Blood pressure variability and brain morphology in elderly women without cardiovascular disease

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Abstract

Objective

To examine the relationship between blood pressure (BP) variability (BPV), brain volumes, and cognitive functioning in postmenopausal women with few modifiable cardiovascular risk factors.

Methods

Study participants consisted of postmenopausal women enrolled in the Women's Health Initiative Memory MRI study (WHIMS-MRI) without cardiovascular disease, diabetes mellitus, hypertension, or current smoking at baseline (1996–1999). BP readings were taken at baseline and each annual follow-up visit. BPV was defined as the SD associated with a participant's mean BP across visits and the SD associated with the participant's regression line with BP regressed across visits. Brain MRI scans were performed between 2004 and 2006. Cognitive functioning was assessed at baseline and annually thereafter with the Modified Mini-Mental State Examination (3MSE) scoring until 2008. The final sample consisted of 558 women (mean age 69 years, median follow-up time [interquartile range] 8 [0.8] years).

Results

In adjusted models including mean systolic BP, women in the highest tertile of systolic BPV had lower hippocampal volumes and higher lesion volumes compared to women in the lowest tertile. No relationship between BPV and 3MSE scoring was detected.

Conclusions

In postmenopausal women with few modifiable cardiovascular risk factors, greater visit-to-visit systolic BPV was associated with reductions in hippocampal volume and increases in lesion volumes at later life. These data add evidence to the emerging importance of BPV as a prognostic indicator even in the absence of documented cardiovascular risk factors.

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Glossary

BP = blood pressure; **BPV** = blood pressure variability; **CHD** = coronary heart disease; **CVD** = cardiovascular disease; **DBP** = diastolic blood pressure; **DBPV** = diastolic blood pressure variability; **ONTARGET** = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; **PROSPER** = Prospective Study of Pravastatin in the Elderly at Risk; **SBP** = systolic blood pressure; **SBPV** = systolic blood pressure variability; **SDreg** = SD about the participant's regression line; **3MSE** = Modified Mini-Mental State Examination; **TRANSCEND** = Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; **WHI** = Women's Health Initiative; **WHIMS** = Women's Health Initiative Memory Study.

Higher visit-to-visit in blood pressure (BP) variability (BPV) is associated with cerebrovascular diseases and impaired cognitive function later in life.^{1–3} Several questions remain. To date, information on the prognostic value of BPV stems mostly from populations at high cardiovascular risk.^{2–8} However, there may be different implications of associations between BPV and vascular outcomes in groups that vary by age and risk factor profiles; different clinical implications may arise for these groups.¹

Studies that involved patients with cardiovascular disease (CVD) found high systolic BP (SBP) variability (SBPV) to be associated with worse cognitive performance, lower hippocampal volume, and higher risk of cortical infarcts and of cerebral microhemorrhages in later life, while diastolic BP (DBP) variability (DBPV) did not play a significant role.^{2,3} So far, there is limited evidence in populations with few modifiable cardiovascular risk factors, including analyses of brain morphology.⁹ It is unclear whether elevated SBPV and DBPV are associated with morphologic brain changes and faster rates of cognitive decline in these individuals. This is important because the strength of the association between BPV and cognitive function and brain health is most likely dependent on the duration and magnitude of the exposure, as well as on the presence of comorbid conditions. Long-term studies with regular standardized BP assessments are largely missing.⁹ Moreover, no study has previously examined these relations in postmenopausal women, who are at increased risk for cerebrovascular diseases such as stroke.

The primary aim of this study was to evaluate the relationships between SBPV and DBPV and brain and lesion volumes using brain MRI scans in a cohort of elderly postmenopausal women with no history of CVD and few or no modifiable cardiovascular risk factors. The secondary aim was to assess the relationship between BPV and global cognitive functioning.

Methods

Study population

Design of the Women's Health Initiative Memory Study trial

The study population consisted of postmenopausal women enrolled in the MRI component of the Women's Health Initiative (WHI) Memory Study (WHIMS).^{10–14} WHIMS examined the effect of postmenopausal hormone treatment

(conjugated equine estrogen alone vs placebo, conjugated equine estrogen plus medroxyprogesterone vs placebo) on cognitive function.^{15–18} Recruitment was initiated between May 1996 and December 1999 at 39 US clinical centers and included women who were ≥ 65 years of age and were free of dementia at enrollment (baseline visit). Details of the study population and of the initial screening process have been reported previously.^{10–12,15–22} After enrollment, women were scheduled for in-clinic visits annually and were sent semi-annual questionnaires to ensure the timely update of selected exposures and to ascertain medical outcomes.

WHIMS-MRI study

Recruitment for the WHIMS-MRI study began in January 2005 and was completed in April 2006. Its aim was to investigate whether postmenopausal hormone treatment affects the brain structure of WHIMS participants.^{10–13} General exclusion criteria for participating in WHIMS-MRI included contraindications to the performance of MRI (pacemakers, prohibited medical implants, and foreign bodies), shortness of breath or inability to lie flat, anxiety panic disorders, and claustrophobia.¹⁰

In the WHIMS-MRI study, brain scans were completed on 1,403 women, 51 of which failed quality check and were excluded from further analysis. For the purposes of this analysis, women with a self-reported history of diabetes mellitus, coronary heart disease (CHD), stroke, atrial fibrillation, or hypertension at baseline were excluded ($n = 663$) because these conditions are known independent causes and contributors to cognitive dysfunction.²³ Current smokers ($n = 57$) were excluded because smoking is highly associated with CHD and stroke risk and has been further identified to contribute to cognitive dysfunction.²³ Women with missing baseline data, dementia at baseline, and missing follow-up data or covariates were also excluded from our primary analysis ($n = 31$). Finally, we excluded ethnicities other than white because of low sample sizes ($n = 43$). Our final study population consisted of 558 women. Institutional review boards at participating institutions approved all study protocols, and all participants provided written informed consent.

Exposure assessment: BPV

BP was measured at baseline and each annual study visit by certified staff using standardized procedures.²² The range number of BP measurements for this analytic sample was 3 to 9

(figure). BP was measured in the right arm with a mercury sphygmomanometer and appropriate cuff size after the participant was seated and had rested for 5 minutes, followed by a second measurement. BPV was calculated from all available BP measures that occurred before MRI assessment. Participants missing ≥ 2 of the first 3 study visits were excluded. Two approaches were used to assess BPV as previously outlined in detail.²⁴ First, we defined BPV as the SD of the participant's mean SBP or mean DBP across visits. Second, we calculated BPV as the SD about the participant's regression line (SDreg) with BP regressed across visits. Whereas the estimation of SD assumes that a participant's BP is constant over follow-up, the estimation of SDreg assumes a linear temporal trend and thereby can account for systematic changes in BP.

Outcome ascertainment

Brain MRI measures

Structural brain MRI scans were performed between January 2005 and April 2006 with a standardized protocol developed at the MRI Quality Control Center in the Department of Radiology, University of Pennsylvania as previously described.^{10–13} Briefly, scans were obtained with a field of view of 22 cm and a matrix of 256 × 256. Included were oblique axial spin density/T2-weighted spin echo (repetition time 3,200 milliseconds, echo time 30/120 milliseconds, slice thickness 3 mm), fluid-attenuated inversion recovery T2-weighted spin echo (repetition time 8,000 milliseconds, TI 2,000 milliseconds, echo time 100 milliseconds, slice thickness 3 mm), and oblique axial 3-dimensional T1-weighted gradient echo (flip angle 30°, repetition time 21 milliseconds, echo time 8 milliseconds, slice thickness 1.5 mm) images from the vertex to the skull base parallel to the anterior commissure–posterior commissure plane.^{10–13} Brain volumes were measured with automated computer-based template warping to sum voxels in anatomic regions of interest.^{10–13} All supratentorial brain tissue was classified as normal or abnormal (ischemic) gray or white matter and assigned to 1 of 92 anatomic regions of interest of the cerebrum. These regions of interest were organized in an anatomically hierarchical system that was collapsed into anatomic regions for this analysis.^{10–13} Statistical analyses on lesions volumes were adjusted for total brain volume.

Table 1 Baseline characteristics of included women enrolled in WHIMS-MRI (1996–1999)

Characteristic	WHIMS-MRI (n = 558)
Age	
Mean age (SD) at enrollment, y	69.3 (3.6)
Mean age (SD) at MRI, y	78.2 (3.6)
BP assessments/visits before MRI, mean (SD), n	7.6 (0.7)
Education, more than school diploma/GED, n (%)	394 (40.6)
WHI menopausal hormone therapy, n (%)	282 (50.5)
SBP (baseline), mean (SD), mm Hg	122 (11)
DBP (baseline), mean (SD), mm Hg	73 (7)
Heart rate (baseline), mean (SD), bpm	69 (9)
Presence of APOE ε4 allele, n (%)	109 (20)
3MSE score (baseline), mean (SD)	96.6 (3.1)
During follow-up, n (%)	
Incident hypertension	245 (48.0)
Incident diabetes mellitus	18 (3.3)
Incident CHD, including stroke	7 (1.3)
Incident atrial fibrillation	1 (0.9)
Outcome, mean (SD), cm³	
Brain volume	866.7 (76.7)
Frontal lobe volume	179.0 (25.7)
Hippocampal volume	5.83 (0.78)
Total lesion volume	5.86 (6.86)
White matter lesion	4.10 (4.19)
Gray matter lesion volume	1.75 (3.09)

Abbreviations: BP = blood pressure; CHD = coronary heart disease; DBP, diastolic blood pressure; GED = general education development; SBP, systolic blood pressure; 3MSE = Modified Mini-Mental State Examination; WHI = Women's Health Initiative; WHIMS-MRI = Women's Health Initiative Memory MRI Study.

Figure Timeline of the study

Table 2 BPV and brain and lesion volumes in the WHIMS-MRI study (n = 558) in adjusted models

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Brain volume, cm ³	Frontal lobe volume, cm ³	Hippocampal volume, cm ³	Total lesion volume, cm ^{3c}	White matter lesion, cm ^{3c}	Gray matter lesion volume, cm ^{3c}
SBPV (SD from the mean)^d										
T1	1.2–8.4	186	7.53	7.96	869.1 (852.4–885.9)	179.8 (174.1–185.4)	5.89 (5.73–6.05)	5.57 (3.99–7.14)	3.84 (2.90–4.79)	1.73 (1.00–2.45)
T2	8.42–11.7	186	7.59	7.95	862.6 (846.5–878.8)	180.2 (174.8–185.7)	5.77 (5.61–5.93)	6.40 (4.88–7.92)	4.18 (3.27–5.10)	2.22 (1.51–2.92)
T3	11.72–26.2	186	7.60	8.01	856.1 (839.5–872.7)	176.9 (171.3–182.5)	5.65 (5.49–5.81)	6.96 (5.40–8.52)	4.65 (3.71–5.58)	2.31 (1.59–3.04)
p Value for trend					0.1241	0.3246	0.0034	0.0805	0.0938	0.1078
SBPV (SDreg from the least-squares regression line)^e										
T1	1.3–7.6	186	7.46	7.91	867.0 (850.2–883.9)	180.7 (175.1–186.4)	5.92 (5.75–6.08)	5.42 (3.84–7.00)	3.60 (2.65–4.54)	1.82 (1.09–2.55)
T2	7.6–11.1	186	7.59	7.99	856.9 (840.4–873.5)	178.0 (172.4–183.6)	5.72 (5.56–5.88)	6.45 (4.90–8.00)	4.23 (3.30–5.16)	2.23 (1.51–2.94)
T3	11.1–29.2	186	7.67	8.02	863.4 (847.4–879.5)	178.5 (173.1–183.9)	5.69 (5.53–5.85)	6.94 (5.44–8.45)	4.72 (3.82–5.62)	2.23 (1.53–2.92)
p Value for trend					0.6422	0.4183	0.0052	0.0496	0.0169	0.2524
DBPV (SD from the mean)^d										
T1	1.7–5.0	186	7.60	8.00	862.9 (846.9–879.0)	178.3 (172.9–183.7)	5.79 (5.63–5.94)	6.39 (4.88–7.90)	4.27 (3.36–5.17)	2.13 (1.43–2.82)
T2	5.0–6.5	186	7.46	7.92	861.9 (845.6–878.2)	179.9 (174.4–185.4)	5.78 (5.62–5.94)	5.66 (4.12–7.19)	3.90 (2.98–4.82)	1.76 (1.05–2.47)
T3	6.5–15.7	186	7.65	8.00	862.2 (845.5–879.0)	178.8 (173.2–184.5)	5.72 (5.55–5.88)	7.06 (5.49–8.63)	4.59 (3.65–5.54)	2.47 (1.74–3.19)
p Value for trend					0.9314	0.8409	0.3705	0.3757	0.4713	0.3261
DBPV (SDreg from the least-squares regression line)^e										
T1	0.9–4.5	186	7.50	7.94	856.1 (839.7–872.4)	176.3 (170.8–181.8)	5.78 (5.62–5.94)	5.48 (3.95–7.02)	3.72 (2.80–4.64)	1.76 (1.05–2.47)
T2	4.6–6.1	186	7.55	7.96	867.6 (850.7–884.4)	182.1 (176.4–187.8)	5.81 (5.64–5.97)	7.01 (5.43–8.59)	4.55 (3.60–5.49)	2.46 (1.73–3.19)

Continued

Table 2 BPV and brain and lesion volumes in the WHIMS-MRI study (n = 558) in adjusted models (continued)

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Brain volume, cm ³	Frontal lobe volume, cm ³	Hippocampal volume, cm ³	Total lesion volume, cm ^{3c}	White matter lesion, cm ^{3c}	Gray matter lesion volume, cm ^{3c}
T3	6.1–15.8	186	7.66	8.02	864.1 (848.1–880.0)	179.0 (173.7–184.4)	5.72 (5.56–5.87)	6.53 (5.03–8.02)	4.42 (3.53–5.32)	2.10 (1.41–2.79)
<i>p</i> Value for trend					0.3196	0.3054	0.3986	0.1686	0.1201	0.3366

Abbreviations: BP = blood pressure; BPV = blood pressure variability; DBPV = diastolic blood pressure variability; SBPV = systolic blood pressure variability; SDreg = SD about the participant's regression line; T = tertile; WHIMS-MRI = Women's Health Initiative Memory MRI Study.

^a BPV was calculated from all available BP measures that occurred before baseline MRI.

^b Follow-up years defined as number of years between study enrollment and MRI baseline assessment.

^c Lesion volumes were adjusted for total brain volume.

^d SD about the participant's mean BP across visits. Model adjusted for age, education, presence of APOE ε4 allele, Women's Health Initiative hormone therapy randomization arm, and mean BP.

^e SD about the participant's regression line with BP across visits. Model adjusted for age, education, presence of APOE ε4 allele, smoking status, Women's Health Initiative hormone therapy randomization arm, mean BP, and slope of blood pressure change across visits.

Global cognitive function

Global cognitive function was assessed at baseline and annually thereafter with the Modified Mini-Mental State Examination (3MSE).^{15,17} Scores ranged from 0 to 100, with a higher score reflecting better cognitive function. The test items measure temporal and spatial orientation, immediate and delayed recall, executive function, naming, verbal fluency, abstract reasoning (similarities), praxis (obeying command, sentence writing), writing, and visual-constructional abilities (copying). The 3MSE was administered at the WHI screening visit and annually thereafter by a trained and centrally certified technician.^{15,17} Administration time averaged 10 to 12 minutes. The 3MSE has demonstrated moderate internal consistency and temporal reliability, with good sensitivity and specificity for detecting cognitive impairment.

Covariates

Information was collected via self-reported surveys or by physical measurements at WHI baseline.²² Hypertension was defined as self-reported current antihypertensive use or values of SBP ≥140 mm Hg or DBP ≥90 mm Hg at the baseline visit. Women were classified as having diabetes mellitus on the basis of self-report of diabetes mellitus or self-report of diabetes treatment. Incident CHD was defined as all nonfatal and silent myocardial infarctions and CHD death, and the diagnosis was physician adjudicated.²² Atrial fibrillation was identified through review of ECG data in years 3, 6, and 9 after baseline. The presence of the APOE ε4 allele was determined by DNA genotyping in a subset of study participants.

Statistical analysis

Descriptive statistics were used to describe demographics and other characteristics. To calculate BPV, SD and SDreg were calculated from all available BP measures that occurred before the MRI scans or before the last known 3MSE score. Each exposure variable of interest (e.g., SD of SBP) was categorized by tertiles based on the distribution of the overall analytic sample.² To assess the associations of BPV, brain and lesion volumes, and global cognitive function, univariate and multivariate linear regression models were used with SD and SDreg as the main independent variables. Multivariable models were adjusted for age, education, presence of APOE ε4 allele(s), hormone therapy randomization arm, and mean BP.^{2,24} The *p* value for trend was evaluated by including tertiles of the main exposure variable (SD/SDreg) in the multivariate regression models as a continuous variable and tested by extra-sum-of-squares *F* test. Sensitivity analyses were undertaken by also adjusting for antihypertensive medication use (time-dependent variable), for incident CVD (CHD, stroke, diabetes mellitus, and atrial fibrillation), and for pulse pressure over time. All statistical tests were 2 sided. To address concerns about multiple comparisons, a conservative Bonferroni correction was used, and values of *p* < 0.003 (0.05/18 simultaneous tests) were considered to be statistically significant. Analyses were performed with SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC).

Table 3 BPV and brain and lesion volumes in the WHIMS-MRI Study

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Brain volume, cm ³	Frontal lobe volume, cm ³	Hippocampal volume, cm ³	Total lesion volume, cm ^{3c}	White matter lesion, cm ^{3c}	Gray matter lesion volume, cm ^{3c}
SBPV (SD from the mean)^d										
T1	1.2–8.38	186	7.53	7.96	868.7 (852.0–885.5)	179.7 (174.0–185.4)	5.89 (5.73–6.05)	5.60 (4.02–7.18)	3.86 (2.91–4.81)	1.74 (1.01–2.47)
T2	8.42–11.72	186	7.59	7.95	862.1 (845.9–878.3)	180.1 (174.6–185.6)	5.77 (5.61–5.93)	6.46 (4.93–7.98)	4.21 (3.30–5.13)	2.24 (1.54–2.95)
T3	11.72–26.2	186	7.60	8.01	856.5 (839.9–873.1)	177.0 (171.4–182.6)	5.65 (5.49–5.81)	6.92 (5.35–8.48)	4.62 (3.68–5.56)	2.29 (1.57–3.02)
p Value for trend					0.1500	0.3678	0.0038	0.1006	0.1149	0.1319
Systolic BPV (SDreg from the least-squares regression line)^e										
T1	1.3–7.6	186	7.46	7.91	866.5 (849.6–883.4)	180.6 (174.9–186.3)	5.92 (5.75–6.08)	5.53 (3.95–7.11)	3.65 (2.70–4.60)	1.88 (1.15–2.61)
T2	7.6–11.09	186	7.59	7.99	856.5 (839.9–873.1)	177.9 (172.3–183.5)	5.72 (5.56–5.88)	6.54 (4.99–8.09)	4.27 (3.34–5.20)	2.27 (1.56–2.99)
T3	11.10–29.2	186	7.67	8.02	863.8 (847.7–879.9)	178.6 (173.2–184.0)	5.69 (5.53–5.85)	6.88 (5.37–8.38)	4.69 (3.78–5.59)	2.19 (1.50–2.88)
p Value for trend					0.7164	0.4577	0.0055	0.0840	0.0276	0.3816
DBPV (SD from the mean)^d										
T1	1.7–4.99	186	7.60	8.00	862.4 (846.3–878.5)	178.1 (172.7–183.6)	5.79 (5.63–5.94)	6.43 (4.92–7.95)	4.29 (3.38–5.20)	2.14 (1.44–2.84)
T2	4.99–6.45	186	7.46	7.92	861.3 (845.0–877.7)	179.7 (174.2–185.2)	5.78 (5.62–5.94)	5.70 (4.16–7.24)	3.92 (3.00–4.85)	1.78 (1.07–2.49)
T3	6.45–15.7	186	7.65	8.00	862.9 (846.2–879.7)	179.0 (173.3–184.7)	5.72 (5.55–5.88)	7.01 (5.43–8.58)	4.56 (3.62–5.51)	2.44 (1.72–3.17)
p Value for trend					0.9516	0.7437	0.4067	0.4643	0.5650	0.4029
DBPV (SDreg from the least-squares regression line)^e										
T1	0.9–4.54	186	7.50	7.94	855.4 (839.0–871.8)	176.1 (170.6–181.6)	5.78 (5.62–5.94)	5.58 (4.04–7.12)	3.77 (2.85–4.69)	1.81 (1.10–2.52)
T2	4.55–6.09	186	7.55	7.96	867.4 (850.6–884.3)	182.1 (176.4–187.7)	5.81 (5.64–5.97)	7.03 (5.45–8.60)	4.56 (3.61–5.50)	2.47 (1.74–3.20)

Continued

Table 3 BPV and brain and lesion volumes in the WHIMS-MRI Study (continued)

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Brain volume, cm ³	Frontal lobe volume, cm ³	Hippocampal volume, cm ³	Total lesion volume, cm ^{3c}	White matter lesion, cm ^{3c}	Gray matter lesion volume, cm ^{3c}
T3	6.09–15.8	186	7.66	8.02	864.4 (848.4–880.4)	179.1 (173.7–184.5)	5.72 (5.56–5.87)	6.48 (4.99–7.98)	4.40 (3.50–5.30)	2.08 (1.39–2.77)
<i>p</i> Value for trend					0.2654	0.2674	0.4086	0.2348	0.1658	0.4406

Abbreviations: BP = blood pressure; BPV = blood pressure variability; DBPV = diastolic blood pressure variability; SBPV = systolic blood pressure variability; SDreg = SD about the participant's regression line; T = tertile; WHIMS-MRI = Women's Health Initiative Memory MRI Study.

Sensitivity analysis also was adjusted for antihypertensive medication use during follow-up.

^a BPV was calculated from all available BP measures that occurred before baseline MRI.

^b Follow-up years defined as number of years between study enrollment and MRI baseline assessment.

^c Lesion volumes were adjusted for total brain volume.

^d SD about the participant's mean BP across visits. Model adjusted for age, education, presence of APOE ε4 allele, Women's Health Initiative hormone therapy randomization arm, mean BP, and antihypertensive medication use.

^e SD about the participant's regression line with BP across visits. Model adjusted for age, education, presence of APOE ε4 allele, smoking status, Women's Health Initiative hormone therapy randomization arm, antihypertensive medication use, mean BP, and slope of BP change across visits.

Standard protocol approvals, registrations, and patient consents

The NIH and the institutional review boards for the WHI Clinical Coordinating Center and each WHI clinical center approved the WHI and WHIMS protocols and consent forms (ClinicalTrials.gov identifier NCT00685009). Written informed consent was obtained for each MRI; the NIH and the institutional review boards of participating institutions approved the protocols and consent forms.

Data availability

The deidentified participant data, analytical methods, and study materials are available to other researchers for purposes of reproducing the results or replicating the procedure. WHI data can be obtained from BioLINCC, a public repository maintained by the US National Heart, Lung, and Blood Institute. The BioLINCC website (accessed via biolincc.nhlbi.nih.gov/) includes detailed information about the available data and the process to obtain such data.

Results

Baseline characteristics of study participants at the time of enrollment are presented in table 1. Included women were ≈69 years old, and the mean BP was 122/73 mm Hg. Participating women were subsequently followed up over a median of 8.0 years. During the follow-up period, 48% developed hypertension, 3% developed diabetes mellitus, and 1% developed CHD, including stroke.

BPV and morphologic MRI assessments

In multivariate analyses, higher tertiles of SDs of SBP were associated with lower hippocampal volume and higher lesion volumes, although the association did not reach significance for lesion volumes (table 2). Similarly, higher tertiles of SBP SDreg were associated with lower hippocampal volume, higher total lesion volumes, and higher white matter lesion volumes. None of the associations with hippocampal volumes significantly changed on adjustment for use of antihypertensive therapy, incident cardiovascular events, or pulse pressure over time, but the associations with lesions volumes were slightly attenuated (tables 3–5). We did not find associations between DBPV and MRI measures.

BPV and cognitive function

Cognitive function was assessed in a subgroup of 160 women with a mean age of 70 years (SD 4.0 years) at baseline until February 2008 with an average of 9 (SD 1.6) 3MSE assessments. Neither SBPV nor DBPV was associated with changes from baseline average 3MSE scores or average annual 3MSE changes (table 6). 3MSE scoring did not correlate with lesion volumes but did correlate with hippocampal volume ($r = 0.31$, $p \leq 0.0001$) (table 7 available from Dryad, doi.org/10.5061/dryad.c0k37q6).

Discussion

Our results add important information to the available evidence on BPV and its relationship to brain morphology and

Table 4 BPV and brain and lesion volumes in the WHIMS-MRI Study

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Brain volume, cm ³	Frontal lobe volume, cm ³	Hippocampal volume, cm ³	Total lesion volume, cm ^{3c}	White matter lesion, cm ^{3c}	Gray matter lesion volume, cm ^{3c}
SBPV (SD from the mean)^d										
T1	1.2–8.4	186	7.53	7.96	869.0 (852.3–885.8)	179.7 (174.0–185.3)	5.89 (5.73–6.05)	5.58 (4.00–7.16)	3.85 (2.91–4.80)	1.73 (1.00–2.46)
T2	8.4–11.7	186	7.59	7.95	862.4 (846.2–878.5)	179.9 (174.5–185.4)	5.77 (5.61–5.93)	6.44 (4.92–7.97)	4.22 (3.31–5.13)	2.23 (1.52–2.93)
T3	11.7–26.2	186	7.60	8.01	855.9 (839.3–872.5)	176.7 (171.1–182.3)	5.65 (5.48–5.81)	7.00 (5.43–8.56)	4.67 (3.74–5.61)	2.32 (1.60–3.05)
p Value for trend					0.1211	0.3014	0.0033	0.0760	0.0870	0.1056
SBPV (SDreg from the least-squares regression line)^e										
T1	1.3–7.6	186	7.46	7.91	866.8 (850.0–883.7)	180.5 (174.8–186.1)	5.91 (5.75–6.08)	5.46 (3.88–7.04)	3.63 (2.68–4.58)	1.83 (1.10–2.56)
T2	7.6–11.1	186	7.59	7.99	856.8 (840.2–873.3)	177.8 (172.3–183.4)	5.72 (5.56–5.88)	6.48 (4.93–8.03)	4.25 (3.32–5.18)	2.23 (1.52–2.95)
T3	11.1–29.2	186	7.67	8.02	863.3 (847.2–879.4)	178.3 (172.9–183.7)	5.69 (5.53–5.85)	6.97 (5.47–8.48)	4.74 (3.84–5.64)	2.23 (1.54–2.93)
p Value for trend					0.6489	0.4352	0.0053	0.0515	0.0178	0.2561
DBPV (SD from the mean)^d										
T1	1.7–5.0	186	7.60	8.00	862.9 (846.8–878.9)	178.2 (172.8–183.6)	5.79 (5.63–5.94)	6.41 (4.90–7.91)	4.28 (3.37–5.18)	2.13 (1.43–2.83)
T2	5.0–6.5	186	7.46	7.92	861.7 (845.3–878.0)	179.6 (174.1–185.1)	5.78 (5.62–5.94)	5.70 (4.16–7.24)	3.93 (3.01–4.85)	1.77 (1.06–2.48)
T3	6.5–15.7	186	7.65	8.00	862.0 (845.2–878.8)	178.5 (172.9–184.2)	5.72 (5.55–5.88)	7.10 (5.53–8.68)	4.63 (3.68–5.57)	2.48 (1.75–3.20)
p-trend					0.9134	0.9015	0.3616	0.3539	0.4381	0.3175
DBPV (SDreg from the least-squares regression line)^e										
T1	0.9–4.5	186	7.50	7.94	855.9 (839.5–872.2)	176.0 (170.5–181.5)	5.78 (5.62–5.94)	5.52 (3.98–7.05)	3.75 (2.83–4.67)	1.77 (1.06–2.48)
T2	4.6–6.1	186	7.55	7.96	867.5 (850.6–884.3)	182.0 (176.4–187.6)	5.80 (5.64–5.97)	7.02 (5.44–8.60)	4.56 (3.61–5.50)	2.46 (1.73–3.19)

Continued

Table 4 BPV and brain and lesion volumes in the WHIMS-MRI Study (continued)

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Brain volume, cm ³	Frontal lobe volume, cm ³	Hippocampal volume, cm ³	Total lesion volume, cm ^{3c}	White matter lesion, cm ^{3c}	Gray matter lesion volume, cm ^{3c}
T3	6.1–15.8	186	7.66	8.02	863.8 (847.9–879.8)	178.8 (173.4–184.1)	5.71 (5.56–5.87)	6.56 (5.06–8.06)	4.45 (3.56–5.35)	2.11 (1.41–2.80)
<i>p</i> Value for trend					0.3214	0.3089	0.3977	0.1671	0.1182	0.3359

Abbreviations: BP = blood pressure; BPV = blood pressure variability; DBPV = diastolic blood pressure variability; SBPV = systolic blood pressure variability; SDreg = SD about the participant's regression line; T = tertile; WHIMS-MRI = Women's Health Initiative Memory MRI Study.

Sensitivity analysis also was adjusted for cardiovascular disease during follow-up.

^a BPV was calculated from all available BP measures that occurred before baseline MRI.

^b Follow-up years were defined as number of years between study enrollment and MRI baseline assessment.

^c Lesion volumes were adjusted for total brain volume.

^d SD about the participant's mean bp across visits. Model adjusted for age, education, presence of APOE ε4 allele, Women's Health Initiative hormone therapy randomization arm, mean BP, and cardiovascular disease.

^e SD about the participant's regression line with blood pressure across visits. Model adjusted for age, education, presence of APOE ε4 allele, smoking status, Women's Health Initiative hormone therapy randomization arm, antihypertensive medication use, cardiovascular disease, mean BP, and slope of BP change across visits.

cognitive functioning. In elderly postmenopausal women without a history of CVD and few modifiable cardiovascular risk factors, long-term SBPV was associated with smaller hippocampal volumes and larger white and gray matter lesion volumes in later life. No association between BPV and cognitive function was detected.

Morphologic brain changes, including white matter lesions, are commonly detected in the elderly. However, they occur more frequently in individuals at high risk for CVD such as patients with hypertension or diabetes mellitus.^{25,26} Most studies on BPV, brain morphology, and risk of vascular or cognitive outcomes involved predominantly individuals with a history of CVD and with a range of modifiable risk factors, although the risk of cognitive impairment is markedly affected by several comorbid conditions and by the duration and type of such comorbid conditions.^{1–3} This study, which involved women without a history of CVD and few modifiable cardiovascular risk factors at baseline, was an attempt to fill this gap. Our results indicate that higher SBPV compared to lower SBPV is related to changes in brain morphology independently of mean SBP. These findings remained after accounting for important confounding variables such as antihypertensive treatment and incident cardiovascular events over time. Thus, the observations point to potentially undetected underlying processes, diseases, or dysfunctions in that we found increases in white and gray matter lesion volumes and a decrease in hippocampal volumes. We did not see significant corresponding functional changes in 3MSE scoring in individuals with high BPV (although a weak correlation between 3 MSE scoring and hippocampal volume was detected).

Our data suggest that long-term SBPV represents an important risk factor contributing to deteriorating brain morphology. Because morphologic changes tend to precede functional disturbances, women with higher long-term SBPV may constitute a population at risk. However, women with fewer cardiovascular risk factors may still have mechanisms available (brain reserve hypothesis) to compensate for a slightly altered brain morphology. Over time, depending on the duration and magnitude of exposure, we expect a decrease in functioning to occur. This study may not have been able to capture this relationship because our follow-up period may have been too short.

Few studies have examined the associations between BPV and cognitive outcomes so far. In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) Study, which included mostly individuals at high risk for CVD, higher SBPV was found to be associated with lower hippocampal volume and higher risk of cortical infarcts.² Moreover, higher SBPV was related to worse cognitive performance, a finding that is in line with pooled cognition data from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) trials and with results from

Table 5 BPV and brain and lesion volumes in the WHIMS-MRI Study

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Brain volume, cm ³	Frontal lobe volume, cm ³	Hippocampal volume, cm ³	Total lesion volume, cm ^{3c}	White matter lesion, cm ^{3c}	Gray matter lesion volume, cm ^{3c}
SBPV (SD from the mean)^d										
T1	1.2–8.4	186	7.53	7.96	869.0 (852.3–885.7)	179.7 (174.1–185.3)	5.89 (5.73–6.05)	5.56 (3.98–7.13)	3.84 (2.89–4.78)	1.72 (0.99–2.45)
T2	8.4–11.7	186	7.59	7.95	862.7 (846.5–878.8)	180.3 (174.8–185.7)	5.77 (5.61–5.93)	6.41 (4.89–7.92)	4.19 (3.28–5.10)	2.22 (1.52–2.92)
T3	11.7–26.2	186	7.60	8.01	856.8 (840.2–873.4)	177.4 (171.9–183.0)	5.64 (5.48–5.81)	7.03 (5.47–8.60)	4.68 (3.74–5.62)	2.36 (1.64–3.08)
p Value for trend					0.1493	0.4333	0.0031	0.0640	0.0812	0.0810
SBPV (SDreg from the least-squares regression line)^e										
T1	1.3–7.6	186	7.46	7.91	866.7 (849.8–883.5)	180.5 (174.8–186.1)	5.92 (5.75–6.08)	5.38 (3.81–6.95)	3.58 (2.63–4.53)	1.80 (1.07–2.52)
T2	7.6–11.1	186	7.59	7.99	857.0 (840.5–873.5)	178.1 (172.5–183.6)	5.72 (5.56–5.88)	6.46 (4.91–8.00)	4.23 (3.30–5.16)	2.23 (1.52–2.94)
T3	11.1–29.2	186	7.67	8.02	864.2 (848.1–880.3)	179.1 (173.7–184.4)	5.69 (5.53–5.84)	7.02 (5.52–8.53)	4.75 (3.85–5.66)	2.27 (1.58–2.96)
p Value for trend					0.7415	0.5979	0.0045	0.0347	0.0128	0.1825
DBPV (SD from the mean)^d										
T1	1.7–5.0	186	7.60	8.00	862.9 (846.8–878.9)	178.2 (172.9–183.6)	5.79 (5.63–5.94)	6.39 (4.88–7.90)	4.27 (3.36–5.17)	2.12 (1.43–2.82)
T2	5.0–6.5	186	7.46	7.92	862.5 (846.2–878.8)	180.3 (174.8–185.8)	5.78 (5.62–5.94)	5.71 (4.18–7.25)	3.92 (3.00–4.84)	1.79 (1.09–2.50)
T3	6.5–15.7	186	7.65	8.00	862.4 (845.7–879.1)	178.9 (173.3–184.5)	5.72 (5.55–5.88)	7.07 (5.50–8.64)	4.60 (3.65–5.54)	2.47 (1.75–3.20)
p Value for trend					0.9503	0.8005	0.3678	0.3619	0.4613	0.3090
DBPV (SDreg from the least-squares regression line)^e										
T1	0.9–4.5	186	7.50	7.94	856.5 (840.2–872.9)	176.6 (171.1–182.1)	5.78 (5.62–5.94)	5.52 (3.99–7.06)	3.73 (2.81–4.66)	1.79 (1.08–2.50)
T2	4.6–6.1	186	7.55	7.96	867.9 (851.1–884.8)	182.4 (176.7–188.0)	5.80 (5.64–5.97)	7.04 (5.46–8.62)	4.56 (3.61–5.51)	2.48 (1.75–3.21)

Continued

Table 5 BPV and brain and lesion volumes in the WHIMS-MRI Study (continued)

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Brain volume, cm ³	Frontal lobe volume, cm ³	Hippocampal volume, cm ³	Total lesion volume, cm ^{3c}	White matter lesion, cm ^{3c}	Gray matter lesion volume, cm ^{3c}
T3	6.1–15.8	186	7.66	8.02	864.1 (848.1–880.0)	179.0 (173.7–184.4)	5.72 (5.56–5.87)	6.52 (5.03–8.02)	4.42 (3.53–5.32)	2.10 (1.41–2.79)
p Value for trend					0.3483	0.3635	0.4113	0.1840	0.1275	0.3705

Abbreviations: BP = blood pressure; BPV = blood pressure variability; DBPV = diastolic blood pressure variability; SBPV = systolic blood pressure variability; SDreg = SD about the participant's regression line; T = tertile; WHIMS-MRI = Women's Health Initiative Memory MRI Study.

^a BPV was calculated from all available BP measures that occurred before follow-up.

^b Sensitivity analysis also was adjusted for pulse pressure during follow-up.

^c Follow-up years were defined as number of years between study enrollment and MRI baseline assessment.

^d Lesions volumes were adjusted for total brain volume.

^e SD about the participant's mean BP across visits. Model adjusted for age, education, presence of APOE ε4 allele, Women's Health Initiative hormone therapy randomization arm, mean BP, mean pulse pressure, and cardiovascular disease.

^f SD about the participant's regression line with BP across visits. Model adjusted for age, education, presence of APOE ε4 allele, smoking status, Women's Health Initiative hormone therapy randomization arm, antihypertensive medication use, mean BP, mean pulse pressure, and slope of P change across visits.

community-dwelling Chinese adults.^{2,3,8} In contrast to SBPV, the relationship of DPBV with brain morphology and cognitive decline is less clear, and data are inconsistent across studies.^{2,8} Some found DPBV to be unrelated to cognitive decline at older age, an observation that also held true in our study population⁸; we did not find a relationship between DBPV, brain morphology, and cognitive functioning.

The pathophysiologic mechanisms linking BPV to brain injuries and impaired cognitive function are unclear.^{27–29} It is hypothesized that SBP fluctuations lead to cerebral hypoperfusion and silent vascular brain lesions.^{30,31} The blood-brain barrier may provide some protection to the brain against these BP fluctuations, which may also be the reason why DBPV seems less influential than SBPV, but ultimately, damage will manifest. Concomitant vascular structural changes, including arterial stiffness, endothelial dysfunction, and subclinical inflammation, have been described also to play a key role.^{8,32} Increased arterial stiffness leads to reduced dampening of BP in response to changes in stroke volume and thereby contributes to the harmful relationship between BPV and silent cerebral injuries, as reflected by white matter hyperintensities.³² Pulse pressure reflects arterial compliance. When we included pulse pressure in our adjusted modeling, our main results did not change significantly. This suggests the presence of other mediating factors. Autonomic dysfunction, including an exaggerated sympathetic nervous system and pressor response to physical and emotional stimuli, as well as blunted arterial baroreflex functioning, may contribute at least in part to the relationship.³³ In fact, prior animal studies using sinoaortic denervation, which causes significant increases in BPV without eliciting changes in mean BP levels, have demonstrated the influence of enhanced BPV on target organ damage.^{34,35} Finally, nonadherence to antihypertensive therapy and being under treatment are other possible contributors, although previous reports indicate that only a small percentage of BPV can be explained by low medication adherence.³⁶

Strengths of our analysis include a large, well-characterized cohort with long-term follow-up that included standardized BP assessments on an annual basis, as well as brain MRI scans and cognitive assessments with strict quality control assurance. These methodologic factors are important given the various reported definitions on BPV, the number of visits used to calculate BPV and the duration of time between visits.^{37–39} Nonetheless, there are several limitations. Most important, because our analyses included women who met the criteria for participation in the WHIMS clinical trial, our findings are not generalizable to other populations, including men and younger individuals.

In elderly postmenopausal women without a history of CVD and with few modifiable cardiovascular risk factors, greater SBPV was associated with significant reductions in hippocampal volume and increases in white and gray matter lesions

Table 6 BPV and change in 3MSE score in the WHIMS-MRI2 study (n = 160)²

	BPV, mm Hg ^a	Individuals, n	Mean BP measures, n	Mean follow-up, y ^b	Mean change in 3MSE score from baseline (95% CI)	Mean 3MSE annual change (95% CI)
SBPV (SD from the mean)^c						
T1	3.5–8.4	49	7.43	8.30	–2.85 (–5.92 to 0.21)	–0.33 (–0.67 to 0.01)
T2	8.4–11.7	51	7.71	9.02	–2.14 (–4.95 to 0.68)	–0.24 (–0.55 to 0.07)
T3	11.7–23.7	60	7.55	8.78	–1.19 (–3.93 to 1.55)	–0.15 (–0.45 to 0.15)
p Value for trend					0.2913	0.3111
SBPV (SDreg from the least-squares regression line)^d						
T1	2.0–7.6	49	7.43	8.45	–2.21 (–5.20 to 0.78)	–0.26 (–0.59 to 0.07)
T2	7.7–11.03	54	7.59	8.67	–1.92 (–4.88 to 1.04)	–0.23 (–0.56 to 0.09)
T3	11.3–23.1	57	7.65	8.97	–1.76 (–4.45 to 0.94)	–0.20 (–0.50 to 0.10)
p Value for trend					0.7746	0.7529
DBPV (SD from the mean)^c						
T1	1.7–4.9	50	7.72	8.91	–0.65 (–3.46 to 2.16)	–0.08 (–0.39 to 0.23)
T2	5.0–6.4	57	7.30	8.33	–2.47 (–5.19 to 0.25)	–0.30 (–0.60, 0.00)
T3	6.4–12.6	53	7.70	8.93	–2.88 (–5.82 to 0.05)	–0.31 (–0.63 to 0.02)
p Value for trend					0.1531	0.2000
DBPV (SDreg from the least-squares regression line)^d						
T1	1.6–4.5	49	7.59	8.68	–1.22 (–4.18 to 1.74)	–0.18 (–0.50 to 0.15)
T2	4.6–6.1	55	7.51	8.78	–1.73 (–4.54 to 1.08)	–0.19 (–0.50 to 0.12)
T3	6.1–11.4	56	7.59	8.67	–2.80 (–5.56 to –0.04)	–0.32 (–0.62 to –0.01)
p Value for trend					0.3052	0.3936

Abbreviations: BP = blood pressure; BPV = blood pressure variability; CI = confidence interval; DBPV = diastolic blood pressure variability; SBPV = systolic blood pressure variability; SDreg = SD about the participant's regression line; T = tertile; 3MSE = Modified Mini-Mental State Examination; WHIMS-MRI2 = Women's Health Initiative Memory MRI Substudy.

^a Blood pressure variability was calculated from all available BP measures that occurred before the last known 3MSE score.

^b Follow-up years defined as number of years between study enrollment and last known 3MSE score.

^c SD about the participant's mean BP across visits. Model adjusted for age, education, presence of *APOE* ε4 allele, WHI hormone therapy randomization arm, and mean BP.

^d SD about the participant's regression line with BP across visits. Model adjusted for age, education, presence of *APOE* ε4 allele, WHI hormone therapy randomization arm, mean BP, and slope of BP change across visits.

but not with cognitive decline. These data suggest a possible role of SBPV as a prognostic indicator even in the absence of a documented history of CVD or cardiovascular risk factors. Monitoring SBPV over time may be a useful strategy for preserving cognitive health in elderly postmenopausal women.

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Jingmin Liu, MS	WHI	Author	Conducted the statistical analysis; revised the manuscript for intellectual content
Elena Salmoirago-Blotcher, MD, PhD	Brown University	Author	Interpreted the data; revised the manuscript for intellectual content
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Gloria Sarto, PhD	University of Wisconsin	Author	Interpreted the data; revised the manuscript for intellectual content
Jacques Roussouw, MD	WHI	Author	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Lew H. Kuller, MD, PhD	University of Pittsburgh	Author	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
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