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Research Article

Beyond Hypertension: Examining Variable Blood Pressure's Role in Cognition and Brain Structure

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Abstract

Objectives: Hypertension or high blood pressure (BP) is one of the 12 modifiable risk factors that contribute to 40% of dementia cases that could be delayed or prevented. Although hypertension is associated with cognitive decline and structural brain changes, less is known about the long-term association between variable BP and cognitive/brain changes. This study examined the relationship between variable BP and longitudinal cognitive, white matter hyperintensity (WMH), gray matter (GM), and white matter (WM) volume change over time and postmortem neuropathology.

Methods: A total of 4,606 participants (32,776 follow-ups) from RADC Research Resource Sharing Hub (RUSH) and 2,114 participants (9,827 follow-ups) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were included. Participants were divided into 1 of 3 groups: normal, high, or variable BP. Linear-mixed models investigated the relationship between BP and cognition, brain structure, and neuropathology.

Results: Older adults with variable BP exhibited the highest rate of cognitive decline followed by high and then normal BP. Increased GM volume loss and WMH burden were also observed in variable compared to high and normal BP. In postmortem neuropathology, both variable and high BP had increased rates compared to normal BP. Results were consistent across the RUSH and ADNI participants, supporting the generalizability of the findings.

Discussion: Damages potentially associated with variable BP may reduce resilience to future dementia-related pathology and increased the risk of dementia more than that caused by high BP. Improved treatment and management of variable BP may help reduce cognitive decline in the older adult population.

Keywords: Cognitive decline, Gray matter, Neuropathology, White matter, White matter hyperintensities

Elevated blood pressure (BP), or hypertension, is a well-established risk factor for cognitive decline and dementia (Livingston et al., 2020). Hypertension is not only associated with cognitive decline but also contributes to structural changes in the brain. For example, hypertension is associated with increased white matter hyperintensity (WMH, Abraham et al., 2016; Morrison et al., 2024; van der Flier et al., 2018) burden and increased neurodegeneration (Glodzik et al., 2012; Schaare et al., 2019), both of which are contributing factors to conversion to dementia (Dadar, Camicioli, et al., 2020; Kamal et al., 2023). Not surprisingly, hypertension has been identified as one of the 12 modifiable risk factors that account for the approximately 40% of dementia cases that could be delayed or prevented (Livingston et al., 2020). Most BP research has examined the detrimental effects of elevated BP; however, older adults can also experience visit-to-visit variability in their BP.

Variability in BP over time has been observed to be associated with an increased risk of developing dementia (Mahinrad et al., 2023; Yoo et al., 2020). In cognitively normal adults with a genetic risk (i.e., APOE ε4 positivity) of developing Alzheimer's disease (AD), BP variability is associated with tau and amyloid alterations (Sible & Nation, 2022b) and medial temporal lobe atrophy (Sible & Nation, 2022a). Furthermore, one study following approximately 13,000 cognitively normal adults for a median of 5 years showed that increased BP variability was associated with increased cognitive decline and vascular pathology (WMHs, atherosclerosis, and infarcts) and AD-related pathology (neurofibrillary tangles; Ma et al., 2021). With respect to AD, BP variability is associated with increased rates of cognitive decline (Lattanzi et al., 2015). Despite these findings, limitations still exist in our understanding of how BP influences cognitive change and brain structure.

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The current study investigated the relationship between long-term BP status (normal vs high vs variable BP), cognition, structural brain changes, and postmortem neuropathology. Our goals were to determine if: (1) variable BP was associated with more cognitive and brain declines than normal and/or high BP, (2) variable BP is associated with increased postmortem neuropathology compared to normal and/or high BP, and (3) findings replicate in a secondary cohort. It is hypothesized that cognitive and structural brain changes as well as postmortem neuropathology will increase from normal to high to variable BP.

Method

RADC Research Resource Sharing Hub

Data were used from the RADC Research Resource Sharing Hub (RUSH; www.radc.rush.edu). The study received ethical approval from the review boards of all participating institutions. Participants provided informed written consent to participate in one of three cohort studies on aging and dementia: (1) Minority Aging Research Study (Barnes et al., 2012), (2) RUSH AD Center African American Clinical Core (Schneider et al., 2009), or (3) the RUSH Memory and Aging Project (Bennett et al., 2018).

Participants

Participants from RUSH had a baseline age of at least 55 and were either cognitively normal or diagnosed with mild cognitive impairment (MCI) or dementia. Cognitive status was determined using a three-stage process including computer scoring of cognitive tests, clinical judgment by a neuropsychologist, and diagnostic classification by a clinician based on the National Institute on Aging and the Alzheimer's Association (McKhann et al., 2011). BP was measured with a mercury sphygmomanometer by trained research assistants at each visit. Mean systolic and diastolic readings were calculated by averaging two seated BP readings, followed by one additional standing BP reading. All BP readings were expressed in mmHg. Mean and standard deviation (*SD*) of systolic BP were computed for each individual, taking into account all their longitudinal time points. The *SD* of the whole sample was then calculated based on individual *SD*s. These *SD*s were then used to determine if each participant exhibited normal, high, or variable BP. For normal, their mean BP had to be less than 130 and their *SD* not more than 1 *SD* away from the sample *SD*. One *SD* away from the mean was equivalent to 13.87 mmHg. For high, their BP must have been greater than or equal to 130 (as per the National Institute of Health and National Institute on Aging guidelines for older adults, Hyman et al., 2012), and their *SD* is less than 1 *SD* away from the sample mean *SD*. Variable BP were participants whose BP *SD* was more than 1 *SD* away from the mean *SD* of the sample. The sample consisted of a total of 4,606 older participants with 32,776 time points. Participants were followed up annually. There were 1,332 older adults with 9,145 time points who had normal BP, 1,377 with 8,602 time points who had high BP, and 1,897 with 15,018 time points with variable BP.

Additional analyses were completed to examine the influence of BP on brain structure with the subset of participants who either had MRI measures from which volumetric measures could be extracted or postmortem neuropathology information. A total of 1,846 participants had postmortem neuropathology information ($n = 486$ normal BP, $n = 473$ high BP, and $n = 886$ variable BP). For MRI measures, a total of 820 participants ($n = 268$ normal BP, $n = 244$ high BP, and $n = 307$ variable BP), with 1,555 follow-ups were included ($n = 532$ normal BP, $n = 458$ high BP, and $n = 563$ variable BP).

Cognitive battery

Participants were administered a comprehensive neuropsychological battery comprised of 18 tests assessing episodic memory, semantic memory, working memory, processing speed, and visuospatial ability (Barnes et al., 2016; Wilson et al., 2002). Episodic memory was assessed using seven tests (immediate and delayed recall of Story A of the Wechsler Memory Scale-Revised; immediate and delayed recall of the East Boston Story; Word List Memory, Recall and Recognition). Semantic memory was assessed using three tests (Verbal Fluency; Boston Naming; and Reading Test). Working memory was assessed using three tests (Digit Span forward and backward; Digit Ordering). Processing speed was assessed using four tests (Symbol Digit Modalities Test; Number Comparison; and two indices from a modified version of the Stroop Test). Visuospatial ability was assessed using two tests (Line Orientation and Progressive Matrices). Composite scores were created for each domain by converting all individual test scores to *z* scores, using the mean and *SD* from the combined cohort at baseline. Then, all *z* scores were averaged for each respective domain. Additionally, a measure of global cognitive function was computed for each participant by averaging individual performance across all 19 tests. More information is provided at https://www.radc.rush.edu/.

MRI and postmortem measures

All MRI and postmortem measurements were calculated based on standard procedures determined by the RADC Rush researchers and neuropsychologists. T1-weighted (T1w) 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) and T2-weighted 2D Fluid-Attenuated Inversion Recovery (FLAIR) were acquired for structural assessments. T1w images were processed using FreeSurfer. Total gray matter (GM) and white matter (WM) volumes as well as intracranial volumes (used for normalization) were calculated using the Computational Anatomy Toolbox (Gaser & Dahnke, 2012) from SPM (Friston et al., 1995). WMHs were segmented using sysu (Li et al., 2018), a previously validated deep learning-based automated WMH segmentation tool.

The methodology used to determine cerebral atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy severity, and presence of infarcts was determined by the RUSH RADC investigators.

Cerebral atherosclerosis rating was completed after a postmortem examination of the extent of involvement of each artery and number of arteries involved. Ratings included 0 = no significant atherosclerosis observed, 1 = Small amounts in up to several arteries (typically less than 25% vessel involvement) without significant occlusion, 2 = In up to half of all visualized major arteries, with less than 50% occlusion of any single vessel, and 3 = In more than half of all visualized arteries, and/or more than 75% occlusion of one or more vessels.

Arteriolosclerosis was used to describe histological changes (e.g., include intimal deterioration, smooth muscle degeneration, and fibrohyalinotic thickening of arterioles with consequent narrowing of the vascular lumen) observed in the small

vessels. The vessels of the anterior basal ganglia were assessed with a semiquantitative grading system: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Cerebral amyloid angiopathy pathology was determined using a semiquantitative rating in four neocortical regions: midfrontal, midtemporal, parietal, and calcarine cortices. Scores were classified into a four-level severity with ratings determined by neuropathologist: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

The presence of one or more gross chronic cerebral infarctions as well as chronic microinfarcts were determined by neuropathologic evaluations performed at RUSH. A board-certified neuropathologist who was blinded to clinical data performed the evaluations to determine the presence of infarctions. Participant outcomes were reported as, 0 = no gross chronic infarction or 1 = one or more infarctions (regardless of location), and 0 = no chronic infarctions or 1 = one or more chronic microinfarctions (regardless of location).

Alzheimer's Disease Neuroimaging Initiative Participants

Data used in the preparation of this article were also obtained from the AD Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD. The study received ethical approval from the review boards of all participating institutions. Written informed consent was obtained from participants or their study partners. Participants were selected only from all ADNI Cohorts (ADNI-1, ADNI-GO, ADNI-2, and ADNI-3).

Participants from ADNI had baseline ages between 55 and 90 (see www.adni-info.org for more information). Cognitively healthy older adults exhibited no evidence of memory decline, as measured by the Wechsler Memory Scale, and no evidence of impaired global cognition as measured by the Mini Mental Status Examination (MMSE) or Clinical Dementia Rating (CDR). MCI participants scored between 24 and 30 on the MMSE, 0.5 on the CDR, and abnormal scores on the Wechsler Memory Scale. Dementia was defined as participants who had abnormal memory function on the Wechsler Memory Scale, an MMSE score between 20 and 26 a CDR of 0.5 or 1.0, and a probable AD clinical diagnosis according to the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria.

Blood pressure (BP) was measured with a mercury sphygmomanometer at each visit while the participant was seated. For each participant, BP was recorded from the dominant forearm positioned horizontally at the 4th intercostal space at the sternum. All BP readings were expressed in mmHg. Participants were included if they had BP measurements from at least two visits and had information for the dependent variables of interest. That is MRIs with ventricle, hippocampal, and entorhinal cortex volume measurements had at least one of the cognitive tests available, the Alzheimer's Disease Assessment Scale-13 (ADAS-13) or Functional Activities Questionnaire (FAQ). A total of 2,114 participants with 9,827 follow-up time points were included. These participants were then divided into one of three groups, normal BP, high BP, or variable BP. Similar to RUSH, the sample *SD* was then calculated and used to divide participants into three groups: (1) normal BP, (2) high BP, and (3) variable BP. The sample consisted of 568 older adults with 2,348 time points who had normal BP, 771 with 2,843 time points who had high BP, and 775 with 4,636 time points with variable BP. One *SD* away from the mean translated to 13.33 mmHg.

Structural MRI acquisition and processing

All longitudinal scans were downloaded from the ADNI website (see http://adni.loni.usc.edu/methods/mri-tool/mri-analysis/ for detailed MRI acquisition protocol). T1w scans for each participant were preprocessed through our standard pipeline including noise reduction (Coupé et al., 2008), intensity inhomogeneity correction (Sled et al., 1998), and intensity normalization into range (0–100). The preprocessed images were then linearly (9 parameters: 3 translation, 3 rotation, and 3 scaling; Dadar et al., 2018) registered to the MNI-ICBM152-2009c average (Fonov et al., 2011).

WMH measurements

A previously validated WMH segmentation technique was employed to generate participant WMH measurements (Dadar et al., 2019). This technique has been validated in ADNI in which a library of manual segmentations based on 50 ADNI participants (independent of those studied here) was created. The technique has also been validated in other multicenter studies such as the Parkinson's Markers Initiative (Dadar, Fereshtehnejad, et al., 2020) and the National Alzheimer's Coordinating Center (Anor et al., 2021). WMHs were automatically segmented using the T1w contrasts, along with a set of location and intensity features obtained from a library of manually segmented scans in combination with a random forest classifier to detect the WMHs in new images (Dadar et al., 2017). WMH load was defined as the volume of all voxels as WMH in the standard stereotaxic space (in mm^3) and is thus normalized for head size. The volumes of the WMHs for frontal, parietal, temporal, and occipital lobes as well as the entire brain were calculated based on regional masks from the Hammers atlas (Dadar et al., 2017; Hammers et al., 2003). The quality of the registrations and WMH segmentation was visually verified by an experienced rater (author M.D.), blinded to participants diagnostic group.

FreeSurfer measurements

T1-weighted (T1w) images were processed using FreeSurfer and quality controlled by the UCSF group, and regional GM and WM volumes were extracted. 1.5T and 3T data were processed with FreeSurfer versions 4.3 and 5.1, respectively, as appropriate.

Statistical Analysis

Analyses were performed using "R" software version 4.0.5. Linear-mixed effects models investigated rates of change differences in the dependent variables across groups (normal, high, and variable BP). The dependent variables included rates of change for global cognition, episodic memory, semantic memory, perceptual speed, perceptual orientation, working memory, and structural brain changes that were observed over time (WMHs, GM, and WM). Baseline age, sex, and baseline diagnosis were included as covariates. The interaction of interest, TimeFromBaseline:Group, examined if change over time differed between Groups (normal, high,

Table 1. Demographic Information for RUSH and ADNI Cohorts

Variable	RUSH				ADNI			
	Full sample (N = 4,606)	Normal BP (n = 1,332)	Variable BP (n = 1,897)	High BP (n = 1,377)	Full sample (N = 2,114)	Normal BP (n = 568)	Variable BP (n = 775)	High BP (n = 771)
Age, $M \pm SD$	76.8 ± 7.7	75.7 ± 8.0	77.7 ± 7.4	76.5 ± 7.7	73.3 ± 7.2	71.6 ± 7.2	74.8 ± 7.2	73.2 ± 7.0
Sex (female), n (%)	3,429 (74%)	958 (72%)	1,463 (77%)	1,004 (73%)	1,132 (53%)	264 (46%)	354 (46%)	367 (48%)
Education in years, $M \pm SD$	15.8 ± 4.0	6.0 ± 4.0	15.5 ± 3.8	15.9 ± 4.1	16.0 ± 2.8	16.1 ± 2.7	16.0 ± 2.8	16.0 ± 2.8
Mean BP, $M \pm SD$		119 ± 7.4	137 ± 13.7	141 ± 10.2		120 ± 9.1	139 ± 19.5	141 ± 10.9
BP group, n (%)								
Normal	1,332 (29%)				568 (27%)			
Variable	1,897 (41%)				775 (37%)			
High	1,377 (30%)				771 (36%)			
Diagnosis, n (%)								
Normal control	3,347 (73%)	983 (74%)	1,348 (71%)	1,013 (73%)	770 (36%)	209 (37%)	245 (32%)	314 (41%)
Mild cognitive impairment	1,063 (23%)	290 (22%)	460 (24%)	313 (23%)	977 (46%)	257 (45%)	396 (51%)	321 (42%)
Dementia	200 (4%)	59 (4%)	89 (5%)	51 (4%)	372 (18%)	102 (18%)	134 (17%)	136 (17%)
Race, n (%)								
Black	1,189 (26%)	278 (21%)	529 (28%)	927 (67%)	95 (5%)	20 (4%)	29 (4%)	45 (6%)
White	3,230 (70%)	988 (74%)	1,313 (69%)	382 (3%)	1,948 (92%)	529 (93%)	721 (93%)	694 (90%)
Other	191 (4%)	66 (5%)	55 (3%)	68 (5%)	73 (3%)	19 (3%)	25 (3%)	32 (4%)

Notes: ADNI = Alzheimer's Disease Neuroimaging Initiative; BP = Blood pressure; RUSH = RADC research resource sharing hub; *SD* = standard deviation.

Table 2. Demographic and Pathology Measures Between Those with One Visit and Those with More Than One

Clinical characteristics	Only one timepoint (n = 182)	More than one timepoint (first visit) (n = 3,869)	More than one timepoint (last visit) (n = 3,869)
Age	76.6 ± 7.8	76.6 ± 7.5	84.5 ± 7.8*
Education	14.9 ± 4.6	15.9 ± 3.9	—
Systolic BP	135.0 ± 20. 7	134.9 ± 18.9	130.8 ± 20.24
	Only one timepoint with pathology outcomes (n = 98)	More than one timepoint with pathology outcomes (n = 1,774)	
Age at death	85.7 ± 7.0	89.9 ± 6.6*	
Education	15.8 ± 4.1	16.3 ± 3.6	
Cerebral atherosclerosis	1.2 ± 0.8	1.2 ± 0.8	
Arteriosclerosis	1.1 ± 1.1	1.1 ± 1.0	
Infarctions	0.3 ± 0.4	0.4 ± 0.5	
Microinfarctions	0.2 ± 0.4	0.3 ± 0.5	
Cerebral amyloid angiopathy	1.1 ± 0.9	1.3 ± 0.9*	

Notes: BP = Blood pressure.
*Indicates a statistically significant difference between that group and those with only one timepoint.

and variable BP). Normal BP was used as the reference group, but the models were repeated a second time using variable BP as the reference to observe differences between high versus variable BP. Participant ID was included as a categorical random effect to account for repeated measures of the same participant.

$$Dependent\ Variable \sim Age\_bl + Sex + Dx\_bl + Time\ From\ Baseline : Group + Time\ From\ Baseline + Group + (1|\ ID)$$

Cerebral atherosclerosis, cerebral amyloid angiopathy, arteriosclerosis, gross chronic cerebral infarcts, and chronic microinfarcts assessments were completed postmortem and were thus analyzed using linear regressions. Age at death, sex, and baseline diagnosis were included as covariates. The effect of interest was group (normal, high, and variable BP), to examine if the dependent variables differed by group.

$$Dependent\ Variable \sim Age\_death + Sex + Dx\_bl + Group$$

MRI data were not collected at consistent intervals for the RUSH data set. For example, some participants had MRIs at their baseline visit and then at years 2 and 4, whereas others had MRI information available at years 19 and 21. Therefore, we discarded the information prior to the MRI visits, considered the first MRI timepoint as a baseline for the MRI analyses and adjusted the *TimeFromBaseline* accordingly. For example, if someone had MRI visits at years 19 and 21, in our MRI analyses, those visits were considered as 0 (baseline) and year 2. All continuous values (except follow-up year) were z scored within the population prior to analyses.

To examine potential sampling biases in the data between those who dropped out versus those who remained in the study we completed t tests examining demographic characteristics between the groups at baseline, last visit, and in pathology measures.

Data Availability

Researchers may obtain access to all study data used in this study by applying online. The RUSH study data by applied through https://www.radc.rush.edu/ and the ADNI study data through adni.loni.usc.edu.

Results

Demographic information for both cohorts is shown in Table 1. For RUSH, normal BP mean was 119, variable BP was 137, and high BP mean was 141. Within ADNI, normal BP mean was 120, variable BP was 139, and high BP mean was 141. Demographic data at baseline and for pathology measures at death between those with only one timepoint and those with more than one follow-up visit are shown in Table 2.

RUSH

Figure 1 shows the trajectories of cognitive change by BP group over time. Figure 2 shows overall GM, WM, and WMH volume by group. Supplementary Table 1 shows a summary of all results.

Cognitive outcomes

Older adults with variable BP had increased rates of decline compared to those with normal and high BP in global cognition, episodic memory, semantic memory, processing speed, and working memory (t belongs to [11.57–2.69], $p < .007$). For visuospatial orientation, those with variable BP had increased rates of decline compared to those with normal BP ($t = 3.71$, $p = .002$), but not high BP ($t = 1.78$, $p = .075$). Those with high BP also had increased rates of cognitive decline compared to those with normal BP in global cognition, episodic memory, semantic memory, processing speed, and working memory (t belongs to [5.44–3.15], $p < .002$). For visuospatial orientation, those with high BP did not differ from normal BP ($t = 1.59$, $p = .11$).

MRI outcomes

Those with normal BP exhibited lower overall WMH burden ($t = -3.71$, $p < .001$) and higher GM volumes ($t = 2.87$, $p = .003$) compared to only those with variable BP. Those with high BP also exhibited lower overall WMH burden ($t = -3.60$, $p < .001$) and higher GM volume than those with

variable BP ($t = 2.59$, $p = .009$). Total WM volume slopes did not differ between the three groups.

Postmortem outcomes

When examining cerebral atherosclerosis, those with normal BP exhibited less severe ratings than both variable ($t = -6.37$, $p < .001$) and high BP ($t = -8.16$, $p < .001$), and high BP was more severe than variable BP ($t = 2.88$, $p = .004$). For arteriosclerosis, those with normal BP had less severe ratings than both variable ($t = -3.40$, $p < .001$) and high BP ($t = -4.54$, $p < .001$), which did not differ. Similarly, for infarctions, normal BP had less severe ratings than both variable ($t = -4.31$, $p < .001$) and high BP ($t = -3.09$, $p = .002$), who did not differ. For microinfarctions, those with normal BP had less severe ratings than only variable BP ($t = -2.28$ $p = .02$). No differences between high BP and either group were observed. There were no significant group differences in cerebral amyloid angiopathy severity.

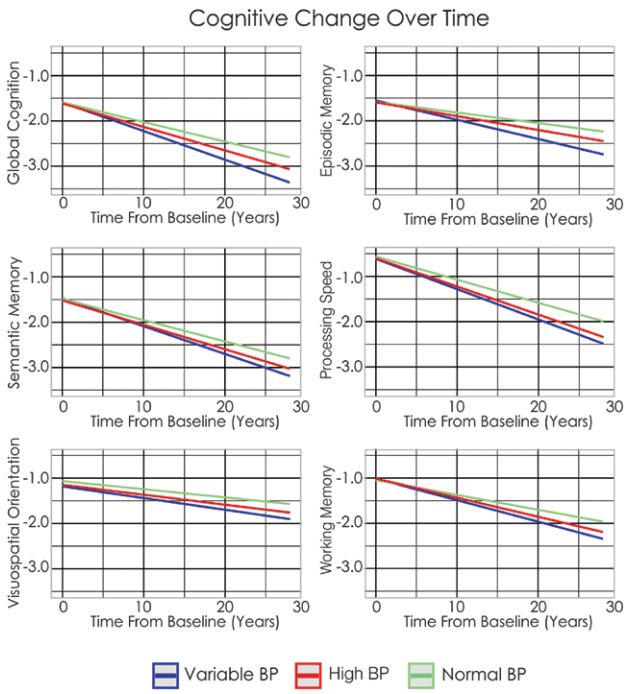

Figure 1. Estimated Cognitive Change Over Time by Group in RUSH (RADC Research Resource Sharing Hub). BP = Blood pressure.

Secondary Analyses in RUSH

To examine whether the grouping methodology influenced the outcomes, secondary analyses were completed separating the RUSH participants into four groups: (1) Normal BP (mean BP < 130 and a $SD < 1$), (2) Normal variable BP (mean BP < 130 and a $SD > 1$), (3) High BP (mean BP ≥ 130 and a $SD < 1$), and (4) High variable BP (mean BP ≥ 130 and a $SD > 1$).

For the cognitive outcomes, we observed that for all cognitive domains (global cognition, episodic memory, semantic memory, processing speed, visuospatial processing, and working memory), both variable BP groups (normal and high) had increased cognitive decline compared to both normal and high BP groups with two exceptions. High variable BP did not have increased cognitive decline compared to high BP in perceptual orientation ($t = 0.65$, $p = .99$) and working memory ($t = 1.59$, $p = .11$).

For the MRI outcomes, we continued to observe that normal BP exhibited lower WMH burden than both normal variable BP ($t = -3.08$, $p = .002$) and high variable BP ($t = -3.05$, $p = .002$) groups. Importantly, the two variable BP groups did not differ. Variable normal BP did not differ in total GM volume from any of the groups. However, variable high BP had steeper total GM loss than both high ($t = -3.02$, $p = .003$) and normal BP ($t = -2.88$, $p = .004$). Also, consistent with previous findings was that total WM slopes did not differ between the groups.

For cerebral atherosclerosis, normal BP was still associated with lower pathology levels than both high and variable high BP (t belongs to [7.77–8.27], $p < .001$) but not normal variable BP. High BP and high variable BP were no longer different, and both had increased pathology compared to normal variable BP (t belongs to [4.63–5.19], $p < .001$). For arteriolosclerosis, normal BP was still associated with lower pathology levels than both high BP and variable high BP (t belongs to [−4.52 to −4.66], $p < .001$) but not normal variable BP. High BP and high variable BP remained similar but were both higher than normal variable BP (t belongs to [3.11–3.28], $p = .001$). For infarctions, normal BP did not differ from normal variable BP but had less severe ratings than both high and variable high BP (t belongs to [−3.24 to −4.89], $p < .001$), who did not differ.

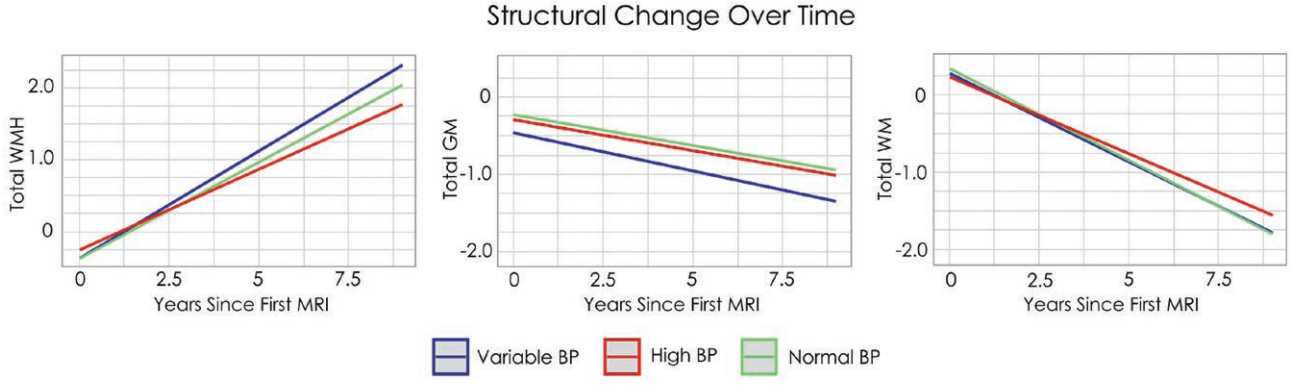

Figure 2. Estimated volume change over time by group in RUSH (RADC Research Resource Sharing Hub). BP = Blood pressure; GM = Gray matter; MRI = magnetic resonance imaging; WM = White matter; WMH = White matter hyperintensity.

Only high variable BP had increased infarctions compared to normal variable BP (t = –2.45, p = .01). For microinfarctions, those with normal BP had less severe ratings than only variable BP (t = –2.18 p = .03). Last, consistent with previous findings, there were no significant group differences in cerebral amyloid angiopathy severity. Compared to the initial analyses the main difference was that normal variable BP no longer differed from normal BP in cerebral atherosclerosis, arteriolosclerosis, and infarctions and was lower compared to high variable BP (cerebral atherosclerosis, arteriolosclerosis, and infarctions) and high BP (arteriolosclerosis and infarctions).

Overall, these secondary analyses suggest that although cognitive decline, GM, WM, and WMH volumes are similar between normal variable and high variable BP groups, postmortem pathology is more severe in high variable BP than normal variable BP.

Another analysis was also conducted using different cutoffs of 1.5 *SD* (20.81 mmHG) and 2.0 *SD* (27.75 mmHG) away from the mean to group the participants in normal, variable, and high BP to assess the potential impact of the cut-off threshold on the findings. Results for both grouping methods using 1.5 and 2.0 *SD* cutoffs were similar for cognitive outcomes in terms of effect size and significance. With respect to the pathology outcomes, most of the results remained for both cutoffs except for cerebral atherosclerosis, using the 2.0 *SD* cut-off variable BP was only significantly worse than normal BP (and no longer worse than high BP). The MRI outcomes were the same for 1.5 *SD*, however, for 2.0 WMH and GM differences between the groups were no longer significant. The differences in MRI measures may be because the groups became more overlapped and imbalanced (e.g., for 2 S.D. n = 120 variable, n = 1,834 normal, and n = 2,651 high) which may have reduced the ability to detect significant differences in WMH and GM.

A final set of analyses was conducted adding two vascular covariates to all the original models, diabetes (0 for no diabetes or 1 for diabetes) and body mass index (BMI, continuous measure). With respect to cognition, group differences remained the same in terms of effect size and significance for global cognition, episodic memory, semantic memory, perceptual orientation, and processing speed. The only difference was that working memory change over time no longer differed between those with high and variable BP (t = 1.67 p = .09). It should also be noted that diabetes was significantly associated with an increased rate of cognitive change for all domains except semantic memory (t belongs to [3.67–2.08], p < .05) and higher BMI was associated with increased rate of cognitive change for global cognition and episodic and semantic memory (t belongs to [2.7–3.5], p < .001). The MRI measures (WMH, GM, and WM) did not differ when including BMI and diabetes in the models. With respect to pathology measures, all group differences remained significant when including diabetes and BMI in the models. A main effect of diabetes was observed for infarctions (t = 2.3, p = .02) and a main effect of BMI was observed for arteriosclerosis (t = 3.12, p = .002).

ADNI

Figure 3A shows trajectory of cognitive scores by group and Figure 3B shows trajectory of total, cortical, and subcortical GM, and WM volume change over time by group. Figure 4 shows WMH trajectory by group.

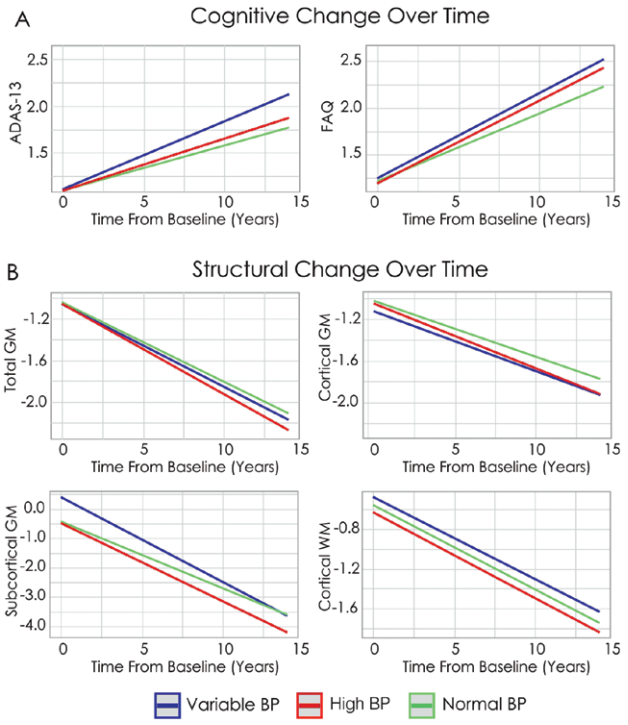

Figure 3. Estimated cognitive and structural brain change over time by group in Alzheimer's Disease Neuroimaging Initiative. ADAS-13 = Alzheimer's Disease Assessment Scale-13; FAQ = Functional Activities Questionnaire; GM = Gray matter; WM = White matter.

Cognitive outcomes

When examining global cognition, as measured by the ADAS-13, normal BP had less change than variable BP (t = –3.45, p < .001), but did not differ from high BP (t = 0.89, p = .37). Furthermore, variable BP exhibited increased cognitive decline compared to high BP (t = 2.46, p = .014). With respect to functional status, as measured by the FAQ, normal BP exhibited greater functional ability compared to variable BP (t = –2.56, p < .001), but did not differ from high BP (t = –1.84, p = .03), and high BP did not differ from variable BP (t = 0.36, p = .72).

GM and WM outcomes

The only difference observed in GM and WM was in subcortical GM. Normal BP exhibited less decline in subcortical GM volume compared to both variable (t = –5.19, p < .001) and high BP (t = –2.85, p = .004). Variable BP exhibited an increased rate of subcortical GM volume loss compared to high BP (t = 2.47, p = .013). No group differences were observed in cortical GM or cortical WM.

WMH outcomes

When examining WMH burden changes over time, we observed many differences between groups. Normal BP exhibited lower WMH burden increases over time at all regions except occipital compared to both variable (t belongs to [–7.50 to –3.80], p < .001) and high BP (t belongs to [–3.85 to –2.62], p < .006). Variable BP exhibited increased total (t = 2.18, p = .029) and frontal WMH burden compared to high BP (t = 3.49, p < .004), these groups did not differ at temporal, parietal, or occipital regions. Finally, there were no group differences in the occipital region.

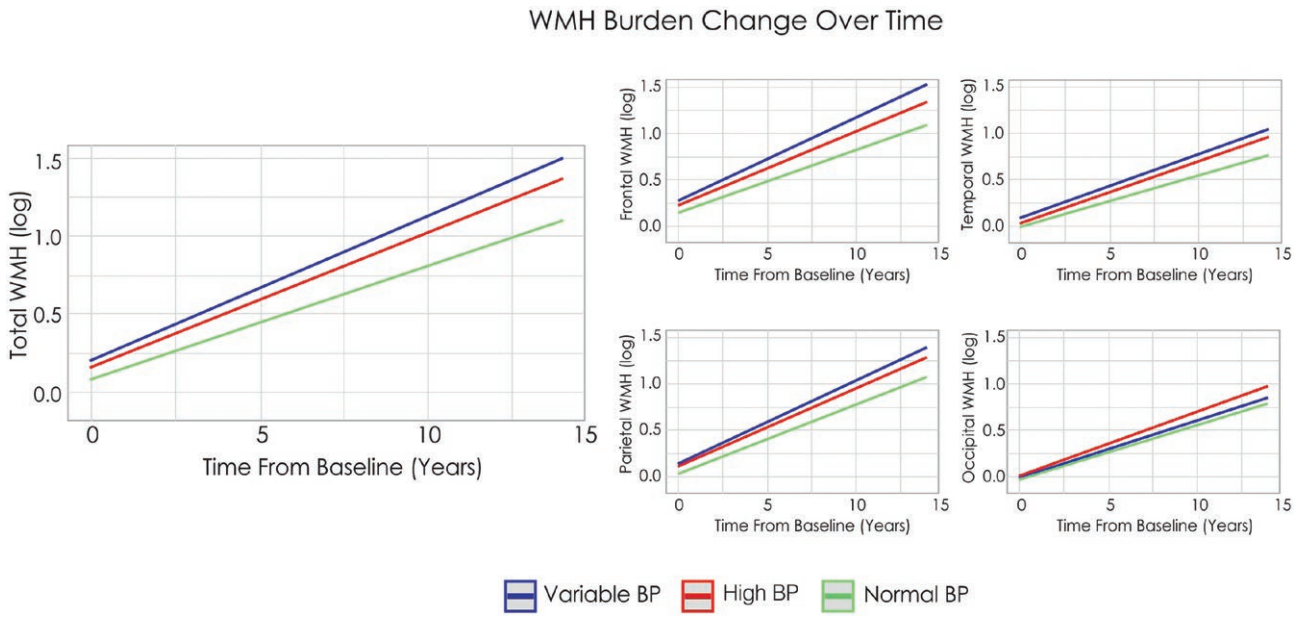

Figure 4. Estimated WMH progression over time by group in Alzheimer's Disease Neuroimaging Initiative. BP = Blood pressure; WMH = White matter hyperintensity.

Discussion

This study examined the relationship between BP and cognition, brain structure, and postmortem neuropathology. The findings show that people with variable and high BP exhibit increased rates of cognitive decline, WMH burden, and vascular pathologies at death than normal BP. Importantly, those with variable BP exhibited heightened rates of cognitive decline, GM volume loss, and increased WMH burden compared to those with normal and high BP. These findings suggest that while both high and variable BP are detrimental to cognitive decline and structural brain changes, variable BP may result in more negative complications due to BP fluctuations. Our findings support the established theory that high BP is a modifiable risk factor that contributes to cognitive decline and dementia (Livingston et al., 2020). Expanding beyond that understanding is that variable BP may have more severe implications for cognition and structural brain changes.

Increased cognitive decline was observed in those with high and variable BP compared to older adults with normal BP. Those with variable BP also exhibited increased decline compared to older adults' high BP. This finding was observed in global cognition, episodic memory, semantic memory, and working memory. When examining visuospatial orientation and functional status, only those with variable BP exhibited increased rates of decline compared to those with normal BP. The increased cognitive decline observed in those with high BP is consistent with numerous findings (e.g., Gąsecki et al., 2013; Gottesman et al., 2014; Kennelly et al., 2009; Walker et al., 2017) which helps explain high BP increases risk for dementia (Mahinrad et al., 2023; Yoo et al., 2020). However, our investigation into how variable BP affects cognition beyond what is observed in high BP is a novel and relatively unexplored area of research with conflicting findings (Walker et al., 2017).

Consistent with previous findings in healthy older adults over a 5-year period (Ma et al., 2021), we observed that BP variability was associated with increased vascular pathology and WMHs. We also observed that high and variable BP was associated with lower GM volume than normal BP. This result is consistent with previous research indicating that high BP is associated with smaller brain volume and reductions in brain volume over time (see Walker et al., 2017 for review) acting as an important factor for neurodegeneration above what is observed in aging (Beauchet et al., 2013). Again, the increased rate of change in variable BP observed in both data sets suggests that variable BP may have more detrimental effects on GM volume and overall neurodegeneration than high BP. Increased rates of WMH burden were also observed in high and variable BP groups compared to normal BP except in the occipital region, with total and frontal WMH burden progressively worse from normal to high to variable BP. Similarly, previous work has observed that high time-averaged BP (averaged across participant visits similar to this study), was also associated with WMH progression (Gottesman et al., 2010; Verhaaren et al., 2013). With respect to regional WMH burden, different patterns of WMH accumulation indicate different etiologies (Bangen et al., 2020; Kamal et al., 2023; McAleese et al., 2017, 2021). For example, more widespread distribution of WMHs is associated with nonamnestic MCI (Bangen et al., 2020; which leads to dementia and other AD) whereas posterior WMHs are strongly associated with conversion to AD (McAleese et al., 2017). Frontal WMHs are more strongly associated with vascular risk factors (such as hypertension), indicating that variable BP has more negative effects on brain structure resulting in increased WMH in frontal regions compared to high BP. It should be noted that in the RUSH data set, we observed that the variable BP group had increased WMHs compared to high and normal BP which did not differ. However, we observed differences between high and normal BP in the ADNI data set. These differences may be associated with the regional method employed to analyze the ADNI data.

With respect to postmortem neuropathology, we observed that variable and high BP were associated with increased

amounts of arteriosclerosis and infarctions compared to normal BP but did not differ from each other. Furthermore, variable BP displayed increased microinfarctions compared to normal BP, whereas high BP did not differ from either normal or variable. This finding suggests that variable BP may be more strongly associated with microinfarctions than high BP. These differences in BP variability are also consistent with previous reports indicating that increased BP variability is associated with arteriosclerosis, infarctions, and microinfarctions (Ma et al., 2021). However, they also observed that high variability was associated with increased cerebral amyloid angiopathy which we did not observe. This difference may be associated with study design, as we separated our participants into three groups (normal, high, and variable BP) whereas they looked at variability between visits as a continuous measure.

The underlying biological mechanism linking BP variability to atrophy and cognitive decline is largely unknown, with several possible mechanisms that could underly this relationship. First, hypertension alters cerebral blood flow (i.e., cerebral autoregulation), which damages the blood vessels in the brain and WM (causing WMHs), and results in overall lower brain volume due to damage and death of the neurons and connections between them (Walker et al., 2017). When BP is chronically evaluated, the blood vessels thicken, reducing vascular elasticity, and increased risk of microbleeds and microinfarctions, as well as risk of cerebral small vessel disease, all of which are known risk factors for dementia (Gąsecki et al., 2013; Walker et al., 2017). Our findings show that variable BP may result in more instability in the brain and cognitive changes than high BP. Taken together, variable BP may be damaging because not only is BP high, but the body is unable to regulate these fluctuations effectively. The repeated episodes of changes in BP (i.e., higher than normal) may cause more significant stress on the cerebral blood vessels and exacerbate damage to brain tissue than continuous high BP. This instability can accelerate neuronal damage and cognitive decline, making BP variability a critical factor in brain health. Taken together, these insights underscore the importance of not only managing high BP but also minimizing fluctuations to protect against cognitive decline and brain atrophy.

This study has a few limitations that should be explored in future research. As the information was not available, this study did not consider antihypertensive medication usage which should be examined in future studies. It is possible that some individuals who were grouped into "normal BP" have high BP that is controlled through medication usage. Future research should explore if the use of antihypertensive medications helps mitigate cognitive decline and brain changes associated with high and variable BP. Furthermore, there are other modifiable risk factors (e.g., sleep disorders) that may contribute to cognitive decline and brain changes in aging and dementia (Kamal et al., 2024). Future research should explore the independent and joint effects of hypertension with these disorders to generate a deeper understanding of factors that influence cognitive and brain change.

This study observed that high and variable BP is associated with increased rates of cognitive decline, neurodegeneration, WMH burden, and postmortem neuropathology. Variable BP was more strongly associated with an increased rate of change than high BP. These declines due to BP may reduce resilience to future pathology and cognitive decline due to dementia. Given that BP can be managed with lifestyle changes and medications, and that no randomized clinical trials have previously considered BP variability as a treatment target, more investigations into management of BP variability as a treatment target for reducing subsequent cognitive decline and dementia are warranted.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

None.

Data Availability

To obtain data from MARS, AA Core, and MAP for research use, please visit the RADC Research Resource Sharing Hub (www.radc.rush.edu). Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.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.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Author Contributions

All authors (C.M., M.O., M.D., and F.K.) were involved with the conceptualization, design, and data interpretation of the study; C.M. and M.D. completed data analysis; F.K. created figures; C.M. wrote the manuscript; and all authors revised and approved the submitted version.

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