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RESEARCH ARTICLE

High visit-to-visit blood pressure variability predicts global cognitive decline: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background: Research of hypertension-related risk factors for Alzheimer's disease has typically focused on blood pressure (BP) levels, despite evidence that high blood pressure variability (BPV) over time may predict poorer cardiovascular, neuropathological, and neurocognitive outcomes. We evaluated associations between BPV and cognitive function in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: Multivariable linear and logistic regression analyses of BP data across six examinations were used to determine associations that BPV (average real variability [ARV], variability independent of the mean [VIM]) and group-based latent BP trajectories have with cognitive function, decline, and impairment, measured by the Cognitive Abilities Screening Instrument (CASI), Digit Symbol Coding (DSC), and Digit Span tests.

Results: Participants (N = 1314; mean baseline age = 57) were 50% female, and 48% White. Higher systolic (β = −0.06, 95% confidence interval [CI]: −0.12, −0.0001) and diastolic (β = −0.08, 95% CI: −0.14, −0.02) ARV predicted increased global cognitive decline after covariate adjustment. Stronger relationships between BPV and global cognition were in older, White and Black participants, apolipoprotein E (*APOE*) ε4 non-carriers, male participants, and non-antihypertensive medication users.

Conclusion: Results suggest that higher systolic and diastolic BPV is an independent risk factor for cognitive dysfunction and decline in this multi-ethnic cohort. This relationship differs across demographic and clinical characteristics.

KEYWORDS
blood pressure, blood pressure measurement/monitoring cognitive impairment, ethnicity, race

1 | INTRODUCTION

Vascular disorders in midlife increase the risk for late-life cognitive dysfunction and dementia.[1–7] In the Multi-Ethnic Study of Atherosclerosis (MESA), we have shown previously that higher baseline blood pressure (BP) and its change over time are associated with poorer performance on tests of global cognitive performance, processing speed, and working memory.[4]

Blood pressure (or BP) can fluctuate across examinations in response to intrinsic regulatory mechanisms and extrinsic

environmental and behavioral factors like poor drug adherence, uncontrolled hypertension, and aging.[8,9] High blood pressure variability (BPV) has been explored as a risk factor for cognitive impairment.[10-13] The Atherosclerosis in Communities (ARIC) study[13] demonstrated that higher long-term systolic BP (SBP) and diastolic BP (DBP) variability is associated with lower global cognition in later life, but not with cognitive decline, whereas the China Health and Nutrition Survey[12] observed an association between high BPV and increased global cognitive decline. BPV has been associated with impaired cognitive function across domains and with adverse neurophysiological changes, such as tau accumulation, white matter lesions, and decreased hippocampal volume.[10,11,14-16] BP control interventions have shown promise in reducing the risk of mild cognitive impairment (MCI) and incident dementia, but have typically been focused on lowering BP levels rather than BPV.[17,18]

There are racial/ethnic differences in BP that may affect the relationship between BP and cognition, including differences in hypertension prevalence, management, and control,[19,20] and in dementia risk, which is modified by hypertension status.[21] Few studies have investigated the impacts of race/ethnicity on the relationship between BPV and cognition. Tsang et al. found that diastolic BPV correlated with incidental and verbal memory but not global cognition in a cross-sectional study of Black participants.[22] The ARIC study did not find significant differences between Black and White participants in the association between BPV and cognition.[7] Although this relationship has been investigated in diverse international settings and cultural groups, few studies have the ability to directly compare multiple racial and ethnic groups within the United States to examine the presence of heterogeneity of effects.

We expand upon prior MESA studies by conducting longitudinal analyses studying the influence of BPV in midlife on cognition in advanced age. We investigate potential modifiers of the relationship of BPV with cognition, race/ethnicity, sex, apolipoprotein E (*APOE*) ε4 carrier status, and anti-hypertensive (AHT) medication use.[7,10,23,24] BP trajectory analyses will demonstrate underlying differences in the shape of change, which have previously predicted negative cardiovascular disease (CVD) and neurocognitive outcomes.[25-28] To our knowledge, group-based trajectories have not been used to address the relationship of midlife BP with late-life cognitive functioning. This data-driven approach may provide valuable information regarding the shape and direction of BP change and offers advantages over "naïve approaches" to trajectory analyses by empirically defining the characteristics of trajectory groups.[29]

1.1 | Expected outcome

We hypothesized that increased BPV would predict poorer cognitive performance, cognitive decline, and impairment, and that these findings would differ according to demographic and genetic risk groups. It is expected that BP trajectory groups would differentially predict cognitive performance.

> **RESEARCH IN CONTEXT**
>
> 1. **Systematic Review**: The authors conducted an extensive search of standard resources such as PubMed and found a number of longitudinal observational studies investigating the relationship between blood pressure variability (BPV) and dementia-related cognitive dysfunction or decline. These studies largely indicate poorer cognitive performance associated with increased BPV, but often lacked observed relationships with cognitive decline, or in multi-ethnic US cohorts.
> 2. **Interpretation**: In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, long-term BPV is an independent modifiable risk factor for dementia-related cognitive decline. This effect is largely consistent across racial/ethnic groups, and is likely influenced by heterogeneous underlying BP trajectories.
> 3. **Future Directions**: Future directions include: (1) further research into this relationship with larger Hispanic and Chinese American samples; (2) larger overall sample to better investigate individual BP trajectory groups; (3) more detailed cognitive and neurobiological measures; and (4) more detailed assessment of anti-hypertensive (AHT) medication types for potential effect moderation.

2 | METHODS

2.1 | Study design and participants

All MESA participants provided informed consent prior to participation and protocols were approved by local institutional review boards. MESA recruited participants who were free of CVD to investigate the longitudinal progression of subclinical to clinical CVD in a multiethnic population.[30] The study collected cardiovascular measures over six examinations spanning nearly 20 years with a mean of 3.11 years between each exam for our sample (Baseline/Exam 1 [2000–2002], Exam 2 [2002–2004], Exam 3 [2004–2005], Exam 4 [2005–2007], Exam 5 [2010–2012], and Exam 6 [2016–2018]). Brief cognitive assessments were administered at Exam 5 and again at Exam 6. BPV measures and BP trajectories were derived from a sample of 6066 participants with three or more BP measures from the first five exam visits. Participants who met BP measurement requirements and participated in cognitive testing at Exams 5 and 6 were included in the analytic sample. Participants with invalid or incomplete cognitive abilities screening instrument (Cognitive Abilities Screening Instrument [CASI]) scores, who had a stroke during the study period, had a diagnosis of dementia prior to Exam

5, or were missing relevant regression model covariate data were excluded.

2.2 | Blood pressure measures

BP measures at each examination were collected using standardized procedures. Resting, seated BP was measured in the right arm with the Dinamap model Pro 100 automated sphygmomanometers. Participants underwent three consecutive BP measurements, and the last two were averaged to create final analysis measures. Details of MESA measures have been described previously.[30] Average real variability (ARV) was calculated to account for the order of the clinic visits in which BP was measured, and was measured using the "average of the absolute differences between consecutive BP readings" across visits.[31,32] Variability independent of the mean (VIM) was calculated to measure random dispersal of BP levels and does not correlate with BP mean, enabling the analysis of BPV independently from the BP mean.[13]

BP trajectories were derived using group-based trajectory modeling.[33,34] These models demonstrate the patterns and shape of BP change from Exams 1 to 5, irrespective of AHT medication use. The maximum number of potential groups for these models was obtained from a combination of prior knowledge and the use-of-fit statistics. Previous BP trajectory studies suggested that the maximum number of possible systolic (SBP) and diastolic (DBP) trajectory groups would be six and five, respectively.[25,27] We sequentially derived BP models with increasing number of groups until this maximum was reached. We used Bayesian information criteria (BIC) values to fit the number of groups and individual group shape over time.[33,34] The minimum threshold for posterior probability of group membership (>0.7)[34] and group size considerations[29] were utilized with BIC values to determine final models.

2.3 | Cognitive measures

Data from three neurocognitive tests serve as outcome measures and have been described in detail previously.[35] The CASI, Digit Span forward and backwards (DS), and Digit Symbol Coding (DSC) tests were used to assess global cognitive function, working memory and attention, and processing speed, respectively.[36–38] The CASI was developed for use in multi-cultural populations. Invalid CASI scores were determined by test administrators, technically invalid scores (<5), and incomplete examinations.[4]

Cognitive performance was assessed at Exams 5 and 6, and for change between these. Standardized z-scores for each test were calculated using means and standard deviations from Exam 5. Change in z-score from Exam 5 to Exam 6 was used to denote change in the CASI, DS, and DSC tests. Low global cognitive functioning (LCF) has been utilized previously in MESA[4] as a measure of cognitive impairment based on CASI score distribution. Individuals in the bottom 10th percentile of each age-, education-, and race-stratified CASI distribution at Exams 5 and 6 were assigned the status of LCF.

2.4 | Additional measures

Questionnaires were used to gather demographic data, tobacco and alcohol use, medical conditions and medication use, and moderate and vigorous physical activity total (metabolic equivalents- minutes per week [MET-MIN/WK]).[30] Education was categorized into four strata (≤HS Graduate, Some College or Technical/Associate Degrees, College Graduate [Bachelor's], Graduate/Professional). Smoking intensity was defined as the average number of cigarettes smoked per day. Participant's height and weight was assessed for the calculation of body mass index (BMI; kg/m2) and total cholesterol and glucose were measured in blood samples taken after a 12-hour fast. Diabetes was defined as fasting glucose ≥7 mmol/L (≥126 mg/dL) or use of hypoglycemic medication. Impaired fasting glucose was 6.11 to 7 mmol/L (≥100 mg/dL to 126 mg/dL). Hypertension was SBP over 140 mmHG or DBP over 90 mmHG, or use of AHT medications. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D); scores of 16 or higher indicated the presence of depressive symptoms. Participants excluded from the analysis had dementia defined by an International Classification of Diseases, Ninth Revision (ICD-9) code documented history of dementia, or a report of taking memory medications. Stroke diagnoses were determined using ICD-9 codes.

2.5 | Statistical analysis

Analyses were conducted using SAS 9.4 Software. Two-sample t-tests and chi-square tests determined differences between those included and excluded from our sample. Means and SDs, or percentages, were reported for baseline characteristics, and chi-square tests and analyses of variance (ANOVAs) determined differences in these characteristics by race and ethnicity. Correlation analyses showed relationships of BP and each BPV index with one another. ANOVAs and correlations demonstrated associations between ARV and baseline characteristics. Multivariable linear and logistic regression models determined relationships between BPV indices and cognition using sequentially adjusted models. The first model was unadjusted. A partially adjusted model included baseline age, education level, sex, race/ethnicity, $APOE$ $\varepsilon4$ carrier status, and study center. Fully adjusted models accounted for Exam 1 characteristics: age, education level, sex, race/ethnicity, $APOE$ $\varepsilon4$ carrier status, study center, and country of birth; and Exam 5 characteristics: income, household size, smoking intensity, depressive symptoms, BMI, glucose, AHT and diabetes medications, and mean SPB or DBP (from visits 1–5). Associations of BPV with Exam 6 outcomes and cognitive change were further adjusted for the time interval between Exams 5 and 6, and the interaction of either SBP or DBP mean with the time between Exams 5 and 6. Stratified analyses were

conducted where significant interaction terms ($P < .05$) were identified for race, age, sex, *APOE ε4* status, or AHT medication use.

We used sequentially adjusted multivariable linear and logistic regressions to determine the differential associations between BP trajectory groups, using the lowest BP group as a reference, with each cognitive measure. The first model was unadjusted and a second, fully adjusted, model accounted for age, sex, *APOE ε4* carrier status, education, and race/ethnicity at baseline, and glucose, BMI, and presence of AHT medication at Exam 5. In sensitivity analysis, another model contained covariates from the fully adjusted models of BPV and cognition. Inverse probability of attrition weighting was used to account for participant dropout and potential selection bias.[39,40]

3 | RESULTS

A total of 6814 participants were enrolled at MESA Exam 1 (Figure 1). Of these, 748 participants who did not have three or more BP measures were excluded from the analysis ($n = 6066$). A total of 3303 participants returned for Exam 6 and 2048 completed cognitive assessments; 1985 of those had cognitive data from Exams 5 and 6. A further 142 participants were excluded with invalid CASI scores ($n = 1843$). Finally, 529 were excluded because of ICD-9 codes for dementia or memory medication use before cognitive testing, stroke diagnosis throughout the study period or missing regression covariate measures, leaving an analytic sample size of 1314 participants representing four racial/ethnic groups.

Participants in our sample were younger (58 vs 63 years), had more education, were wealthier, and were healthier, including lower BPV and better cognitive scores, than excluded participants (Table S1). Table 1 shows the baseline characteristics of the sample by race/ethnic groups. Demographics, health behaviors, clinical characteristics, and BP measures differed significantly between race/ethnic groups. Black and Hispanic groups generally had higher BPV and were disproportionately represented in higher BP trajectory groups. At the time of the first cognitive assessment, the average age was 66.7 (8.3) years.

BPV differed by age, income, physical activity, cardio-metabolic diseases, and BP trajectory groups (Tables S2,S3). Group-based trajectory modeling criteria were used to select BP trajectories models with five SBP groups and four DBP groups (Figures 2 and 3). Systolic trajectory groups 1 to 5 can be described as low-normal stable, normal stable, high-normal stable, hypertensive-increasing, and hypertensive-decreasing, respectively. Diastolic groups 1 to 4 all showed moderate decline across the study period and were numbered sequentially from low to high normal BP.

Because of the high degree of collinearity between systolic ($R2 = 0.76$) and diastolic ($R2 = 0.80$) ARV and VIM, and because VIM cannot be compared across study populations because of its reliance on cohort BP distribution,[13] ARV served as the primary exposure variable and VIM was reserved for sensitivity analyses. Table 2 displays unadjusted and fully adjusted models of ARV and cognition. Increased systolic ($\beta = -0.06$, 95% confidence interval [CI]: -0.12, -0.0001) and diastolic ($\beta = -0.08$, 95% CI: -0.14, -0.02) BPV were predictive of

N = 6,814

Excluded, n = 748
Missing at least 3 or more BP measures

n = 6,066

Excluded, n = 4,081
Missing cognitive testing exams 5 or 6

n = 1,985

Excluded, n = 142
Invalid CASI scores at exam 5 or 6.

n = 1,843

Excluded, n = 529
AD prior to exam 5 (n=18)
Stroke throughout study period (n=43)
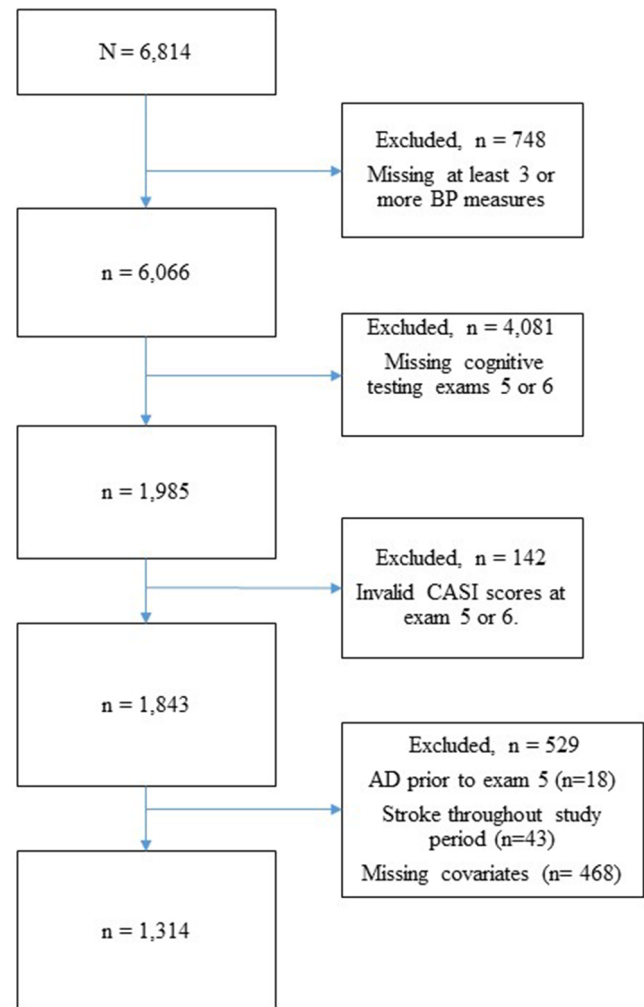Missing covariates (n= 468)

n = 1,314

FIGURE 1 A total of 6814 participants were enrolled at the Multi-Ethnic Study of Atherosclerosis (MESA) Exam 1. Of these, 748 participants who did not have at least three blood pressure (BP) measurements were excluded from analysis ($n = 6066$). A total of 3303 participants returned for Exam 6 and 2048 completed cognitive assessments; 1985 of those had cognitive test data from both Exams 5 and 6. A further 142 participants were excluded with invalid Cognitive Abilities Screening Instrument (CASI) scores ($n = 1843$). Finally, 529 were excluded because Alzheimer's diagnosis or medication use before cognitive testing, stroke diagnosis throughout the study period, or missing regression covariate measures, leaving an analytic sample size of 1314 participants representing four racial/ethnic groups.

increased global cognitive decline from Exams 5 to 6 in fully adjusted models. These results were nearly identical in partially adjusted models (results not shown), indicating that differences in unadjusted and fully adjusted models were due largely to adjustment for age, sex, education, race/ethnicity, *APOE ε4* carrier status, and study site. Increased systolic ($\beta = -0.06$, 95% CI: -0.11, -0.004) and diastolic ($\beta = -0.10$, 95% CI: -0.15, -0.04) VIM were associated with increased global decline but also with higher global performance at Exam 5 ($\beta = 0.06$, 95% CI: 0.004, 0.10).

Fully adjusted sensitivity analyses of ARV with global cognitive functioning at Exam 6 were stratified by age, and analyses of ARV with

TABLE 1 Clinical/demographic characteristics, BPV, and cognition by race/ethnicity

	White (N = 636)	Chinese (N = 89)	Black (N = 381)	Hispanic (N = 208)	Overall (N = 1314)	
	Mean (SD)/(%)	Mean (SD)/(%)	Mean (SD)/(%)	Mean (SD)/(%)	Mean (SD)/(%)	P-value
Age (years)	57.36 (8.28)	57.30 (8.84)	57.52 (8.45)	56.85 (8.69)	57.32 (8.43)	.83
Sex (female)	50.63%	37.08%	55.38%	41.35%	49.62%	<.001
APOE ε4 (at least 1 copy)	23.90%	12.36%	35.43%	23.08%	26.33%	<.001
Education						<.001
≤HS Grad	12.11%	25.84%	17.85%	54.33%	21.39%	
Some college	26.42%	16.85%	39.90%	33.65%	30.82%	
College grad	27.83%	26.97%	19.95%	5.29%	21.92%	
Post grad	33.65%	30.34%	22.31%	6.73%	25.88%	
No health insurance	2.99%	16.85%	5.51%	14.42%	6.47%	<.001
Income (<$25,000)	8.65%	26.97%	18.37%	35.10%	16.89%	<.001
Birth place (U.S.)	93.08%	8.99%	90.03%	40.38%	78.16%	<.001
Number in household	2.18 (1.13)	2.99 (1.31)	2.12 (1.19)	2.60 (1.44)	2.29 (1.23)	.001
Ever smoker (yes)	7.08%	5.62%	11.29%	6.73%	8.14%	.06
Average cigs smoked/day	10.09 (14.14)	4.49 (9.94)	8.13 (11.21)	5.71 (10.24)	8.45 (12.64)	<.001
MV physical activity	5457.46 (4937.82)	4428.99 (4304.62)	7120.31 (6974.33)	8759.38 (8199.73)	6392.63 (6279.90)	<.001
CES-D	7.56 (7.25)	7.33 (6.86)	7.28 (6.83)	8.34 (7.95)	7.58 (7.22)	.38
BMI	27.61 (5.17)	23.76 (3.02)	30.08 (5.52)	29.63 (4.95)	28.39 (5.39)	<.001
Hypertension	26.42%	25.84%	45.93%	30.77%	32.72%	<.001
AHT medication	24.06%	22.47%	39.63%	24.04%	28.46%	<.001
Diabetes medication	2.36%	6.74%	6.56%	9.13%	4.95%	.002
Diabetes	3.3%	7.87%	9.19%	10.58%	6.47%	<.001
Glucose	88.84 (19.33)	95.54 (16.57)	93.90 (24.77)	97.51 (29.61)	92.14 (22.9)	
BPV measures	Mean (SD) /No. (%)	Mean (SD) /No. (%)	Mean (SD) /No. (%)	Mean (SD) /No. (%)	Mean (SD) /No. (%)	
Average BP						
SBP	116.72 (14.42)	119.59 (13.96)	125.34 (15.22)	121.17 (17.35)	120.12 (15.55)	<.001
DBP	68.63 (8.25)	71.28 (7.43)	72.61 (8.17)	70.81 (8.72)	70.31 (8.42)	<.001
VIM						
SBP	10.70 (5.11)	9.67 (4.36)	11.39 (5.36)	10.32 (5.54)	10.77 (5.22)	.01
DBP	5.39 (2.55)	5.02 (2.22)	5.56 (2.66)	5.32 (2.59)	5.40 (2.57)	.30
ARV						
SBP	14.70 (8.45)	13.87 (7.73)	18.05 (10.93)	15.99 (10.87)	15.82 (9.70)	<.001
DBP	7.56 (3.70)	7.20 (3.26)	8.33 (4.39)	7.99 (4.42)	7.83 (4.02)	.01
SBP Groups						<.001
Group 1	32.39%	25.84%	13.39%	25.96%	25.42%	
Group 2	46.86%	49.44%	49.87%	44.71%	47.56%	
Group 3	17.92%	21.35%	28.35%	21.15%	21.69%	
Group 4	1.89%	1.12%	5.25%	4.81%	3.27%	
Group 5	0.94%	2.25%	3.15%	3.37%	2.05%	
DBP groups						<.001
Group 1	17.45%	10.11%	7.09%	10.58%	12.86%	
Group 2	41.67%	37.08%	33.07%	41.35%	38.81%	
Group 3	35.06%	43.82%	45.41%	35.10%	38.66%	
Group 4	5.82%	8.99%	14.44%	12.98%	9.67%	

(Continues)

TABLE 1 (Continued)

Cognitive measures	Mean (SD)/No. (%)	Mean (SD)/No. (%)	Mean (SD)/No. (%)	Mean (SD)/No. (%)	Mean (SD)/No. (%)	P-value
CASI						
Exam 5	93.24 (4.87)	88.52 (6.05)	89.17 (6.26)	85.88 (8.10)	90.58 (6.59)	<.001
Exam 6	93.35 (5.78)	89.58 (6.34)	89.28 (6.63)	86.18 (8.12)	90.78 (7.02)	<.001
Change	0.01 (0.76)	0.13 (0.77)	0.01 (0.74)	0.04 (0.89)	0.03 (0.78)	.58
DS						
Exam 5	17.30 (4.23)	18.17 (4.66)	15.44 (3.91)	12.77 (4.06)	16.11 (4.47)	<.001
Exam 6	16.72 (4.10)	17.39 (4.34)	14.84 (3.56)	12.20 (3.32)	15.50 (4.20)	<.001
Change	−0.13 (0.75)	−0.16 (0.86)	−0.14 (0.66)	−0.13 (0.66)	−0.13 (0.72)	.98
DSC						
Exam 5	61.68 (14.23)	61.66 (17.45)	51.04 (15.50)	47.79 (18.04)	56.27 (16.65)	<.001
Exam 6	58.16 (16.03)	56.02 (18.23)	47.46 (15.11)	40.13 (18.40)	52.13 (17.68)	<.001
Change	−0.19 (0.63)	−0.36 (0.57)	−0.22 (0.60)	−0.44 (0.65)	−0.26 (0.63)	<.001
LCF Exam 5	3.62%	7.87%	3.67%	6.37%	4.41%	.09
LCF Exam 6	9.43%	12.36%	8.92%	7.21%	9.13%	.54

Note: Average cigarettes smoked per day includes both smokers and non-smokers; hypertension defined as an SBP greater than 140 mm HG and/or DBP greater than 90 mm HG.

Abbreviations: AHT, anti-hypertensive; ARV, average real variability; BMI, body mass index; CASI, Cognitive Abilities Screening Instrument; CES-D, Center for Epidemiologic Studies Depression Scale; DBP, diastolic blood pressure; DSB, digit span backwards; DSF, digit span forward; DSC, digit symbol coding; HS, high school; LCF, low global cognitive functioning; MV physical activity, moderate and vigorous physical activity; SD, standard deviation; SBP, systolic blood pressure; VIM, variability independent of the mean.
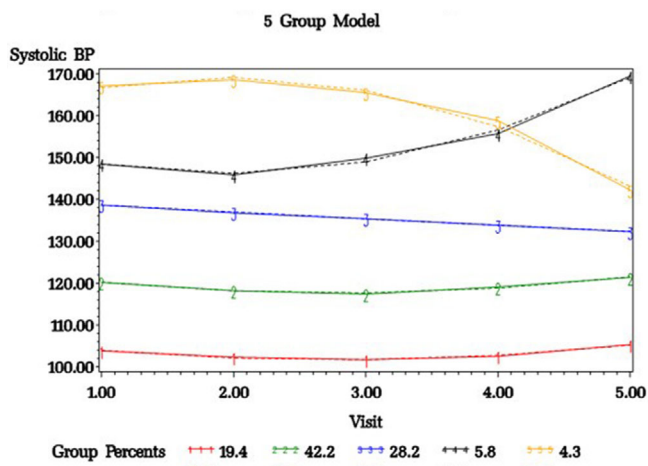

FIGURE 2 Long-term systolic blood pressure trajectory groups during Exams 1 to 5 (2000–2012). Systolic trajectory groups 1 to 5 can be described as low-normal stable (red), normal stable (green), high-normal stable (blue), hypertensive-increasing (black), and hypertensive-decreasing (yellow), respectively.
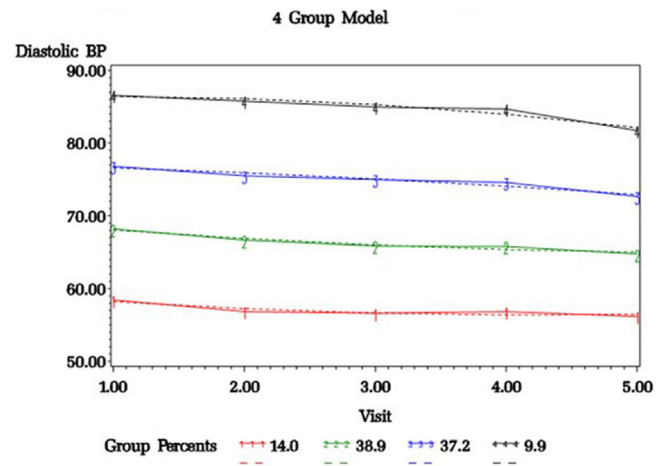

FIGURE 3 Long-term diastolic blood pressure trajectory groups during Exams 1 to 5 (2000–2012). Diastolic groups 1 to 4 all showed moderate decline across the study period and were numbered sequentially from low to high normal BP: low (red), low-normal (green), normal (blue), and high-normal (black).

global cognitive decline were stratified by age, race/ethnicity, *APOE ε4* carrier status, sex, and AHT medication use, all of which interacted with these relationships at a $P < .05$ level. In older participants (≥65 years at baseline), increased systolic ($\beta = -0.11$, 95% CI: −0.23, −0.001) and diastolic ($\beta = -0.13$, 95% CI: −0.24, −0.03) BPV predicted decreased global performance (Table S4). Increased systolic ($\beta = -0.15$, 95% CI: −0.27, −0.03) and diastolic BPV ($\beta = -0.21$, 95% CI: −0.32, −0.09)

predicted increased global cognitive decline in older participants. High systolic ($\beta = -0.12$, 95% CI: −0.22, −0.04) and diastolic ($\beta = -0.18$, 95% CI: −0.21, −0.05) BPV were associated with increased global cognitive decline for White participants in stratified analyses, and high diastolic BPV was associated with increased global decline for Black participants ($\beta = -0.12$, 95% CI: −0.22, −0.01) (Table S5). Higher diastolic BPV predicted increased cognitive decline in male ($\beta = -0.10$, 95% CI: −0.18, −0.02) and marginally reduced decline in female ($\beta = -0.08$,

TABLE 2 Association of ARV with cognitive scores, decline, and impairment

	Models			
	Unadjusted		Fully adjusted	
	SBP	DBP	SBP	DBP
Cognitive measure	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Global cognition (CASI)				
Exam 5	**−0.09 (−0.15, −0.04)**	0.00 (−0.06, 0.05)	0.02 (−0.03, 0.07)	0.04 (−0.01, 0.09)
Exam6	**−0.17 (−0.22, −0.12)**	**−0.07 (−0.12, −0.01)**	−0.03 (−0.08, 0.02)	−0.04 (−0.08, 0.01)
Change	**−0.09 (−0.14, −0.04)**	**−0.07 (−0.13, −0.02)**	**−0.06 (−0.12, −0.0001)**	**−0.08 (−0.14, −0.02)**
Executive Function (DS total)				
Exam 5	**−0.12 (−0.17, −0.07)**	**−0.07 (−0.12, −0.01)**	0.01 (−0.07, 0.04)	0.00 (−0.05, 0.05)
Exam6	**−0.12 (−0.18, −0.07)**	**−0.06 (−0.11, −0.006)**	0.00 (−0.05 0.06)	−0.01 (−0.06, 0.05)
Change	0.01 (−0.04, 0.06)	0.01 (−0.05, 0.06)	0.00 (−0.03, 0.09)	−0.01 (−0.07, 0.04)
Processing speed (DS coding)				
Exam 5	**−0.18 (−0.23, −0.12)**	**−0.06 (−0.12, −0.006)**	−0.01 (−0.06, 0.04)	0.01 (−0.04, 0.05)
Exam6	**−0.17 (−0.23, −0.12)**	**−0.07 (−0.13, −0.01)**	−0.001 (−0.05, 0.05)	0.00 (−0.05, 0.04)
Change	−0.03 (−0.09, 0.03)	−0.02 (−0.08, 0.04)	0.00 (−0.06, 0.07)	−0.02 (−0.08, 0.04)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Low cognitive functioning				
Exam 5	**1.03 (1.01-1.05)**	0.99 (0.95-1.04)	0.99 (0.97-1.02)	0.96 (0.90-1.03)
Exam 6	**1.04 (1.02-1.05)**	0.96 (0.90-1.03)	1.01 (0.99-1.03)	1.01 (0.96-1.06)

Note: Fully adjusted models account for demographic and genetic variables at Exam 1: age, education level, sex, race/ethnicity, *APOE ε*4 carrier status, study center, and country of birth; and demographic and clinical characteristics at Exam 5: income level, household size, smoking intensity, depressive symptoms, BMI, glucose, anti-hypertensive medications, diabetes medications, and mean SPB or DPB (from visits 1–5). Associations of BPV with Exam 6 outcomes and cognitive change measures were further adjusted by the time interval between visits 5 and 6, and the interaction of either systolic of diastolic BP mean with the time between visits 5 and 6 (Time in years*Mean SBP or DBP). Adjusted β's (95% CIs) associated with 1 SD increases of each BP and cognitive parameter are shown. The 1 SD increases of systolic and diastolic average real variability are, per 9.7 mm Hg and per 4.02 mm Hg, respectively. The 1 SD increases of each cognitive outcome are: per 6.59, 7.02, 0.78 for CASI scores at Exam 5, Exam 6, and CASI Change, respectively; per 4.47, 4.40, 0.72 for DS scores at Exam 5, Exam 6, and DS Change, respectively; and per 16.65, 17.68, and 0.63 for DSC scores at Exam 5, Exam 6, and DSC Change, respectively. Statistical significance at *P* < .05 level is indicated with bold text.

95% CI: −0.16, 0.002) participants. Higher systolic (β = −0.07, 95% CI: −0.14, −0.001) and diastolic (β = −0.08, 95% CI: −0.14, −0.01) BPV was associated with increased global cognitive decline in *APOE ε*4 non-carriers (Table S6). Increased diastolic BPV predicted reduced global performance (β = −0.08, 95% CI: −0.15, −0.01) and increased cognitive decline (β = −0.11, 95% CI: −0.19, −0.03) in those not using AHT medication. Age (p-interaction <0.001) and race (p-interaction <0.001) significantly interacted with diastolic VIM to predict global cognitive function at Exam 5. Stratified analyses indicated that higher variability in VIM marginally predicted increased CASI scores for White participants (β = 0.08, 95% CI: −0.002, 0.16), but not for Chinese (β = 0.02, 95% CI: −0.18, 0.24), Black (β = 0.05, 95% CI: −0.04, 0.15), or Hispanic participants (β = 0.05, 95% CI: -0.09, 0.19). Higher variability in VIM did not predict CASI scores in either older (β = 0.07, 95% CI: -0.03, 0.17) or younger adults (β = 0.05, 95% CI: −0.01, 0.10). Interactions with VIM to predicted Exam 5 CASI scores were not identified for sex (p-interaction = 0.77), *APOE ε*4 carrier status (p-interaction = 0.47), or AHT use (p-interaction = 0.36).

Table 3 shows the relative association of each BP trajectory group with each cognitive outcome. After full adjustment, SBP groups

were differentially associated with global cognition, executive function, and information processing. SBP groups 4 and 5, hypertensive-increasing and hypertensive-decreasing, respectively, were most consistently associated with decreased performance. DBP group 4, pre-hypertensive and declining, was associated with reduced global cognition and executive function. Adjustment for sensitivity analysis covariates, including BP mean, yielded no diastolic BP group differences in association with cognitive performance. SBP group 4 (β = 0.08, 95% CI: −0.13, −0.03) and group 5 (β = −0.07, 95% CI: −0.12, −0.02) predicted poorer global performance at Exam 6.

Table 4 shows the differential odds of cognitive impairment between BP trajectories. After full adjustment, DBP trajectory group 4 (odds ratio [OR] = 7.51, 1.88–30.00) was associated with increased impairment odds at Exam 5, compared to group 1. After sensitivity analysis covariate adjustment, DBP groups 2 (OR = 3.96, 1.54–10.23; 3: OR = 6.70, 1.59–28.24; and 4: OR = 24.59, 3.01–200.99) were associated with increased odds of cognitive impairment at Exam 6 compared to group 1. The large ORs and wide CIs for DBP group 4 caution the interpretation of these results and may be related to the small size and comparatively large heterogeneity within this group.

TABLE 3 Association of BP trajectories with cognitive performance and decline—models 1 and 2

	Cognitive domain								
	Global cognition (CASI)			Executive function (DS total)			Processing speed (DS coding)		
BP groups	Exam 5 β (95% CI)	Exam 6 β (95% CI)	Change β (95% CI)	Exam 5 β (95% CI)	Exam 6 β (95% CI)	Change β (95% CI)	Exam 5 β (95% CI)	Exam 6 β (95% CI)	Change β (95% CI)
Unadjusted									
Systolic									
Group 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Group 2	**−0.10 (−0.16, −0.03)**	**−0.08 (−0.15, −0.02)**	0.01 (−0.05, 0.08)	**−0.10 (−0.17, −0.03)**	**−0.09 (−0.15, −0.02)**	0.02 (−0.05, 0.09)	**−0.20 (−0.26, −0.13)**	**−0.20 (−0.26, −0.13)**	−0.03 (−0.11, 0.04)
Group 3	**−0.17 (−0.23, −0.11)**	**−0.17 (−0.23, −0.11)**	−0.01 (−0.08, 0.05)	**−0.14 (−0.20, −0.07)**	**−0.14 (−0.20, −0.07)**	0.01 (−0.06, 0.07)	**−0.28 (−0.34, −0.21)**	**−0.27 (−0.33, −0.20)**	−0.03 (−0.10, 0.04)
Group 4	**−0.12 (−0.18, −0.07)**	**−0.18 (−0.23, −0.13)**	**−0.07 (−0.13, −0.02)**	**−0.14 (−0.20, −0.09)**	**−0.15 (−0.20, −0.09)**	0.01 (−0.05, 0.06)	**−0.16 (−0.22, −0.10)**	**−0.18 (−0.24, −0.12)**	−0.06 (−0.12, 0.00)
Group 5	**−0.10 (−0.16, −0.05)**	**−0.17 (−0.22, −0.12)**	**−0.08 (−0.14, −0.03)**	**−0.12 (−0.17, −0.06)**	**−0.12 (−0.17, −0.06)**	0.01 (−0.05, 0.06)	**−0.17 (−0.22, −0.11)**	**−0.15 (−0.21, −0.09)**	−0.03 (−0.09, 0.03)
Diastolic									
Group 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Group 2	**−0.11 (−0.19, −0.02)**	**−0.10 (−0.15, −0.02)**	−0.001 (−0.09, 0.08)	−0.001 (−0.09, 0.08)	−0.07 (−0.16, 0.01)	**−0.09 (−0.17, −.001)**	**−0.14 (−0.23, −0.05)**	**−0.10 (−0.19, −0.01)**	0.05 (−0.04, 0.15)
Group 3	−0.08 (−0.16, 0.01)	−0.03 (−0.12, 0.05)	0.04 (−0.04, 0.13)	−0.01 (−0.09, 0.08)	−0.05 (−0.13, 0.04)	−0.06 (−0.14, 0.03)	**−0.16 (−0.25, −0.07)**	**−0.10 (−0.18, −0.01)**	0.08 (−0.01, 0.17)
Group 4	**−0.15 (−0.22, −0.08)**	**−0.09 (−0.16, −0.03)**	0.05 (−0.02, 0.12)	**−0.11 (−0.18, −0.04)**	**−0.13 (−0.20, −0.07)**	−0.02 (−0.09, 0.05)	**−0.15 (−0.22, −0.08)**	**−0.12 (−0.19, −0.05)**	0.03 (−0.05, 0.10)
Fully adjusted									
Systolic									
Group 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Group 2	0.00 (−0.06, 0.06)	0.03 (−0.03, 0.09)	0.03 (−0.04, 0.10)	−0.02 (−0.09, 0.04)	0.00 (−0.06, 0.06)	0.03 (−0.04, 0.10)	**−0.06 (−0.12, −0.001)**	−0.06 (−0.11, 0.00)	−0.01 (−0.09, 0.07)
Group 3	−0.02 (−0.08, 0.05)	0.00 (−0.06, 0.06)	0.02 (−0.05, 0.10)	−0.02 (−0.09, 0.05)	0.00 (−0.07, 0.07)	0.02 (−0.06, 0.10)	**−0.07 (−0.14, −0.01)**	**−0.06 (−0.12, −0.004)**	0.01 (−0.07, 0.09)
Group 4	−0.04 (−0.09, 0.01)	**−0.08 (−0.13, −0.03)**	−0.05 (−0.11, 0.00)	**−0.07 (−0.12, −0.01)**	**−0.06 (−0.11, −.003)**	0.01 (−0.05, 0.07)	**−0.05 (−0.10, −0.001)**	**−0.06 (−0.11, −0.02)**	−0.03 (−0.09, 0.03)
Group 5	−0.01 (−0.06, 0.04)	**−0.07 (−0.12, −0.02)**	**−0.06 (−0.12, −.001)**	−0.05 (−0.10, 0.00)	−0.04 (−0.09, 0.01)	0.02 (−0.04, 0.08)	**−0.06 (−0.11, −0.01)**	−0.05 (−0.09, 0.00)	0.00 (−0.06, 0.07)
Diastolic									
Group 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Group 2	−0.05 (−0.12, 0.03)	−0.04 (−0.12, 0.02)	0.00 (−0.09, 0.08)	0.04 (−0.04, 0.12)	−0.02 (−0.10, 0.05)	**−0.09 (−0.17, 0.00)**	−0.05 (−0.13, 0.02)	−0.02 (−0.08, 0.05)	0.06 (−0.03, 0.15)
Group 3	−0.02 (−0.09, 0.07)	0.01 (−0.07, 0.09)	0.03 (−0.06, 0.12)	0.03 (−0.05, 0.11)	−0.01 (−0.09, 0.07)	−0.06 (−0.15, 0.03)	−0.05 (−0.12, 0.04)	0.00 (−0.07, 0.07)	0.06 (−0.03, 0.16)
Group 4	**−0.08 (−0.14, −0.02)**	−0.04 (−0.11, 0.02)	0.03 (−0.04, 0.11)	−0.06 (−0.13, 0.01)	**−0.09 (−0.15, −0.02)**	−0.03 (−0.10, 0.05)	−0.05 (−0.11, 0.01)	−0.04 (−0.11, 0.01)	0.00 (−0.08, 0.08)

Note: Model 1 is unadjusted for covariates. Model 2 covariates are: age, sex, APOE ε4 carrier status, education, and race/ethnicity at baseline; clinical characteristics at Exam 5: glucose, BMI, and presence of anti-hypertensive medication at Exam 5. Statistical significance was defined as $P < .05^*$, $P < .05†$, $P < .01‡$, $P < .001$. Adjusted β's (95% CIs) associated with 1 SD increases of each cognitive parameter are shown. The 1 SD increases of each cognitive outcome are: per 6.59, 7.02, and 0.78 for CASI scores at Exam 5, Exam 6, and CASI Change, respectively; per 4.47, 4.40, and 0.72 for DS scores at Exam 5, Exam 6, and DS Change, respectively; and per 16.65, 17.68, and 0.63 for DSC scores at Exam 5, Exam 6, and DSC Change, respectively. Statistical significance at $P < .05$ level is indicated by bold text.

TABLE 4 Association of BP trajectories with global cognitive impairment

BP trajectories	Cognitive domain	
	Low cognitive functioning (Exam 5)	Low cognitive functioning (Exam 6)
	OR (95% CI)	OR (95% CI)
Unadjusted		
Systolic		
Group 1 (N = 334)	1.00	1.00
Group 2 (N = 625)	1.35 (0.59–3.09)	1.21 (0.71–2.06)
Group 3 (N = 285)	3.41* (1.49–7.78)	2.16† (1.23–3.79)
Group 4 (N = 43)	4.18† (1.20–14.52)	4.52‡ (1.96–10.40)
Group 5 (N = 27)	7.09* (1.99–25.30)	4.26† (1.55–11.68)
Diastolic		
Group 1 (N = 169)	1.00	1.00
Group 2 (N = 510)	2.73 (0.81–9.19)	1.42 (0.77–2.62)
Group 3 (N = 508)	2.03 (0.59–6.99)	0.84 (0.44–1.61)
Group 4 (N = 127)	6.31† (1.76–22.65)	1.16 (0.52–2.59)
Fully adjusted		
Systolic		
Group 1 (N = 334)	1.00	1.00
Group 2 (N = 625)	0.91 (0.37–2.21)	0.73 (0.41–1.32)
Group 3 (N=285)	1.77 (0.69–4.56)	0.87 (0.45–1.69)
Group 4 (N = 43)	2.20 (0.56–8.71)	1.92 (0.74–5.00)
Group 5 (N = 27)	3.67 (0.90–14.96)	1.34 (0.43–4.16)
Diastolic		
Group 1 (N = 169)	1.00	1.00
Group 2 (N = 510)	2.60 (0.75–8.97)	1.38 (0.72–2.67)
Group 3 (N = 508)	2.26 (0.62–8.25)	0.92 (0.45–1.88)
Group 4 (N = 127)	7.51† (1.88–30.00)	1.66 (0.66–4.15)

Note: Adjusted by model 2 covariates: age, sex, *APOE* ε4 carrier status, education, and race/ethnicity at baseline; clinical characteristics at Exam 5 glucose, BMI, and presence of anti-hypertensive medication at Exam 5. Statistical significance was defined as $P < .05$*, $P < .05$†, $P < .01$‡, $P < .001$.

4 | DISCUSSION

Higher long-term BPV independently predicted global cognitive decline in this relatively healthy, multi-ethnic sample. This relationship may be modified by age, race, sex, AHT medication use, and *APOE* ε4 carrier status, and is likely influenced by underlying differences in BP trajectories, which differentially predicted cognitive performance.

These results align with similar studies, which have observed relationships between high BPV and cognition.[10,12,14,22,41–43] This relationship may be driven by long-term hemodynamic instability and associated microvascular damage, atherosclerosis, and organ hypoperfusion, leading to increased white matter lesions, cortical infarcts, and other neuropathological contributions to cognitive dysfunction.[44] Confidence in these results is strengthened by the consistency of

this pattern across ARV and VIM, with VIM indicating an association independent of BP level. Similar effect sizes were observed between systolic ARV and VIM, whereas diastolic VIM appeared to have a somewhat stronger effect. The effect of VIM on cognition was more variable, suggesting that ARV may be a more consistent predictor of cognitive impairment. Further studies are needed to identify the most informative BPV index and mechanistic differences between them.[13,42]

The finding that BPV is associated with cognitive decline in this younger, healthy and multi-ethnic sample is novel, as studies in the United States generally lack the multiple cognitive measures necessary to make such observations or have reported inconsistent results.[12,13] BPV-associated cognitive impairments have been observed in bi-racial and young adult samples.[7,45] However, the current study demonstrates cognitive decline over time, a key criterion for AD[46] in a sample with multiple ethnic groups, an important knowledge gap in this relationship.[43] The lack of association between BPV with other cognitive measures is notable. It has been suggested that this association may be attenuated in healthier populations.[14] This is possible in MESA, which excluded participants with CVD to investigate subclinical cardiometabolic contributions to chronic diseases.

Increased BPV was predictive of increased global cognitive decline among older participants, aligning with studies that found worse BPV-related cognitive outcomes in older age.[47,48] This differs from studies that showed no modification by age[13,41] or stronger associations at younger ages, attributed to decreased competing risk factors.[12] The cognitive effects of this risk factor may be most noticeable among older ages, in which cognitive decline is more frequently observed, although BPV likely remains a risk factor for younger populations. The relationship was stronger among those not using AHT medications. Treatments like calcium-channel blockers may reduce BPV[49] and improve BPV-related neurocognitive outcomes in hypertensive patients.[10,50] Consistent with a previous study of cardio-metabolic[4] relationships with cognition in MESA, the association of BPV and cognitive decline appears stronger in *APOE* ε4–negative participants, possibly indicating a pathway independent of this genetic risk factor. Similar effect sizes between *APOE* ε4 carriers and non-carriers, smaller group size for carriers, and potential for *APOE* as a competing risk factor for BPV caution this interpretation. The stronger effects indicated in men could be explained by generally poorer male cardiovascular health, including higher BPV. However, effect sizes were generally comparable, suggesting common effects across sexes.

Stratified analyses across racial/ethnic groups indicated possible effect modification. Results were largely similar across racial/ethnic groups, with most groups showing a general decrease in global cognitive decline with increased BPV, except for in Chinese participants. These results are similar to those of other studies showing that Black and White participants similarly had poorer cognition with increased BPV.[7,22] One study of BP change over time indicated that increased BP changes predict dementia risk more strongly in White participants,[28] but this may have been due to the greater attrition of Black participants. Differences seen in Chinese and Hispanic participants may be related to cultural differences (i.e., language and acculturation) but are more likely due to smaller group sizes, particularly for Chinese

participants, as similar associations were shown in the China Health and Nutrition Survey.[12]

BP groups differentially predicted global cognition, executive function, and information processing. Many of these results remained similar after adjustment for mean BP, indicating an independent BPV-related influence cognition. Although the hypertensive-decreasing SBP trajectory (group 5) had a higher mean and BPV than the hypertensive-increasing (group 4), group 4 was more strongly associated with worse cognition, supporting results from the SPRINT trial that indicate that SBP reduction in hypertensive patients may benefit cognitive health.[18] These results align with previous findings that higher and more variable BP patterns predict worse cognitive performance.[26,28] We expand upon prior work by applying a latent trajectory approach to account for underlying differences in shape and direction of long-term BPV.

This study had several limitations. This is an observational study and we cannot interpret any causative relationships; yet, this analysis provides temporal relationships between BPV over time and change in cognitive performance. Cognitive testing for this sample was not conducted prior to Exam 5, thus we lack cognitive information from the first 10 years of risk factor assessment. Our sample was younger and healthier on average than other studies of cognitive aging due to the MESA study design and our inclusion criteria. Bias may exist in this association due to a higher attrition among participants with poorer health, including those with higher and more variable BP trajectories. This could have reduced the observed effect, as BPV-related cognitive impairment is particularly seen in less healthy populations, although it is possible that those who dropped out with high BPV may have had preserved cognitive abilities. We addressed this bias using inverse probability weighting; there were no significant changes to our results. Observations of spurious associations due to multiple comparisons is possible; however, interdependence of our cognitive and BP measures, and the consistent direction of effects, limits this concern. BP trajectory model development adjusting for AHT medications may be of interest, but their influence could be complex with elements like number, dosage, type, and duration of use potentially influencing trajectories. We chose to derive groups irrespective of other factors, but to adjust for covariates in linear modeling. Relatively small BP trajectory group sizes may have limited the power to detect effects, but do not affect the appropriateness of the models as confirmed using the aforementioned criteria.

5 | CONCLUSION

High visit-to-visit BPV over nearly 20 years is predictive of increased global cognitive decline, independent of mean BP, in this multi-ethnic cohort that was relatively healthy at baseline. This study attempted to address the gaps in knowledge regarding the similarity of this association across multiple ethno-racial groups in the United States, and the results indicate a commonality of effects in BPV-related cognitive decline, after robust adjustment for sociodemographic factors. The observed effects were strongest in participants aged 65 or older at baseline and not using AHT medications. Higher and more variable BP

trajectories predicted poorer cognitive performance across multiple domains, highlighting the utility of this method to track underlying differences in the shape of BP change. Future studies should investigate this association with larger samples to investigate differences within heterogeneous ethnic groups and in the relatively small, but high and variable BP trajectory groups.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.