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Original Article

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Associations of Blood Pressure Level and Variability With Cortical Thickness: A Cross-Sectional Analysis From the Maracaibo Aging Study

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BACKGROUND: Although high blood pressure (BP) level and variability are associated with Alzheimer's disease (AD), their relationship with cortical thickness in brain regions that are associated with AD is unclear. Furthermore, the role of 24-h BP has not been examined. We investigated the associations of office and ambulatory BP measures with cortical thickness in brain regions implicated in AD.

METHODS: We performed a cross-sectional analysis of 304 participants without dementia from a population-based study with office and 24-h BP and magnetic resonance imaging data. We considered cortical thickness values derived from 10 regions throughout the frontal, parietal, and temporal lobes, and the posterior cingulate cortex that are associated with risk and progression of AD. The association between BP and cortical thickness was tested using adjusted linear regression models.

RESULTS: The mean age was 58.1 years and 231 (76%) were women. Higher office systolic BP was associated with thinner temporal (β = –0.059; 95% confidence interval [CI], –0.112, –0.005) and posterior cingulate cortex (β = –0.095; 95% CI, –0.145, –0.045). 24-h and nighttime BP levels were associated with thinner seven regions, with β-estimates ranging from –0.103 (95% CI, –0.182, –0.012) to –0.045 (95% CI, –0.080, –0.010). A higher 24-h BP variability was associated with thinner middle frontal (β = –0.156; 95% CI, –0.282, –0.030) and middle temporal (β = –0.146; 95% CI, –0.268, –0.024) gyri, and posterior cingulate cortex (β = –0.134; 95% CI, –0.026, –0.009).

CONCLUSIONS: Increased ambulatory BP level and variability are associated with cortical thinning in regions associated with AD. Better BP evaluation with out-of-office approaches might reduce brain structural changes associated with AD.

Keywords: AD signatures; ambulatory blood pressure monitoring; blood pressure; blood pressure level; blood pressure variability; brain MRI; hypertension; population-based study.

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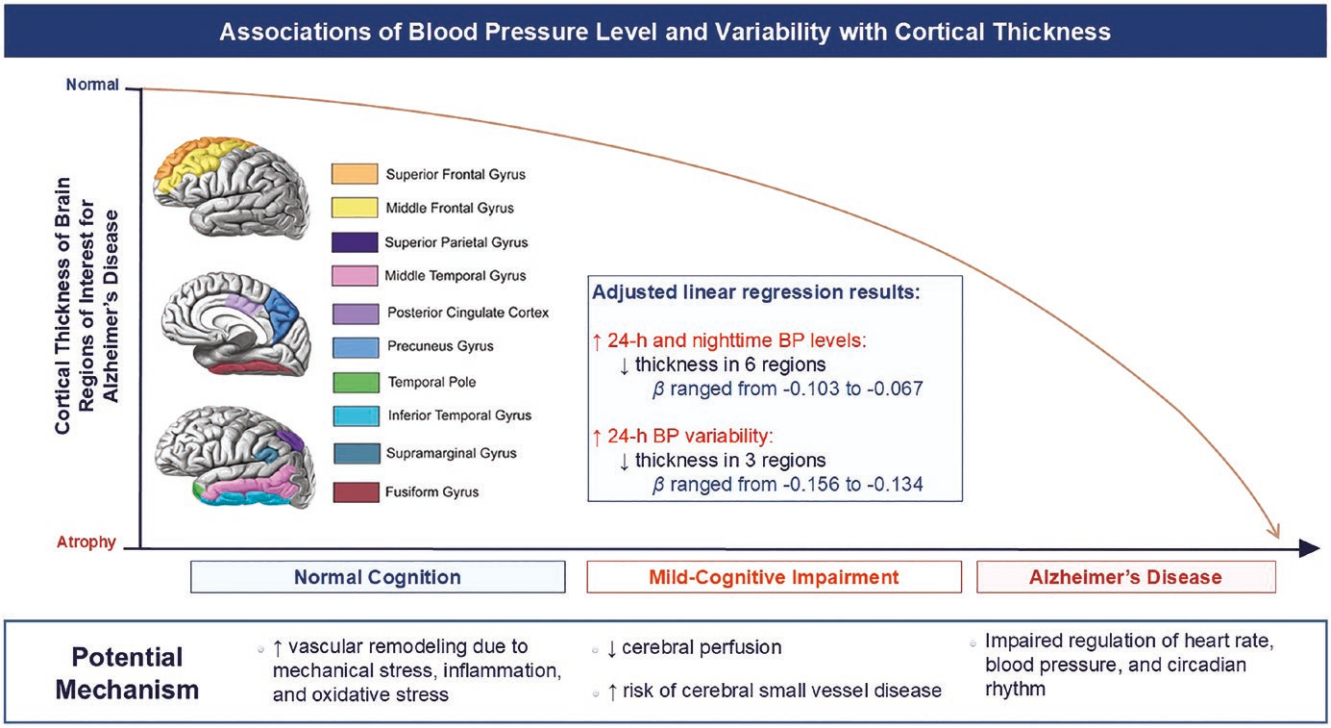
Graphical Abstract



Thinning or atrophy in certain cortical brain regions is associated with risk and progression of Alzheimer's Disease (AD).[1] Investigating cortical thickness in these regions using magnetic resonance imaging (MRI) provides an opportunity for early detection and the identification of modifiable risk factors during the initial stages of dementia. Elevated blood pressure (BP) is a modifiable risk factor that is associated with lower cortical thickness,[2] cognitive impairment and dementia.[3] In addition to BP level, high BP variability has been associated with accumulation of beta-amyloid,[4] cerebral small vessel disease,[5] brain atrophy,[6] and dementia.[7]

Although BP is often measured at the office or clinic visits, out-of-office BP assessments including the 24-h ambulatory BP monitoring provide more accurate values of individuals' BP by recording daytime and nighttime BP.[8] For instance, 24-h and nighttime BP are strongly associated with cerebral small vessel disease[9–11] and dementia risk.[12] We recently demonstrated that a higher 24-h BP variability over time was associated with cognitive decline.[13] A post hoc analysis of the Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT-MIND) study further showed that increased 24-h BP variability in the control group was associated with a higher risk of dementia.[14] While assessment of 24-h ambulatory BP monitoring may be less convenient than office BP in advanced AD, assessing cortical thickness before AD onset offers a valuable opportunity to investigate the relationship between BP and cortical atrophy in regions associated with AD risk and progression. Therefore, we aimed to investigate the associations of office and 24-h ambulatory BP monitoring with cortical thickness in regions relevant to AD.

METHODS

Material and methods

The Institutional Review Boards of the Cardiovascular Institute at the University of Zulia, Maracaibo, and Columbia University, New York, approved the study, which complied with the Helsinki Declaration for investigations into human subjects.[15] An informed consent form was signed by each participant. We followed the Oxford Equator Network STROBE guidelines https://www.equator-network.org/.

Study participants

The Maracaibo Aging Study is a prospective study of 2915 community participants ≥40 years of age recruited from the Santa Lucia and Santa Rosa neighborhoods in Maracaibo, Venezuela.[16] The baseline assessment was conducted between 1998 and 2001 for the Santa Lucia participants, and between 2010 and 2015 for the Santa Rosa participants. The purpose of the study is to investigate age-related diseases, particularly neurological and cardiovascular conditions.[16] Of the 2915 participants in the database, we included 304 participants dementia-free at baseline who underwent brain MRI scans, 24-h ambulatory BP monitoring, and had a minimum of six and three nocturnal readings which are sufficient to maintain the prognostic information of daytime and nocturnal BP level,[17] and at least 48 BP readings over 24-h for BP variability.[18]

Brain MRI acquisition

MRI scans were obtained on a 1.5-T scanner (GE Healthcare). They included T1-weighted, T2-weighted, gradient echo, diffusion-weighted imaging, angiography, and T2-weighted fluid-attenuated inversion recovery (FLAIR) scans. The FLAIR image parameters were TR = 8,000 ms, TE = 123 ms, 2,000 [ms] inversion time, 25-cm FOV, 2 NEX, 256 × 192 matrix with 2-mm slice thickness, 0 mm spacing, 63 slices; 6:01; COIL 8NHEAD_A, and an oblique orientation. Participants with a pacemaker, aneurysm clip, neurostimulator, cochlear implant, or body weight >110 kg did not undergo brain MRI scans. The MRI scans were subsequently transferred to Columbia University for analysis of the scans.[19]

Brain MRI regions of interest for AD

Brain MRI scans were analyzed to derive regional cortical thickness using FreeSurfer.[19] There are cortical regions in the brain that appear to be thinner in individuals who subsequently develop AD compared with those who stay cognitively stable decades prior to symptom onset.[1] These regions, distributed throughout the cortical mantle, are often described as an "AD signature" because they are associated with AD risk and progression.[1] They include the following gyri: superior frontal, middle frontal, supramarginal, superior parietal, precuneus, temporal, middle temporal, inferior temporal, entorhinal, fusiform (**Figure 1**). We additionally included the posterior cingulate cortex as baseline atrophy associates with AD.[20,21] We averaged the right and left sides of both cerebral hemispheres for each one of the cortical thickness regions.

BP assessments

Training nurses or physicians measured office BP readings with a validated oscillometric device (Dynamap). Office BP measurement was the average of five consecutive BP readings after 5 min of rest in a seated position. The assessment of the 24-h ambulatory BP monitoring has been previously discussed in detail.[13] Briefly, the 24-h BP readings were obtained with oscillometric automated devices (validated oscillometric 90202 or 90207 Spacelabs monitors).[22] Readings were programmed at 15-min intervals during the day from 06:00 AM to 11:00 PM, and at 30-min intervals from 11:00 PM to 6:00 AM. The within-subject 24-h systolic BP level and variability were time-weighted as time intervals between BP readings vary. BP variability was captured as the average real variability (ARV) index.[23] Our analysis focused on the ARV as it is the only metric that captures variability among consecutive BP readings.[24] ARV was calculated as the average of the absolute changes between consecutive BP readings, as follows:

$$ARV = \frac{1}{\sum w}\sum_{k=1}^{n-1} w \times |BP_{k+1} - BP_k|$$

where k ranges from 1 to $n - 1$, w is the time interval between BPk and BP$k + 1$, and n is the number of BP readings. BP level and variability were derived for 24-h, daytime, and nighttime measures. The dipping ratio was calculated by dividing the nighttime BP by the daytime BP.[25]

Covariates

Clinical variables including age (years), sex, height (in cm) and weight (in kg), self-reported smoking status (yes/no), history of diabetes mellitus (yes/no), serum total cholesterol (mg/dL), self-reported previous history of cardiovascular disease or stroke (yes/no), and use of antihypertensive and antidiabetic medications (yes/np) were collected. We followed the 2017 American Heart Association/American Collage of Cardiology guidelines for the management of hypertension to define categories of hypertension.[26] Office hypertension was defined as a systolic or diastolic BP over 130/80 mm Hg; respectively. Twenty-four-hour hypertension was a 24-h systolic or diastolic BP level over 125/75 mm Hg. Diabetes was defined as a serum fasting glucose level ≥126 mg/dL or a history of the use of antidiabetic medication (yes/no).

Statistical analysis

Continuous data are presented as the mean and SD for normally distributed variables and as the median (Q1–Q4) for nonnormally distributed variables. Categorical data are shown as frequencies (%). Baseline characteristics, office and ambulatory BP measurements, and the distribution of brain MRI regions of interest for AD were reported for the whole study sample.

Adjusted linear regression models were used to investigate the associations of office and ambulatory BP level and variability (exposure variables) with cortical thickness associated with AD (outcomes). Covariates were selected based on their biological relevance with BP level and variability, and cortical thickness. Covariates included age, sex, years of education, body mass index, intracranial volume, smoking, alcohol intake, total serum cholesterol, history of cardiovascular disease, diabetes mellitus, and use of antihypertensive medication. For BP variability and night-to-day ratio, models were additionally adjusted by the corresponding mean BP level. Exploratory analysis were conducted to replicate whether BP level and variability were associated with cortical thickness in adjusted logistic regression models. Using the 10th percentile of AD regions cortical thickness as a cutoff point, we generated a proxy to categorize individuals with atrophy (below the 10th percentile) and normal thickness (≥10th percentile) for this specific population. Odds ratios and 95% confidence interval (CI) were displayed in a forest plot. We used SAS software, version 9.4, and maintenance level 5. Statistical significance was indicated by a two-tailed α-level of 0.05 or less.

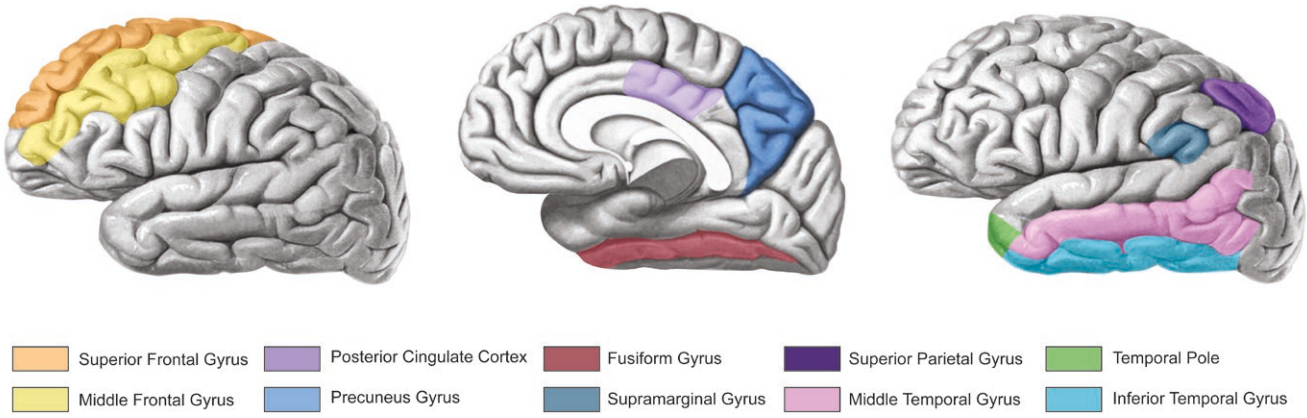


Figure 1. Brain atlas highlighting the cortical regions of interest for Alzheimer's disease.

RESULTS

Baseline characteristics

The mean age was 58.1 ± 12.2 and 231 (76.0%) were women (**Table 1**). The proportion of current smoking, alcohol intake, office and 24-h hypertension, use of antihypertensive medication, diabetes mellitus, and history of cardiovascular diseases was 28.3%, 48.4%, 55.9%, 42.4%, 36.2%, 15.1%, and 8.2%, respectively. **Table 2** contains the mean and SD of the brain MRI regions of interest.

Associations of office and ambulatory BP level with cortical thickness

Office ($P \leq 0.031$), 24-h ($P \leq 0.0.30$), daytime ($P \leq 0.035$), and nighttime ($P \leq 0.013$) BP levels were associated with MRI regions of interest for AD (**Table 3**). For office systolic BP, every + 1SD (mm Hg) increase was associated with −0.059 mm (95% CI, −0.122 and −0.005) thinner temporal pole and −0.095 mm (95% CI, −0.145 and −0.045) thinner posterior cingulate cortex. Each + 1 SD increase in 24-h, daytime, and nighttime BP was associated

Table 1. Baseline characteristics of the study sample

Baseline characteristics	Study sample (*n* = 304)
Demographics	
Age, years	58.1 ± 12.2
Women, *n* (%)	231 (76.0)
Education, years	6 (5-11)
Clinical variables	
Body mass index, kg/mt2	27.7 ± 5.2
Current smoking, *n* (%)	86 (28.3)
Alcohol intake, *n* (%)	147 (48.4)
Office hypertension, *n* (%)	170 (55.9)
24-h hypertension, *n* (%)	129 (42.4)
Antihypertensive treatment, *n* (%)	110 (36.2)
Diabetes mellitus, *n* (%)	46 (15.1)
History of cardiovascular diseases, *n* (%)	25 (8.2)
Biochemistry features	
Serum glucose, mg/dL	108.5 ± 35.7
Serum total cholesterol, mg/dL	196.8 ± 44.1
Blood pressure measurements, mm Hg	
Office systolic blood pressure level	139.8 ± 25.1
Ambulatory systolic blood pressure level	
24-h	120.8 ± 15.0
Daytime	122.8 ± 14.4
Nighttime	116.1 ± 17.8
Ambulatory systolic blood pressure variability	
24-h average real variability	8.55 ± 1.86
Daytime average real variability	8.83 ± 2.10
Nighttime average real variability	8.01 ± 2.55
Night-to-day ratio	0.94 ± 0.07

Abbreviation: AD, Alzheimer's disease. Values are means and SD and frequencies (%) or are reported as median and interquartile range if following a nonparametric distribution. Previous history of cardiovascular disease included ischemic heart disease, heart failure, and stroke.

Table 2. Cortical thickness of brain MRI regions of interest for Alzheimer's disease

Brain MRI regions of interest for Alzheimer's disease	Study sample (*n* = 304)
Frontal lobe, mm	
Superior frontal gyrus	2.79 ± 0.15
Middle frontal gyrus	2.47 ± 0.13
Parietal lobe, mm	
Supramarginal gyrus	2.34 ± 0.13
Superior parietal gyrus	2.12 ± 0.11
Precuneus gyrus	2.25 ± 0.12
Temporal lobe, mm	
Temporal pole	3.57 ± 0.32
Middle temporal gyrus	2.86 ± 0.14
Inferior temporal gyrus	3.00 ± 0.17
Entorhinal cortex	3.24 ± 0.28
Fusiform gyrus	2.74 ± 0.14
Posterior cingulate cortex	2.54 ± 0.16

Abbreviation: MRI, magnetic resonance imaging.
Values are means and standard deviation (SD).
Figure 1 displays a brain atlas highlighting the brain MRI regions of interest for AD.

Table 3. Association of BP level with cortical thickness of brain MRI regions of interest for Alzheimer's disease

Brain MRI AD regions	Office and ambulatory systolic BP level measurements			
	Office BP (+ 10 mm Hg)	24-h BP (+ 10 mm Hg)	Daytime BP (+ 10 mm Hg)	Nighttime BP (+ 10 mm Hg)
	β-coefficient (95% CI)[a]	β-coefficient (95% CI)[a]	β-coefficient (95% CI)[a]	β-coefficient (95% CI)[a]
Frontal lobe, mm				
Superior frontal gyrus	−0.036 (−0.083, 0.010)	−0.026 (−0.098, 0.045)	−0.025 (−0.098, 0.049)	−0.026 (−0.086, 0.034)
Middle frontal gyrus	−0.041 (−0.093, 0.010)	−0.033 (−0.112, 0.046)	−0.032 (−0.114, 0.049)	−0.030 (−0.096, 0.037)
Parietal lobe, mm				
Supramarginal gyrus	−0.028 (−0.077, 0.022)	−0.083 (−0.158, −0.008)*	−0.083 (−0.161, −0.006)*	−0.069 (−0.132, −0.005)*
Superior parietal gyrus	−0.015 (−0.069, 0.040)	−0.007 (−0.090, 0.077)	−0.009 (−0.095, 0.077)	−0.002 (−0.073, 0.068)
Precuneus gyrus	−0.026 (−0.077, 0.025)	−0.031 (−0.109, 0.048)	−0.032 (−0.113, 0.048)	−0.023 (−0.089, 0.043)
Temporal lobe, mm				
Temporal pole	−0.059 (−0.112, −0.005)*	−0.090 (−0.172, −0.009)*	−0.080 (−0.165, 0.004)	−0.088 (−0.156, −0.019)*
Middle temporal gyrus	−0.034 (−0.084, 0.016)	−0.094 (−0.170, −0.018)*	−0.097 (−0.176, −0.019)*	−0.072 (−0.136, −0.008)*
Inferior temporal gyrus	−0.044 (−0.095, 0.007)	−0.092 (−0.170, −0.014)*	−0.083 (−0.164, −0.003)*	−0.089 (−0.154, −0.023)**
Entorhinal cortex	−0.034 (−0.086, 0.017)	−0.079 (−0.157, 0.001)	−0.078 (−0.159, 0.003)	−0.065 (−0.131, 0.001)
Fusiform gyrus	−0.032 (−0.084, 0.020)	−0.103 (−0.182, −0.024)*	−0.094 (−0.175, −0.012)*	−0.099 (−0.165, −0.032)**
Posterior cingulate cortex	−0.095 (−0.145, −0.045)***	−0.090 (−0.168, −0.012)*	−0.095 (−0.175, −0.014)*	−0.067 (−0.133, −0.001)*

Abbreviations: MRI, magnetic resonance imaging; AD, Alzheimer's disease; BP, blood pressure; CI, confidence interval.
Estimates (β-coefficient and 95% CI) express the association of each 10 mm Hg increase in office and ambulatory systolic BP level with 1SD unit change in brain MRI AD regions. Negative estimates indicate that a higher systolic BP level relates with thinner (atrophy) MRI AD regions.
[a]Adjusted linear regression models were accounted for age, sex, years of education, body mass index, intracranial volume, smoking, alcohol intake, total serum cholesterol, history of cardiovascular disease, diabetes mellitus, and use of antihypertensive medication.
*P<0.05; **P<0.01; ***P<0.001.

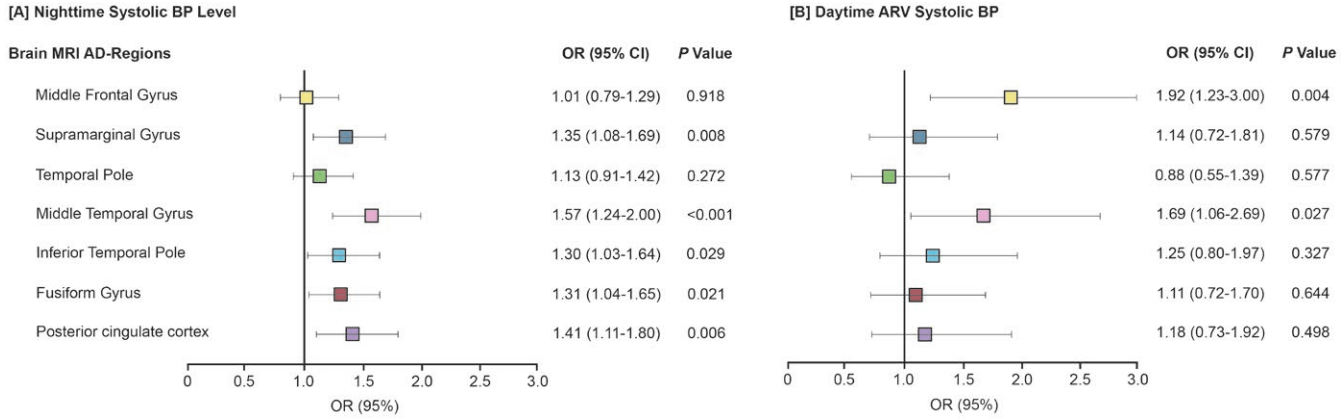


Figure 2. Association of nighttime systolic BP level (**a**) and daytime systolic ARV (**b**) with Cortical atrophy of MRI regions of interest for AD. Using the 10th percentile, we generated a proxy of cortical atrophy defined as individuals with cortical thickness below the 10th percentile, and normal ≥10th percentile. Adjusted logistic regression models were accounted for age, sex, years of education, body mass index, intracranial volume, smoking, alcohol intake, total serum cholesterol, history of cardiovascular disease, diabetes mellitus, and use of antihypertensive medication hypertension. For daytime systolic ARV, models additionally accounted for the mean daytime systolic BP level. OR are expressed per + 10 mm Hg increase in the nighttime systolic BP level and + 1SD (2.10 mm Hg) increase in the daytime systolic ARV.

with lower thickness of the supramarginal gyrus, temporal pole, middle temporal gyrus, inferior temporal gyrus, fusiform gyrus, and posterior cingulate cortex. The adjusted β-coefficient varied from -0.103 mm (95% CI, −0.182 and −0.024) to −0.059 mm (95% CI, −0.112, −0.005). In logistic regression analysis (**Figure 2**), each + 10 mm Hg increase in the nighttime systolic BP was associated with higher odds of having cortical atrophy in the supramarginal gyrus, middle temporal gyrus, inferior temporal gyrus, fusiform gyrus, and posterior cingulate cortex; odds ratios ranged from 1.31 (95% CI, 1.04–1.65) to 1.57 (95% CI, 1.24–2.00).

Associations of ambulatory BP variability with cortical thickness

Increased 24-h systolic ARV was associated with lower cortical thickness in the middle frontal gyrus (β-coefficient per + 1SD increase in 24-h systolic ARV, −0.156 mm; 95% CI, −0.282 and −0.030; **Table 4**), middle temporal gyrus (β-coefficient, −0.146 mm; 95% CI, −0.268 and −0.024), and posterior cingulate cortex (β-coefficient, −0.134 mm; 95% CI, −0.260 and −0.009). We observed similar findings for daytime systolic ARV with β-coefficients ranging from −0.183 mm to −0.082 mm. Nighttime systolic ARV and night-to-day ratio were not associated with cortical thickness (β-coefficients were less than −0.107; $P \geq 0.088$). In logistic models (**Figure 2**), high 24-h systolic ARV was associated with brain atrophy in the middle frontal (odds ratio per + 1SD increase in 24-h systolic ARV, 1.92; 95% CI, 1.23–3.00), and middle temporal gyri (odds ratio, 1.69; 95% CI, 1.06–2.69).

DISCUSSION

In this population-based study of 304 participants, increased BP levels were associated with thinner brain regions that are associated with risk and progression of AD. We observed that 24-h

Table 4. Association of ambulatory BP variability with cortical thickness of MRI regions of interest for Alzheimer's disease

Brain MRI regions of interest for Alzheimer's disease	Measurements of ambulatory systolic BP variability					
	24-h systolic ARV (+ 1SD = 1.86 mm Hg)		Daytime systolic ARV (+ 1SD = 2.10 mm Hg)		Nighttime systolic ARV (+ 1SD = 2.55 mm Hg)	
	β-coefficient (95% CI)[a]	P value	β-coefficient (95% CI)[a]	P value	β-coefficient (95% CI)[a]	P value
Frontal lobe, mm^3						
Superior frontal gyrus	−0.089 (−0.204, 0.026)	0.128	−0.092 (−0.206, 0.021)	0.111	−0.056 (−0.162, 0.050)	0.300
Middle frontal gyrus	−0.156 (−0.282, −0.030)	0.016	−0.183 (−0.307, −0.059)	0.004	−0.033 (−0.151, 0.084)	0.578
Parietal lobe, mm^3						
Supramarginal gyrus	0.024 (−0.098, 0.145)	0.702	−0.003 (−0.123, 0.117)	0.961	0.060 (−0.052, 0.172)	0.293
Superior parietal gyrus	−0.058 (−0.193, 0.076)	0.393	−0.057 (−0.190, 0.075)	0.395	−0.052 (−0.176, 0.072)	0.409
Precuneus gyrus	−0.034 (−0.161, 0.092)	0.593	−0.012 (−0.137, 0.112)	0.846	−0.067 (−0.183, 0.049)	0.259
Temporal lobe, mm						
Temporal pole	0.017 (−0.115, 0.149)	0.797	−0.025 (−0.155, 0.105)	0.707	0.094 (−0.027, 0.215)	0.128
Middle temporal gyrus	−0.146 (−0.268, −0.024)	0.019	−0.164 (−0.284, −0.044)	0.008	−0.031 (−0.145, 0.082)	0.588
Inferior temporal gyrus	−0.031 (−0.157, 0.095)	0.628	−0.044 (−0.169, 0.081)	0.488	−0.011 (−0.127, 0.105)	0.855
Entorhinal cortex	−0.122 (−0.248, 0.004)	0.059	−0.109 (−0.234, 0.016)	0.088	−0.060 (−0.177, 0.057)	0.313
Fusiform gyrus	−0.043 (−0.170, 0.084)	0.507	−0.063 (−0.189, 0.063)	0.327	0.002 (−0.116, 0.119)	0.978
Posterior cingulate cortex	−0.134 (−0.260, −0.009)	0.036	−0.140 (−0.264, −0.016)	0.027	−0.053 (−0.170, 0.063)	0.369

Abbreviations: MRI, magnetic resonance imaging; ARV, average real variability; CI, confidence interval.
Estimates (β-coefficient and 95% CI) express the association of each + 1 SD mm Hg increase ambulatory systolic BP variability with 1 SD unit change in brain MRI AD regions. Negative estimates indicate that a higher systolic BP variability relates with thinner (atrophy) MRI AD regions. Night-to-day ratio was not related with MRI AD regions ($P \geq 0.171$).
[a]Adjusted linear regression models were accounted for age, sex, years of education, body mass index, intracranial volume, smoking, alcohol intake, total serum cholesterol, history of cardiovascular disease, diabetes mellitus, and use of antihypertensive medication.*

and nighttime BP levels were the indices with the strongest association with the MRI outcomes. Additionally, 24-h and daytime BP variability were also related to cortical thinning, especially regions in the temporal lobe, regardless of the mean BP level.

Elevated BP is associated with brain atrophy.[27,28] Some studies evaluated ambulatory BP level in relation to brain atrophy but without focusing on cortical thickness of regions implicated in AD.[29,30] Examining 24-h ambulatory BP data has clinical (by improving management of hypertension) and scientific (by capturing greater number of BP readings, BP variability, and circadian rhythms) relevance in many fields, including AD research. Our study provides novel data showing that 24-h BP (including daytime and nocturnal BP) relate to cortical thickness of areas associated with risk and progression of AD. Given that individuals who developed AD have, on average, atrophy of these regions decades prior to disease onset,[1] it is possible that lowering the probability of brain atrophy related to uncontrolled out-of-office BP might decrease the risk of developing AD. Recent findings from the SPRINT-MIND showed that intensive BP control reduces the risk of cognitive impairment and dementia.[14] Although office BP will continue being the primary strategy for assessing hypertension, consideration of out-of-office values opens the opportunity for improving our understanding of the role of vascular risk factors in dementia.

Elevated nighttime but not daytime BP was associated with cortical thickness. Numerous studies showed that nighttime BP level has the strongest association with outcomes including cerebral small vessel disease,[9,10] cardiovascular complications, and mortality.[31] We demonstrated that elevated nighttime BP is related to a higher risk of AD.[12] Similar to its association with cardiovascular complications, our study suggests that nighttime BP provides more information relevant to cortical thickness than other BP indices. Moreover, the inclusion of nighttime BP measures could be particularly important because circadian rhythms in BP can be examined using daytime and nighttime BP levels, and regulation of the circadian rhythms is impaired in AD.[32] Research on this topic is still limited, but new technologies might overcome challenges related to performing 24-h ambulatory BP monitoring.

Another key finding was the association of 24-h BP variability with MRI outcomes. Currently, there are only two studies examining 24-h BP variability in relation to AD. A post hoc analysis of the SPRINT-MIND study showed that elevated 24-h BP variability increased the risk of developing dementia in the intensive BP group.[33] The other study includes a recent publication from our group. Using a different subset (baseline was between 1998 and 2001) of 437 subjects with both longitudinal 24-h BP data and cognitive testing, we reported that a higher increase in 24-h BP variability over time was associated with cognitive decline during follow-up.[13] Nonetheless, there is emerging discussion about the importance of BP variability and risk for dementia.[7] The mechanism remains unclear, regulation of physiological functions including heart rate and BP may be impaired in dementia.[34] With the notion that AD is related to impaired circadian rhythms and loss of physiological regulation, capturing 24-h BP variability could potentially be utilized as a marker of vascular dysregulation in AD.

Various physiopathological mechanisms could underlie the impact of hypertension on brain parenchyma, including vascular remodeling.[35] Changes in the cerebral circulation are driven by inflammation, mechanical stress, and the activation of factors that can lead to increased oxidative stress.[35] The resulting changes in the cerebrovascular circulation can impair cerebral blood flow, and damage the cerebral microcirculation (e.g., promoting cerebral small vessel disease) and parenchyma (e.g., resulting in atrophy), increasing the risk of cognitive and decline stroke. Given hypertension is associated with these physiopathological changes occurring before and after AD onset, relying solely on in-office BP might not be sufficient to reduce vascular injury associated with AD development and progression. A clear understanding of hypertension and BP dysregulation in AD might help reduce atrophy of regions vulnerable to vascular damage.

Dysregulation of the cardiovascular system plays a potential role in the physiopathological mechanism of AD.[7] The exact mechanisms remain unclear and understanding the role of vascular dysregulation is complex. Nevertheless, some plausible hypotheses state that vascular dysregulation affects cerebral autoregulation. Systemic BP is one of the determinants of cerebral blood flow.[36] Therefore, when drastic and constant changes in the systemic BP occur, the cerebral circulation of individuals with AD might adapt inadequately to, for example, elevated 24-h BP variability.[37] The resulting event is an impaired cerebral blood flow affecting perfusion pressure.[37] Brain atrophy is associated with cerebral hypoperfusion related to drops in the systemic BP in conditions such as orthostatic hypotension.[38] Another potential mechanistic hypothesis states that high BP variability may be due to increased arterial stiffness, which is a strong risk factor for cognitive impairment and clinical AD.[39] Elevated BP variability could have an indirect effect on brain tissue as it relates to the presence and development of cerebral small vessel disease.[40]

Limitations and strengths

This study should be interpreted within the context of its limitations. First, the cross-sectional design of our study limits establishing whether elevated 24-h BP level and variability can lead to atrophy of AD brain regions.Moreover, it is possible that atrophy of AD brain regions may lead to 24-h BP dysregulation. Although our longitudinal data and previous studies demonstrated that elevated 24-h BP variability leads to cognitive impairment, longitudinal brain MRI data will be fundamental to test causality. Second, due to the lack of longitudinal data, it is unknown whether individuals who have evidence of brain atrophy are at a higher risk of developing AD. Third, although Hispanics are at higher risk of developing AD and also have a higher proportion of vascular risk factors including hypertension compared to non-Hispanic white people, our findings should be tested and replicated in other cohorts of individuals from different ethnicity groups. Fourth, we found that no associations between BP level or variability and AD-related brain MRI regions remained statistically significant after multiple testing correction using the Benjamini–Hochberg procedure.[41] However, in our study, these findings should be interpreted with caution as both the AD-related brain regions and ambulatory BP measures are correlated and multiple testing procedures assume independence among variables.[42,43] The pathophysiological mechanisms linking elevated BP and variability to regional brain atrophy also involve shared biological pathways. Therefore, applying multiple testing corrections may lead to overcorrection and reduced statistical power, potentially masking meaningful associations. The strengths of our study included the assessment of 24-h BP variability, which is currently the only approach that captures BP fluctuations among consecutive BP readings, the analysis of volumetric brain MRI data, and the inclusion of a multidisciplinary team constituted by primary care physicians, neurologists, psychiatrists, cardiologists, and geriatricians.

Conclusions

Elevated BP levels were associated with cortical thining of brain MRI regions associated with AD risk, particularly high 24-h and nighttime BP levels. We also observed that ambulatory BP variability was related to brain atrophy independently of the mean BP level. An improved reduction in vascular insult related to 24-h vascular dysregulation may lead to decreased cerebral small vessel disease, and in turn, reduce thinning of cortical regions associated with AD. Nonetheless, prospective studies are needed to test whether 24-h BP dysregulation leads to brain atrophy and whether controlling BP level and having lower BP variability at baseline resulted in lower atrophy of AD regions.

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Conflict of Interest

The authors declared no conflict of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author [JDM], upon reasonable request.

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