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

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## Abstract

The objective was to investigate the association between variability in blood pressure and cognitive function for sitting, standing and reclining blood pressure values, and variability derived from all 15 measures. In previous studies only sitting blood pressure values have been examined, and only a few cognitive measures have been employed. A secondary objective was to examine associations between blood pressure 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 blood pressure clinic measures (5 sitting, 5 recumbant and 5 standing) were obtained, prior to testing of cognitive performance. Using all 15 measures, higher variability in systolic and diastolic blood pressure 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 blood pressure values were compared, only variability in standing blood pressure was related to measures of cognitive performance. However, for diastolic blood pressure, variability in all three positions was related to cognitive performance. Mean blood pressure values were weaker predictors of cognition. Furthermore, higher overall variability in both systolic and diastolic blood pressure was associated with poorer cognitive performance in unsuccessfully treated hypertensive individuals (with blood pressure ≥140/90 mmHg), but these associations were not evident in those with controlled hypertension.

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None.

**Keywords**

blood pressure variability; cognitive function; hypertension

## Introduction

Measures of blood pressure (BP) in the office or clinic are typically used to assess an individuals 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.[1–3] 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 relations 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.[7,8] More recently, studies suggest that higher BP variability may be associated with poorer cognitive function[4,9–11] 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/or night.[9,10,14] Despite the advantages of ambulatory BP, the practice of office-type measurements and other non-ambulatory measurements in research will continue. Guidelines for treatment of hypertension emphasize multiple BP assessments, in a number of 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] Further, correlations between office BP with ambulatory BP may vary according to office position.[18]

We are unaware of any studies that have investigated whether or not relations 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 paper in *Hypertension*, Matsumoto et al.[9] followed 486 participants from the Ohshama study, a community-based study of Japanese individuals over 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, Matusumato et al.[9] found no associations between variabiliy 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 unscuccessfully 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 relations 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 6$^{th}$ wave of the Maine Syracuse Study (MSLS), conducted in central New York. Details of initial study recruitment have been previously described.[19–22] Volunteers for studies of aging were recruited by various forms of public announcements 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), undertaking dialysis 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 (NINCDS-ADRDA) criteria.[23] The University of Maine Institutional Review Board approved this study and informed consent was obtained from all participants.

### Procedure

A blood sample was obtained following fast from midnight. Standard assay methods were employed to obtain total cholesterol, HDL, LDL, 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 (BMI) was calculated as weight in kilograms divided by height in metres squared ($kg/m^2$). Smoking status (never, former, current) was based on self-report from the Nutrition and Health Questionnaire, as was alcohol consumption. Diabetes was defined as fasting glucose level of ≥126mg/dL, or being treated with anti-diabetic medication.The physical assessment was followed by a light breakfast and then the neuropsychological examination.

### Predictor variables: blood pressure

The BP measurements were taken in the morning after a supine rest for 15 minutes, following the brief physical examination. Automated BP measures (GE DINAMAP 100DPC-120XEN, GE Healthcare) were taken 5 times 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 (mmHg) 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 were calculated as the standard deviation (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 two sitting BP measures taken were also calculated (both systolic and diastolic). Pulse pressure (mmHg) 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 mmHg, and uncontrolled hypertension (treated unsuccessfully) as those on medication and with BP of ≥140/90 mmHg. A second criterion of uncontrolled BP (≥135/85 mmHg) employed by Matsumoto et al,[9] was used in a sensitivity analysis.

### Dependent variables: cognitive function

Cognitive testing was conducted in the afternoon following a light mid-day lunch and a one 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 relations between cardiovascular risk factors and cognitive performance.[7,19,21,22,24] The four composite scores are: Visual Spatial Memory and Organization, Scanning and Tracking, Verbal Episodic Memory, and Working Memory.[21] The WAIS Similarities Test,[25] a measure of abstract reasoning, loaded on all composite scores (factors) and was thus employed 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,[13] a global measure of mental status, was employed.

**Additional predictor variables—**Covariables included age (continuous, years), gender, education (years), ethnicity (African American/other), pulse pressure (mmHg), diabetes (Y/N), BMI (kg/m$^2$), total cholesterol (mg/dL), smoking (Y/N), and alcohol consumption (Y/N). This is the covariate set employed by Matsumoto et al.[9] 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 means were performed to determine whether means 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 Chi-square tests were used to compare demographic, health, and BP variables, according to hypertension status (controlled versus uncontrolled).

For the primary analyses, the means 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 persons 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, gender, education, ethnicity;

Covariate set 2 - Basic + diabetes, pulse pressure, BMI, 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 employed in the Matsumoto et al.[9] study and each of these variables were 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, Illinois). $P$<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 Online Table S1. However the proportion of persons with orthostatic hypertension and orthostatic hypotension (4.7% and 3.2% respectively) were small, and there was no evidence of relations between either 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 three 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. Means taken from sitting, reclining and standing BP values were seen for three 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 were the same and thus are not included in this table.

In those with uncontrolled HT, that is, on medication but not treated successfully (n=195), variability in systolic and diastolic BP were 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=−.019, *P*=.007), Visual Spatial Memory and Organization (b=−.023, *P*=.002), Similarities (b=−.018, *P*=.023), and the MMSE (b=−.024, *P*=.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.[9] 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 assocations 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 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 decribed above using the just the first two assessments of sitting BP (means and SD of systolic and diastolic BP) following Matsumoto et al.[9] with respect to their office measurements. There were no significant associations between the predictors (mean and variablity in BP) and cognition based on two 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 both for systolic and diastolic BP. 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 al. found no evidence that cognition prospectively predicted variability in BP or mean BP.[26,27]

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, reclining, 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.[3] While systolic BP has been a focus of attention with respect to variability in BP and cognition,[9] it is quite 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 over a 3-year period (measured in sitting, 3-monthly) was associated with worse cognitive performance in over 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 were 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 relations between variability in BP and mean BP and cognition are 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 ‘time saving’ compromise between reclining and standing pressures.

Matsumoto et al,[9] 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 futher 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 two definitions of successful treatment, BP <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[33] 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 3 or more classes of hypertensive medication) in comparison to 24 percent of the successfully treated (Fisher's exact test, $P<0.08$). Ninety-one percent of the unsuccessfully treated hypertensives took their medications each day, as compared to 96 percent of the successfully medicated hypertensive individuals (Fisher's exact test $P<0.08$).

One may raise a question as to whether better cogntive performance predicted membership in the successfully treated group. Torres et al.[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 contolled hypertensive group.

Clinical trials suggest that Angiotensin II blocking agents and angiotensin-converting enzyme (ACE) inhibitors are related to improved memory performance.[34,35] We did not conduct a controlled clinic trial, did not control for dosage levels, and did not examine improvment in performance in this crosss-sectional, treatment-as-usual study. However, it is of interest to note that studies of treatment-resistent hypertension[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 persons treated with this antihypertensive medication class was relatively low; 14 percent in the controlled hypertensives and 10 percent in the uncontrolled hypertensives.

Regardless of why successful hypertension management was not achieved in a subtest of our study participants, the notable finding is that we do not see relations 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 mmHg systolic and 56–107 mmHg diastolic) than in the successfully medicated group (range = 87–140 mmHg systolic and 46–89 mmHg diastolic), thus allowing the variability relation to be observed.

Importantly, statisically significant asociations between variability (or mean) and cognitive measures were *not* obtained when only two measures of BP were employed. This is in contrast to two other studies, both reporting associations between greater variability in systolic BP, obtained from two sitting measures, and poorer performance on the MMSE.[9,10] It seems logical that variability (SD) is less likely to be related to sensitive and specific measures of cognitive performance when only two measurements of BP are obtained and the present study indicates that more measurements are better than a few. Where two or fewer measurements have been related to cognitive performance these measurements have been averaged over multiple years of observation.[30] Indeed Matsumoto et al.[9] found weak relations between two sitting office BP measurements and MMSE performance and concluded their article by outlining the need for more assessments. Our finding of few associations between varibility in performance and MMSE may relate to the different study populations used in our study and by Matsumoto et al.[9] As pointed out by Palatini,[33] a Japanese population may not be representative of non-Asian subjects and population-

comparative studies are important. While ambulatory BP 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.[7,36] 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) and Scanning and Tracking (Table 4 only) 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.[33] 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,[12,37,38] 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.[33] Clearly more research is needed on the direction of the relation between BP variability and brain injury. However, we speculate that the relations 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 relations between brain injury and BP pressure variability. Very clearly, efforts to reduce BP variability should not be constrained to systolic BP.

## Limitations

The study was cross-sectional and therefore any inference regarding the direction of the relations 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 following 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 stuctural brain injury, including cerebral microbleeds and white matter lesions,[4,39] however it remains unclear as to whether BP irregularity is a cause or consequence of brain changes. Palatini[33] 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 relations 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 to one or several measures. A completely unique aspect of the study is that we investigated BP measures obtained in different postures, in addition to overall variability calculated from 15 repeated BP measurements. Finally, a novel aspect of this study was our stratified analyses according to hypertension treatment status.

### Perspectives

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, are associated with poorer cognitive performance in a sample including hypertensive and normotensive individuals, especially in persons 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. Very expensive and time consuming studies in terms of data collection and controls for hypertension-related mortality and morbidity, have been limited by one or two measurements of BP.[7] Further, the relation of variability in BP to cognition must include assessment of multiple cognitive abilities in order 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 relations are bidirectional.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet. 2010; 375:938–948. [PubMed: 20226991]
2. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010; 375:895–905. [PubMed: 20226988]
3. Floras JS. Blood pressure variability: a novel and important risk factor. Can J Cardiol. 2013; 29:557–563. [PubMed: 23618505]
4. Sabayan B, Wijsman LW, Foster-Dingley JC, Stott DJ, Ford I, Buckley BM, Sattar N, Jukema JW, van Osch MJP, van der Grond J, van Buchem MA, Westendorp RGJ, de Craen AJM, Mooijaart SP. Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study. Br Med J. 2013; 347:f4600. [PubMed: 23900315]

5. Gunstad J, Cohen RA, Tate DF, Paul RH, Poppas A, Hoth K, Macgregor KL, Jefferson AL. Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. Blood Press. 2005; 14:353–358. [PubMed: 16403689]

6. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu-Asia Aging study. Stroke. 2002; 33:26–30. [PubMed: 11779884]

7. Elias MF, Goodell AL, Dore GA. Hypertension and cognitive functioning: a perspective in historical context. Hypertension. 2012; 60:260–268. [PubMed: 22753214]

8. Gifford KA, Badaracco M, Liu D, Tripodis Y, Gentile A, Lu Z, Palmisano J, Jefferson AL. Blood Pressure and Cognition Among Older Adults: A Meta-Analysis. Arch Clin Neuropsychol. 2013; 28:649–664. [PubMed: 23838685]

9. Matsumoto A, Satoh M, Kikuya M et al. Day-to-Day Variability in Home Blood Pressure Is Associated With Cognitive Decline: The Ohasama Study. Hypertension. 2014; 63:1333–1338. [PubMed: 24688128]

10. Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. J Hypertens. 2012; 30:1556–1563. [PubMed: 22728907]

11. Sakakura K, Ishikawa J, Okuno M, Shimada K, Kario K. Exaggerated ambulatory blood pressure variability is associated with cognitive dysfunction in the very elderly and quality of life in the younger elderly. Am J Hypertens. 2007; 20:720–727. [PubMed: 17586405]

12. Alperovitch A, Blachier M, Soumare A, Ritchie K, Dartigues JF, Richard-Harston S, Tzourio C. Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. Alzheimers Dement. 2013

13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

14. Nagai M, Hoshide S, Nishikawa M, Masahisa S, Kario K. Visit-to-visit blood pressure variability in the elderly: Associations with cognitive impairment and carotid artery remodeling. Atherosclerosis. 2014; 233:19–26. [PubMed: 24529116]

15. 1993 guidelines for the management of mild hypertension. Memorandum from a World Health Organization/International Society of Hypertension meeting. Guidelines Subcommittee of the WHO/ISH Mild Hypertension Liaison Committee. Hypertension. 1993; 22:392–403. [PubMed: 8349333]

16. Netea RT, Lenders JW, Smits P, Thien T. Both body and arm position significantly influence blood pressure measurement. J Hum Hypertens. 2003; 17:459–462. [PubMed: 12821952]

17. Netea RT, Smits P, Lenders JW, Thien T. Does it matter whether blood pressure measurements are taken with subjects sitting or supine? J Hypertens. 1998; 16:263–268. [PubMed: 9557918]

18. Zachariah PK, Sheps SG, Moore AG. Office blood pressures in supine, sitting, and standing positions - correlation with ambulatory blood pressures. Int J Cardiol. 1990; 28:353–360. [PubMed: 2210901]

19. Dore GA, Elias MF, Robbins MA, Budge MM, Elias PK. Relation between central adiposity and cognitive function in the Maine-Syracuse Study: attenuation by physical activity. Ann Behav Med. 2008; 35:341–350. [PubMed: 18584267]

20. Elias MF, Robbins MA, Budge MM, Abhayaratna WP, Dore GA, Elias PK. Arterial pulse wave velocity and cognition with advancing age. Hypertension. 2009; 53:668–673. [PubMed: 19237680]

21. Elias MF, Robbins MA, Budge MM, Elias PK, Brennan SL, Johnston C, Nagy Z, Bates CJ. Homocysteine, folate, and vitamins B6 and B12 blood levels in relation to cognitive performance: the Maine-Syracuse study. Psychosom Med. 2006; 68:547–554. [PubMed: 16868263]

22. Robbins MA, Elias MF, Elias PK, Budge MM. Blood pressure and cognitive function in an African-American and a Caucasian-American sample: the Maine-Syracuse Study. Psychosom Med. 2005; 67:707–714. [PubMed: 16204428]

23. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of

Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]

24. Elias MF, Goodell AL, Waldstein SR. Obesity, cognitive functioning and dementia: back to the future. J Alzheimer's Dis. 2012; 30(Suppl 2):S113–S125. [PubMed: 22057026]
25. Lezak, MD.; Howieson, DB.; Loring, DW. Neuropsychological Assessment. 4th edn. New York, NY, USA: Oxford University Press; 2004.
26. Torres, RV.; Elias, MF.; Sullivan, KJ. Treatment resistant hypertension and cognitive performance: the Maine-Syracuse Longitudinal Study. New England Psychological Association Annual Meeting; Lewiston, Maine. 2014.
27. Torres, RV.; Elias, MF.; Sullivan, KJ.; Robbins, MA. Cardiovascular variables related to treatment resistant hypertension. 41st Annual Maine Biological and Medical Sciences Symposium; Mount Desert Island, Maine. 2014.
28. Elias MF, Dore GA, Davey A, Robbins MA, Elias PK. From blood pressure to physical disability: the role of cognition. Hypertension. 2010; 55:1360–1365. [PubMed: 20404216]
29. Elias MF, Elias PK, Dore GA, Robbins MA. High-normal blood pressure and cognition: supplying the missing data. Hypertension. 2008; 52:e1–e2. [PubMed: 18474833]
30. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: The Framingham Heart Study. Int J Obesity. 2003; 27:260–268.
31. Pase MP, Grima NA, Stough C, Scholey A, Pipingas A. Association of pulsatile and mean cerebral blood flow velocity with age and neuropsychological performance. Physiol Behav. 2014; 130:23–27. [PubMed: 24657738]
32. Tsivgoulis G, Alexandrov AV, Wadley VG, Unverzagt FW, Go RC, Moy CS, Kissela B, Howard G. Association of higher diastolic blood pressure levels with cognitive impairment. Neurology. 2009; 73:589–595. [PubMed: 19704077]
33. Palatini P. Day-by-Day Blood Pressure Variability: Cause or Consequence of Vascular Brain Injury? Hypertension. 2014; 63:1163–1165. [PubMed: 24688122]
34. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens. 2013; 31:1073–1082. [PubMed: 23552124]
35. Yamada K, Horita T, Takayama M, Takahashi S, Takaba K, Nagata Y, Suzuki N, Kanda T. Effect of a centrally active angiotensin converting enzyme inhibitor, perindopril, on cognitive performance in chronic cerebral hypo-perfusion rats. Brain Res. 2011; 1421:110–120. [PubMed: 21981801]
36. Godefroy O, group G-Vs, Leclercq C, Bugnicourt JM, Roussel M, Moroni C, Quaglino V, Beaunieux H, Taillia H, Nedelec-Ciceri C, Bonnin C, Thomas-Anterion C, Varvat J, Aboulafia-Brakha T, Assal F. Neuropsychological assessment and cerebral vascular disease: the new standards. Rev Neurol (Paris). 2013; 169:779–785. [PubMed: 23999023]
37. Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, DeCarli C, Brown TR, Mayeux R. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. Arch Neurol. 2010; 67:564–569. [PubMed: 20457955]
38. Tartaro A, Budassi S, Pascali D, Marini E, Di Iorio A, Abate G, Bonomo L. Correlation between computed tomography findings of leukoaraiosis and 24-hour blood pressure variability in elderly subjects. J Stroke Cerebrovasc Dis. 1999; 8:66–70. [PubMed: 17895142]
39. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and the brain: a 5-year follow-up. Neurology. 2005; 64:1846–1852. [PubMed: 15955932]

## Novelty and Significance

**1) What is new?**

- First study to examine and compare associations between variability in BP taken in different postures (sitting, reclining, 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.

**2) 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.
- While ambulatory BP with multiple measures has many diagnostic advantages, multiple measurements in the laborory and office yield data as to relations 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.

**3) Summary**

- Variability in sitting, reclining and standing diastolic BP was inversely related to measures of cognitive performance, particularly executive function/fluid 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.

**Table 1**

Demographic and health characteristics, and cognitive scores of whole sample (N=972), according to hypertension status

| Variable | All N=972 | | Hypertension, uncontrolled,* n=195 (20.1%) | | Hypertension, controlled,* n=289 (29.7%) | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | *P*† |
| Age (years) | 62.0 | 12.8 | 67.6 | 11.0 | 62.3 | 11.8 | <0.001 |
| Education (years) | 14.7 | 2.7 | 14.0 | 2.6 | 14.5 | 2.8 | 0.045 |
| Mean systolic BP (mmHg) | 130.9 | 21.6 | 157.2 | 13.9 | 123.1 | 11.4 | <0.001 |
| Mean diastolic BP (mmHg) | 70.5 | 10.0 | 77.5 | 9.0 | 68.5 | 8.5 | <0.001 |
| Variability systolic BP (SD)§ | 9.2 | 3.3 | 10.8 | 3.5 | 9.1 | 3.3 | <0.001 |
| Variability diastolic BP (SD)§ | 5.6 | 2.1 | 6.5 | 2.6 | 5.4 | 1.9 | <0.001 |
| Pulse pressure (mmHg) | 60.4 | 12.8 | 79.7 | 15.0 | 54.6 | 10.3 | <0.001 |
| Mean arterial pressure (mmHg) | 90.6 | 12.6 | 104.1 | 8.2 | 86.7 | 8.2 | <0.001 |
| BMI (kg/m$^2$) | 29.3 | 5.9 | 30.9 | 7.1 | 30.4 | 5.9 | 0.414 |
| Total cholesterol (mg/dL) | 201.3 | 39.6 | 196.3 | 36.4 | 191.0 | 38.2 | 0.133 |
| Physical activity (MET mins/wk) | 1232 | 1653 | 871 | 1429 | 1030 | 1525 | 0.251 |
| | % | | % | | % | | *P*‡ |
| Gender | | | | | | | 0.166 |
| Males | 41.0 | | 40.0 | | 46.4 | | |
| Females | 59.0 | | 60.0 | | 53.6 | | |
| Ethnicity | | | | | | | 0.409 |
| African American | 7.5 | | 9.7 | | 7.6 | | |
| Other | 92.5 | | 90.3 | | 92.4 | | |
| Smoking (current smoker) | 9.3 | | 9.2 | | 9.0 | | 0.930 |
| Alcohol (currently drinks alcohol) | 50.7 | | 42.1 | | 50.2 | | 0.079 |
| Cardiovascular disease‖ | 14.3 | | 28.7 | | 22.5 | | 0.121 |
| Diabetes¶ | 12.4 | | 23.6 | | 16.6 | | 0.057 |

BMI indicates body mass index; BP, blood pressure; MET, metabolic equivalent; MMSE, Mini-Mental State Examination.

[*] Hypertension defined as ≥140/90 mmHg, or being treated with anti-hypertensive medication; controlled defined as BP <140/90 mmHg while on medication; uncontrolled defined as BP ≥140/90 mmHg while on medication

[†] Analysis of variance for continuous variables.

[‡] Chi square for categorical variables.

[§] Variability calculated as the standard deviation of all individual BP measures (15).

[//] Cardiovascular disease was defined as present if there was self-reported history of coronary artery disease, myocardial infarction, congestive heart failure, transient ischemic attack, or angina pectoris.

[¶] Diabetes was defined as fasting glucose level of ≥126 mg/dL, or being treated with anti-diabetic medication.

**Table 2**

Raw (unstandardized) regression coefficients (b) and standard error (SE) summarizing associations between mean systolic BP* (mm Hg) and variability in systolic BP† (SD) and cognitive functioning measures

| Outcome | Predictor | Position and number of BP measures | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sitting (×5) | | | Reclining (×5) | | | Standing (×5) | | | Overall (×15) | | |
| | | b | SE | *P* | b | SE | *P* | b | SE | *P* | b | SE | *P* |
| Global Composite | Mean SBP | −.003 | .002 | .190 | −.002 | .002 | .285 | −.004 | .002 | .035 | −.002 | .001 | .193 |
| | Variability SBP | −.005 | .008 | .544 | −.011 | .008 | .162 | −.013 | .006 | .032 | −.018 | .008 | .026 |
| Visual Spatial Memory and Organization | Mean SBP | −.002 | .001 | .164 | −.002 | .001 | .172 | −.003 | .001 | .027 | −.002 | .001 | .081 |
| | Variability SBP | −.007 | .009 | .420 | −.015 | .009 | .093 | −.016 | .007 | .015 | −.017 | .008 | .048 |
| Similarities | Mean SBP | −.002 | .001 | .113 | −.002 | .001 | .179 | −.003 | .001 | .031 | −.002 | .001 | .089 |
| | Variability SBP | −.016 | .010 | .096 | −.011 | .009 | .267 | −.011 | .007 | .142 | −.024 | .009 | .009 |
| Mini-Mental State Examination | Mean SBP | −.002 | .001 | .169 | −.002 | .001 | .129 | −.002 | .001 | .224 | −.002 | .001 | .157 |
| | Variability SBP | −.019 | .010 | .061 | −.022 | .010 | .023 | −.016 | .007 | .026 | −.024 | .009 | .012 |

SBP indicates systolic blood pressure.

Presented data are for the extended model; regression coefficients were adjusted for age, education, gender, ethnicity, diabetes, pulse pressure, BMI, total cholesterol, smoking (Y/N), alcohol (Y/N). Note the same pattern of significant results with similar regression coefficients were obtined for the basic model, and thus are not shown.

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

†Variability calculated as the SD of the 5 individual systolic BP measures taken in each position (sitting, recumbant, standing), and overall variability calculated as the SD of all 15 individual systolic BP measures.

**Table 3**

Raw (unstandardized) regression coefficients (b) and standard error (SE) summarizing associations between mean diastolic BP* (mm Hg) and variability in diastolic BP† (SD) and cognitive functioning measures

| Outcome | Predictor | Position and number of BP measures | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sitting (×5) | | | Reclining (×5) | | | Standing (×5) | | | Overall (×15) | | |
| | | b | SE | *P* | b | SE | *P* | b | SE | *P* | b | SE | *P* |
| Global Composite | Mean DBP | −.004 | .002 | .070 | −.004 | .003 | .110 | −.004 | .002 | .067 | −.005 | .002 | .048 |
| | Variability DBP | −.018 | .010 | .080 | −.022 | .011 | .049 | −.029 | .010 | .004 | −.038 | .012 | .001 |
| Visual Spatial Memory and Organization | Mean DBP | −.005 | .003 | .069 | −.006 | .003 | .038 | −.006 | .002 | .015 | −.006 | .003 | .024 |
| | Variability DBP | −.026 | .011 | .018 | −.037 | .012 | .002 | −.030 | .011 | .007 | −.048 | .012 | <.001 |
| Similarities | Mean DBP | −.009 | .003 | .002 | −.008 | .003 | .006 | −.008 | .003 | .002 | −.009 | .003 | .001 |
| | Variability DBP | −.034 | .012 | .005 | −.028 | .013 | .029 | −.037 | .012 | .002 | −.043 | .014 | .001 |
| Mini-Mental State Examination | Mean DBP | −.006 | .003 | .021 | −.007 | .003 | .014 | −.005 | .003 | .057 | −.007 | .003 | .021 |
| | Variability DBP | −.030 | .012 | .013 | −.022 | .013 | .091 | −.014 | .012 | .242 | −.023 | .014 | .095 |

DBP indicates diastolic blood pressure.

Presented data are for the extended model; regression coefficients were adjusted for age, education, gender, ethnicity, diabetes, pulse pressure, BMI, total cholesterol, smoking (Y/N), alcohol (Y/N). Note the same pattern of significant results with similar regression coefficients were obtined for the basic model, and thus are not shown.

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

†Variability calculated as the SD of the 5 individual diastolic BP measures taken in each position (sitting, recumbant, standing), and overall variability calculated as the SD of all 15 individual diastolic BP measures.

**Table 4**

Raw (unstandardized) regression coefficients (b) and standard error (SE) summarizing associations between overall variability in BP* (SD) and cognitive functioning measures, stratified by hypertension status†

| Cognitive outcome | Predictor | Hypertension, controlled,† n=289 (29.7%) | | | Hypertension, uncontrolled,† n=195 (20.1%) | | |
|---|---|---|---|---|---|---|---|
| | | b | SE | *P* | b | SE | *P* |
| Global Composite | Variability SBP | −.010 | .014 | .490 | −.040 | .017 | .021 |
| | Variability DBP | −.021 | .024 | .386 | −.073 | .023 | .002 |
| Visual Spatial Memory and Organization | Variability SBP | −.014 | .015 | .354 | −.029 | .018 | .097 |
| | Variability DBP | −.028 | .026 | .277 | −.085 | .023 | <.001 |
| Similarities | Variability SBP | −.001 | .016 | .932 | −.045 | .019 | .020 |
| | Variability DBP | .033 | .027 | .226 | −.072 | .026 | .005 |
| Mini-Mental State Examination | Variability SBP | −.006 | .014 | .696 | −.070 | .022 | .002 |
| | Variability DBP | .002 | .024 | .935 | −.058 | .030 | .057 |

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

Presented data are for the extended model; regression coefficients were adjusted for age, education, gender, ethnicity, diabetes, pulse pressure, BMI, total cholesterol, smoking (Y/N), alcohol (Y/N).

*Overall variability calculated as the SD of all 15 individual BP measures.

†Hypertension defined as BP ≥140/90 mmHg or being treated with anti-hypertensive medication; controlled defined as BP <140/90 mmHg while on medication; uncontrolled defined as BP ≥140/90 mmHg while on medication.