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Association of longitudinal changes in 24-h blood pressure level and variability with cognitive decline

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Objective: A high office blood pressure (BP) is associated with cognitive decline. However, evidence of 24-h ambulatory BP monitoring is limited, and no studies have investigated whether longitudinal changes in 24-h BP are associated with cognitive decline. We aimed to test whether higher longitudinal changes in 24-h ambulatory BP measurements are associated with cognitive decline.

Methods: We included 437 dementia-free participants from the Maracaibo Aging Study with prospective data on 24-h ambulatory BP monitoring and cognitive function, which was assessed using the selective reminding test (SRT) and the Mini-Mental State Examination (MMSE). Using multivariate linear mixed regression models, we analyzed the association between longitudinal changes in measures of 24-h ambulatory BP levels and variability with cognitive decline.

Results: Over a median follow-up of 4 years (interquartile range, 2–5 years), longitudinal changes in 24-h BP level were not associated with cognitive function ($P \geq 0.09$). Higher longitudinal changes in 24-h and daytime BP variability were related to a decline in SRT-delayed recall score; the adjusted scores lowered from −0.10 points [95% confidence interval (CI), −0.16 to −0.04) to −0.07 points (95% CI, −0.13 to −0.02). We observed that a higher nighttime BP variability during follow-up was associated with a decline in the MMSE score (adjusted score lowered from −0.08 to −0.06 points).

Conclusion: Higher 24-h BP variability, but not BP level, was associated with cognitive decline. Prior to or in the early stages of cognitive decline, 24-h ambulatory BP monitoring might guide strategies to reduce the risk of major dementia-related disorders including Alzheimer's disease.

Graphical abstract: http://links.lww.com/HJH/C545

Keywords: ambulatory blood pressure monitoring, blood pressure variability, cognitive decline, longitudinal data, mixed models, older adults, population-based study

Abbreviations: ARV, average real variability; BP, blood pressure; CI, confidence Interval; MMD, maximum−minimum difference; MMSE, mini-mental state examination; SRT, selective reminding test; VIM, variability independent of the mean

INTRODUCTION

Dementia affects over six million people in the United States, and this number is expected to double by 2050 because of the rapid aging of the population [1]. Primary and secondary prevention strategies rely on the identification of risk factors associated with cognitive decline [2], with many studies focusing on modifiable vascular risk factors including elevated blood pressure (BP) [3,4]. Although office and out-of-office BP measurements are used to identify, treat, and control elevated BP, most studies are based on office BP to prevent cognitive decline [3,5]. Focusing on out-of-office BP measurements such as 24-h ambulatory BP monitoring might offer opportunities to better study associations with dementia-related disorders. Prevention of cognitive decline reduces the risk of developing major dementia-related

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disorders, including Alzheimer's disease and vascular dementia.

Currently, there are studies on 24-h ambulatory BP monitoring in relation to cognitive function; however, they are cross-sectional and emphasize BP level rather than variability [6,7]. Considering that BP variability is an emerging vascular risk factor for cognitive decline and dementia [8] – even more important than the BP level [9] – the study of 24-h BP data will provide a more comprehensive assessment of the relationship between BP variability and cognitive decline. For instance, ambulatory BP monitoring allows for the study of 24-h BP dysregulations, including abnormal circadian rhythms [10,11], variability among consecutive measures [12], extreme nocturnal fall [13], and nocturnal high BP. Additionally, a prospective study of 24-h BP could address whether exacerbation of 24-h BP level and dysregulation over time confers a greater risk of cognitive decline [14]. However, evidence for this hypothesis remains undocumented because there are no studies examining longitudinal data on 24-h ambulatory BP monitoring and cognitive decline [8,9]. Therefore, we used prospective 24-h ambulatory BP monitoring and cognitive data to study the association of longitudinal changes in 24-h ambulatory BP monitoring measures with cognitive function assessed during follow-up.

METHODS

Study participants

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The Maracaibo Aging Study is a prospective, population-based cohort study of individuals aged at least 55 years old, residing in Maracaibo, Santa Lucia County, Zulia, Venezuela ($n = 2439$) [15]. Baseline assessment was conducted between 1998 and 2001 whereas follow-up assessments were conducted between 2001 and 2010. The detailed methodology of the study has been described elsewhere [15]. The study was approved by the Institutional Review Boards of the Cardiovascular Institute at the University of Zulia in Maracaibo and complied with the Helsinki Declaration for investigations in human participants [16]. All the participants signed an informed consent form. For the present study, we included subjects with at least two longitudinal ambulatory BP monitoring and cognitive assessments availability; a minimum number of 16/6 daytime and nighttime BP recordings [17]; at least 48 BP recordings during 24-h to maintain the prognostic information of BP variability [18]; and a clinical dementia rating scale equal to zero at baseline. A total of 437 participants with prospective data on both 24-h ambulatory BP monitoring and cognitive function were analyzed. The 24-h ambulatory BP monitoring and cognitive evaluations were performed within days to 1 month apart, and the follow-up evaluation was conducted at least 1 year after the baseline assessment.

Twenty-four-hour ambulatory blood pressure monitoring

Validated [19] oscillometric 90207 Spacelabs monitors (Snoqualmie, Washington, USA) were programmed to obtain BP readings at 15 min intervals from 6 a.m. to 11 p.m. and at 30 min intervals from 11 a.m. to 6 a.m. Ambulatory BP monitoring data were checked and cleaned to avoid errors. The within-subject 24-h BP was time-weighted, giving weights to each individual reading proportional to the preceding time interval, to generate weighted mean, standard deviation, variability independent of the mean (VIM), and average real variability (ARV) measures.

The BP level was studied as the mean BP and night-to-day ratio [20]. To assess 24-h ambulatory BP variability, we followed standardized recommendations to evaluate short-term overall BP variability using indices of dispersion (quantified with VIM), sequence (quantified with ARV), and instability [estimated as the maximum and minus BP difference (MMD)] [21]. VIM was calculated as the standard deviation of the BP readings divided by the mean to the power x and multiplied by the population mean to the power x [22]. The power x was obtained by fitting a curve through a plot of standard deviation against mean, using the model standard deviation $= a*\text{mean}^x$, where x is derived by nonlinear regression analysis. In this study, the obtained x ranged from 0.41 to 0.92. The MMD was calculated as the maximum BP reading minus the minimum BP reading [23]. The ARV index was the average of the absolute changes between consecutive BP readings [12], as follows:

$$\text{ARV} = \frac{1}{\sum w_k} \sum_{k=1}^{n-1} w_k \times |\text{BP}_{k+1} - \text{BP}_k|$$

where k ranges from 1 to $n-1$ and w is the time interval between BP_k and BP_{k+1}, and n is the number of BP readings. Ambulatory BP monitoring measures of level and variability were calculated for SBP and DBP and per 24 h, daytime, and nighttime periods.

Cognitive function

The assessment of cognitive functioning in the Maracaibo Aging Study is described elsewhere [15,24]. To measure cognitive decline, we included a global cognition score based on the Mini-Mental State Examination (MMSE) (score range 0–30), and three memory domains obtained from the Selective Reminding Test (SRT) to evaluate memory impairment [25], which included total recall, long-term retrieval, and delayed recall. The SRT total recall measures the number of words recalled from a 12-word list during six trials (score range 0–72) and the SRT long-term retrieval quantifies words recalled in two consecutive trials without reminding (score range 0–72). The SRT-delayed recall measures words recalled 15 min after completing the test (score range 0–12).

Other measurements

Through interviews, physical examinations, and fasting blood sampling, we collected data on demographics and clinical variables including sex, height and weight, smoking status (current and previous smoker), office BP readings, diabetes mellitus, serum cholesterol, previous history of cardiovascular disease (including coronary artery disease, peripheral artery disease, and heart failure) or stroke, and use of antihypertensive and antidiabetic medications. BMI was calculated as weight in kilograms divided by height in

meters squared (mt^2). The 24-h hypertension was defined as an averaged 24-h SBP or DBP of at least 125/75 mmHg [26]. Diabetes mellitus was defined as a serum fasting glucose levels of at least 126 mg/dl or the use of antidiabetic medication.

Statistical analysis

Descriptive information is presented as mean ± standard deviation for continuous variables, and as frequency and percentage for categorical variables. The baseline characteristics were reported in the studied sample. Additionally, we also included information of the excluded participants from the Maracaibo Aging Study and compared the baseline characteristics between the studied and excluded participants by applying chi-square for categorical comparisons and Student *t* or Mann–Whitney *U*-test for comparison among continuous variables with a parametric and nonparametric distribution.

We first analyzed the association of baseline ambulatory BP measurements with decline in cognitive function. Subsequently, we constructed mixed models by including longitudinal ambulatory BP measurements. Linear mixed effects regression models were fitted with a subject-specific random intercept and a subject-specific random slope with an unstructured covariance matrix. The cognitive function score at each visit was the dependent variable whereas the covariables information measured at baseline and 24-h ambulatory BP monitoring measures were the independent variables. The follow-up time was measured in years and analyzed as a continuous variable. Multicollinearity and interaction effects between the covariates included in the models were assessed during the model building process. Covariables were selected based on their biological relevance to cognitive decline and included age, sex, years of education, alcohol intake, smoking status, BMI, dyslipidemia, previous cardiovascular diseases, diabetes mellitus, and use of antihypertensive medication. Models examining the association of MMD and ARV with cognitive decline were additionally adjusted for BP level to account for potential effects explained by BP level [27]. We conducted the following set of exploratory analysis. First, by considering office and ambulatory BP levels, and rates of antihypertensive treatment, we categorized hypertension into: normotension (defined as individuals with normal office and 24-h BP without treatment), treated and controlled (individuals with normal office and 24-h BP taking antihypertensive treatment), treated and uncontrolled (high office or 24-h BP despite taking medication) and untreated hypertension (individuals with high BP without taking medication). We compared the baseline office and ambulatory BP level among the groups using ANOVA. Second, we additionally examined the association between ambulatory BP variability assessed with the standard deviation and cognitive decline. For database management and statistical analysis, we used SAS software, version 9.4, maintenance level 5 (SAS Institute Inc., Cary, North Carolina, USA. All statistical tests were two-sided and performed with a significance (alpha) level of 0.05.

RESULTS

Baseline characteristics of the participants

Table 1 shows the baseline characteristics of the 437 participants included in this study and those who were

TABLE 1. Baseline characteristics of the participants

Baseline characteristics	Whole sample ($n = 2439$)	Studied participants ($n = 437$)	Excluded participants ($n = 2002$)	*P* value[a]
Demographic characteristics				
Age (years)	67.5 ± 9.0	65.2 ± 7.1	68.0 ± 9.3	<0.001
Women [*n* (%)]	1631 (66.9)	292 (66.8)	1339 (66.9)	0.979
Education (years)	5.7 ± 4.4	6.62 ± 3.91	5.54 ± 4.47	<0.001
Clinical variables				
BMI (kg/m^2)	27.3 ± 5.5	27.8 ± 4.8	27.2 ± 5.7	0.037
Smoking status [*n* (%)]	1186 (48.6)	219 (50.1)	967 (48.3)	0.661
Alcohol intake [*n* (%)]	713 (29.2)	98 (22.4)	615 (30.7)	0.032
24-h hypertension [*n* (%)]	705 (61.9)[b]	273 (62.5)	432 (61.5)[b]	0.753
Antihypertensive treatment [*n* (%)]	705 (28.9)	129 (29.5)	576 (28.8)	0.095
Diuretics	79 (3.3)	69 (3.5)	10 (2.5)	0.332
Calcium channel blockers	205 (8.6)	173 (8.7)	32 (8.0)	0.675
Beta-blockers	157 (6.5)	129 (6.5)	28 (7.0)	0.681
ACE inhibitors	370 (15.4)	306 (15.3)	64 (16.0)	0.717
Diabetes mellitus [*n* (%)]	472 (19.4)	73 (16.7)	399 (19.9)	0.032
Dyslipidemia [*n* (%)]	831 (34.1)	109 (24.9)	722 (36.1)	<0.001
Previous history of CVD [*n* (%)]	401 (16.4)	46 (10.5)	355 (17.7)	<0.001
Biochemistry features				
Serum glucose (mg/dl)	110.9 ± 45.7	102.8 ± 35.2	112.4 ± 47.4	<0.001
Serum total cholesterol (mg/dl)	191.5 ± 51.4	189.5 ± 53.8	192.1 ± 50.9	0.255
Serum triacylglycerides (mg/dl)	134 (99–183)	122 (101–160)	136 (99–186)	0.002
Serum creatinine (mg/dl)	0.92 ± 0.42	0.90 ± 0.28	0.92 ± 0.45	0.335

CVD, cardiovascular disease. Values are presented as mean and standard deviation (±) and frequencies with percentages (%). Smoking status including participants currently smoking or past smokers. 24-h hypertension was defined as a 24-h SBP or DBP level ≥125/75 mmHg or the use of antihypertensive treatment. A previous history of cardiovascular disease included ischemic heart disease, heart failure, and stroke.
[a]*P* value of the comparison of baseline characteristics between studied and excluded participants from the Maracaibo Aging Study.
[b]We estimated the prevalence of 24-h hypertension using 702 out of the 2002 participants who underwent ambulatory blood pressure monitoring.

excluded ($n = 2002$). In the studied sample, the mean age at baseline was 65.2 ± 7.1 years old, and 66.8% ($n = 292$) were women. Among the participants included in the analysis, 50.1% ($n = 219$) were current smokers, 22.4% ($n = 98$) reported alcohol intake, 62.5% ($n = 273$) had 24 h hypertension, 29.5% ($n = 129$) were taking antihypertensive treatment, 16.7% ($n = 73$) had diabetes mellitus, 24.9% ($n = 109$) had dyslipidemia, and 10.5% ($n = 46$) experienced previous cardiovascular diseases. Compared with the studied sample, excluded participants were older, had lower year of education and BMI, had higher rates of alcohol intake, diabetes mellitus, dyslipidemia, and previous cardiovascular diseases ($P \leq 0.037$). The proportion of women, smoking, 24-h hypertension, and use of antihypertensive treatment was similar between studied and excluded participants ($P \geq 0.095$). The proportion of individuals taking diuretics, calcium channel blockers, beta-blockers, and ACE inhibitors in the whole sample was 3.3, 8.6, 6.5, and 15.4%; respectively – there was not significance difference of the type of antihypertensive medication between studied and excluded participants ($P \geq 0.332$).

In exploratory analysis, we reported in Table S1, http://links.lww.com/HJH/C546 the distribution of office and ambulatory BP levels based on treatment and control rates. Out of the 473 participants, 48 (11%) had normotensive office and ambulatory BP level without using antihypertensive treatment. Whereas 14 (3.2%), 115 (26.3%), and 260 (59.5%) had treated and controlled hypertension, treated and uncontrolled hypertension, and untreated hypertension; respectively. The mean office and ambulatory SBP and DBP levels distributed differently among the four groups.

Description of 24-h blood pressure and cognitive function

Over a median follow-up of 4 years (interquartile range, 2–5 years), the baseline assessment and last follow-up global cognitive function were 24.4 ± 3.6 and 23.3 ± 3.7 points, respectively (Table 2). For SRT total retrieval, long-term retrieval, and delayed recall, the baseline and last follow-up scores were 38.6 ± 8.8 and 36.9 ± 9.2 points, 24.9 ± 11.2 and 23.3 ± 11.3 points, and 5.50 ± 2.18 and 5.33 ± 2.20 points; respectively. The baseline and last follow-up values for 24-h, daytime, and nighttime SBP and DBP levels and variability (VIM, MMD, and ARV) are reported in Table 2. The 24-h, daytime, and nighttime SBP increase between 0.7 ± 14.1 and 2.6 ± 15.5 mmHg whereas DBP decreases

TABLE 2. Cognitive function and ambulatory blood pressure monitoring measures at baseline and last follow-up

Variables	Baseline assessment ($n = 437$)	Last follow-up[a] ($n = 437$)	Δ-change from baseline to last follow-up
Cognitive function			
Global cognitive function	24.4 ± 3.6	24.3 ± 3.7	−0.2 ± 2.8
SRT total retrieval	38.6 ± 8.8	36.9 ± 9.2	−1.6 ± 8.2
SRT long-term retrieval	24.9 ± 11.2	23.3 ± 11.3	−0.2 ± 2.1
SRT-delayed recall	5.50 ± 2.18	5.33 ± 2.20	−1.4 ± 11.3
Ambulatory BP monitoring measures (mmHg)			
Mean BP level			
24-h SBP	128.0 ± 15.9	129.2 ± 16.3	1.1 ± 13.9
Daytime SBP	129.1 ± 15.9	130.3 ± 16.3	0.7 ± 14.1
Nighttime SBP	121.4 ± 17.6	124.4 ± 18.7	2.6 ± 15.5
24-h DBP	74.8 ± 9.8	73.0 ± 9.2	−1.8 ± 8.3
Daytime DBP	76.3 ± 9.9	74.3 ± 9.2	−2.1 ± 8.5
Nighttime DBP	68.9 ± 10.7	68.2 ± 10.3	−0.6 ± 9.2
Indices of dispersion			
Variability independent of the mean			
24-h SBP	13.9 ± 3.3	13.6 ± 3.3	−0.3 ± 4.0
Daytime SBP	13.8 ± 3.7	13.5 ± 3.6	−0.3 ± 4.3
Nighttime SBP	9.8 ± 3.2	10.3 ± 3.7	0.5 ± 4.4
24-h DBP	10.5 ± 2.2	10.2 ± 2.1	−0.3 ± 2.5
Daytime DBP	10.3 ± 2.5	9.9 ± 2.3	−0.3 ± 2.8
Nighttime DBP	7.8 ± 2.7	8.1 ± 2.9	0.3 ± 3.7
Indices of sequence			
Average real variability			
24-h SBP	9.1 ± 2.0	9.5 ± 2.1	0.4 ± 2.1
Daytime SBP	7.4 ± 1.9	7.7 ± 1.9	0.3 ± 2.10
Nighttime SBP	2.1 ± 1.0	2.1 ± 0.8	0.1 ± 1.2
24-h DBP	7.6 ± 1.6	7.5 ± 1.7	−0.03 ± 1.9
Daytime DBP	6.1 ± 1.5	6.1 ± 1.6	0.02 ± 1.9
Nighttime DBP	1.7 ± 0.9	1.6 ± 0.7	−0.1 ± 1.0
Indices of instability			
Maximum – minimum BP difference			
24-h SBP	66.2 ± 17.9	67.8 ± 19.6	1.5 ± 20.9
Daytime SBP	63.2 ± 18.3	64.6 ± 19.4	1.4 ± 20.8
Nighttime SBP	32.2 ± 11.7	34.8 ± 13.9	2.7 ± 15.9
24-h DBP	48.2 ± 11.2	47.7 ± 11.9	−0.5 ± 14.2
Daytime DBP	45.3 ± 11.4	45.1 ± 12.1	−0.3 ± 14.7
Nighttime DBP	26.3 ± 9.4	26.9 ± 10.3	0.8 ± 13.2

Values are presented as mean and standard deviation (±) and frequency (%).ABPM, ambulatory blood pressure monitoring; BP, blood pressure.
[a]The median follow-up time was 4 years (interquartile range, 2–5 years).

between -2.1 ± 8.5 and -0.6 ± 9.2 mmHg. Overall, the changes in indices of ambulatory BP variability ranged from −0.3 and 2.7 mmHg.

Ambulatory blood pressure level and decline in cognitive function

Linear mixed models controlled for the effect of the covariables showed that longitudinal changes in SBP or DBP levels during 24 h, daytime, or night-time periods were not associated with a decline in any measure of cognitive function ($P \geq 0.133$, Table 3). We also observed that the night-to-day ratio was not related to cognitive function measures ($P \geq 0.090$, Table 3). In exploratory analysis (Table S2, http://links.lww.com/HJH/C546), we did not observe an association between baseline ambulatory BP level and decline in cognitive function.

Baseline ambulatory blood pressure variability and decline in cognitive function

Table 4 shows the estimates of the association between baseline ambulatory BP variability indices and a decline in cognitive function. Each 1-SD increase in 24 h and daytime VIM of DBP at baseline was associated with a decline in SRTs, with estimates ranging from −0.14 [95% confidence interval (CI), −0.22 to −0.06] to −0.12 (95% CI, −0.20 to −0.03). An increase in VIM of daytime SBP was associated with lower cognitive function in SRT total recall (adjusted change, −0.08; 95% CI, −0.16 to −0.01) and SRT long-term retrieval (adjusted change, −0.08; 95% CI, −0.17 to −0.01). A higher ARV of daytime DBP was associated with a decline in SRT total recall (adjusted change, −0.09; 95% CI, −0.17 to −0.01) and in SRT long-term retrieval (adjusted change, −0.10; 95% CI, −0.18 to −0.02). A higher ARV of nighttime SBP was associated with a decline in global cognitive function (adjusted change, −0.07; 95% CI, −0.15 to −0.01). For indices of instability, MMD of the 24-h and daytime SBP and DBP were associated with SRTs; estimates of adjusted changes ranged from −0.14 (95% CI, −0.22 to −0.06) to −0.09 (95% CI, −0.17 to −0.01). An increase in nighttime MMD of DBP was associated with a decline in SRT-delayed recall (adjusted change, −0.10; 95% CI, −0.18 to −0.02).

Longitudinal changes in ambulatory blood pressure variability and decline in cognitive function

For indices of dispersion, in adjusted linear mixed models, longitudinal changes in the VIM of the 24-h, daytime, and night-time periods were associated with a decline in cognitive function ($P \leq 0.041$, Table 5). For instance, each unit (+3.44 mmHg) increase in nighttime VIM of SBP during follow-up was associated with a −0.05 (95% CI, −0.11 to <0.01; $P = 0.041$) decline in SRT total recall and −0.05 (95% CI, −0.09 to <0.01; $P = 0.035$) in global cognitive function scores. Longitudinal changes in VIM of SBP were associated with decline in SRT-delayed recall with estimates ranging from −0.09 lower SRT-delayed recall score (95% CI, −0.15 to −0.03; $P = 0.005$) per +3.30 mmHg higher 24-h VIM SBP and −0.08 lower SRT-delayed recall score (95% CI, −0.14 to −0.02; $P = 0.008$) per +3.59 mmHg higher daytime VIM SBP. A higher VIM of 24-h (adjusted change, −0.10, 95% CI, −0.16 to −0.04; $P = 0.002$) and daytime (adjusted change, −0.09; 95% CI, −0.16 to −0.03; $P = 0.003$) DBP was associated with a decline in SRT-delayed recall score.

For indices of overall BP variability sequence, longitudinal changes in 24-h, daytime, and nighttime ARV of SBP and DBP were not associated with lower cognitive scores during follow-up ($P \geq 0.065$, Table 5). A higher longitudinal change in nighttime systolic and diastolic ARV was associated with a lower global cognitive function score. The estimates were −0.08 (95% CI, −0.14 to −0.03; $P = 0.004$) and −0.06 (95% CI, −0.011 to <−0.01; $P = 0.044$) lower global cognitive function score per +0.94 and +0.76 mmHg increase in nighttime SBP and DBP ARV during follow-up; respectively.

For indices of instability, each +12.7 mmHg longitudinal increase in nighttime MMD SBP was associated with a −0.06 lower score in SRT total recall (95% CI, −0.11 to <−0.01;

TABLE 3. Longitudinal changes in ambulatory blood pressure level in relation to cognitive decline

Ambulatory BP level measures	SRT total recall		SRT-delayed recall		SRT long-term retrieval		Global cognitive function	
	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value
24-h level								
SBP (+15.9 mmHg)	−0.01 (−0.07 to 0.06)	0.785	−0.03 (−0.10 to 0.03)	0.320	<0.01 (−0.06 to 0.07)	0.897	−0.01 (−0.07 to 0.05)	0.726
DBP (+9.5 mmHg)	0.03 (−0.03 to 0.10)	0.320	−0.02 (−0.09 to 0.05)	0.618	0.05 (−0.02 to 0.12)	0.176	−0.03 (−0.09 to 0.03)	0.321
Daytime level								
SBP (+15.9 mmHg)	−0.01 (−0.07 to 0.06)	0.835	−0.03 (−0.10 to 0.03)	0.299	0.01 (−0.06 to 0.08)	0.789	−0.01 (−0.07 to 0.05)	0.764
DBP (9.6 mmHg)	0.04 (−0.03 to 0.10)	0.295	−0.03 (−0.10 to 0.04)	0.466	0.05 (−0.02 to 0.12)	0.133	−0.03 (−0.09 to 0.03)	0.326
Night-time level								
SBP (+17.7 mmHg)	−0.02 (−0.08 to 0.05)	0.587	−0.02 (−0.09 to 0.04)	0.460	−0.01 (−0.08 to 0.05)	0.657	−0.01 (−0.07 to 0.05)	0.749
DBP (+10.5 mmHg)	0.02 (−0.05 to 0.09)	0.607	0.02 (−0.05 to 0.09)	0.619	0.02 (−0.05 to 0.09)	0.538	−0.02 (−0.08 to 0.04)	0.505
Night-to-day ratio								
SBP (+6.86%)	<0.01 (−0.06 to 0.06)	0.998	<0.01 (−0.06 to 0.06)	0.998	0.04 (−0.02 to 0.10)	0.207	<0.01 (−0.05 to 0.06)	0.885
Diastolic BP (+8.02%)	0.02 (−0.04 to 0.08)	0.528	−0.06 (−0.12 to 0.01)	0.090	0.03 (−0.04 to 0.09)	0.428	−0.01 (−0.06 to 0.050)	0.802

Negative estimates indicate that each standard deviation increment (specified within parentheses) in the BP level is associated with a decline in cognitive function, whereas positive estimates indicate that exposure variables associate with better cognitive function. The association between baseline ambulatory BP level with cognitive decline is reported in Table S3, http://links.lww.com/HJH/C546. Overall, ambulatory BP level at baseline was not associated with decline in cognitive function evaluated during follow-up; *P* values ranged from 0.064 to 0.997. BP, blood pressure; SE, standard error; SRT, selective reminding test.

[a]Models were adjusted for age, sex, education, alcohol intake, smoking status, BMI, dyslipidemia, previous cardiovascular disease, use of antihypertensive medication, diabetes mellitus, and time as intercept.

TABLE 4. Association of baseline indices of ambulatory blood pressure variability with cognitive decline

Indices of ambulatory BP variability	SRT total recall		SRT-delayed recall		SRT long-term retrieval		Global cognitive function	
	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value
Indices of dispersion								
24-h VIMsbp (+3.3 mmHg)	−0.08 (−0.16 to 0.01)	0.045	−0.06 (−0.15 to 0.02)	0.120	−0.07 (−0.15 to 0.01)	0.067	0.01 (−0.08 to 0.07)	0.927
24-h VIMdbp (+2.38 mmHg)	−0.13 (−0.20 to −0.05)	0.002	−0.12 (−0.20 to −0.03)	0.006	−0.13 (−0.21 to −0.05)	0.001	−0.04 (−0.11 to 0.04)	0.296
Daytime VIMsbp (+3.59 mmHg)	−0.08 (−0.16 to −0.01)	0.046	−0.07 (−0.15 to 0.02)	0.116	−0.08 (−0.17 to −0.01)	0.041	0.01 (−0.08 to 0.07)	0.938
Daytime VIMdbp (+2.38 mmHg)	−0.12 (−0.20 to −0.04)	0.003	−0.12 (−0.20 to −0.04)	0.005	−0.14 (−0.22 to −0.06)	0.001	−0.02 (−0.09 to 0.06)	0.652
Nighttime VIMsbp (+3.44 mmHg)	−0.04 (−0.12 to 0.04)	0.333	−0.02 (−0.10 to 0.07)	0.700	−0.03 (−0.11 to 0.05)	0.396	−0.03 (−0.10 to 0.05)	0.489
Nighttime VIMdbp (+2.76 mmHg)	0.06 (−0.02 to 0.14)	0.123	0.08 (−0.01 to 0.16)	0.070	0.05 (−0.03 to 0.13)	0.184	−0.02 (−0.09 to 0.05)	0.577
Indices of sequence								
24-h ARVsbp (+2.01 mmHg)	−0.06 (−0.15 to 0.02)	0.155	−0.05 (−0.14 to 0.04)	0.293	−0.05 (−0.14 to 0.04)	0.282	−0.04 (−0.13 to 0.04)	0.286
24-h ARVdbp (+1.65 mmHg)	−0.07 (−0.15 to 0.02)	0.112	−0.05 (−0.14 to 0.04)	0.264	−0.09 (−0.17 to −0.01)	0.039	−0.01 (−0.09 to 0.06)	0.735
Daytime ARVsbp (+1.89 mmHg)	−0.06 (−0.15 to 0.03)	0.164	−0.03 (−0.12 to 0.06)	0.474	−0.05 (−0.13 to 0.03)	0.248	−0.02 (−0.10 to 0.06)	0.576
Daytime ARVdbp (+1.50 mmHg)	−0.09 (−0.17 to −0.01)	0.039	−0.07 (−0.16 to 0.01)	0.104	−0.10 (−0.18 to −0.02)	0.017	0.01 (−0.07 to 0.08)	0.953
Nighttime ARVsbp (+0.94 mmHg)	−0.03 (−0.10 to 0.05)	0.499	−0.04 (−0.12 to 0.04)	0.371	−0.03 (−0.11 to 0.05)	0.452	−0.07 (−0.15 to −0.01)	0.042
Nighttime ARVdbp (+0.76 mmHg)	−0.01 (−0.08 to 0.07)	0.875	0.01 (−0.07 to 0.09)	0.746	−0.02 (−0.01 to 0.06)	0.626	−0.05 (−0.12 to 0.02)	0.162
Indices of instability								
24-h MMDsbp (+18.4 mmHg)	−0.09 (−0.17 to −0.01)	0.041	−0.08 (−0.16 to 0.01)	0.090	−0.08 (−0.16 to 0.01)	0.070	−0.02 (−0.10 to 0.06)	0.579
24-h MMDdbp (+11.5 mmHg)	−0.11 (−0.19 to −0.02)	0.011	−0.09 (−0.18 to −0.01)	0.035	−0.12 (−0.20 to −0.04)	0.004	−0.07 (−0.14 to 0.01)	0.083
Daytime MMDsbp (+18.6 mmHg)	−0.09 (−0.18 to −0.01)	0.035	−0.08 (−0.17 to 0.01)	0.086	−0.09 (−0.18 to −0.01)	0.033	−0.01 (−0.09 to 0.07)	0.831
Daytime MMDdbp (+11.7 mmHg)	−0.11 (−0.19 to −0.03)	0.009	−0.11 (−0.20 to −0.03)	0.009	−0.14 (−0.22 to −0.06)	0.001	−0.04 (−0.11 to 0.04)	0.317
Nighttime MMDsbp (+12.7 mmHg)	−0.02 (−0.10 to 0.07)	0.709	0.01 (−0.08 to 0.09)	0.903	0.01 (−0.09 to 0.08)	0.965	−0.03 (−0.11 to 0.04)	0.408
Nighttime MMDdbp (+9.8 mmHg)	0.07 (−0.01 to 0.15)	0.079	−0.10 (−0.18 to −0.02)	0.021	0.07 (−0.01 to 0.16)	0.067	−0.02 (−0.09 to 0.06)	0.638

Negative estimates indicate that each standard deviation increment (specified within parentheses) in the indices of variability is associated with decline in a cognitive function, whereas positive estimates indicate that exposure variables associate with better cognitive function. ARV, average real variability; BP, blood pressure; CI, confidence interval; dbp, DBP; MMD, maximum and minimum difference; sbp, SBP; SRT, selective reminding test; VIM, variability independent of the mean.
[a]Models were adjusted for age, sex, education, alcohol intake, smoking status, BMI, dyslipidemia, previous cardiovascular disease, use of antihypertensive medication, diabetes mellitus, and time as intercept.

$P = 0.035$). A higher (+18.4 mmHg for 24 h and +18.6 mmHg for daytime) MMD of SBP was associated with lower score in SRT-delayed recall, with estimates of −0.09 lower score for 24-h (95% CI, −0.15 to −0.03; $P = 0.003$) and −0.08 lower score for daytime (95% CI, −0.15 to −0.02; $P = 0.009$). A decline in the SRT-delayed recall test was also associated with a higher longitudinal change in the MMD of the 24-h and daytime DBP ($P \leq 0.017$). Exploratory analysis for standard deviation (Table S3, http://links.lww.com/HJH/C546) showed that an increase in the standard deviation of 24-h, daytime, or nighttime SBP and DBP were also related to a decline in

TABLE 5. Longitudinal changes in indices of ambulatory blood pressure variability in relation to cognitive decline

Indices of ambulatory BP variability	SRT total recall		SRT-delayed recall		SRT long-term retrieval		Global cognitive function	
	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value
Indices of dispersion								
24-h VIMsbp (+3.3 mmHg)	−0.02 (−0.08, 0.03)	0.398	−0.09 (−0.15 to −0.03)	0.005	−0.03 (−0.10 to 0.03)	0.278	−0.05 (−0.10 to <0.01)	0.058
24-h VIMdbp (+2.38 mmHg)	−0.03 (−0.09 to 0.03)	0.261	−0.10 (−0.16 to −0.04)	0.002	−0.03 (−0.09 to 0.03)	0.325	−0.04 (−0.09 to 0.01)	0.106
Daytime VIMsbp (+3.59 mmHg)	−0.01 (−0.07 to 0.05)	0.665	−0.08 (−0.14 to −0.02)	0.008	−0.02 (−0.09 to 0.04)	0.479	−0.04 (−0.09 to 0.01)	0.118
Daytime VIMdbp (+2.38 mmHg)	−0.04 (−0.10 to 0.02)	0.175	−0.09 (−0.16 to −0.03)	0.003	−0.04 (−0.11 to 0.02)	0.166	−0.03 (−0.09 to 0.02)	0.196
Nighttime VIMsbp (+3.44 mmHg)	−0.05 (−0.11 to <0.01)	0.041	−0.05 (−0.10 to <0.01)	0.054	−0.04 (−0.10 to 0.01)	0.109	−0.05 (−0.09 to <−0.01)	0.035
Nighttime VIMdbp (+2.76 mmHg)	0.02 (−0.03 to 0.07)	0.444	−0.01 (−0.06 to 0.05)	0.796	0.03 (−0.02 to 0.09)	0.252	−0.03 (−0.08 to 0.01)	0.159
Indices of sequence								
24-h ARVsbp (+2.01 mmHg)	<0.01 (−0.07 to 0.06)	0.956	−0.04 (−0.11 to 0.02)	0.213	0.03 (−0.04 to 0.09)	0.419	−0.04 (−0.10 to 0.02)	0.150
24-h ARVdbp (+1.65 mmHg)	0.01 (−0.05 to 0.07)	0.841	−0.02 (−0.08 to 0.04)	0.558	0.01 (−0.06 to 0.07)	0.851	−0.02 (−0.07 to 0.03)	0.417
Daytime ARVsbp (+1.89 mmHg)	0.03 (−0.04 to 0.09)	0.390	−0.02 (−0.09 to 0.04)	0.454	0.03 (−0.03 to 0.10)	0.316	−0.02 (−0.08 to 0.03)	0.417
Daytime ARVdbp (+1.50 mmHg)	0.01 (−0.05 to 0.07)	0.742	−0.01 (−0.06 to 0.05)	0.841	<0.01 (−0.06 to 0.06)	0.896	−0.01 (−0.06 to 0.04)	0.825
Nighttime ARVsbp (+0.94 mmHg)	−0.06 (−0.12 to <0.01)	0.065	−0.02 (−0.09 to 0.04)	0.441	−0.01 (−0.08 to 0.05)	0.723	−0.08 (−0.14 to −0.03)	0.004
Nighttime ARVdbp (+0.76 mmHg)	−0.02 (−0.08 to 0.05)	0.600	−0.02 (−0.09 to 0.04)	0.442	0.00 (−0.06 to 0.07)	0.905	−0.06 (−0.11 to <0.01)	0.044
Indices of instability								
24-h MMDsbp (+18.4 mmHg)	−0.05 (−0.11 to 0.01)	0.116	−0.09 (−0.15 to −0.03)	0.003	−0.05 (−0.11 to 0.02)	0.144	−0.04 (−0.09 to 0.01)	0.110
24-h MMDdbp (+11.5 mmHg)	−0.02 (−0.08 to 0.03)	0.423	−0.07 (−0.13 to −0.01)	0.017	−0.03 (−0.09 to 0.03)	0.350	−0.04 (−0.09 to 0.01)	0.130
Daytime MMDsbp (+18.6 mmHg)	−0.02 (−0.08 to 0.04)	0.514	−0.08 (−0.15 to −0.02)	0.009	−0.03 (−0.10 to 0.03)	0.321	−0.03 (−0.08 to 0.02)	0.282
Daytime MMDdbp (+11.7 mmHg)	−0.02 (−0.07 to 0.04)	0.541	−0.07 (−0.13 to −0.02)	0.013	−0.03 (−0.09 to 0.02)	0.240	−0.03 (−0.08 to 0.02)	0.197
Nighttime MMDsbp (+12.7 mmHg)	−0.06 (−0.11 to <0.01)	0.035	−0.05 (−0.11 to <0.01)	0.054	−0.04 (−0.10 to 0.02)	0.182	−0.05 (−0.09 to <0.01)	0.058
Nighttime MMDdbp (+9.8 mmHg)	0.01 (−0.04 to 0.06)	0.711	0.00 (−0.05 to 0.06)	0.949	0.02 (−0.03 to 0.08)	0.432	−0.02 (−0.07 to 0.02)	0.340

Negative estimates indicate that each standard deviation increment (specified within parentheses) in the indices of variability is associated with decline in a cognitive function, whereas positive estimates indicate that exposure variables associate with better cognitive function. ARV, average real variability; BP, blood pressure; CI, confidence interval; dbp, DBP; MMD, maximum and minimum difference; sbp, SBP; SRT, selective reminding test; VIM, variability independent of the mean.
[a]Models were adjusted for age, sex, education, alcohol intake, smoking status, body mass index, dyslipidemia, previous cardiovascular disease, use of antihypertensive medication, diabetes mellitus and time as intercept.

cognitive functions; with estimates ranging from −0.10 (95% CI, −0.16 to −0.03) to −0.05 (95% CI, −0.10 to −0.01).

DISCUSSION

In this prospective population-based study, we reported that baseline and longitudinal changes in ambulatory BP level were not associated with cognitive decline. Instead, a higher baseline ambulatory BP variability was associated with cognitive decline. We also observed similar associations when analyzing both ambulatory and cognitive longitudinal data. A longitudinal increase in 24-h, daytime, and nighttime SBP and DBP variability was related to a decline in cognitive function. Specifically, we observed that the decline in memory domains was more related to indices of overall variability (VIM) and extreme values (MMD), whereas variability among consecutive BP measures (ARV) was only related to global cognitive function.

We found that an increase in ambulatory BP level at baseline or during follow-up was not associated with cognitive decline. Although these findings have been previously reported [28,29], they are conflicting as numerous studies have reported the relevance of controlling BP levels to prevent cognitive decline and dementia [30,31]. Moreover, a recent meta-analysis including 20 studies with a total sample of nearly eight million individuals reported that the contribution of BP variability to cognitive decline and dementia exceeds that of BP level [9]. Other studies, including the SPRINT MIND study, have reported that BP variability is associated with the development of mild cognitive impairment and probable dementia regardless of well controlled BP level, and decline in cerebral perfusion [28,32,33]. To note, those previous studies analyzed visit-to-visit BP variability [9,28,32,33], and information on 24-h BP variability is limited. Nevertheless, these studies support the need to test similar hypotheses using 24-h ambulatory BP monitoring data. Until further evidence on 24-h BP variability in relation to structural and functional brain MRI markers, the role of controlling BP levels to prevent cognitive decline and major related complications, including dementia should not be dismissed. Future studies should evaluate operative markers of excessive 24-h BP variability that could be utilized in clinical practice to prevent or delay cognitive decline.

The study of BP variability and cognitive decline has been of particular interest over the past few decades. BP variability provides additional clinical and pathophysiological information that can be utilized to prevent cognitive decline [8]. From a clinical perspective, high BP variability suggests uncontrolled BP, especially when metrics of visit-to-visit variability are applied [22]. This has been the case for other vascular risk factors including elevated visit-to-visit cholesterol variability, which has been associated with increased cardiovascular risk [34,35]. Most studies on cognition have examined BP variability using relatively crude metrics such as visit-to-visit variability. To the best of our knowledge, information on longitudinal changes in 24-h BP variability – also described as short-term variability – in relation to cognitive decline has not been documented. Therefore, we report novel findings that longitudinal changes in 24-h ambulatory BP variability are associated with cognitive decline.

The physiopathology of BP variability in relation to cognitive decline or dementia seems to be linked with microvascular brain damage and impaired brain perfusion pressure [8,33,36]. The first potential mechanism comes from the association between high BP variability – augmented by arteriosclerosis – and brain microvasculature damage including brain atrophy and cerebral small vessel disease; accumulation of these lesions contributes to cognitive decline and dementia [37]. The second potential mechanism relates to cerebral hypoperfusion [8,33]. Normal functioning of the brain circulation ensures maintenance of blood supply to the brain tissue across a range of physiological BP levels [38]. Cerebral autoregulation is impaired in neurodegenerative disorders [8], facilitating the ischemic impact of excessive BP variability on the brain tissue. The neurological and clinical consequences of orthostatic hypotension support this mechanism [39]. Hence, chronic exposure to abnormal BP circadian rhythms can lead to hypotensive-related damage in the brain tissue and microcirculation, increasing the risk of dementia. Although conclusive mechanisms are needed, accruing evidence supports a link between 24-h BP dysregulation and neurodegenerative disorders of a presumed vascular origin.

We observed that variability seemed to affect memory domains more than global cognitive function. Individuals with dementia-related disorders experience an overall decline in cognition; however, memory is the most prominent domain affected in Alzheimer's disease-related disorders [40]. Although concrete evidence is still needed, we hypothesize that an exacerbation of 24-h BP dysregulations over time can potentially be linked to impaired autoregulation of BP. Evidence supports that individuals with Alzheimer's disease have impaired autoregulation [8,14], which might affect the ability to maintain a stable cerebral perfusion pressure during the course of the day. The impact of BP variability on cognition seems compelling but further studies are needed to test whether 24-h BP variability is associated with dementia prevalence and incidence. Additionally, it is necessary to investigate the role of 24-h ambulatory BP monitoring measurements with blood biomarkers of Alzheimer's disease-related disorders to elucidate the underlying mechanisms.

Limitations and strengths

The present study should be interpreted within the context of its limitations. First, markers of cerebral small vessel disease to assess their potential role as mediators in the relationships between BP variability and cognitive decline were not available. This might be especially important considering the rates of hypertension were high in our studied participants, with poor rates of controlled and treated BP. Second, the number of participants with longitudinal data on 24-h ambulatory BP monitoring and cognition with ApoE profile was not sufficient to test whether ApoE-ε4 influences the association of longitudinal changes in ambulatory BP indices and cognitive decline. Third, the short, median follow-up time might not allow significant longitudinal changes in both 24-h ambulatory BP measurements and cognitive function. Fourth, we studied a small

subsample of the Maracaibo Aging Study (∼20%) who followed our inclusion criteria. To consider, the excluded sample were older and seemed to have a higher cardiovascular risk due to the higher rates of BMI, diabetes mellitus, dyslipidemia, and previous cardiovascular diseases compared with the studied subsample. Nevertheless, the study had several strengths: the use of 24-h ambulatory BP monitoring data to study short-term variability and abnormal BP circadian rhythms; the availability of repeated 24-h ambulatory BP monitoring assessment in a cohort of Hispanics who are disproportionally affected by Alzheimer's disease-related disorders; and the extensive and adequate assessment of cognitive data that included different memory domains.

In conclusion, we found that an increase in 24-h ambulatory BP variability – but not in BP level – was associated with a decline in cognitive functioning in community-dwelling older adults. Our findings point towards 24-h BP dysregulation that aggravates with aging. During aging, metrics of 24-h BP variability may provide an opportunity to elucidate whether BP variability is a potentially preventable and treatable risk factor for neurological complications of presumed vascular origin, including cognitive decline, stroke, and dementia.

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Conflicts of interest

There are no conflicts of interest.

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