
The Maine Syracuse Study

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Abstract—The objective was to investigate the association between variability in blood pressure (BP) and cognitive function for sitting, standing, and reclining BP values and variability derived from all 15 measures. In previous studies, only sitting BP values have been examined, and only a few cognitive measures have been used. A secondary objective was to examine associations between BP variability and cognitive performance in hypertensive individuals stratified by treatment success. Cross-sectional analyses were performed on 972 participants of the Maine Syracuse Study for whom 15 serial BP clinic measures (5 sitting, 5 recumbent, and 5 standing) were obtained before testing of cognitive performance. Using all 15 measures, higher variability in systolic and diastolic BP was associated with poorer performance on multiple measures of cognitive performance, independent of demographic factors, cardiovascular risk factors, and pulse pressure. When sitting, reclining, and standing systolic BP values were compared, only variability in standing BP was related to measures of cognitive performance. However, for diastolic BP, variability in all 3 positions was related to cognitive performance. Mean BP values were weaker predictors of cognition. Furthermore, higher overall variability in both systolic and diastolic BP was associated with poorer cognitive performance in unsuccessfully treated hypertensive individuals (with BP ≥140/90 mm Hg), but these associations were not evident in those with controlled hypertension. (Hypertension. 2014;64:00-00.) ● Online Data Supplement

Key Words: blood pressure • cognition • hypertension

Measures of blood pressure (BP) in the office or clinic are typically used to assess an individual’s risk for BP-related cardiovascular events, diagnose hypertension, and subsequently guide the need for antihypertensive drugs.1 However, variability in BP measures is being increasingly recognized as a potentially important consideration in risk prediction for stroke and vascular events.2–4 Less is known about the relationship between BP variability and cognitive function. Given that BP variability has been associated with lower hippocampal volume, the presence of cerebral microbleeds and cortical infarcts,4 and white matter hyperintensities,5,6 it is important to examine relationships between BP variability and cognitive performance.

Reviews of the literature indicate that BP averaged over multiple BP assessments is associated with lower cognitive performance and dementia.3,7 More recently, studies suggest that higher BP variability may be associated with poorer cognitive function6–11 and risk of dementia.11,12 These studies have used a single screening measure to assess cognitive function, such as the Mini-Mental State Examination (MMSE),13 have based their variability indicators on only few BP measures, or have used ambulatory BP measures with measurements taken throughout the day and night.9,10,14 Despite the advantages of ambulatory BP, the practice of office-type measurements and other nonambulatory measurements in research will continue. Guidelines for treatment of hypertension emphasize multiple BP assessments, in several different positions.15 However, even if the arm of the patient is placed at the correct heart level,15 the assumption that BP in sitting and supine assessment can be considered similar is incorrect.16,17 Furthermore, correlations between office BP with ambulatory BP may vary according to office position.18

We are unaware of any studies that have investigated whether relationships between variability in BP and cognitive function differ according to the position in which BP is measured, namely sitting, reclining, and standing. Given the increasing recognition of variability in BP as a stronger predictor for vascular events than average BP, we are also interested in examining whether variability is superior to mean BP assessment in predicting cognitive performance for multiple cognitive domains of functioning.

In a recent article in Hypertension, Matsumoto et al19 followed up 486 participants from the Ohasama study, a community-based study of Japanese individuals during a median of 7.8 years using a single measure of cognitive ability, the MMSE. Day-to-day...
variability in systolic BP was significantly associated with cognitive decline at follow-up (increased risk of 51%), and this was true after adjustment for demographic factors, cardiovascular risk factors, and pulse pressure. However, these investigators did not report findings for diastolic BP, a goal of the present study. More importantly, Matusumoto et al.10 found no associations between variability in BP and MMSE scores within treated hypertensives. This may have been because the MMSE is less sensitive to cognitive performance in higher performing individuals who do not have clinical cognitive deficits or because treated hypertensives were not stratified by those who were successfully treated and those who were not. We are unaware of any study that has examined variability in BP with cognitive performance for successfully and unsuccessfully treated hypertensive individuals.

The Maine Syracuse Longitudinal Study (MSLS) provides a good data set for this study because participants underwent multiple BP measurements and cognitive assessment at each wave of the study and all hypertensive individuals (BP in excess of 140/90) were referred to their own physician for treatment as usual. Thus, we are able to compare those who were successfully and unsuccessfully treated.

We hypothesized that variability in both systolic and diastolic BP would be related to poorer performance in multiple cognitive domains using values obtained from 5 sitting, 5 recumbent, and 5 standing assessments, and an overall variability score obtained from all 15 BP measures would be inversely related to cognitive performance. We hypothesized that variability in performance would be related to cognitive function only for those for whom BP was not normalized by medication, and finally that mean systolic and diastolic BP would show weaker relationships with cognitive performance than variability in BP based on the same number of BP assessments.

Methods

Participants

Subjects were community-dwelling individuals participating in the sixth wave of the MSLS, conducted in central New York. Details of initial study recruitment have been described previously.19–22 Volunteers for studies of aging were recruited by various forms of public announcement including media. Those with diagnosed alcoholism and psychiatric disorder were not admitted to the study. Participants for the present study were those who completed a comprehensive assessment of cognition (2001–2006) and where data on a broad array of cardiovascular risk factors were obtained by objective measures (wave 6). From an initial sample of 1049 adults at wave 6, we excluded those missing data on cardiovascular health (n=34), history of acute stroke (n=28), diagnosis of probable dementia (n=8), undertaing denial treatment (n=5), unable to read English (n=1), or reporting alcohol abuse (n=1), leaving 972 participants. Dementia, stroke, and dialysis cases were excluded as we were interested in examining relationships between BP and cognitive performance in people without severe cognitive impairment.

Acute stroke was defined as a focal neurological deficit persisting for >24 hours and probable dementia was defined by cognitive measures, medical records, and a multidisciplinary dementia review using the National Institute of Neurological Diseases and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders criteria.21 The University of Maine Institutional Review Board approved this study and informed consent was obtained from all participants.

Procedure

A blood sample was obtained after fast from midnight. Standard assay methods were used to obtain total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and fasting plasma glucose. Body weight was measured to the nearest 0.1 kg with participants wearing light clothing, and height was measured with a vertical ruler to the nearest 0.1 cm. Body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m²). Smoking status (never, former, and current) was based on self-report from the Nutrition and Health Questionnaire, as was alcohol consumption. Diabetes mellitus was defined as fasting glucose level of ≥126 mg/dL or being treated with antidiabetic medication. The physical assessment was followed by a light breakfast and then the neuropsychological examination.

Predictor Variables: BP

The BP measurements were taken in the morning after a supine rest for 15 minutes, after the brief physical examination. Automated BP measures (GE DINAMAP 100DPC-120XEN, GE Healthcare) were taken 5x each in sitting, reclining, and standing positions using hospital level instrumentation so as to standardize measurement procedures. The average (mean) systolic BP and diastolic BP (mm Hg) taken from the 5 sitting, standing, and reclining measures in each position was calculated, as was the total mean systolic BP and diastolic BP from all 15 measures. Following the literature, variability in systolic and diastolic BP was calculated as the SD of the 5 measures in each position, and an overall variability score was calculated from all 15 measures. The mean and SD from the first 2 sitting BP measures taken were also calculated (both systolic and diastolic). Pulse pressure (mm Hg) was calculated as the difference in mean systolic BP and mean diastolic BP (taken from 15 measures).

Hypertension was defined as BP of ≥140/90 or taking medications for hypertension. Controlled hypertension (treated successfully) was defined as those on medication and with BP of <140/90 mm Hg, and uncontrolled hypertension (treated unsuccessfully) as those on medication and with BP of ≥140/90 mm Hg. A second criterion of uncontrolled BP (≥135/85 mm Hg) used by Matsumoto et al.10 was used in a sensitivity analysis.

Dependent Variables: Cognitive Function

Cognitive testing was conducted in the afternoon after a light mid-day lunch and a 1 hour half-hour rest period. The MSLS neuropsychological test battery comprises 18 individual tests designed to measure a wide range of cognitive abilities. Composite scores have been developed based on factor analysis and have been used in many previous studies of the relationships between cardiovascular risk factors and cognitive performance.7,19,21,22,24 The 4 composite scores are Visual Spatial Memory and Organization, Scanning and Tracking, Verbal Episodic Memory, and Working Memory.21 The Wechsler Adult Intelligence Scale Similarities Test,23 a measure of abstract reasoning, loaded on all composite scores (factors) and was thus used separately. The tests used to define each composite and the factor analytic methods used to derive these composites have been described previously.21 A Global Cognition Composite score was also derived by averaging the z scores for all individual tests in the battery. In addition, the MMSE,23 a global measure of mental status, was used.

Additional Predictor Variables

Covariates included age (continuous, years), sex, education (years), ethnicity (black/other), pulse pressure (mm Hg), diabetes mellitus (Y/N), body mass index (kg/m²), total cholesterol (mg/dL), smoking (Y/N), and alcohol consumption (Y/N). This is the covariate set used by Matsumoto et al.10 in their recent variability study. Of the risk factors, alcohol consumption and smoking were based on self-report.

Statistical Analyses

First, analyses with t test comparisons between pairs of mean values were performed to determine whether mean values and variability across the sitting, reclining, and standing BP measures differed (P<0.05). Then, according to the type of variable (continuous or categorical), independent samples t tests and χ² tests were used to compare demographic, health, and BP variables, according to hypertension status (controlled versus uncontrolled).

For the primary analyses, the mean values and variability in systolic and diastolic BP were each related to the cognitive functioning measures via multiple linear regression analyses. These analyses were performed in the whole sample (n=972), including people with normal BP and for successfully (n=289) and unsuccessfully treated (medicated) hypertensive individuals (n=195). The following
regression covariate sets were used, but findings are reported only for covariate set 2 because results were the same for both sets:

Covariate set 1—basic: age, sex, education, and ethnicity.

Covariate set 2—basic+diabetes mellitus, pulse pressure, body mass index, total cholesterol, smoking (Y/N), and alcohol consumption (Y/N). Pulse pressure was excluded from the extended model when testing associations between mean BP and cognitive function. Covariate set 2 was used in the Matsumoto et al9 study and each of these variables was related to the predictors or outcomes in the present study.

All statistical analyses were performed with PASW for Windows version 21.0 software (formerly SPSS Statistics Inc, Chicago, IL). P<0.05 was considered statistically significant.

Results

Preliminary Analyses

Preliminary analyses indicated higher variability (SD) values for standing than for sitting and reclining (paired t tests, all P values <0.001), thus underscoring the importance of examining sitting, standing, and reclining BP associations with cognitive performance separately. Mean systolic BP in sitting was significantly higher than mean systolic BP in either reclining or standing (both P<0.001). The mean and variability in systolic and diastolic BP, taken in each position, can be seen in Table S1 in the online-only Data Supplement. However, the proportion of people with orthostatic hypertension and orthostatic hypotension (4.7% and 3.2%, respectively) were small, and there was no evidence of relationships between either orthostatic hypertension or hypotension with cognitive function in preliminary analyses.

Participant Characteristics

Table 1 shows the demographic and health characteristics, and BP-related measures of the sample, according to hypertension control status. Those with controlled hypertension were younger, had higher education, and had lower variability in both systolic and diastolic BP (all P<0.05).

Systolic BP and Cognitive Function

Table 2 shows raw regression coefficients, SE, and P values summarizing the significant associations between systolic BP and cognitive performance. Higher variability in systolic BP (SD) was related significantly to poorer scores on the Global Composite.
Visual Spatial Memory and Organization, Similarities (measure of abstract reasoning), and the MMSE for all BP measures combined and for the standing BP assessment (with exception of Similarities; all \( P < 0.05 \)). Mean systolic BP was inversely associated with the Global Composite, Visual Spatial Memory and Organization, and Similarities, taken in standing only. These associations were significant with full adjustment for demographic, cardiovascular risk factors, and pulse pressure.

**Diastolic BP and Cognitive Function**

Overall variability in diastolic BP was significantly and inversely related to the Global Composite, Visual Spatial Memory and Organization, and Similarities (all \( P < 0.01 \), shown in Table 3). It was also related to assessments taken in all 3 postures for Visual Spatial Memory and Organization and for Similarities and for reclining and standing for the Global Composite score. Relations for sitting BP were in the same direction as the other postures but did not achieve conventional statistical significance (\( P = 0.08 \)). In contrast to systolic BP, overall variability in diastolic BP was unrelated to the MMSE, but variability obtained from the sitting measures was (\( P < 0.05 \)).

Mean diastolic BP taken from all 15 BP measures was inversely associated with the Global Composite, Visual Spatial Memory and Organization, Similarities, and the MMSE. Consistent findings across these measures of cognition were only seen when the average of all BP measures was used. Mean values taken from sitting, reclining, and standing BP values were seen for 3 measures; Visual Spatial Memory and Organization, Similarities, and the MMSE. There were no significant associations between mean BP or variability in BP (systolic or diastolic) with Verbal Episodic Memory or Working Memory.

**BP Variability and Cognitive Performance According to Treatment Status**

As shown in Table 4, in those with controlled hypertension, that is, on medication and treated successfully (\( n = 289 \)), there were no associations between variability in either SBP or DBP and any cognitive outcome measure (basic or extended models). The pattern of results for the basic model was the same and thus is not included in this table.

In those with uncontrolled hypertension, that is, on medication but not treated successfully (\( n = 195 \)), variability in systolic and diastolic BP was each inversely associated with scores on the Global Composite and with the Similarities test (all \( P < 0.05 \), extended model). Diastolic variability was also inversely related to Visual Spatial Memory and Organization, and systolic variability was related to the MMSE. For example, an increase in systolic variability of 10 SDs was associated with a reduction in MMSE score of 0.7 \( z \) score units.

Mean systolic BP, from all 15 measures, was unrelated to any cognitive outcome (basic or extended model), in either those with controlled or uncontrolled hypertension (data not shown). Mean diastolic BP was inversely associated with the Global Composite (\( b = -0.019; P = 0.007 \), Visual Spatial Memory and Organization (\( b = -0.023; P = 0.002 \), Similarities (\( b = -0.018; P = 0.023 \)), and the MMSE (\( b = -0.024; P = 0.011 \)), only in those with uncontrolled hypertension (extended model, pulse pressure excluded from model, data not shown).

**Sensitivity Analyses**

Sensitivity analyses were further performed using a cut score of \( < 135/85 \) for controlled BP levels (ie, successfully treated), as used by Matsumoto et al. The pattern of results seen when comparing successfully and unsuccessfully controlled hypertension groups was the same.

To determine whether results for variability would hold with adjustment for mean BP, analyses were performed replacing pulse pressure with mean systolic or mean diastolic BP in the extended model. Inverse associations between overall variability in systolic BP and scores on Similarities and the MMSE remained significant (both \( P < 0.05 \)). Higher overall variability in diastolic BP and lower scores on the

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictor</th>
<th>Position and Number of BP Measures</th>
<th>Mean SBP</th>
<th>SE</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sitting (5( \times ))</td>
<td>Reclining (5( \times ))</td>
<td>Standing (5( \times ))</td>
<td>Overall (15( \times ))</td>
</tr>
<tr>
<td>Global Composite</td>
<td>Mean SBP</td>
<td>(-0.003)</td>
<td>0.002</td>
<td>0.190</td>
<td>(-0.002)</td>
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<tr>
<td>Similarities</td>
<td>Variability SBP</td>
<td>(-0.005)</td>
<td>0.008</td>
<td>0.544</td>
<td>(-0.011)</td>
</tr>
<tr>
<td>Visual Spatial Memory and Organization</td>
<td>Mean SBP</td>
<td>(-0.002)</td>
<td>0.001</td>
<td>0.164</td>
<td>(-0.002)</td>
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<tr>
<td></td>
<td>Variability SBP</td>
<td>(-0.007)</td>
<td>0.009</td>
<td>0.420</td>
<td>(-0.015)</td>
</tr>
<tr>
<td></td>
<td>Mean SBP</td>
<td>(-0.002)</td>
<td>0.001</td>
<td>0.113</td>
<td>(-0.002)</td>
</tr>
<tr>
<td>Similarities</td>
<td>Variability SBP</td>
<td>(-0.016)</td>
<td>0.010</td>
<td>0.096</td>
<td>(-0.011)</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>Mean SBP</td>
<td>(-0.002)</td>
<td>0.001</td>
<td>0.169</td>
<td>(-0.002)</td>
</tr>
<tr>
<td></td>
<td>Variability SBP</td>
<td>(-0.019)</td>
<td>0.010</td>
<td>0.061</td>
<td>(-0.022)</td>
</tr>
</tbody>
</table>

Presented data are for the extended model; regression coefficients were adjusted for age, education, gender, ethnicity, diabetes mellitus, pulse pressure, body mass index, total cholesterol, smoking (Y/N), and alcohol (Y/N). Note the same pattern of significant results with similar regression coefficients was obtained for the basic model and thus is not shown. BP indicates blood pressure; and SBP, systolic blood pressure.

*Mean calculated from the 5 individual SBP measures taken in each position (sitting, recludent, and standing), and total mean calculated from all 15 individual SBP measures.

†Variability calculated as the SD of the 5 individual SBP measures taken in each position (sitting, recludent, and standing), and overall variability calculated as the SD of all 15 individual SBP measures.
Table 3. Raw (Unstandardized) Regression Coefficients (b) and SE summarizing Associations Between Mean DBP* (mm Hg) and Variability in DBP† (SD) and Cognitive Functioning Measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictor</th>
<th>Sitting (5×)</th>
<th>b</th>
<th>SE</th>
<th>P Value</th>
<th>Reclining (5×)</th>
<th>b</th>
<th>SE</th>
<th>P Value</th>
<th>Standing (5×)</th>
<th>b</th>
<th>SE</th>
<th>P Value</th>
<th>Overall (15×)</th>
<th>b</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Composite</td>
<td>Mean DBP</td>
<td>−0.004</td>
<td>0.002</td>
<td>0.070</td>
<td>P &lt;0.05</td>
<td>−0.004</td>
<td>0.003</td>
<td>0.110</td>
<td></td>
<td>−0.004</td>
<td>0.002</td>
<td>0.067</td>
<td></td>
<td>−0.005</td>
<td>0.002</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variability DBP</td>
<td>−0.018</td>
<td>0.010</td>
<td>0.080</td>
<td></td>
<td>−0.022</td>
<td>0.011</td>
<td>0.049</td>
<td></td>
<td>−0.029</td>
<td>0.010</td>
<td>0.004</td>
<td></td>
<td>−0.038</td>
<td>0.012</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Visual Spatial Memory and Organization</td>
<td>Mean DBP</td>
<td>−0.005</td>
<td>0.003</td>
<td>0.069</td>
<td></td>
<td>−0.006</td>
<td>0.003</td>
<td>0.038</td>
<td></td>
<td>−0.006</td>
<td>0.002</td>
<td>0.015</td>
<td></td>
<td>−0.006</td>
<td>0.003</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variability DBP</td>
<td>−0.026</td>
<td>0.011</td>
<td>0.018</td>
<td></td>
<td>−0.037</td>
<td>0.012</td>
<td>0.002</td>
<td></td>
<td>−0.030</td>
<td>0.011</td>
<td>0.007</td>
<td></td>
<td>−0.048</td>
<td>0.012</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>Mean DBP</td>
<td>−0.009</td>
<td>0.003</td>
<td>0.002</td>
<td></td>
<td>−0.008</td>
<td>0.003</td>
<td>0.006</td>
<td></td>
<td>−0.008</td>
<td>0.003</td>
<td>0.002</td>
<td></td>
<td>−0.009</td>
<td>0.003</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variability DBP</td>
<td>−0.034</td>
<td>0.012</td>
<td>0.005</td>
<td></td>
<td>−0.028</td>
<td>0.013</td>
<td>0.029</td>
<td></td>
<td>−0.037</td>
<td>0.012</td>
<td>0.002</td>
<td></td>
<td>−0.043</td>
<td>0.014</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Mini-Mental State Examination</td>
<td>Mean DBP</td>
<td>−0.006</td>
<td>0.003</td>
<td>0.021</td>
<td></td>
<td>−0.007</td>
<td>0.003</td>
<td>0.014</td>
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<td>−0.005</td>
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<tr>
<td></td>
<td>Variability DBP</td>
<td>−0.030</td>
<td>0.012</td>
<td>0.013</td>
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<td>−0.014</td>
<td>0.012</td>
<td>0.242</td>
<td></td>
<td>−0.023</td>
<td>0.014</td>
<td>0.095</td>
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</tbody>
</table>

Presented data are for the extended model; regression coefficients were adjusted for age, education, gender, ethnicity, diabetes mellitus, pulse pressure, body mass index, total cholesterol, smoking (Y/N), and alcohol (Y/N). Note the same pattern of significant results with similar regression coefficients was obtained for the basic model and thus is not shown. BP indicates blood pressure; and DBP, diastolic blood pressure.

*Mean calculated from the 5 individual DBP measures taken in each position (sitting, recumbent, and standing), and total mean calculated from all 15 individual DBP measures.
†Variability calculated as the SD of the 5 individual DBP measures taken in each position (sitting, recumbent, and standing), and overall variability calculated as the SD of all 15 individual DBP measures.

Global Composite, Visual Spatial Memory and Organization, and Similarities remained when pulse pressure was replaced with mean diastolic BP (all P<0.05). The significant findings in those with uncontrolled hypertension (Table 4) remained unchanged for both systolic and diastolic variability measures.

We repeated all of the main analyses described above using the just the first 2 assessments of sitting BP (mean values and SD of systolic and diastolic BP) following Matsumoto et al18 with respect to their office measurements. There were no significant associations between the predictors (mean and variability in BP) and cognition based on 2 BP assessments.

Discussion

We found that variability in BP is associated with poorer cognitive function. These associations are independent of demographic factors (age, education, sex, and ethnicity), major risk factors for cardiovascular disease, and pulse pressure, or alternatively mean BP. Consistent with previous findings, variability in BP yields stronger associations with cognitive performance than mean BP,9,10,12 and in the present study we find that this is true for both systolic and diastolic BP variability. A question might be raised as to whether cognitive performance predicted greater BP variability or mean BP rather than the other way round. We feel this is unlikely as BP was assessed during the morning session and cognitive function during the afternoon. Moreover, in ongoing studies of treatment-resistant hypertension in the MSLS, Torres et al28,29 found no evidence that cognition prospectively predicted variability in BP or mean BP.

In the present study, the strongest associations between variability in BP and cognitive performance were observed for diastolic BP where statistically significant associations were observed for all measures combined, and for sitting, recumbent, and standing BP assessments. However, variability in systolic BP related to MMSE scores measured in all positions. Diastolic BP has also been shown to be a stronger predictor of cognitive performance than averaged systolic pressure,28,29 and this has also been true in the Framingham Heart Study.30 A parsimonious explanation of stronger and more consistent findings for diastolic variability in the present study is that diastolic BP is generally a better predictor of cognitive functioning in samples that vary over a wide range of adult ages and are not focused on the elderly.30 Although systolic BP has been a focus of attention with respect to variability in BP and cognition,8 it is clear that pulsatile variations in diastolic BP and chronic high diastolic BP have a deleterious influence on the brain and vessel walls via white matter lesions and atherosclerotic processes and that the small cerebral arteries undergo progressive vascular atrophy in relation to high levels of diastolic BP.31,32

Our findings support results from the PROspective Study of Pravastatin (PROSPER), where higher variability in both systolic and diastolic BP during a 3-year period (measured in sitting, 3 monthly) was associated with worse cognitive performance in >5000 elderly participants (mean age, 75.3 years).4 In analyses adjusted for mean BP and cardiovascular risk factors, higher visit-to-visit variability in systolic and diastolic BP was associated with poorer performance on tests of attention, processing speed, immediate and delayed memory, as well as lower hippocampal volume and cortical infarcts.

The most robust set of relationships between variability in BP and mean BP and cognition is seen when sitting, recumbent, and standing BP values were combined into an all measurements index. It is clear that we are inducing more variability by basing 15 measures of BP in different postures for the overall measure of variability. However, if variability is a useful diagnostic tool, it would seem that using methods that promote variability is not a disadvantage, and it is well known that sitting BP has become a disadvantage, and it is well known that sitting BP is a better predictor of cognitive performance than mean BP.

Matsumoto et al18 found that variability in BP was related to cognition only in untreated individuals. We had too few hypertensive subjects who were untreated to perform a meaningful analysis for this group but clearly variability in BP is related to cognition in unsuccessfully treated hypertensive
individuals. By wave 6, nearly all participants in the MSLS with hypertension are treated with medications (80.9%). Those who were untreated were simply observed further or treated initially with lifestyle changes. However, we were able to compare uncontrolled and controlled hypertensive individuals. As hypothesized, in the MSLS, measures of variability were unrelated to any measure of cognition in the successfully treated (medicated) individuals, and this was true with 2 definitions of successful treatment, BP $\geq 140/90$ and $<135/85$, but significant associations between mean BP and variability in BP were observed in unsuccessfully treated hypertensive individuals.

In an editorial commentary on mechanisms related to variability in day-to-day BP, Palatini\textsuperscript{13} points out that elevated BP variability may be related to poor adherence to treatment. Thirty percent of the unsuccessfully medicated hypertensives met the criteria for treatment-resistant hypertension (taking $\geq 3$ classes of hypertensive medication) in comparison with 24% of the successfully treated (Fisher exact test, $P<0.08$). Ninety-one percent of the unsuccessfully treated hypertensives took their medications each day, as compared with 96% of the successfully medicated hypertensive individuals (Fisher exact test, $P<0.08$).

One may raise a question as to whether better cognitive performance predicted membership in the successfully treated group. Torres et al\textsuperscript{26,27} found that only the Verbal Memory composite score was positively associated with membership in the controlled hypertension group. However, none of the cognitive outcomes related to systolic or diastolic BP variability were predictors of membership in the controlled hypertensive group.

Clinical trials suggest that angiotensin II blocking agents and angiotensin-converting enzyme inhibitors are related to improved memory performance.\textsuperscript{34,35} We did not conduct a controlled clinical trial, did not control for dosage levels, and did not examine improvement in performance in this cross-sectional, treatment-as-usual study. However, it is of interest to note that studies of treatment-resistant hypertension\textsuperscript{26,27} performed in our wave 6 sample of participants found that the only class of medication for which cognitive performance (Global Composite and Working Memory) was above the mean and superior relative to other classes of medication was the angiotensin II receptor blocker class. This was observed only for the controlled hypertensive individuals. The proportion of people treated with this antihypertensive medication class was relatively low; 14% in the controlled hypertensives and 10% in the uncontrolled hypertensives. Regardless of why successful hypertension management was not achieved in a subset of our study participants, the notable finding is that we do not see relationships between BP variability and cognitive function in those who have been successfully controlled. A parsimonious explanation for these findings in unsuccessfully treated hypertensive individuals is that the range of BP values was higher in this group of participants (range, 131–203 mm Hg systolic and 56–107 mm Hg diastolic) than in the successfully medicated group (range, 87–140 mm Hg systolic and 46–89 mm Hg diastolic), thus allowing the variability relation to be observed.

Importantly, statistically significant associations between variability (or mean) and cognitive measures were not obtained when only 2 measures of BP were used. This is in contrast to 2 other studies, both reporting associations between greater variability (or mean) and cognitive measures were not obtained when only 2 measurements of BP are obtained, and the present study indicates that more measurements are better than a few. Where $\leq 2$ measurements have been related to cognitive performance, these measurements have been averaged over multiple years of observation.\textsuperscript{30} Indeed, Matsumoto et al.\textsuperscript{9} found weak relationships between 2 sitting office BP measurements and MMSE.\textsuperscript{9,10} It seems logical that variability (SD) is less likely to be related to sensitive and specific measures of cognitive performance when only 2 measurements of BP are obtained, and the present study indicates that more measurements are better than a few. Where $\leq 2$ measurements have been related to cognitive performance, these measurements have been averaged over multiple years of observation.\textsuperscript{30} Indeed, Matsumoto et al.\textsuperscript{9} found weak relationships between 2 sitting office BP measurements and MMSE performance and concluded their article by outlining the need for more assessments. Our finding of few associations between variability in performance and MMSE may relate to the different study populations used in our study and by Matsumoto et al.\textsuperscript{9} As pointed out by Palatini,\textsuperscript{33} a Japanese population may not be representative of non-Asian subjects and population-comparative studies are important. Although ambulatory BP

### Table 4. Raw (Unstandardized) Regression Coefficients ($b$) and SE Summarizing Associations Between Overall Variability in BP* (SD) and Cognitive Functioning Measures, Stratified by Hypertension Status†

<table>
<thead>
<tr>
<th>Cognitive Outcome</th>
<th>Predictor</th>
<th>Hypertension, Controlled;‡</th>
<th>Hypertension, Uncontrolled;‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n=289 (29.7%)</td>
<td>n=195 (20.1%)</td>
</tr>
<tr>
<td>Global Composite</td>
<td>Variability SBP</td>
<td>$-0.010$</td>
<td>$0.014$</td>
</tr>
<tr>
<td></td>
<td>Variability DBP</td>
<td>$-0.021$</td>
<td>$0.024$</td>
</tr>
<tr>
<td>Visual Spatial Memory and Organization</td>
<td>Variability SBP</td>
<td>$-0.014$</td>
<td>$0.015$</td>
</tr>
<tr>
<td>Similarities</td>
<td>Variability SBP</td>
<td>$-0.028$</td>
<td>$0.026$</td>
</tr>
<tr>
<td></td>
<td>Variability DBP</td>
<td>$-0.001$</td>
<td>$0.016$</td>
</tr>
<tr>
<td></td>
<td>Variability DBP</td>
<td>$0.033$</td>
<td>$0.027$</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>Variability SBP</td>
<td>$-0.006$</td>
<td>$0.014$</td>
</tr>
<tr>
<td></td>
<td>Variability DBP</td>
<td>$0.002$</td>
<td>$0.024$</td>
</tr>
</tbody>
</table>

*Overall variability calculated as the SD of all 15 individual BP measures.
†Hypertension defined as BP $\geq 140/90$ mm Hg or being treated with antihypertensive medication; controlled defined as BP $<140/90$ mm Hg while on medication; uncontrolled defined as BP $\geq 140/90$ mm Hg while on medication.
‡Presented data are for the extended model; regression coefficients were adjusted for age, education, sex, ethnicity, diabetes mellitus, pulse pressure, body mass index, total cholesterol, smoking (Y/N), and alcohol (Y/N). BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

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with multiple day-to-day measures are an important source of data, especially eliminating white-coat hypertension, our study and others indicate that measure-to-measure variability (on the same day) in the office, the clinic, or the research laboratory is a useful diagnostic tool with respect to cognitive performance. The pattern of results for the composite scores, especially for diastolic BP, is consistent with a type of deficit in cognitive performance that can lead to vascular dementia. Working Memory and Verbal Memory were not related to variability in BP, but measures reflecting executive function (Visual Spatial Memory and Organization) and abstract reasoning (the Similarities test) were related to variability and mean BP. This is necessarily speculative but is consistent with the emphasis on vascular brain injury as a mechanism related to cognitive deficit in relation to variability. Previous investigations indicate that both short-term and long-term variability in BP are related to white matter lesions, brain atrophy, and silent cerebral infarctions, but increased BP variability could be the result of brain injury rather than the cause of it, and high BP variability may reflect underlying atherosclerotic processes. Clearly more research is needed on the direction of the relationship between BP variability and brain injury. However, we speculate that the relationships may be bidirectional and thus efforts to reduce variability should be a clinical goal, at least until further studies have been done to clarify the direction of relationships between brain injury and BP pressure variability. Clearly, efforts to reduce BP variability should not be constrained to systolic BP.

Limitations
The study was cross-sectional and therefore any inference on the direction of the relationships between predictors and outcomes cannot be made, but it seems logical to speculate that variability in BP is related to cognitive performance and that cognitive performance does not produce variability in BP, especially when assessed after BP measurements. Brain imaging was not performed in the present study. 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; however, it remains unclear as to whether BP irregularity is a cause or consequence of brain changes. Palatini asks this question and summarizes many mechanisms that may intervene between day-to-day BP variability and vascular brain injury. This discussion applies equally well to measure-to-measure variability, which was the topic of our study.

Strengths
We have assessed relationships between average BP and variability in BP, including both systolic and diastolic measures and cognitive function using an extensive neuropsychological test battery measuring multiple cognitive domains as compared with 1 or several measures. A completely unique aspect of the study is that we investigated BP measures obtained in different postures, a useful diagnostic tool with respect to cognitive performance. The present study indicates that higher variability in both systolic and diastolic BP, obtained from multiple measures taken at a single visit on the same day, is associated with poorer cognitive performance in a sample including hypertensive and normotensive individuals, especially in people with unsuccessfully treated hypertension. This finding indicates the potential importance of controlling variability in BP as well as averaged BP values. The findings also highlight the benefits of more rather than fewer number of measurements of BP given at a single occasion in a diagnostic, treatment or research context, especially when dealing with uncontrolled BP levels. Expensive and time-consuming studies in terms of data collection and controls for hypertension-related mortality and morbidity have been limited by 1 or 2 measurements of BP. Furthermore, the relationship of variability in BP to cognition must include assessment of multiple cognitive abilities to determine which cognitive domains are more vulnerable to cognitive deficits. Our studies suggest that measures of executive function or fluid ability are related to BP variability. Trials examining whether reducing BP variability, as well as mean levels of BP, can prevent or delay cognitive decline are warranted, and it will be important to determine whether variability follows from brain injury, brain injury follows from variability, or whether relationships are bidirectional.

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Disclosures
None.

References
1. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet. 2010;375:938–948.
Novelty and Significance

What Is New?

- First study to examine and compare associations between variability in blood pressure (BP) taken in different postures (sitting, reclining, and lying), in addition to variability from all measures, and cognitive function.
- First study to specifically examine associations between BP variability and cognitive function in individuals being treated for hypertension, comparing those with controlled versus uncontrolled hypertension.
- Cognitive function was assessed using multiple measures of cognitive domains in addition to specific tests including the Mini-Mental State Examination.

What Is Relevant?

- Our study adds important data to the literature on BP variability and cognition.
- Studies evaluating the relationship between BP variability using office or clinic measures and cognition to date have used few BP measures in the sitting position and have used one or a few cognitive tests.
- Studies have not examined variability in BP in relation to cognitive performance for those with hypertension who are successfully treated and those who are not.

- Although ambulatory BP with multiple measures has many diagnostic advantages, multiple measurements in the laboratory and office yield data as to relationships between variability in BP and cognition that are diagnostically important with respect to cognitive performance.
- Where findings as to variability in BP have not been seen with measure-to-measure variations in BP, too few BP assessments were undertaken and restricted to the sitting position.

Summary

Variability in sitting, reclining, and standing diastolic BP was inversely related to measures of cognitive performance, particularly executive function/fluency ability. Mean BP values were weaker predictors of cognition. Higher overall variability in both systolic and diastolic BP was associated with poorer cognitive performance in unsuccessfully treated hypertensive individuals.
Georgina E. Crichton, Merrill F. Elias, Gregory A. Dore, Rachael V. Torres and Michael A. Robbins

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MEASUREMENT-TO-MEASUREMENT BLOOD PRESSURE VARIABILITY IS RELATED TO COGNITIVE PERFORMANCE: THE MAINE-SYRACUSE STUDY

Online Data Supplement: Table S1

Georgina E. Crichton\textsuperscript{a,b,*}, Merrill F. Elias\textsuperscript{c,d}, Gregory A. Dore\textsuperscript{e}, Rachael V. Torres\textsuperscript{e}, Michael A. Robbins\textsuperscript{c,d}

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Table S1. Mean and variability (SD) in systolic and diastolic blood pressure, taken in sitting, reclining, standing, and overall, in the whole sample (N=972)

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Sitting (x5)</th>
<th>Reclining (x5)</th>
<th>Standing (x5)</th>
<th>Overall (x15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mmHg)</td>
<td>133.0</td>
<td>128.8</td>
<td>130.6</td>
<td>130.9</td>
</tr>
<tr>
<td>Variability (SD)</td>
<td>6.7</td>
<td>5.9</td>
<td>8.6</td>
<td>9.2</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mmHg)</td>
<td>71.1</td>
<td>67.5</td>
<td>72.8</td>
<td>70.5</td>
</tr>
<tr>
<td>Variability (SD)</td>
<td>3.9</td>
<td>3.6</td>
<td>4.9</td>
<td>5.6</td>
</tr>
</tbody>
</table>