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Visit-to-visit Blood Pressure Variability in Young Adulthood and Hippocampal Volume and Integrity at Middle Age: Coronary Artery Risk Development in Young Adults (CARDIA) study:

Blood Pressure Variability and Hippocampus

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Abstract

The aims of this study are to assess the relationships of visit-to-visit blood pressure (BP) variability in young adulthood to hippocampal volume and integrity at middle age. We used data over eight examinations spanning 25 years collected in the Coronary Artery Risk Development in Young Adults (CARDIA) Study of black and white adults (age 18–30 years) started in 1985–1986.

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Visit-to-visit BP variability was defined as by standard deviation (SD_{BP}) and average real variability (ARV_{BP}, defined as the absolute differences of BP between successive BP measurements). Hippocampal tissue volume standardized by intracranial volume (%) and integrity assessed by fractional anisotropy (FA) were measured by 3-Tesla MRI at the Year 25 examination (n=545, mean age 51 years; 54% women; and 34% African Americans). Mean systolic BP (SBP)/diastolic BP (DBP) levels were 110/69 mmHg at Year 0 (baseline), 117/73 mmHg at Year 25, and ARV_{SBP} and SD_{SBP} were 7.7 and 7.9 mmHg, respectively. In multivariable-adjusted linear models, higher ARV_{SBP} was associated with lower hippocampal volume (unstandardized regression coefficient [standard error] with 1 SD higher ARV_{SBP}: −0.006 [0.003]), and higher SD_{SBP} with lower hippocampal FA (−0.02 [0.01]; all $P<0.05$), independent of cumulative exposure to SBP during follow-up. Conversely, cumulative exposure to SBP and DBP was not associated with hippocampal volume. There was no interaction by sex or race between ARV_{SBP} or SD_{SBP} with hippocampal volume or integrity. In conclusion, visit-to-visit BP variability during young adulthood may be useful in assessing the potential risk for reductions in hippocampal volume and integrity in midlife.

Keywords

Blood pressure variability; brain; hippocampus; young adult

Introduction

Higher blood pressure (BP) levels and variability appear to enhance vascular damage or lead to periods of organ hypoperfusion.[1–6] Chronically higher BP is linked to lower cognitive function in individuals <50 years of age.[7–9] In addition to BP levels, our previous study revealed that BP variability over multiple time points (i.e., long-term visit-to-visit BP variability) in young adulthood may be associated with lower cognitive function, and memory function in particular, at middle age.[10] However, whether visit-to-visit BP variability in young adulthood is associated with brain structural and functional changes is unknown.

Reductions in hippocampal volume and microstructural integrity are of particular interest as they are correlated with cognitive dysfunction,[11–14] Alzheimer's disease,[15,16] and vascular dementia.[17] Sabayan et al., evaluated several brain MRI measures in relation to visit-to-visit BP variability in adults >70 years of age. These investigators observed that greater visit-to-visit BP variability was associated with lower hippocampal volumes.[18] Given that hippocampal neurons are highly vulnerable to disturbances of the cerebral circulation,[18,19] we hypothesized that higher visit-to-visit BP variability may be linked to lower hippocampal volume and integrity. Whether early exposure to higher BP levels and variability are associated with hippocampal volume and integrity in later life is unknown.

To understand the association of BP during young adulthood with brain structural changes at middle age, a lifespan approach is crucial. However, conducting lifespan studies is challenging due to the many years of follow-up required. We are uniquely positioned to fill these knowledge gaps, using data from the Coronary Artery Risk Development in Young

Adults (CARDIA) Study. CARDIA enrolled black and white adults in young adulthood and followed them for 25 years via 8 clinical examinations. As a part of the Year 25 examination, brain MRI scans were obtained in 710 participants. Using data from CARDIA, we sought to assess the relationships between visit-to-visit BP variability in young adulthood and hippocampal volume and integrity at middle age, and to determine whether these associations are independent of cumulative exposure to BP levels in young adulthood.

Methods

The CARDIA study began in 1985–1986 with the examination of 5,115 black and white adults ages 18 to 30 years from 4 US field centers: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California.[20] All participants provided written informed consent, and institutional review boards at each field center and the coordinating center approved the study annually. By design, the cohort was balanced with respect to race (52% of the participants are black), sex (55% are women), and educational level (40% have ≤12 years of education). Serial follow-up examinations were conducted 2 (Y_2), 5 (Y_5), 7 (Y_7), 10 (Y_{10}), 15 (Y_{15}), 20 (Y_{20}) and 25 (Y_{25}) years after baseline (Y_0). At Y_{25}, 72% of the surviving cohort were re-examined, and as part of this, a sub-sample was invited to participate in the CARDIA brain magnetic resonance imaging (MRI) sub-study.[21] Participants for this sub-study were recruited from 3 of the 4 CARDIA field centers (Birmingham, Minneapolis, and Oakland). Exclusion criteria at the time of sample selection, or at the MRI site, were a contraindication to MRI, suspected pregnancy, or a body size that was too large for the MRI tube bore. Separate written consent for participation in the brain MRI sub-study was obtained, and separate approval was given by the institutional review boards governing participating sites. Of a total of 719 participants, 710 participants provided adequate MRI images for analysis.

BP and other measurements

Participants were asked to fast and to abstain from smoking or heavy physical activity for at least 12 hours before each examination. From the Y_0 to Y_{15} examinations, trained research staff measured right-arm brachial artery BP three times at 1-minute intervals after the participant had been sitting in a quiet room for 5 minutes, using a Hawksley random-zero sphygmomanometer (Hawksley, Sussex, UK).[10] The average of the second and third measurements were used for the analysis. At the Y_{20} and Y_{25} examinations, concerns about mercury contained in the apparatus required a switch to an automated oscillometric BP monitor (Omron HEM-907XL; Online Fitness, Santa Monica, CA). A calibration study was performed, and values standardized to the sphygmomanometric measures were used for Y_{20} and Y_{25} BP measurements, so that no machine bias remained.[10] The details are described in the online-only Data Supplement. Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or use of antihypertensive medication.

The primary exposure of the current study is visit-to-visit BP variability calculated from Y_0 to Y_{25} BP measurements. We calculated the standard deviation (SD_{BP}: SD_{SBP} and SD_{DBP}), coefficient of variation, the maximum and minimum BP difference, and average real variability (ARV_{BP}: ARV_{SBP} and ARV_{DBP}) across 8 visits (Figure 1). ARV was calculated

as (ΔBP1+ΔBP2+ΔBP3+ΔBP4+ΔBP5+ΔBP6+ΔBP7)/7 where ΔBP is the absolute difference between successive BP measurements. These measures have been used to describe visit-to-visit BP variability in previous studies.[1–6,10,22] However, these parameters are partially dependent on the overall BP level and change in mean BP levels over time. Distinguishing BP variability from systemic changes in BP level over time (e.g., slope) could thus be difficult.[4] The issue may not be resolved even if we use mean BP level over visits as an adjustment factor. Cumulative exposure to BP (mm Hg×years), defined as the summed average BP for each pair of consecutive examinations multiplied by the time between these two consecutive visits in years (Figure 1),[10] reflects not only mean BP level but also systemic change in BP level over time.[23] Therefore, we used cumulative exposure to BP as an adjustment factor.

Other data, including education, height, weight, smoking, alcohol consumption, physical activity, medication use, clinical history of CVD, and fasting laboratory values were collected using standardized protocols and quality control procedures across study centers.[20,24] APOE phenotype was determined from plasma samples by a modification of the methods of Kamboh et al.[25] Participants were classified according to APOE phenotype (E2.2, E3.2, E3.3, E4.2, E4.3 and E4.4).[26]

MRI acquisition and processing

MRI scans were obtained for participants using 3-Tesla MR scanners located proximal to each CARDIA clinical site. Details of the scanners, training of MRI technologists at the different sites, implementation of study protocols, and quality assurance of scanner stability and performance are described in the online-only Data Supplement.[21] Normal tissue volumes of hippocampus, gray matter, white matter, and total brain (sum of the gray and white matter) and total intracranial volume (total brain plus cerebral spinal fluid volumes) were estimated from sagittal 3D T1 images. Each brain normal tissue volume was standardized by dividing each by the intracranial volume. Brain microstructural tissue integrity and organization were estimated from axial Diffusion Tensor Images (DTI). Here we analyzed the values of the DTI-derived fractional anisotropy (FA). FA ranges from 0 to 1 and estimates the degree (or uniformity) to which water diffuses along the direction of myelinated tracks in the brain; a “0” indicates equal probability of diffusion in all directions (i.e. there is no structural restriction to the flow of molecules), and a ‘1’ indicates the diffusion occurs along one axis (e.g., the white matter tract).[21,27] The clinical relevance of hippocampal FA as a measure of hippocampal integrity has been reported.[28,29]

Image processing was performed by the Section of Biomedical Image Analysis, Department of Radiology, University of Pennsylvania. The quality control procedures were described in online-only Data Supplement. The technical error of measurement, an accuracy index that reflects measurement quality of both acquisition and processing of scans, was estimated from scans of 3 persons measured 3 times in the 3 centers; results were 1.2% for total brain tissue volume and 3.4% for white-matter FA.

Statistical analyses

Descriptive statistics are presented as means and SD, proportions, and medians with interquartile ranges where appropriate. Correlations between visit-to-visit BP variability measurements and clinical characteristics were calculated by Pearson correlation method. Multivariable-adjusted linear regression models were used to assess the association between visit-to-visit BP variability measurements and brain MRI variables (all as continuous variables). The primary outcomes were measures of hippocampal normal tissue volume and integrity (i.e., [hippocampus volume×100]/intracranial volume and hippocampal FA). The primary exposures were measures of visit-to-visit BP variability (i.e., SD_{SBP}, SD_{DBP}, ARV_{SBP}, and ARV_{DBP}). To determine whether associations were driven by total brain tissue, we also examined as secondary outcomes, associations of BP variability to total brain, gray matter, and white matter.

FA measures were log-transformed before analyses because of the skewed distributions. Possible violations of the assumptions of multiple linear regression were examined by visual inspection of the distribution of residuals through both histograms and normal probability plots. We further checked for deviations of linearity and homoscedasticity by visually inspecting scatterplots of standardized residuals by standardized predicted values. In addition, we assessed variance inflation factors to examine the possibility of multicollinearity and values >2.5 were considered to indicate collinearity. Covariates included demographic variables: age, sex, race, education attainment, and clinical characteristics at Y_{25}: body mass index (BMI), smoking, physical activity, fasting glucose, and use of antihypertensive medications. These covariates were selected *a priori* because they have known correlations with BP variability[1–6,10,22,30] and brain structural abnormalities[31] and could potentially confound the association between these two variables. Analyses for heterogeneity of effect between visit-to-visit BP variability measurements and brain MRI variables by sex or race were performed, with inclusion of additive interaction terms.

We conducted sensitivity analyses by: (1) excluding individuals taking antihypertensive medications over follow-up; (2) defining BP measurements through Y_0 to Y_{20}, avoiding the inclusion of the late assessment of BP (Y_{25}) that might already have been affected by comorbidities (e.g., atherosclerotic and brain function changes);[1,2] and (3) imputing missing data on BP and covariates. We used multiple imputation chained equations with 20 iterations as described by Raghunathan.[32] All statistical analyses were performed with STATA version 12.1 (STATACorp; College Station, TX). Statistical significance was defined by a *P* value <0.05 using 2-sided tests.

Results

Of the 710 participants, we excluded 5 participants who experienced stroke prior to the Y_{25} examination, 132 participants with at least 1 missing BP measurement during the follow-up period, and 26 participants with any missing covariates at Y_{25}, leaving a sample of 547 participants for analysis. Of the 547 participants, 54% were women, 34% were black race, mean (SD) age at baseline was 26 (3) years, and 22% reported antihypertensive medication use during follow-up (Table 1). The race- or sex-specific prevalence of hypertension at Y_{25}

was: black individuals 38.0%; white individuals 20%; men 26.2%; and women 26.1%. The coefficient of variation and the maximum and minimum BP differences were strongly correlated with SD_{BP} (Pearson's r>0.95; Supplementary Table S1), and therefore we only report SD_{BP} and ARV_{BP} as a measure of BP variability. ARV_{SBP} and SD_{SBP} were positively associated with cumulative exposure to SBP (Pearson's r 0.2–0.4).

Supplementary Tables S2–S4 show the associations of ARV_{BP} and SD_{BP} with clinical characteristics. ARV_{SBP} and SD_{SBP} were higher, whereas cumulative exposure to SBP was lower in women than in men. Black race, higher BMI, smoking, and antihypertensive medication use during follow-up were associated with higher ARV_{SBP} and SD_{SBP} ($P<0.05$ for all). Apolipoprotein E ε4 allele was not associated with ARV_{BP} and SD_{BP}.

With adjustments for covariates including cumulative exposure to SBP, higher ARV_{SBP} was associated with lower normal tissue volumes of the hippocampus, gray matter, and total brain, whereas higher ARV_{DBP} and SD_{DBP} were associated with lower white-matter and total brain volumes (Table 2). In Model 1A or 2A in Table 2, a one-SD increase in cumulative exposure to SBP (+232.2 mmHg×years) or DBP (+186.6 mmHg×years) was not associated with normal tissue volumes of the hippocampus (unstandardized regression coefficient [SE]: 0.005 [0.003] and 0.0001 [0.003]), gray matter (unstandardized regression coefficient [SE]: 0.100 [0.001] and 0.052 [0.094]), white matter (unstandardized regression coefficient [SE]: −0.111 [0.107] and −0.117 [0.100]), and total brain (unstandardized regression coefficient [SE]: −0.013 [0.125] and −0.065 [0.117]; all $P>0.12$). Higher SD_{SBP} was associated with lower value of hippocampal FA, independent of cumulative exposure to SBP (**Model 1B in** Table 3). Additional adjustments by apolipoprotein E ε4 allele (0 versus ≥1), pulse pressure at Y_{25}, drinking status at Y_{25}, and total cholesterol and high- density lipoprotein cholesterol levels at Y_{25} did not change the results (data not shown).

There was no evidence of interaction between ARV_{BP} (or SD_{BP}) and sex or race in association with brain MRI variables (all $P>0.15$). Results were similar when participants taking antihypertensive medications were excluded (analytic sample n=425, Supplementary Table S5 and S6). Visit-to-visit BP variability measurements calculated across 7 (Y_0–Y_{20}) visits were closely associated with those calculated across all 8 (Y_0–Y_{25}) visits (Pearson's r >0.8). Results were generally similar when BP variability measurements based upon these 7 visits were used as the exposure (data not shown). We imputed missing BP measurements and covariates, giving a sample of 710 participants for analysis. The observation numbers of imputed BP and covariates are shown in Supplementary Table S7. In 710 participants, the estimated mean (SD) age at baseline was 25 (4) years, 53% were women, 40 % were blacks, and 24% had antihypertensive medication use at Y_{15}. Mean values of ARV_{BP} and SD_{BP} using imputation were similar to those without imputation (Supplementary Table S8). Results with and without imputing missing BP and covariates were similar in terms of the point estimate for ARV_{BP} and SD_{BP} (Supplementary Table S9 and S10).

Discussion

In this community-based, biracial cohort of young adults followed for 25 years, higher ARV_{SBP} in young adulthood was associated with lower normal tissue volumes of the

hippocampus, gray matter, and total brain. In contrast, higher ARV_{DBP} was associated with lower white matter normal tissue volume. We also found higher SD_{SBP} in young adulthood to be associated with lower hippocampal integrity at middle age. These associations were independent of cumulative exposure to SBP over time. No heterogeneity of effect between visit-to-visit BP variability measurements and hippocampus volume and integrity measures by sex or race was observed.

Associations between visit-to-visit BP variability measurements and brain volume and integrity measures have been described but only in middle-aged and older adults.[19,33,34] In the Honolulu-Asia Aging study that recruited 575 Japanese-American men, higher visit-to-visit SBP variability in midlife (45–70 years old) was associated with white matter hyperintensities and brain ventricular atrophy in their eighties.[33] In the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) study, higher visit-to-visit SBP variability at an old age (>70 years) was associated with lower hippocampal volume (7.6 cm^2 in the 1st tertile vs. 7.5 cm^2 in the 2nd tertile vs. 7.4 cm^2 in the 3rd tertile of BP variability: *P* for trend=0.01).[18] However, BP variability in middle-aged and older populations might be affected by comorbidities (e.g., [silent] brain abnormalities and atherosclerosis). The design of our study, recruiting young adults without known stroke, minimized these potential confounding issues.

Cross-sectional observations from the Framingham Heart Study illustrated that, among 579 white young and middle-aged adults (19–63 years old), higher SBP levels were linearly associated with lower gray matter volume and white matter integrity (assessed by FA).[35] Hippocampal volume and integrity were not assessed. In addition, BP was measured on a single occasion,[35] a “snapshot” of BP that may not fully characterize an individual’s BP phenotypes in young adulthood that are linked to brain structural abnormalities later in life. We extend the finding by demonstrating that in a biracial cohort, those with higher visit-to-visit SBP variability instead of cumulative exposure to SBP in young adulthood were more likely to have lower hippocampal volume and integrity in middle age.[10]

There are several potential mechanisms that may underlie the observed visit-to-visit SBP variability - hippocampus association. First, excess BP variability appears to enhance vascular damage and lead to periods of organ hypoperfusion.[1,2] This may be true when short-term (e.g., beat-to-beat) BP variability is high. In contrast, whether this phenomenon also happens when visit-to-visit BP variability is high remains unclear. This is because short-term and long-term BP variability are weakly correlated and thus their pathophysiology may not be identical.[2,22] Second, large-artery stiffness, a major contributor to visit-to-visit SBP variability increase,[36] may mediate relations between higher visit-to-visit SBP variability and hippocampal structural abnormalities. Large-artery stiffness was shown to correlate with brain structural abnormalities,[37,38] potentially through microvascular injury by exposing the cerebrovasculature to high pressure fluctuations and flow pulsatility.[39,40] To test this possibility, analyses were performed adjusting for pulse pressure, with similar results observed. However, pulse pressure is an indirect marker of large arterial stiffness.[41] Third, higher visit-to-visit SBP variability may be merely epiphenomena of other contributing conditions. For example, adverse stressors (e.g., psychosocial stress and sleep deprivation), neurohormonal activation (e.g., sympathetic nerve activation), lower socioeconomic status,

and/or poor diet could lead to both visit-to-visit SBP variability increase and hippocampal damages.[1,2,42,43]

We observed that cumulative exposure to SBP or DBP was not associated with hippocampal volume. Mean±SD cumulative exposure to SBP and DBP over 25 years of follow-up was 2761.7±232.4 mmHg×years (110.4 mmHg per year) and 1765.0±186.8 mmHg×years (70.6 mmHg per year), respectively. Furthermore, the prevalence of hypertension at Y_{25} in this population appears to be lower than the prevalence in the US general population of the same age.[44] Although the reason is unclear, the difference might result from research participation effects (i.e., the Hawthorne effect).[45] This effect might mitigate BP increases during follow-up in CARDIA participants, which potentially dilutes any true association between cumulative exposure to BP and brain outcomes.

ARV_{SBP} was more consistently associated than SD_{SBP} with normal tissue volumes of the hippocampus, gray matter, and total brain, whereas SD_{SBP} but not ARV_{SBP} was associated with hippocampal integrity. Despite the strong correlation between ARV_{SBP} and SD_{SBP} (Pearson's r 0.7), their clinical implication may not be identical. ARV_{BP} weights for the between-reading time intervals and takes into account the order of the clinic visits at which BP was measured.[1,2] Conversely, SD_{BP} is influenced by outliers or extreme BP values.[1,2,46] We also observed that higher ARV_{SBP} was associated with lower gray matter normal tissue volume, whereas higher ARV_{DBP} with lower white matter normal tissue volume. Different BP components reflect distinctive hemodynamics and pathophysiology.[47] DBP, at least up to age 50, reflect a steady-state load of BP and are representative of resistant vessel structure and function alterations.[48,49] In contrast, SBP is an integrated measure of steady and pulsatile pressure load and representative of large arterial (aortic) stiffness and cardiac output.[48,50] To understand how hemodynamic physiology differs between gray and white matter, and whether the effect of each BP metrics is in fact regionally specific will require further investigations.

Strengths of this study include the well-characterized, community-based biracial cohort and the standardized data collection protocols and rigorous quality control of the CARDIA Study. However, there are limitations. First, since this is an observational study, we are unable to determine the direction of the relationships observed. We cannot conclude whether BP-lowering therapies for young adults with greater visit-to-visit BP variability are useful to prevent or slow cognitive decline. Visit-to-visit BP variability has been shown to be associated with lifestyle factors, including diet, exercise, smoking, and sleep.[10,22,51,52] Therefore, visit-to-visit BP variability measurements may be useful to identify young adults who may benefit from lifestyle modifications to maintain healthy brain function across their lifespans. Second, we could not assess changes in hippocampal volume and integrity from baseline to follow-up, and thus we cannot conclude whether low hippocampal volume or integrity at middle age reflects structural changes. Third, although statistically significant, the effect sizes of visit-to-visit SBP variability on hippocampal volume and integrity might be relatively small. Even subtle changes in hippocampal volume and integrity could result in a significant change in cognitive function, [14–17] it is unknown whether lower hippocampal volume and integrity associated with greater visit-to-visit SBP variability are linked to clinical outcomes. We need data from future CARDIA examinations, including cognitive

function measures, in order to explore longitudinal cognitive function in participants who had greater visit-to-visit BP variability. Fourth, we did not adjust for multiple testing. However, our analyses were not hypothesis free, i.e., this study was executed based on our prior work that illustrated the associations of higher visit-to-visit SBP variability in young adulthood with lower verbal memory at middle age.[10] Most of the significant hippocampus-BP variability associations we found were indicated by P values <0.05. Therefore, our results should be interpreted cautiously. Lastly, our findings may not be generalizable to other racial/ethnic groups (e.g., Asians).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspective

We highlight the clinical relevance of visit-to-visit BP variability in young adulthood, i.e., both BP levels overall, and BP variability specifically, appear important in identifying risk for brain structural abnormalities later in life. Validation of our findings in different studies/cohorts is warranted. Further studies will be required to determine whether reductions in visit-to-visit BP variability in young adulthood can help to limit declines in brain volume and integrity with aging.

Novelty and Significance

1) What Is New

Greater visit-to-visit SBP variability in young adulthood is associated with lower hippocampal volume and integrity in middle age.

2) What Is Relevant?

Visit-to-visit BP variability measurements may be useful to identify young adults who may benefit from lifestyle modifications to maintain healthy brain function across their lifespans.

3) Summary

We highlight the clinical relevance of visit-to-visit BP variability in young adulthood, i.e., both BP levels overall, and BP variability specifically, appear important in identifying risk for brain structural abnormalities later in life.

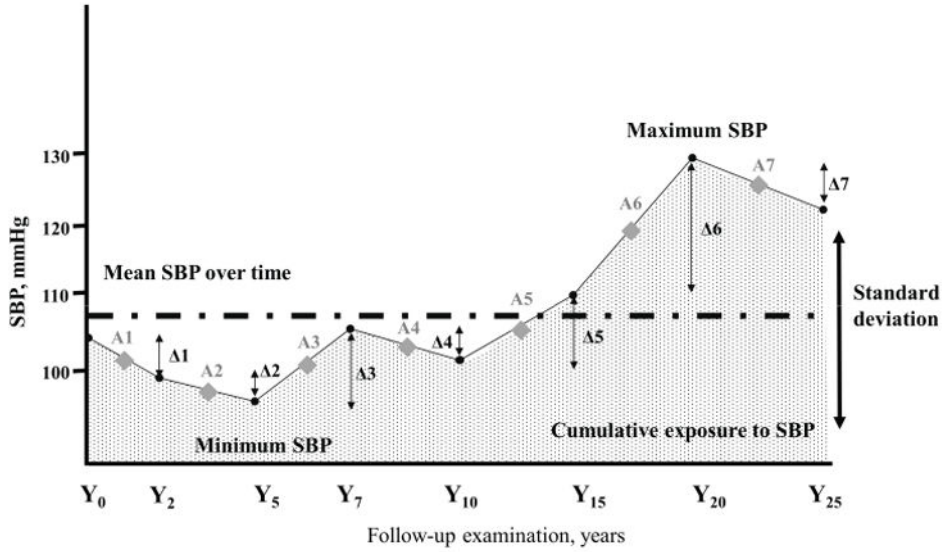

Figure 1. Illustration of visit-to-visit SBP variability measurements and cumulative exposure to SBP from Y_0 to Y_{25}

The figure shows one example of individual follow-up data of SBP across 8 visits (the Y_0−Y_{25} examinations). The absolute differences of SBP between successive SBP measurements are shown as Δ1–Δ7. For example, Δ1 represents the absolute difference in SBP between Y_0 and Y_2 SBPs. Average real variability (ARV) will be calculated as (Δ1+Δ2+Δ3+Δ4+Δ5+Δ6+Δ7)/7. Maximum and minimum SBP difference will be calculated as maximum SBP minus minimum SBP from Y_0 to Y_{25}. Mean BP and standard deviation over time will be calculated from 8 SBP measurements (Y_0−Y_{25}) for each individual, and coefficient of variation will be calculated as standard deviation/mean SBP over time. The average SBP between successive BP measurements is shown as A1–A7. Cumulative exposure to SBP will be calculated as (Cumulative exposure to BP was calculated as (A1×2 years+A2×3 years+A3×2 years+A4×3 years+A5×5 years+A6×5 years+A7×5 years) and is shown by the dotted area, representing in mm Hg×years.

Table 1

Clinical characteristics of study cohort (n=547)

Characteristics	Baseline (Y_0)	Follow-up (Y_{25})
Age, years	25.6±3.4	50.6±3.4
Men, %	46.1	
Black individuals %	34.2	
Educational attainment, years	14.2±2.1	
Body mass index, kg/m^2	23.6±4.0	28.7±5.8
Current smoker, %	22.7	12.8
Current drinker, %	63.2	59.8
Physical activity, exercise units	411.4±281.2	376.5±281.4
Fasting glucose, mg/dL	82.5±11.8	96.0±22.6
Total cholesterol, mg/dL	176.8±33.2	193.4±34.8
High-density lipoprotein, mg/dL	54.0±13.0	58.2±16.7
Antihypertensive medication use, %	0	21.2
APOE ε4 (≥1), %	29.6	
BP parameters at each visit		
SBP, mmHg	109.9±10.7	116.6±13.7
DBP, mmHg	68.9±9.2	72.5±10.4
BP parameters over 8 visits		
Visit-to-visit ARV_{SBP}	7.7±3.0	
Visit-to-visit ARV_{DBP}	7.1±2.8	
Visit-to-visit SD_{SBP}	7.9±3.4	
Visit-to-visit SD_{DBP}	6.8±2.7	
Cumulative exposure to SBP, mmHg×years	2761.7±232.4	
Cumulative exposure to DBP, mmHg×years	1765.0±186.8	
Brain MRI variables		
Normal tissue volume*		
Hippocampus, % ICV	N/A	0.57±0.06
Total brain, % ICV	N/A	81.27±2.35
Gray matter, % ICV	N/A	42.88±1.90
White matter, % ICV	N/A	38.39±1.95
Brain integrity**		
Hippocampus FA	N/A	0.32 (0.29 to 0.34)
Total brain FA	N/A	0.22 (0.22 to 0.23)
Gray matter FA	N/A	0.15 (0.14 to 0.16)
White matter FA	N/A	0.31 (0.29 to 0.32)

Data are expressed as the means ± standard deviations and percentages. Variable* (brain normal tissue volume) were standardized by dividing each by the intracranial volume. Variable** (FA measures), shown as medians with interquartile ranges, were not obtained from all participants (n=540).

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ARV, average real variability; SD, standard deviation; ICV, intracranial volume; FA, fractional anisotropy; N/A, not applicable.

Table 2

Associations between visit-to-visit BPV in young adulthood and normal brain tissue volume at middle age (n=547)

	Hippocampus, % ICV		Total brain, % ICV		Gray matter, % ICV		White matter, % ICV	
BPV measures	**β (SE)**	**R^2, %**	**β (SE)**	**R^2, %**	**β (SE)**	**R^2, %**	**β (SE)**	**R^2, %**
Model 1: SBP								
Model 1A								
Visit-to-visit $ARV_{SBP,}$ per 1SD increase	**−0.006 (0.003)** *	14.7	**−0.223 (0.108)** *	9.3	**−0.199 (0.087)** *	14.7	−0.024 (0.093)	3.6
Model 1B								
Visit-to-visit $SD_{SBP,}$ per 1SD increase	−0.005 (0.003)	14.3	−0.049 (0.127)	8.6	−0.054 (0.102)	10.5	0.005 (0.109)	3.6
Model 2: DBP								
Model 2A								
Visit-to-visit $ARV_{DBP,}$ per 1SD increase	0.001 (0.003)	13.8	**−0.332 (0.105)** †	10.3	−0.121 (0.085)	10.7	**−0.211 (0.090)** *	4.7
Model 2B								
Visit-to-visit $SD_{DBP,}$ per 1SD increase	0.001 (0.003)	13.8	**−0.246 (0.120)** *	9.4	−0.091 (0.097)	10.6	−0.155 (0.103)	4.1

β represents unstandardized regression coefficient, and R^2 represents a measure for the model prediction. Each normal brain volume was standardized by dividing each by the intracranial volume (ICV). Adjusted β (95% CIs) associated with a 1 SD increment of each BP parameter are shown. 1 SD increment of each variable is as follows: ARV_{SBP}, 3.0 mm Hg; ARV_{DBP}, 2.8 mm Hg; SD_{SBP}, 3.7 mm Hg; and SD_{DBP}, 2.9 mm Hg. As adjustment factors, all models include demographic variables (age at Y_{25}, sex, race, and education) and clinical characteristics at Y_{25} (BMI, smoking, physical activity, fasting glucose), antihypertensive medication use from Y_0 to Y_{25}, and cumulative exposure to BP from Y_0 to Y_{25} (SBP was used in model 1, and DBP was used in model 2). ARV indicates average real variability; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure. Statistical significance was defined as $P<0.05$.

*$P<0.05$;

†$P<0.01$;

‡$P<0.001$.

Table 3

Associations between visit-to-visit BPV in young adulthood and brain integrity at middle age (n=540)

	Hippocampus		White matter	
BPV measures	**β (SE)**	**R^2, %**	**β (SE)**	**R^2, %**
Model 1: SBP				
Model 1A				
Visit-to-visit $ARV_{SBP,}$ per 1SD increase	−0.007 (0.006)	10.8	0.002 (0.003)	9.3
Model 1B				
Visit-to-visit $SD_{SBP,}$ per 1SD increase	**−0.020 (0.007)**†	12.2	0.0003 (0.003)	9.2
Model 2: DBP				
Model 2A				
Visit-to-visit $ARV_{DBP,}$ per 1SD increase	−0.001 (0.005)	10.1	−0.002 (0.003)	8.1
Model 2B				
Visit-to-visit $SD_{DBP,}$ per 1SD increase	−0.006 (0.006)	10.3	−0.006 (0.003)	8.6

Fractional anisotropy values of the hippocampus and white matter were log-transformed before analyses. β represents unstandardized regression coefficient, and R^2 represents a measure for the model prediction. Adjusted β (95% CIs) associated with a 1 SD increment of each BP parameter are shown. 1 SD increment of each variable is as follows: visit-to-visit ARV_{SBP}, 3.0 mm Hg; visit-to-visit ARV_{DBP}, 2.8 mm Hg; visit-to-visit SD_{SBP}, 3.7 mm Hg; and visit-to-visit SD_{DBP}, 2.9 mm Hg. As adjustment factors, all models include demographic variables (age at Y_{25}, sex, race, and education) and clinical characteristics at Y_{25} (BMI, smoking, physical activity, fasting glucose), antihypertensive medication use from Y_0 to Y_{25}, and cumulative exposure to BP from Y_0 to Y_{25} (SBP was used in model 1, and DBP was used in model 2). ARV indicates average real variability; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure. Statistical significance was defined as $P<0.05$. Statistical significance was defined as $P<0.05$.

$^{*}P<0.05$;

$^{\dagger}P<0.01$;

$^{\ddagger}P<0.001$.