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J Am Geriatr Soc. Author manuscript; available in PMC 2014 December 01.

Published in final edited form as:
J Am Geriatr Soc. 2013 December ; 61(12): 2168–2173.

Cognitive Dysfunction is Associated with Increased Visit to Visit Systolic Blood Pressure Variability

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Abstract

Objectives—Hypertension is a modifiable risk factor for cognitive decline. We tested the hypothesis that greater variability in blood pressure is negatively associated with performance on cognitive testing.

Design—Multinational, longitudinal, observational cohort study.

Setting—The Alzheimer's Disease Neuroimaging Initiative study.

Participants—A total of 626 subjects had a screening diagnosis of mild cognitive impairment or normal cognition.

Measurements—Blood pressure mean, variance, and maximum were calculated based on measures collected from screening to 36 months. Analysis of covariance models were used to determine the association between blood pressure measures and cognitive scores at 36 months after adjusting for covariates.

Results—Greater variability in systolic ($p < 0.05$) but not diastolic ($p > 0.18$) blood pressure was associated with worse global (ADAS-COG and CDR)and executive functioning (Trail Making B, Animal Fluency, and Vegetable Fluency)and episodic memory (Rey Auditory Verbal Learning Test Total Score).

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[†]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Author Contributions: Dr. Epstein conceived of the idea, developed the protocol, collected the data and wrote the manuscript. Dr. Gao, professor of biostatistics, supervised the statistical analysis and Katie Lane, who is a biostatistician with a master's degree, performed the statistical analysis. Drs. Saykin, Risacher, and Farlow provided advice on study design. All authors edited and approved the final manuscript.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Conclusion—There is a clinically significant association between increased systolic blood pressure variability and greater cognitive dysfunction. These results should be verified in other well-characterized cohorts, and the neuroanatomical pathophysiology underlying the observed greater cognitive impairment should be further explored.

Keywords

Hypertension; Stroke and Cognition

INTRODUCTION

There are currently no disease modifying treatments for Alzheimer's disease (AD) (1). Mild cognitive impairment (MCI) is the stage that immediately precedes AD and other dementias (2). Diverse pathologies have been described in demented patients suggesting that etiologic cause is often multi-factorial (3). The limited correlation between AD pathology and severity of cognitive symptoms also suggests that other pathologies may contribute to decline (4). In epidemiological studies, multiple vascular risk factors, including diabetes (DM) (5), obesity (6), and blood pressure (BP) (7) have been associated with cognitive decline. A NIH technology assessment on preventing AD and cognitive decline concluded that there is an association between hypertension and cognitive decline (8).

Previous studies have focused on the effect of sustained hypertension on cognitive decline, not visit to visit BP variability. Yet visit to visit blood pressure variability is potentially a modifiable risk factor. Maximum BP and BP variance have both been found to be associated with increased stroke risk (9) and suggested to be associated with vascular dementia (10). Our study tested two hypotheses: first, that variability in BP is negatively associated with several domains of cognitive function and, second, increased variability in BP is associated with reduced global functioning as measured by Clinical Dementia Rating, Mini-Mental Status Exam and the Alzheimer's Disease Assessment Scale.

METHODS

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a large cohort study designed to test how neuroimaging, genetic, and clinical markers potentially predict the progression of MCI. More than 800 voluntary participants were recruited, including 400 Petersen criteria MCI, 184 AD, and 226 healthy controls, aged 55-90 years. Inclusion criteria included good general health, low Hachinski Ischemic Scale and Geriatric Depression scores (GDS), and at least 6 years of education. ADNI subjects were followed for 2-3 years. For additional information see www.adni-info.org.

Cognitive function was evaluated in ADNI participants at screening, baseline, 6, 12, 18, 24, and 36 months. Global functioning was measured by Clinical Dementia Rating sum of boxes (CDR) (11), the Mini-Mental Status Exam (MMSE) and the Modified Alzheimer's Disease Assessment Scale Cognitive Component (ADAS-COG). Executive function was measured by Trail Making B (12), Animal Fluency, and Vegetable Fluency (13). Processing speed was measured by the Digit Symbol Test Raw Score (14), and episodic memory was measured by the Rey Auditory Verbal Learning Test Total Score (Rey) (15).

Systolic (SBP) and diastolic BP (DBP) were measured in mmHg at screening, baseline, 6, 12, 18, 24, and 36 months. All arterial BP measurements were resting, measured with clinic sphygmomanometers and taken consistently in the dominant arm whenever possible. The forearm was placed at the level of the heart. Diagnosis, demographics, risk factors, medication usage, and *APOE* genotype data were collected (download version 05/17/2011).

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Hypercholesterolemia was defined as random cholesterol ≥200 mg/dL, self-reported hypercholesterolemia, or treatment with lipid medication. DM was defined as random glucose ≥200 mg/dL, self-reported DM, or treatment with DM medication. Depression was defined as GDS ≥10 or treatment with medication. History of vascular disease was defined as history of coronary artery disease, congestive heart failure, cerebrovascular disease, carotid artery stenosis, or peripheral vascular disease. Atrial fibrillation was defined by history. Education was assessed as a continuous variable in years. Smoking was defined as any history of smoking. Height in meters and weight in kilograms were measured by ADNI site coordinators. *APOE* ε4 carriers were defined as participants positive for at least one ε4 allele. Medication use was self-reported and all anti-hypertensives were recorded.

Statistical Analysis

We defined several variables using BP measures collected from screening through 36 months. For each subject, we calculated mean BP and intra-individual variability in BP as measured by standard deviation (SD), coefficient of variation (CV), and maximum (max). We only included subjects with at least 3 BP measures during the 36 month follow-up period.

Cognitive test scores for ADAS-COG, MMSE, CDR, Rey, and Digit Symbol obtained at the 36-month visit were used as the outcome measure. Since three tests (Trail Making B, Animal Fluency, and Vegetable Fluency) were measuring executive function, we combined these test scores to create a composite *z*-score for executive function. An individual *z*-score for each test was first calculated as the test score at 36-months minus the mean baseline score divided by the baseline standard deviation. The executive function composite *z*-score was the average of the three individual *z*-scores. Higher scores represented better cognition on all executive tests (i.e., Trail Making B scores were reversed prior to averaging). This transformation allowed scores with different units or ranges to be combined into a single domain score. In our analyses, we chose to transform the original scores into SD units of baseline mean because of the stable estimates produced due to the larger sample sizes at baseline, nevertheless, the relative ranking between individuals remains the same regardless which standardizing constants were used.

T-tests and chi-square tests (or Fisher's exact tests, as appropriate) were used to compare the baseline subject characteristics, comorbidities, medication use, cognitive scores, and BP measurements between those with and without 36-month cognitive measures. T-tests were also used to test the association of anti-hypertensive medication use/non-use at 36 months with the BP variables.

Analysis of covariance (ANCOVA) models were used to examine the association between BP and cognitive scores at 36 months while adjusting for covariates including baseline scores, subject demographics, comorbidities, and medication use at 36 months. Potential covariates with p-values ≤ 0.15 in univariate models were included in the multivariate ANCOVA models but only remained in the models if significant at the alpha = 0.05 level in any of the models on any outcome. Interactions between the BP variability variables and *APOE* ε4 status were investigated in the final multivariate ANCOVA models but only included if significant at the alpha = 0.05 level. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

There were 626 subjects with screening MCI or normal cognition, 16 of who died before the 36-month evaluation. Of the survivors, 428 (70.2%) received cognitive testing at the 36-month visit and were analyzed. The 198 subjects who did not present for 36-month cognitive

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testing were more likely to have MCI, *APOE* ε4, vascular disease, higher DBP, depression, worse scores on the cognitive tests at baseline, and to take BP medication ($p<0.05$ for all).

Cohort characteristics and cognitive scores at 36 months are presented in Table 1. Almost all subjects had BP measured at each time point (92%). Only 7% of the subjects were missing 1 measurement and 1% of the subjects were missing 2 measurements.

Table 2 summarizes BP variability measures from screening through 36 months. Of the 428 subjects, 422 (98.6%) had BP measured at the 36-month evaluation, 5 (1.2%) subjects had their last BP measurement at 24 months, and 1 (0.2%) subject had the last BP measurement at 12 months. There was no association between anti-hypertensive medication use at 36 months and DBP variability measures ($p>0.1220$ for all). However, those treated with antihypertensive medication had significantly higher mean SBP and greater variability in SBP as measured by the SD and maximum of the systolic measurements ($p<0.01$ for mean SBP, SD SBP and max SBP; $p=0.07$ for CV SBP). About 80% of subjects treated with antihypertensives had at least 2 BP measurement that were above JNC treatment guidelines during follow-up, while 51% of subjects who were not treated with antihypertensives met JNC diagnostic criteria for hypertension during follow-up. The mean number of BP medications per person in the treated group was 1.6 (SD 0.8). Angiotensin converting enzyme inhibitors or angiotensin receptor blockers where the most frequent (57%), followed by diuretics (48%), then beta blockers (35%) and lastly calcium channel blockers (27%).

In univariate models higher SD, CV, and max SBP were significantly associated with poorer cognitive scores on all 6 cognitive tests ($p<0.05$), with the exception that max SBP was only marginally associated with lower MMSE ($p=0.0580$). The mean SBP only showed marginal association with executive Z-score ($p=0.1083$). None of the DBP measures showed a statistical association with any of the cognitive scores ($p>0.18$ for all).

To identify covariates to include in the multivariate models, we performed univariate ANCOVA models on each of the 36-month cognitive outcomes. Depression, and the presence of an *APOE* ε4 allele were significantly associated with worse performance on each of the cognitive tests ($p<0.0001$). Female gender was significantly associated with higher Rey, Digit Symbol, and executive z-score ($p\leq0.0003$ for all), and marginally associated with lower CDR ($p=0.1083$). Vascular disease was significantly associated with lower Rey and Digit Symbol ($p<0.05$ for both) and marginally associated with higher modified ADAS-COG and CDR ($p<0.15$ for both). Increased education was significantly associated with higher Digit Symbol scores and a greater executive z-score ($p<0.01$ for both). Increased education was also marginally associated with higher MMSE and Rey ($p<0.15$ for both). Greater age was significantly associated with lower Digit Symbol scores ($p=0.0042$). Increased BMI was marginally associated with lower CDR ($p=0.0579$). DM, hypercholesterolemia, atrial fibrillation, antihypertensive or statin medication use, and history of smoking were not significantly associated with any of the cognitive tests ($p>0.11$ for all).

Results from the final ANCOVA models on separate cognitive tests are presented in Table 3. We first modeled each cognitive test score using one summary BP measure while controlling for covariates, including baseline scores, years of education, age, BMI at 36 months, gender, *APOE* ε4, depression, and vascular disease at 36 months. No significant interactions between BP variability and *APOE* ε4 were found. Greater variability in SBP using SD and CV was significantly associated with poorer cognitive scores at 36 months on ADAS-COG, CDR, REY and the executive z-score ($p<0.05$ for all). Maximum BP per person was significantly associated with lower scores on REY and the executive z-score ($p<0.05$). Mean SBP was not associated with any cognitive test score. In order to examine

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the combined association of SBP variability and mean SBP on each of the cognitive scores, models with SD SBP and mean SBP in the same model are also presented in Table 3. Higher SBP variability was significantly associated with lower cognitive score on ADAS-COG, CDR, REY and the executive *z*-score, (p-value <0.05 for all), while mean SBP was not. No significant association with BP measures was found with MMSE or Digit Symbol scores.

DISCUSSION

We demonstrated a statistically significant association between greater visit to visit SBP variability and cognitive dysfunction on a number of cognitive tests. Given the results of the combined SBP mean and variance model, it is likely that variability and not higher BP or diagnosis of hypertension is most strongly associated with cognitive dysfunction. Because hypertension is a modifiable risk factor, treatment has been studied with occasional suggestion of benefit, but inconsistent results (8). To our knowledge, this is the first report investigating the relationship between visit to visit variability and cognitive dysfunction in subjects without a high risk of cardiovascular disease and stroke.

We adjusted for BMI (16), depression (17), and tobacco use (18) and statin use (19). Non-modifiable risk factors associated with cognitive decline, including education (20), gender (21), age, and *APOE* ε4 genotype (22), were also adjusted for. Identifying modifiable risk factors appropriate for clinical trials is aided by well-designed observational studies. A well-designed study should be multivariate and control for as many covariates and interactions as possible. ADNI meets these criteria.

This study proposed that the brain may be vulnerable to systolic BP variability and that gradual subclinical injury over time due to greater variability in systolic BP would lead to detectable cognitive dysfunction in a large well-characterized sample. A potential mechanism for the association between systolic BP variability and cognitive dysfunction may be decreased elasticity in the vascular bed with age and hypertension resulting in lesser ability to adjust blood flow and brain metabolism in face of changes in systemic pressure. This association would likely be stronger in a group of elderly subjects who have less elasticity in their vascular beds. Prior research on 24-hour BP variability with comparatively small sample sizes has shown mixed results, with one study (23) showing a correlation between increased BP variability and improved cognitive function, and another (24) showing an association between increased variability and cognitive dysfunction. The present study has a larger sample size and showed a strong correlation between increased visit to visit BP variability and cognitive dysfunction. We interpret the various findings to be due to the different time scales of measurement and sample sizes examined.

While there is evidence that antihypertensive agents may influence BP mean and variability, data on the association between within subject blood pressure variability and antihypertensives is limited. However, it may be the calcium channel blockers are more effective in controlling BP variability than beta blockers (25). Our study did not show a relationship between antihypertensive use and cognitive function. We did find that increased mean BP and BP variability were associated with antihypertensive use at 36 months. These findings are likely due to medication type and dose, confounding by indication and other factors such as poor compliance, time since last medication use and drug food interactions which could not be studied in the present cohort as it was not recorded. Clinical trials to date have found antihypertensive treatment to be inconsistently associated with protection against cognitive decline. Consequently, while these studies give some indication of a beneficial effect on cognition from antihypertensive treatment, there are some limitations to the conclusion that can be drawn from pre-existing literature.

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Our findings are clinically significant given that the change in cognitive scores associated with increased BP variability are similar to those known to be associated with cholinesterase inhibitor treatment (26). In most of the pivotal approval trials, the effect size of cholinesterase inhibitor treatment was about a 2 to 4 point improvement in ADAS-COG. A SBP variance decrease of 1 SD (5 mmHg SBP) would be associated with an improvement in ADAS-COG of one point. Given that SBP variance is modifiable with antihypertensive medication and has high population prevalence, shifting the mean population BP variance by 1 SD could be an important way to preserve cognitive health. New medications could also be developed with stronger effects on SBP variability. Alternatively some medications already available may be better at controlling SBP variability and could be better utilized in this population (28). Better control of BP variability through treatment may lead to less cognitive decline over time and this finding could be of public health significance.

Limitations of this study include potential selection biases, such as more men than women and low Hachinski scores in the sample. Other important limitations of this study are that cerebral degeneration (particularly the insula or structures in the Central Autonomic System) could have caused higher BP variability which could lead to additional ischemic lesions vicariously produced by neuro-degenerative effects on BP dynamics and that a prodromal fall in BP could inflate the magnitude of variance. Another limitation of this study is that we could not measure obstructive sleep apnea and this could have been associated with both blood pressure variability and cognitive dysfunction. This analysis was a pre-specified protocol but multiple comparisons could have been a source of error. Diurnal variation in blood pressure could have been source of intra-individual BP variability as well. One strength of this study was the prospective nature of the data collection, which likely reduced sample bias. In addition, the subjects who did not drop out had lower rates of vascular disease, hypertension, depression, and mild cognitive impairment so these factors are unlikely to be biasing the results. Other strengths of this study include the large number of measurements for each subject (due to repeated BP measurements), the comparatively large number of well-characterized subjects, and comprehensive standardized cognitive testing. It has been suggested (8) but not proven that the frontal lobe which is mainly responsible for executive function is especially sensitive to hypertension. Future studies targeting the association of BP variability with changes in brain structure, particularly in the frontal lobe, as well as the relationship of BP variability, frontal lobe atrophy, and cognition are warranted. Near-term future research to confirm our findings in other large well-characterized cohorts is also needed. Finally, mediation models of the relationship between neuroanatomical pathophysiology underlying greater cognitive impairment such as the possible presence of subcortical ischemic disease secondary to hypertensive small-vessel disease and variable systolic blood pressure would be particularly beneficial.

Acknowledgments

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf Statistical support for this project was provided by the NIH-funded Indiana Alzheimer's Disease Center, Award Number P30AG10133 from the National Alzheimer's Coordinating Center and NIA. Dr. Risacher received support from the NIH CTSI Pre-doctoral Training Fellowship Grant TL1 RR025759. Dr. Saykin serves as Editor-in-Chief of Brain Imaging and Behavior; has served as a consultant to Baxter International Inc., Bristol-Myers Squibb, and Pfizer Inc.; and has received research support from Eli Lilly and Company, Siemens AG, Welch Allyn Inc., the NIH (R01 CA101318 [PI], R01 AG19771 [PI], RC2 AG036535 [Core Leader], P30 AG10133–18S1 [Core Leader], and U01 AG032984 [Site PI and Chair, Genetics Working Group]), the Indiana Economic Development Corporation (IEDC #87884), and the Foundation for the NIH. Dr. Farlow receives research funding from: BristolMyersSquibb Company, Danone Research, Elan Pharmaceuticals, Inc., Eli Lilly and Company, Genentech, Novartis Pharmaceuticals Corporation, OctaPharma AG, Pfizer Inc., Sanofi-aventis, and Sonexa Therapeutics, Inc., receives honoraria as scientific consultant for: Accera, Inc., Astellas

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Pharma US Inc., Baxter Healthcare Corp., Bayer Pharmaceuticals Corporation, BristolMyersSquibb, DDB Remedy, Eisai Medical Research, Inc., GE Healthcare , Helicon, Medavante, Medivation, Inc., Merck & Co., Inc., Novartis Pharmaceuticals Corp., Pfizer, Inc., Prana Biotechnology Ltd., QR Pharma., Inc., The Sanofi-aventis Group, and Toyama Chemical Co., Ltd.., is speaker for: Eisai Medical Research, Inc., Forest Laboratories, Pfizer Inc. and Novartis Pharmaceuticals Corporation and is a partial owner of Chemigen, Inc., Core leader for P30 similar to Dr. Saykin and site PI for ADNI.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Amorfix Life Sciences Ltd.; AstraZeneca; Bayer HealthCare; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the Rev. August 16, 2011. University of California, Los Angeles. This research was also supported by NIH grants P30, AG010129, K01 AG030514, and the Dana Foundation.

Sponsor's Role: No sponsor.

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Table 1

Participant Characteristics (n=428).

Variables	Summary Statistics
Baseline diagnosis, n(%)	
Normal	181 (42.3%)
MCI	247 (57.7%)
Gender, n(%)	
Male	256 (59.8%)
Female	172 (40.2%)
Baseline age (years), mean ± SD	75.2 ± 6.4
Years of education, mean ± SD	15.9 ± 2.9
BMI at 36 months, mean ± SD	26.0 ± 4.1 (n=416)
BMI at 36 months, n(%)	(n=416)
Underweight	5 (1.2%)
Normal	172 (41.3%)
Overweight	171 (41.1%)
Obese	68 (16.3%)
APOE ε4 allele carriers, n(%)	176 (41.1%)
History of Smoking, n(%)	166 (38.8%)
Comorbidities at 36 Months, n(%)	
Diabetes	37 (8.6%)
High Cholesterol	309 (72.2%)
Atrial Fibrillation	33 (7.7%)
Vascular disease	60 (14.0%)
Depression	93 (21.7%)
Medication Use at 36 Months, n(%)	
Blood pressure medication	204 (47.7%)
Statin Medication	191 (44.6%)
Cognitive Scores at 36 Months, mean ± sd (n)	
ADAS-COG	17.0 ± 11.4 (n=402)
MMSE	26.5 ± 4.4 (n=427)
CDR	2.2 ± 2.8 (n=418)
Rey Auditory Verbal Learning Test	32.4 ± 13.0 (n=423)
Digit Symbol	40.0 ± 15.0 (n=419)
Executive Z-score	0.16 ± 0.90 (n=403)
Trails B (sec)	118.9 ± 77.8 (n=404)
Vegetable Fluency	11.4 ± 5.2 (n=424)
Animal Fluency	16.6 ± 6.5 (n=425)

Mild cognitive impairment (MCI), body mass index in kg/m^2 (BMI), Clinical Dementia Rating Sum of Boxes (CDR), Mini-Mental Status Exam (MMSE), Modified Alzheimer's Disease Assessment Scale Cognitive Impairment (ADAS-COG) and Trail Making B (Trails B),. Underweight was defined as BMI ≤18.5, normal weight as BMI = 18.5–24.9, overweight as BMI = 25–29.9, and obese as BMI of 30 or greater.

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Table 2

Summary Blood Pressure Measures (in mmHg) from Screening through 36 Months by Antihypertensive Medication Use.

Blood Pressure	Systolic Blood Pressure				Diastolic Blood Pressure			
	Overall (n=428)	Using Antihypertensive (n=204)	Not using Antihypertensive (n=224)	p-value[a]	Overall (n=428)	Using Antihypertensive (n=204)	Not using Antihypertensive (n=224)	p-value[b]
Mean, mean ± sd	133.1±12.6	136.4 ± 13.0	130.1 ± 11.4	<0.0001	73.4±7.3	73.9 ± 7.2	73.0 ± 7.4	0.1962
Standard Deviation, mean ± sd	11.4 ± 4.9	12.2 ± 5.0	10.7 ± 4.6	0.0033	6.6 ± 2.6	6.7 ± 2.7	6.4 ± 2.4	0.1942
Coefficient of Variation, mean ± sd	8.6 ± 3.5	8.9 ± 3.5	8.3 ± 3.5	0.0743	9.0 ± 3.6	9.2 ± 3.7	8.9 ± 3.5	0.4153
Maximum, mean ± sd	149.1±16.3	153.8 ± 17.3	144.8±14.1	<0.0001	82.4±8.2	83.0 ± 8.2	81.8 ± 8.2	0.1220

[a] p-value derived using two sample *t*-tests comparing systolic blood pressure summary measures between participants using anti-hypertensive medications and those not using anti-hypertensive medications.

[b] p-value derived using two sample *t*-tests comparing diatolic blood pressure summary measures between participants using anti-hypertensive medications and those not using anti-hypertensive medications.

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Table 3

Results from Final Analysis of Covariance Models with each 36 Month Cognitive Score collected at 36 months as the Outcome and Various Within-person Systolic Blood Pressure Summary Statistics Calculated using Measurements from Screening through 36 Months as Predictor Variables*

Models		Cognitive Outcomes					
		Modified ADAS-COG	MMSE	CDR	REY	Digit Symbol	Executive Z-score
1	Mean SBP	0.01 ± 0.03	−0.01 ± 0.01	−0.003 ± 0.008	−0.06 ± 0.03	−0.02 ± 0.03	−0.002 ± 0.002
		0.7738	0.5045	0.7463	0.0714	0.4704	0.3143
2	SD SBP	0.18 ± 0.07	−0.03 ± 0.03	0.05 ± 0.02	−0.23 ± 0.09	−0.12 ± 0.09	−0.019 ± 0.006
		0.0122	0.3597	0.0314	0.0069	0.1886	0.0033
3	CV SBP	0.25 ± 0.10	−0.04 ± 0.05	0.07 ± 0.03	−0.27 ± 0.12	−0.16 ± 0.12	−0.024 ± 0.009
		0.0110	0.4304	0.0229	0.0241	0.1860	0.0064
4	Max SBP	0.04 ± 0.02	−0.01 ± 0.01	0.01 ± 0.01	−0.06 ± 0.03	−0.04 ± 0.03	−0.004 ± 0.002
		0.0755	0.2378	0.3133	0.0309	0.1384	0.0492
5	SD SBP	0.19 ± 0.07	−0.03 ± 0.04	0.05 ± 0.02	−0.21 ± 0.09	−0.11 ± 0.09	−0.018 ± 0.006
	Mean SBP	0.0124	0.4371	0.0221	0.0188	0.2377	0.0054
		−0.01 ± 0.03	−0.01 ± 0.01	−0.01 ± 0.01	−0.04 ± 0.03	−0.02 ± 0.04	−0.001 ± 0.002
		0.7850	0.6456	0.3956	0.2220	0.6628	0.7189

Clinical Dementia Rating Sum of Boxes (CDR), Mini-Mental Status Exam (MMSE), the Modified Alzheimer's Disease Assessment Scale Cognitive Impairment (ADAS-COG), executive function (Executive z-score), Rey Auditory Verbal Learning Test (Rey), systolic blood pressure (SBP), standard deviation of SBP (SD SBP), coefficient of variation in SBP (CV SBP), and maximum SBP (Max SBP). The analysis in model 5 includes both mean SBP and SBP variance measures.

*Results shown are Parameter Estimate ± Standard Error on the first line and p-value on the second line. All models are adjusted for baseline scores, age, years of education, gender, and presence of *APOE* ε4 allele, in addition to vascular disease, BMI, and depression at 36 months