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The aim of the present study was to examine the relationship between orthostatic changes in blood pressure (BP) and cognition, with consideration given to cardiovascular risk factors and lifestyle variables. The cross-sectional analysis included 961 community-dwelling participants of the Maine-Syracuse Longitudinal Study, for whom BP clinic measures (five sitting, five recumbent, and five standing) were obtained. Eighteen percent of participants had orthostatic hypotension (fall in systolic BP ≥20 mm Hg or diastolic BP ≥10 mm Hg upon standing) and 6% had orthostatic hypertension (rise in systolic BP ≥20 mm Hg). Orthostatic hypotension and hypertension defined using traditional criteria were unrelated to cognition with covariate adjustment. However, an examination of systolic and diastolic BP change independently revealed that participants with systolic orthostatic hypotension had poorer global cognition, verbal memory, and scanning and tracking scores than those with normal systolic BP change. The authors conclude that systolic orthostatic hypotension is significantly associated with reduced cognitive function.

1 | INTRODUCTION

Lowered cognitive function ranging from mild, age-related decline to severe dementia is common and presents significant challenges to the aging population. Hypertension and other forms of blood pressure (BP) dysregulation are risk factors for lowered cognitive performance and these associations are clinically relevant across all ages.[1]

Recently, there has been increasing interest in the association between orthostatic BP changes and health outcomes, including cognition. Standing causes a central-to-peripheral blood volume shift, reducing central venous pressure, cardiac output, and mean arterial pressure. Return to baseline BP in healthy individuals is rapidly achieved through several control mechanisms, as has been discussed by Perlmuter and colleagues[2] and others: (1) baroreceptors in the aortic arch and carotid sinus sense reduced arterial pressure, signaling

the vasomotor center to induce vasoconstriction and raise heart rate and contractility through increased sympathetic and decreased parasympathetic tone; (2) standing activates skeletal muscle pumps that prevent blood from pooling in the lower extremities; and (3) activation of the renin-angiotensin-aldosterone system by the kidneys promotes sodium and water retention to increase blood volume. Risk for dysfunction of these mechanisms increases with age and is higher in patients with certain diseases (eg, cardiac failure and kidney disease) or who take certain medications (eg, antihypertensives and antidiabetic agents).

Orthostatic hypertension is most commonly defined as an increase in systolic BP of ≥20 mm Hg upon assuming an erect posture from a recumbent or seated position and has been associated with increased risk for cardiovascular disease and mortality.[3-5] Orthostatic hypotension occurs when BP drops significantly after assuming an erect posture, the most commonly accepted definition being a fall in systolic BP of ≥20 mm Hg or a fall in diastolic BP of ≥10 mm Hg within 3 minutes of standing.[3] Orthostatic hypotension defined using systolic and diastolic BP criteria has been associated with increased risk for stroke, heart failure, and mortality.[6-9] However, other research has shown that the prognostic significance of orthostatic hypotension in terms of risk for cardiovascular events and mortality differs based on whether individuals experience postural change in systolic or diastolic BP.[10,11]

For example, Luukinen and colleagues[10] found that risk for cardiovascular mortality was significantly increased in older individuals with diastolic orthostatic hypotension 1 minute after standing and systolic orthostatic hypotension 3 minutes after standing. Further investigation revealed that these conditions differ in prevalence and associated comorbidities, leading the investigators to suggest that they may be the result of different pathophysiologic mechanisms. A more recent study by Fagard and De Cort[11] indicates that systolic and diastolic orthostatic hypotension also independently predicts risk for cardiovascular events, with systolic orthostatic hypotension having the greatest predictive power.

Studies examining orthostatic BP changes and cognition are less consistent than studies of other health outcomes. Associations between orthostatic hypotension and cognitive decline in the elderly have been demonstrated in at least one study,[12] while others have failed to find associations.[4,13,14] These studies have all been conducted in elderly populations and focused on cognitive impairment according to performance on a global screening measure, such as the Mini-Mental State Examination. Fewer studies have examined orthostatic hypertension in relation to cognitive function, although one study found that orthostatic hypertension significantly predicted the onset of cognitive decline.[15]

We are unaware of any studies that have investigated the relationship between orthostatic BP change and cognition across multiple domains of functioning, including separate examinations of systolic and diastolic BP. Using data from participants in the MSLS (Maine-Syracuse Longitudinal Study),[15,16] the aim of the present study was to examine associations between orthostatic BP changes and cognitive function in a community-dwelling adult population,

with consideration given to cardiovascular risk factors and lifestyle variables. We hypothesized that both orthostatic hypertension and orthostatic hypotension would be associated with lower performance on a global measure of cognition and for specific cognitive domains.

2 | METHODS

2.1 | Participants

The MSLS was a community-based longitudinal study designed to measure BP, cognitive functioning, and cardiovascular risk factors in adults,[17,18] with participants living independently in the central New York area surrounding Syracuse at the time of recruitment. At wave 1 of the study, the only exclusion criteria were diagnosis of or treatment for psychiatric illness, alcoholism, and inability to comprehend English. Investigations using these data have selected exclusionary criteria as demanded by study objectives.

Participants in the present study were those who completed a comprehensive assessment of cognition (2001–2006) and had data on a broad array of cardiovascular risk factors obtained by objective measurement. From an initial sample of 1049 adults at wave 6, we excluded those missing data on BP, cognition, or other health variables (n = 45); those who had a history of acute stroke (n = 28), diagnosis of probable dementia (n = 8), or were undertaking dialysis treatment (n = 5); and those who were unable to read English (n = 1) or reported alcohol abuse (n = 1). Dementia, stroke, and dialysis cases were excluded because we were interested in examining the relationship between BP and cognitive performance in people without severe cognitive impairment. The final sample consisted of 961 participants.

Stroke, defined as a focal neurological deficit of acute onset persisting for more than 24 hours, was based on self-report and confirmed by a record review. Clinical diagnoses of dementia were determined by a team including two neuropsychologists, a social psychologist, and a geriatric physician using cognitive data, medical records, and criteria established by the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[19] Recently the diagnostic decisions were confirmed using the International Classification of Diseases, 10th Edition, guidelines.[20]

This study was conducted according to the guidelines established by the Declaration of Helsinki and all procedures were approved by the University of Maine's institutional review board. Written informed consent was obtained from all participants.

2.2 | Orthostatic BP change

The sequence and timing of BP measurement was designed to allow for assessment of orthostatic hypotension and orthostatic hypertension, as well as provide a more accurate measure of averaged systolic and diastolic BP. The BP measurements were taken in the morning after a supine rest for 15 minutes, following a brief physical

examination. Automated BP measurements (GE DINAMAP 100DPC-120XEN, GE Healthcare) were performed five times each in the sitting, recumbent, and standing positions. Within each position there were 1-minute intervals between BP measurements. More time was allowed for participants to change position, with a maximum of 3 minutes between the last recumbent and first standing BP measurement. Hospital-level instrumentation was used to standardize measurement procedures. Average systolic and diastolic BPs taken from the five sitting, recumbent, and standing measures were calculated for each position.

To determine the presence or absence of orthostatic hypotension and hypertension, the predictors used in this study, the last of five recumbent BP measures was compared with the first of five standing BP measures within 3 minutes of standing. These differences were calculated such that a negative value represents a fall in BP. Following the methods of Curreri and colleagues,[13] orthostatic hypertension was defined as a rise in systolic BP of ≥20 mm Hg and orthostatic hypotension was defined as a fall in systolic BP of ≥20 mm Hg or diastolic BP of ≥10 mm Hg. In addition to examining orthostatic hypotension using this definition, systolic orthostatic hypotension (fall in systolic BP ≥20 mm Hg) and diastolic orthostatic hypotension (fall in diastolic BP ≥10 mm Hg) were also examined independently.

2.3 | Cognitive outcomes

Following BP assessment was a one half-hour rest period and neurocognitive testing. The MSLS neuropsychological test battery is comprised of 18 individual tests designed to measure a wide range of cognitive abilities. Composite scores constructed via unit weighting have been developed based on factor analysis and used in many previous studies examining the relationship between cardiovascular risk factors and cognitive performance.[1,15,18,21,22] Table 1 summarizes the cognitive domains and the individual measures used to index them.

The four composite scores included visual spatial memory and organization, scanning and tracking, Verbal episodic memory, and working memory.[15] The Wechsler Adult Intelligence Scale (WAIS) Similarities Test,[23] a measure of abstract reasoning, was loaded on all composite scores (factors) and employed separately. A global cognition composite score was also derived by averaging the z scores for all individual tests in the battery. Each measure was examined as an outcome in the present study.

2.4 | Demographics and physical health assessment

Demographic, socioeconomic, and lifestyle characteristics were obtained from the Nutrition and Health Questionnaire.[24,25] Data obtained included smoking history, marital status, and medical history. Physical activity was measured with the Nurses' Health Study Activity Questionnaire.[26] To account for frequency, duration, and intensity of activity, total metabolic equivalent hours of physical activity per week were calculated as previously described.[27] Participants were divided into five categories: <3, 3 to 8.9, 9 to 17.9, 18 to 26.9, and ≥27 metabolic equivalent hours per week. Hypertension was defined as average

TABLE 1 Individual cognitive tests used to index the cognitive composite scores

Test composite/tests included in the composite[a]	Cognitive ability measured
Verbal episodic memory	
Logical Memory-immediate recall[b]	Immediate memory, verbal
Logical Memory-delayed recall[b]	Delayed memory, verbal
Hopkins Verbal Learning Test	Verbal learning and memory
Visual-spatial memory and organization	
Visual Reproductions-immediate recall[b]	Immediate recall, visual memory, and visual-spatial problem solving
Visual Reproductions-delayed recall[b]	Delayed recall, visual memory, and visual-spatial problem solving
Matrix Reasoning[c]	Abstract reasoning and pattern recognition
Block Design[d]	Visual-spatial perception, organization, and construction
Object Assembly[d]	Speed of visual-spatial organization
Hooper Visual Organization	Visual-spatial organization; some demands on executive function
Scanning and tracking	
Trail Making A[e]	Visual scanning and tracking; concentration and attention
Trail Making B[e]	Trails A plus demands on executive function abilities
Digit Symbol Substitution[d]	Psychomotor performance
Symbol Search[c]	Visual processing speed
Working memory	
Digit Span forward[d]	Attention and concentration
Digit Span backward[d]	Attention, concentration, and working memory
Letter-Number Sequence[c]	Information processing while holding information in memory
Controlled Oral Word Associations	Verbal fluency and executive functioning

[a]The tests employed in each composite score/domain define the abilities measured by that domain.
[b]Origin Wechsler Memory Scale-Revised.
[c]Origin Wechsler Adult Intelligence Scale III.
[d]Origin Wechsler Adult Intelligence Scale.
[e]Origin Halstead-Reitan Neuropsychological Test Battery.

sitting systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg. BP values were adjusted for treatment using the Tobin method: 10 mm Hg were added to systolic BP and 5 mm Hg to diastolic BP for those taking antihypertensive medications.[28] Education level was obtained through self-report and ranged from 4 to 20 years.

Standard assay methods were employed to obtain fasting plasma glucose (mg/dL), total cholesterol (mg/dL), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL),

triglyceride (mg/dL), and C-reactive protein (mg/L) levels following an overnight fast.[15] Body weight was measured to the nearest 0.1 kg with participants wearing light clothing and height was measured to the nearest 0.1 cm with a vertical ruler. Body mass index was calculated as weight in kilograms divided by height in meters squared. Waist circumference (in cm) was taken over light clothing using a nonextendable measuring tape at the level of the iliac crest. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL or being treated with antidiabetic medication. Glycated hemoglobin level was not obtained, but medical records containing this information were reviewed and all patients with diabetes mellitus were found to have a history of the disease based on metabolic profile. Obesity was defined as body mass index ≥30 kg/m^2 and cardiovascular disease was based on self-reported history of coronary artery disease, myocardial infarction, congestive heart failure, transient ischemic attack, or angina pectoris and confirmed using medical records.

2.5 | Statistical analyses

Participant demographics, health, and cognition variables were compared according to orthostatic BP change classification at wave 6. Chi-square was used to examine differences between groups for categorical variables and analysis of variance was used for continuous variables. Separate analyses were performed for orthostatic hypotension (absence vs presence) and orthostatic hypertension (absence vs presence).

Multiple regression was employed to relate orthostatic hypotension and orthostatic hypertension variables to each domain of cognitive function using three covariate models. Covariates included were significantly related to orthostatic BP change classification variables and one or more of the cognitive domains, or were deemed clinically and theoretically relevant based on the literature. The following models were employed to adjust for confounding in the primary analyses.

Model 1: age (years) + sex + education (years) + ethnicity;

Model 2: Model 1 + smoking (cigarettes per day) + physical activity (metabolic equivalent hours per week category) + body mass index (kg/m^2) + total homocysteine (μmol/L);

Model 3: Model 2 + diabetes mellitus + hypertension;

As the global composite score involves all of the outcome measures, we used it as a protection with respect to the number of analyses performed for different domains. Hypertension was substituted with mean sitting systolic BP in sensitivity analyses. Accounting for many variables in a statistical analysis reduces variance and can lead to overadjustment bias. To further evaluate the role of diabetes mellitus and hypertension in relation to orthostatic BP change and cognitive performance, each variable was independently added to model 1 in additional sensitivity analyses. Analyses were also performed to determine the role of antihypertensive medication use in the relationship between orthostatic BP change and cognitive performance. All statistical analyses were performed with STATA version 14.1 software (StataCorp, College Station). $P < .05$ (two-tailed) was considered statistically significant.

3 | RESULTS

3.1 | Participant characteristics

Table 2 shows the demographic, health, and cognitive characteristics of MSLS participants (N = 961) with normal postural change (76% of the sample), orthostatic hypotension (18%), and orthostatic hypertension (6%). Mean systolic and diastolic BPs across all 15 measurements for each postural change group can be found in Table S1. Compared with patients with normal orthostatic changes, those with orthostatic hypotension were older; had higher medication-adjusted mean sitting systolic and diastolic BPs; higher fasting plasma glucose, triglyceride, and homocysteine levels; lower physical activity levels; and higher prevalence of cardiovascular disease and diabetes mellitus (all $P < .05$). These participants also had significantly lower scores on all six cognitive outcome measures (all $P < .05$). Of the 169 participants with orthostatic hypotension, 96 had systolic orthostatic hypotension only, 34 had diastolic orthostatic hypotension only and 39 had both. Similar characteristics were observed when participants were grouped by systolic and diastolic orthostatic BP changes separately. Participants with orthostatic hypertension were younger and had significantly higher body mass index than those without exaggerated BP changes. Approximately 23% of participants with orthostatic hypotension, 20% with orthostatic hypertension, and 19% with normal orthostatic BP change self-reported sometimes feeling faint or blacking out when standing up suddenly. It must be noted that patients did not provide this information during collection of BP data. BP measurements were automated and the two trained examiners were blinded to any orthostatic changes.

3.2 | Primary analyses

Significant findings from primary analyses are reported in Table 3 as raw regression coefficients. As each cognitive domain score is standardized, coefficients reflect the adjusted difference between postural change groups in z score metric. Orthostatic hypotension defined as a fall in systolic BP of ≥20 mm Hg or diastolic BP of ≥10 mm Hg was not significantly associated with any measure of cognition using any covariate model. When systolic and diastolic orthostatic BP change classification variables were examined as predictors independently, participants with systolic orthostatic hypotension were found to have significantly lower scanning and tracking scores than those with normal systolic change with use of all three models (all $P < .05$). Participants with systolic orthostatic hypotension also had lower global composite scores with use of models 1 and 2, and lower verbal memory scores with adjustment for model 2 only (all $P < .05$). No significant differences in cognition were observed between participants with diastolic orthostatic hypotension and those with normal diastolic change with use of any model. Moreover, orthostatic hypertension was not significantly related to any cognitive domain with covariate adjustment.

Figures depicting relationships between change in systolic BP upon standing from lying and cognitive domain scores can be found

TABLE 2 Baseline characteristics according to orthostatic changes in blood pressure (N = 961)

Variable (wave 6)	Postural change						Comparisons	
	Normal postural changes (n = 733, 76%)		Orthostatic hypotension[a] (n = 169, 18%)		Orthostatic hypertension[b] (n = 59, 6%)		Normal postural changes vs orthostatic hypotension	Normal postural changes vs orthostatic hypertension
	Mean	SD	Mean	SD	Mean	SD	P value*	P value*
Age, y	61.0	12.7	68.3	11.5	54.9	11.0	<.001	<.001
Education, y	14.7	2.7	14.4	2.8	14.8	2.8	.203	.884
Smoking, cigarettes per d	1.2	5.1	1.7	5.8	2.0	5.6	.239	.286
Body mass index, kg/m^2	29.1	5.6	28.6	5.9	32.5	7.0	.318	<.001
Total cholesterol, mg/dL	200.5	39.5	203.3	43.4	205.1	30.3	.413	.389
Systolic blood pressure, mm Hg[c]	134.5	23.0	151.9	25.6	139.0	20.6	<.001	.146
Diastolic blood pressure, mm Hg[c]	72.6	11.0	77.1	11.7	75.1	9.1	<.001	.095
Fasting blood glucose, mg/dL	97.6	23.4	104.8	39.7	99.8	37.5	.002	.510
Triglycerides, mg/dL	139.4	107.1	159.4	141.7	135.6	74.1	.043	.790
C-reactive protein, mg/L	0.42	0.46	0.41	0.42	0.54	0.65	.824	.076
Plasma homocysteine, µmol/L	9.7	3.4	10.7	4.2	9.4	2.4	.001	.458
Cognitive function variables[d]								
Global composite	0.08	0.96	−0.35	1.04	0.27	0.98	<.001	.155
Visual spatial organization	0.07	0.97	−0.31	1.07	0.29	0.93	<.001	.094
Verbal memory	0.06	0.96	−0.28	1.06	0.21	1.01	<.001	.256
Working memory	0.05	1.00	−0.16	0.95	0.13	1.01	.014	.546
Scanning and tracking	0.09	0.96	−0.37	1.07	0.18	0.98	<.001	.463
Abstract reasoning	0.03	0.97	−0.13	1.05	0.23	1.01	.047	.142
Sex, %								
Male	40.2		40.8		52.5		.889	.065
Female	59.8		59.2		47.5			
Ethnicity, %								
Black	7.5		6.5		10.2		.654	.460
Other	92.5		93.5		89.8			
Physical activity, %								
<3 MET, h/wk	20.5		31.4		25.4		.021	.652
3–8.9 MET, h/wk	23.7		21.3		20.3			
9–17.9 MET, h/wk	18.0		13.0		11.9			
18–26.9 MET, h/wk	11.2		13.0		13.6			
>27 MET, h/wk	26.6		21.3		28.8			
CVD, %[e]	13.0		22.5		6.8		.002	.167
Hypertension, %[f]	40.5		66.3		49.2		<.001	.195
Type 2 diabetes mellitus, %[g]	11.2		16.6		13.6		.054	.581

MET, metabolic equivalent; SD, standard deviation.

*P values for continuous variables were obtained using analysis of variance and for categorical variables using chi-square.

[a]Defined as decline in systolic blood pressure (BP) ≥20 mm Hg or diastolic BP ≥10 mm Hg upon standing from lying down.

[b]Defined as an increase in systolic BP ≥20 mm Hg upon standing from lying down.

[c]Defined as the average of five sitting values, adjusted for antihypertension medication use by adding 10 mm Hg systolic and 5 mm Hg diastolic if taking medication.

[d]Mean z scores and SD.

[e]Cardiovascular disease (CVD) based on self-reported history of coronary artery disease, myocardial infarction, congestive heart failure, transient ischemic attack, or angina pectoris, confirmed by medical records.

[f]Hypertension defined as treatment-adjusted sitting systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg.

[g]Type 2 diabetes mellitus defined as fasting glucose level of ≥126 mg/dL or being treated with antidiabetic medication.

TABLE 3 Cognitive domains significantly associated with systolic orthostatic hypotension at wave 6

Cognitive outcome measure (wave 6)	Model	Raw regression coefficient	95% CI	Model R^2	P value
Global composite	Model 1	−0.160	−0.299 to −0.021	0.44	.025
	Model 2	−0.147	−0.287 to −0.006	0.45	.041
	Model 3	−0.128	−0.269 to 0.013	0.46	.075
Scanning and tracking	Model 1	−0.178	−0.317 to −0.040	0.45	.012
	Model 2	−0.159	−0.298 to −0.020	0.46	.025
	Model 3	−0.141	−0.281 to −0.001	0.47	.048
Verbal memory	Model 1	−0.152	−0.318 to 0.013	0.22	.071
	Model 2	−0.168	−0.334 to −0.002	0.23	.048
	Model 3	−0.161	−0.330 to 0.007	0.23	.060

CI, confidence interval.
Model 1: age (years) + sex + education (years) + ethnicity.
Model 2: Model 1 + smoking (cigarettes per d) + physical activity (metabolic equivalents, h/wk category) + body mass index (kg/m^2) + total homocysteine (μmol/L).
Model 3: Model 2 + diabetes mellitus + hypertension.

in the supplemental material. Investigation of variance inflation factors indicated that there was no collinearity between predictor variables in any of the analyses performed (all variance inflation factors <2).

3.3 | Sensitivity analyses

Substitution of hypertension with mean sitting systolic BP did not alter the pattern of findings observed in primary analyses. With the addition of diabetes mellitus to model 1, participants with systolic orthostatic hypotension exhibited significantly lower global composite and scanning and tracking scores than those with normal systolic orthostatic BP change (both P < .05). The same pattern of findings was observed when hypertension was added to model 1, with similar P values and raw regression coefficients reported.

Sensitivity analyses were performed to determine the role of medication classes in significant associations between systolic orthostatic hypotension and cognition. Medication classes examined were diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, α-blockers, and calcium channel blockers. While many antihypertensive drugs have been associated with a fall in BP when standing,[29] we found significant differences in the proportion of persons taking angiotensin receptor blockers and calcium channel blockers (P < .05). Thirteen percent of the study participants with systolic orthostatic hypotension and 7% with normal postural changes were taking an angiotensin receptor blocker (P < .02), and 26% of participants in the systolic orthostatic hypotension group and 13% in the normal posture change group were taking a calcium channel blocker (P < .001). However, these two medications were not related to cognitive performance when added to the basic model and the relationship between systolic orthostatic hypotension and cognitive measures reported above remained the same with adjustment for each of the medications separately and together (R^2 values >0.44, P < .05 for all [data not shown]).

4 | DISCUSSION

In this cross-sectional study, we found that systolic orthostatic hypotension but not orthostatic hypotension based on change in systolic and diastolic BP was significantly associated with poorer cognitive performance among community-dwelling adults of the MSLS. The relationship between postural change in BP, including orthostatic hypotension and hypertension, and cognitive function were examined using cognitive domain scores created from a previous factor analysis.[30] In contrast to the literature to date, we assessed multiple cognitive domains, utilized a sample with a wider age range (including participants younger than 60 years), and statistically adjusted for a number of cardiovascular and medication class variables that may modify the magnitude of relationship between orthostatic BP change and cognitive function.

With use of models 1 and 2, systolic orthostatic hypotension was significantly associated with lower global composite and scanning and tracking scores. The relationship between systolic orthostatic hypotension and global composite was attenuated with the addition of diabetes mellitus and hypertension in model 3. However, the addition of diabetes mellitus and hypertension to model 1 in separate sensitivity analyses did not attenuate the association, indicating that these variables were not solely responsible for the loss of significance. The relationship between systolic orthostatic hypotension and verbal memory was only significant with use of model 2. Differences in mean cognitive scores for the systolic orthostatic hypotensive and normal orthostatic change groups were in the same direction for each of the models employed, with lower scores observed for those with hypotension.

Robust associations between systolic orthostatic hypotension and scanning and tracking may reflect the fact that this combination of variables could be labeled as executive functioning given that its individual components (ie, Trail Making A, Trail Making B, Digit Symbol, and Symbol Search) place heavy demands on attention and executive function. It is not clear why systolic orthostatic hypotension was related to verbal memory but not to working memory. We suggest that this may be because deficits in verbal learning and memory are present in mild cognitive impairment and may presage future development of dementia, especially Alzheimer's disease in persons who convert to dementia.[31] Our suggestion is speculative and must be subject to further investigation.

While almost all classes of medications are related to orthostatic hypotension,[29] angiotensin receptor blockers and calcium channel blockers were taken disproportionately more by the participants with systolic orthostatic hypotension in this study than those with normal systolic BP change. However, adjustment for use of these classes of antihypertensive medication did not render associations between systolic orthostatic hypotension and cognition nonsignificant.

Findings in the present study support the work of others. Matsubayashi and colleagues[32] showed that elderly individuals (75 years or older) with postural hypotension (as well as those with postural hypertension) had poorer scores on neurobehavioral function tests and more advanced periventricular hyperintensities than those without exaggerated postural changes in systolic BP. Elmstahl and Widerstrom[12] showed that orthostatic hypotension and its symptoms were related to risk of mild cognitive impairment over a 6-year follow-up among patients aged 60 to 93 years. Orthostatic hypotension has significant, clinical importance. The evidence to date suggests that in persons with existing cardiovascular disease risk factors or diabetes mellitus, orthostatic hypotension may further exacerbate the risk for heart failure and total death (ACCORD BP [Action to Control Cardiovascular Risk in Diabetes Blood Pressure] trial).[6]

In contrast, the Progetto Veneto Anziani Study showed that orthostatic hypertension predicts the onset of cognitive decline but showed no relationship between orthostatic hypotension and cognitive function in the elderly.[13] However, this study used only the Mini-Mental State Examination as opposed to a range of more specific cognitive functions and all participants were older than 65 years.

4.1 | Study Limitations

Limitations of the present study must be acknowledged. The study was cross-sectional and therefore any inference regarding causality and the direction of the relationship between dysregulation in orthostatic systolic BP and cognitive performance cannot be made. Use of 24-hour ambulatory BP monitoring would have enhanced the study, albeit all BP measurements in the MSLS were performed in the office. The MSLS also lacked the capacity to perform brain imaging. We previously demonstrated that greater variability in BP is associated with poorer cognition,[33] which is in line with the current findings. Although it is clear from the literature that there are positive associations between higher BP variability and structural brain injury, including cerebral microbleeds and white matter lesions,[34,35] it remains unclear as to whether BP irregularity is a cause or consequence of brain changes. The relatively small number of persons with orthostatic hypotension and orthostatic hypertension is a study limitation. Despite this limitation, we still demonstrated that orthostatic hypotension was related to the global composite score, scanning and tracking, and verbal memory.

4.2 | Study Strengths

The proportion of individuals with orthostatic hypotension relative to total sample size was lower than that reported in other studies.[13,36,37] However, our sample included slightly younger individuals, and those who were found to have BP abnormalities during data collection at any wave of the study were referred to a physician for treatment. The fact that individuals were unaware of their normal or exaggerated postural BP when they came into the study is a strength. Previous research has found that orthostatic hypertension significantly predicts the onset of cognitive decline.[13] No associations between orthostatic hypertension and cognition were found in the present study, although this could be attributed to power limitations given the low number of participants with this condition.

Physiological mechanisms underlying the relationship between orthostatic hypotension and cognitive performance have been identified in previous research.[36-40] Cerebral blood flow is reduced by rapid and significant changes in BP, including orthostatic dysregulation. Reduced cerebral perfusion is associated with vascular brain lesions and reduced cerebral white matter density, which have been previously associated with cognitive impairment.[39,40] Alternatively, BP lowering may be an early sign of cognitive decline, and atherosclerosis may contribute to both BP reduction and cognitive impairment. Clinical conditions leading to hypotension may further accelerate underlying neurodegenerative processes. Additional research is needed to evaluate complex relationships between neurodegeneration and significant alterations in BP.

5 | CONCLUSIONS

The present investigation found cross-sectional associations between systolic orthostatic hypotension and reduced function in three cognitive domains. Associations remained significant with statistical adjustment for potential confounders, including age, education, sex, ethnicity, antihypertensive medication class, and cardiovascular risk factors that related both to orthostatic BP and cognition. Further research on postural change and health outcomes is needed.

CONFLICTS OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.