KF, Harvey D, Beckett L, Park LQ, Farias ST, Reed BR, Decarli C, Mungas D (2013) Demographic predictors of cognitive change in ethnically diverse older persons. *Psychol Aging* **28**, 633-645.

[53] Manly JJ, Gilmore-Bykovskyi A, Deters KD (2021) Inclusion of underrepresented groups in preclinical Alzheimer disease trials—opportunities abound. *JAMA Network Open* **4**, e2114606.

[54] Sloan FA, Wang J (2005) Disparities among older adults in measures of cognitive function by race or ethnicity. *J Gerontol B Psychol Sci Soc Sci* **60**, P242-P250.

[55] Wilson RS, Capuano AW, Marquez DX, Amofa P, Barnes LL, Bennett DA (2016) Change in cognitive abilities in older Latinos. *J Int Neuropsychol Soc* **22**, 58-65.

[56] Brewster PWH, Melrose RJ, Marquine MJ, Johnson JK, Napoles A, MacKay-Brandt A, Farias S, Reed B, Mungas D (2014) Life experience and demographic influences on cognitive function in older adults. *Neuropsychology* **28**, 846-858.

[57] Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, Tennstedt SL (2006) The ACTIVE cognitive training trial and health-related quality of life: Protection that lasts for 5 years. *J Gerontol A Biol Sci Med Sci* **61**, 1324-1329.

[58] Rossetti HC, Munro Cullum C, Hynan LS, Lacritz LH (2010) The CERAD Neuropsychologic Battery Total Score and the progression of Alzheimer disease. *Alzheimer Dis Assoc Disord* **24**, 138-142.

[59] Unger JM, van Belle G, Heyman A (1999) Cross-sectional versus longitudinal estimates of cognitive change in nondemented older people: A CERAD study. *J Am Geriatr Soc* **47**, 559-563.

[60] Bennett HP, Corbett AJ, Gaden S, Grayson DA, Kril JJ, Broe GA (2002) Subcortical vascular disease and functional decline: A 6-year predictor study. *J Am Geriatr Soc* **50**, 1969-1977.

[61] Clark LJ, Gatz M, Zheng L, Chen Y-L, McCleary C, Mack WJ (2009) Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease. *Am J Alzheimers Dis Other Demen* **24**, 461-468.

[62] Cosentino S, Scarmeas N, Albert SM, Stern Y (2006) Verbal fluency predicts mortality in Alzheimer disease. *Cogn Behav Neurol* **19**, 123-129.

[63] Zahodne LB, Schofield PW, Farrell MT, Stern Y, Manly JJ (2014) Bilingualism does not alter cognitive decline or dementia risk among Spanish-speaking immigrants. *Neuropsychology* **28**, 238-246.

[64] Babulal GM, Quiroz YT, Albensi BC, Arenaza-Urquijo E, Astell AJ, Babiloni C, Bahar-Fuchs A, Bell J, Bowman GL, Brickman AM, Chételat G, Ciro C, Cohen AD, Dilworth-Anderson P, Dodge HH, Dreux S, Edland S, Esbensen A, Evered L, Ewers M, Fargo KN, Fortea J, Gonzalez H, Gustafson DR, Head E, Hendrix JA, Hofer SM, Johnson LA, Jutten R, Kilborn K, Lanctôt KL, Manly JJ, Martins RN, Mielke MM, Morris MC, Murray ME, Oh ES,

Parra MA, Rissman RA, Roe CM, Santos OA, Scarmeas N, Schneider LS, Schupf N, Sikkes S, Snyder HM, Sohrabi HR, Stern Y, Strydom A, Tang Y, Terrera GM, Teunissen C, Melo van Lent D, Weinborn M, Wesselman L, Wilcock DM, Zetterberg H, O'Bryant SE; International Society to Advance Alzheimer's Research and Treatment, Alzheimer's Association (2019) Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: Update and areas of immediate need. *Alzheimers Dement* **15**, 292-312.

[65] Blue EE, Horimoto ARVR, Mukherjee S, Wijsman EM, Thornton TA (2019) Local ancestry at APOE modifies Alzheimer's disease risk in Caribbean Hispanics. *Alzheimers Dement* **15**, 1524-1532.

[66] Bostean G (2013) Does selective migration explain the Hispanic paradox? A comparative analysis of Mexicans in the U.S. and Mexico. *J Immigr Minor Health* **15**, 624-635.

[67] Weden MM, Miles JNV, Friedman E, Escarce JJ, Peterson C, Langa KM, Shih RA (2017) The Hispanic paradox: Race/ethnicity and nativity, immigrant enclave residence and cognitive impairment among older US adults. *J Am Geriatr Soc* **65**, 1085-1091.

[68] Jorm AF, Rodgers B, Henderson AS, Korten AE, Jacomb PA, Christensen H, Mackinnon A (1998) Occupation type as a predictor of cognitive decline and dementia in old age. *Age Ageing* **27**, 477-483.

[69] Zahodne LB, Glymour MM, Sparks C, Bontempo D, Dixon RA, MacDonald SWS, Manly JJ (2011) Education does not slow cognitive decline with aging: 12-year evidence from the Victoria Longitudinal Study. *J Int Neuropsychol Soc* **17**, 1039-1046.

[70] Euser SM, Schram MT, Hofman A, Westendorp RGJ, Breteler MMB (2008) Measuring cognitive function with age: The influence of selection by health and survival. *Epidemiology* **19**, 440-447.

[71] Salthouse TA (2014) Selectivity of attrition in longitudinal studies of cognitive functioning. *J Gerontol B Psychol Sci Soc Sci* **69**, 567-574.

[72] González HM, Tarraf W, Gouskova N, Gallo LC, Penedo FJ, Davis SM, Lipton RB, Argüelles W, Choca JP, Catellier DJ, Mosley TH (2015) Neurocognitive function among middle-aged and older Hispanic/Latinos: Results from the Hispanic Community Health Study/Study of Latinos. *Arch Clin Neuropsychol* **30**, 68-77.

[73] Pedraza O, Mungas D (2008) Measurement in cross-cultural neuropsychology. *Neuropsychol Rev* **18**, 184-193.

[74] de Heus RAA, Tzourio C, Lee EJL, Opozda M, Vincent AD, Anstey KJ, Hofman A, Kario K, Lattanzi S, Launer LJ, Ma Y, Mahajan R, Mooijaart SP, Nagai M, Peters R, Turnbull D, Yano Y, Claassen J, Tully PJ (2021) Association between blood pressure variability with dementia and cognitive impairment: A systematic review and meta-analysis. *Hypertension* **78**, 1478-1489.