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In Vivo Brain Plaque and Tangle Burden Mediates the Association Between Diastolic Blood Pressure and Cognitive Functioning in Nondemented Adults

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Objective: *Growing evidence supports an association between increased blood pressure and: (a) poor cognitive performance in older adults, and (b) various biomarkers of increased Alzheimer's disease (AD) neuropathology. The objective of this study was to determine whether systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly associated with cognitive functioning in non-demented adults, and to examine* in vivo *AD pathology as a possible mediator of this association.* **Methods:** *Positron emission tomography (PET) scans with 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl) amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) provide* in vivo *measurements of plaque and tangle burden. A total of 101 non-demented older subjects with blood pressure data and FDDNP-PET scans were drawn from a larger study of predictors of cognitive decline. A neuropsychological test battery was used to compute "global cognitive scores" (averaged across five key domains), which served as an index of general cognitive functioning.* **Results:** *Higher DBP (but not SBP) was significantly associated with lower cognitive scores, controlling for age, sex, antihypertensive medication use, and* ApoE *genotype (η^2 = 0.06). However, this relationship was no longer significant after introducing FDDNP-PET binding as an additional covariate in the statistical models.* In vivo *plaque and tangle burden accounted for over 30% of the observed association between higher DBP and poorer cognitive performance.* **Conclusions:** *By suggesting a mediation of the relationship between DBP and cognitive functioning by FDDNP-PET binding, this study advances our understanding of some potential predictors of cognitive decline in non-demented adults, and underscores the importance of devising early multimodal interventions to more effectively combat degenerative brain disorders.* (Am J Geriatr Psychiatry 2017; ■■:■■–■■)

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Key Words: FDDNP-PET, plaques, tangles, diastolic blood pressure, age-related cognitive decline

Article Highlights

- Diastolic (but not systolic) blood pressure is significantly associated with cognitive functioning in nondemented middle-aged and older adults.
- Higher diastolic blood pressure is associated with poorer cognitive performance, independently of age, sex, use of antihypertensive medications, and *ApoE* genotype.
- This association is no longer significant after introducing FDDNP-PET binding as an additional covariate in the statistical models.
- The relationship between higher diastolic blood pressure and poorer cognitive performance may be mediated by increased in vivo plaque and tangle burden.

INTRODUCTION

Epidemiologic and clinicopathologic data demonstrate considerable overlap between cerebrovascular disease and Alzheimer disease (AD) and indicate that vascular and AD-type pathologies are leading causes of cognitive impairment in the elderly.[1] The main neuropathologic hallmarks of AD are senile plaques and neurofibrillary tangles. β-Amyloid (Aβ) peptides can aggregate to form insoluble fibers that are resistant to degradation. Plaques result from the accumulation of amyloid fibrils between neurons, whereas tangles are intracellular aggregates of hyperphosphorylated tau protein. Human autopsy studies indicate that plaques and tangles accumulate in a predictable spatial pattern in aging and AD.[2,3] These changes may begin before age 30[4] and gradually increase in prevalence with age.

Recently developed positron emission tomography (PET) ligands allow *in vivo* measurement of AD pathology in the brain. Notably, our group developed a small molecule, 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP), for use as an *in vivo* chemical marker of cerebral aggregates of Aβ and tau proteins.[4] FDDNP-PET is the first and only method to provide a measure of both plaque and tangle binding levels in the living human brain, and the *in vivo* distribution of FDDNP in the brain follows patterns of plaque and tangle distribution seen at autopsy.[5]

Structural magnetic resonance imaging (MRI) studies have demonstrated associations between vascular pathology[6–8] and cognitive decline and indicated synergistic relationships between Aβ burden and cerebrovascular disease on cognitive impairment.[9] Contributors to vascular risk, such as diabetes,[10] smoking status,[11] and hyperhomocysteinemia[12] have been associated with cognitive deficits and elevated risk of developing dementia. Converging evidence from autopsy, neuroimaging, and cerebrospinal fluid biomarker studies indicates that vascular and AD-type pathologies exert additive or synergistic effects on cognitive decline, but the relationships between individual vascular factors and plaque/tangle burden remain unclear.[1]

Although early reports found no relationship between blood pressure and cognitive functioning,[13,14] growing evidence supports an association between increased blood pressure and lower cognitive performance in older adults.[15] Recent studies also suggest a link between elevated blood pressure and various biomarkers of increased plaque and tangle load.[16] However, to our knowledge, no previous study has examined *in vivo* AD pathology as a potential mediator of the association between blood pressure and cognitive performance in pre-dementia states.

To address this knowledge gap, we first determined whether systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly associated with cognitive functioning in our sample of 101 nondemented middle-aged and older adults, controlling for age, sex, use of antihypertensive medications, and *ApoE* genotype. We also tested the hypothesis that our cross-sectional study may point to *in vivo* plaque and tangle burden as a possible mediator of the relationship between higher DBP and poorer cognitive functioning.

METHODS

Subjects

A total of 101 nondemented subjects who had complete neuropsychological testing, blood pressure data, and FDDNP-PET scans were drawn from a larger study of predictors of cognitive decline.[17,18] Data were collected between September 1998 and February 2016. Briefly, volunteers from the community were recruited through advertisements, media coverage of the study, and referrals by physicians and families. Members of the research staff screened potential volunteers via telephone interviews. All subjects underwent FDDNP-PET scans and clinical and cognitive assessments performed blinded to the results of FDDNP-PET scans. Written informed consent was obtained in accordance with the University of California, Los Angeles Human Subjects Protection Committee procedures. Cumulative radiation dosimetry for all scans was below the mandated maximum annual dose and in compliance with state and federal regulations. Exclusion criteria included MRI intolerance, evidence of stroke or brain tumor on MRI, traumatic brain injury, cognitively altering medications, and excessive head motion during scanning. For the purpose of the current study, which focused on nondemented adults, participants with a diagnosis of AD or other dementias were also excluded, leaving a total of 101 nondemented subjects for the current analyses.

Neuropsychological Testing

A neuropsychological test battery was administered to assess five specific cognitive domains: (1) memory, which included the Wechsler Memory Scale, Third Edition logical memory (delayed score), Buschke selective reminding (total score), and Rey-Osterrieth complex figure recall (3-minute delayed recall score); (2) language, which included the Boston naming test, and letter (F.A.S.) and category (Animal naming test) fluency; (3) attention and information-processing speed, which included the Trail-Making Task A, Stroop Color Naming (Kaplan version), and Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) digit symbol; (4) executive functioning, which included the Trail-Making Task B and Stroop Interference (Kaplan version); and (5) visuospatial ability, which included the WAIS-III block design and Rey-Osterrieth complex figure copy. We converted raw test scores to z scores by standardizing them to a mean of 0 and a standard deviation of 1. We computed domain z scores by averaging those z scores belonging to the cognitive tests in that domain. Because this study focused on participants' overall cognitive functioning and its association with blood pressure measures (in the absence of *a priori* hypotheses about specific cognitive domains), we obtained global cognitive scores by averaging the five domain z scores.

Demographic, Blood Pressure, and Genetic Data

During study intake for each subject, gender and age were recorded and medical history obtained to determine use of antihypertensive medications. Right arm blood pressure was measured once by a registered nurse with the subject seated, following standard clinical protocols. In most cases, a single blood pressure measurement was recorded. However, for participants who expressed that an activity or emotional state was affecting them or if a significantly abnormal blood pressure (per subject report) was measured, participants were requested to rest for at least several minutes before another reading was obtained. In these instances only the second measurement was recorded. All DNA was obtained from blood samples. The *ApoE* genotypes were determined using standard techniques as previously described.[19]

Imaging Methods

Global plaque and tangle load from an FDDNP-PET scan was the single pathology score used for each subject in this study. Global FDDNP-PET binding was calculated by averaging the load from five brain regions of interest (ROIs) known to accumulate pathology in AD (medial temporal, lateral temporal, posterior cingulate, parietal, and frontal cortices). Global load was the average over all ROIs.

FDDNP was prepared at very high specific activities (>37 GBq/mol), as described in detail elsewhere.[20] All scans were performed with the ECAT HR or EXACT HR + tomograph (Siemens-CTI, Knoxville, TN) with subjects supine and the imaging plane parallel to the orbitomeatal line. A bolus of FDDNP (320–550 MBq) was injected via an indwelling venous catheter, and consecutive dynamic PET scans were

performed for 2 hours. Scans were decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5-mm full width at half maximum) with scatter and measured attenuation correction. The resulting images contained 47 contiguous slices with plane separation of 3.37 mm (ECAT HR) or 63 contiguous slices with plane separation of 2.42 mm (EXACT HR+). Determinations of data reproducibility were performed when the new scanner was introduced in the Nuclear Medicine clinic using phantoms and comparing results between scanners. Nonparametric Wilcoxon two-sample tests found no significant differences in regional FDDNP signals between the two PET scanners.

All subjects received MRI scans that were coregistered to PET scans for determination of ROIs. These anatomic brain scans were obtained using either a 1.5-T or 3-T magnet (General Electric-Signa, Milwaukee, WI) scanner. Fifty-four transverse planes were collected throughout the brain, superior to the cerebellum, using a double-echo, fast-spin echo series with a 24-cm field of view and 256 × 256 matrix with 3 mm/0 gap (TR = 6000 [3 T] and 2000 [1.5 T]; TE = 17/85 [3 T] and 30/90 [1.5 T]). Rules for ROI drawing were based on the identification of gyral and sulcal landmarks with respect to the atlas of Talairach and Tournoux.[21] All PET and MRI scans were read, and the ROIs were drawn by investigators blind to clinical assessments. Previous inter-rater reliability studies have confirmed high consistency and reliability using this method.[22]

FDDNP-PET binding levels were quantified as previously described.[17] Briefly, we performed Logan graphical analysis with the cerebellum as the reference region for time points between 30 and 125 minutes.[23] The slope of the linear portion of the Logan plot is the relative distribution volume (DVR), which is equal to the distribution volume of the tracer in an ROI divided by that in the reference region. We generated DVR parametric images and analyzed them using gray matter ROIs drawn manually on the FDDNP-PET image obtained in the first 5 minutes after injection (the perfusion image). This image shows the perfusion pattern and has sufficient anatomic information to identify the cerebellum and cerebellar gray matter. ROIs were drawn bilaterally on the medial temporal (containing limbic regions, including hippocampus, parahippocampal, and entorhinal areas), lateral temporal, posterior cingulate, parietal, frontal, and cerebellar regions, as previously described.[24] Each cerebral regional DVR or binding value was expressed as an average of left and right regions, and global DVR values were calculated as averages of the values for all these regions.

Statistical Analyses

Data were screened for outliers, whose values may fall beyond 2.5 standard deviations from the mean, for all variables included in these analyses. We used general linear models to examine associations between blood pressure and global cognitive scores in our sample of 101 nondemented middle-aged and older adults. Separate general linear models were used to determine if SBP and DBP were significantly associated with global cognitive scores, controlling for age, sex, use of antihypertensive medications, and *ApoE* genotype, and whether these associations remained significant after including global FDDNP-PET binding as an additional covariate in the statistical models.

Simple mediation analyses were conducted using Andrew Hayes's PROCESS Procedure (v2.15) for SPSS 23.0 (Armonk, NY: IBM Corp.). We obtained path coefficients (a, b, c, and c′) representing the linear regression coefficients for each path in the mediation model. We standardized all variables to facilitate the interpretation of path coefficients, now bounded by –1 and 1 across all measures. The a-path represents the association between the predictor and mediator variables. The b-path denotes the relationship between the mediator and outcome variables, while also controlling for the predictor variable. The c′-path (also called "direct effect") and the c-path (also known as "total effect") represent the associations between the predictor and outcome variables including and excluding the mediator variable, respectively. If the difference between c and c′ is statistically significant, then there is a significant mediation effect. It has been shown that $a \times b = c - c'$;[25] therefore, we tested the significance of $a \times b$ (also known as "indirect effect") using bootstrapped confidence intervals with 1,000 simulated samples.[26] If the 95% confidence interval for $a \times b$ does not include 0 and the association between the predictor and outcome variables including the mediator variable (i.e., the c′-path) is no longer significant, then a significant ($p < 0.05$) mediation has occurred. We used percent mediation as a measure of effect size.[27,28]

RESULTS

Demographic and Clinical Characteristics of the Sample

This cohort of nondemented middle-aged and older adults included a higher proportion of women (55%) (Table 1). Most participants (80%) were not under antihypertensive therapy at time of the study. Forty-five subjects carried at least one ApoE-ε4 allele (45%).

TABLE 1. Demographic and Clinical Characteristics of the Sample (N = 101)

Variable	Frequency
Sex	M: 45 (45%) F: 56 (55%)
Under antihypertensive therapy	No: 81 (80%) Yes: 20 (20%)
ApoE genotype (no. of ε4 alleles)	0 ε4: 56 (55%) 1 ε4: 40 (40%) 2 ε4: 5 (5%)

	Mean (Standard Deviation)	Median	Range
Age, yr	63.68 (12.29)	64	39 – 87
Global cognitive scores	0.04 (0.65)	0.06	−1.94 – 1.30
SBP	129.09 (19.44)	130	85 – 177
DBP	72.06 (10.77)	72	39 – 94
Global FDDNP-PET binding	1.09 (0.03)	1.09	1.01 – 1.16

All continuous variables examined in this study appeared to be normally distributed. All individual values fell within 2.5 standard deviations from the mean for all variables included in these analyses. Descriptive statistics are provided in Table 1.

Associations Between Blood Pressure and Cognitive Functioning

Multiple regression analyses revealed that higher SBP was not significantly associated with lower global cognitive scores, when controlling for age, sex, *ApoE* genotype, and blood pressure medication status. *F*-statistics followed by degrees of freedom in parentheses and *p*-values for all variables in the models are reported in Table 2. Similar results were observed when global FDDNP-PET binding was included as an additional covariate in the statistical models (Table 2). Unlike SBP, higher DBP was significantly associated with lower global cognitive scores, controlling for age, sex, *ApoE* genotype, and blood pressure medication status (Table 2). The partial eta-squared ($\eta^2 = 0.06$) suggested a small to medium effect size. However, this association was no longer significant after introducing global FDDNP-PET binding as an additional regressor (Table 2). In this model, higher global FDDNP-PET binding showed a significant association of moderate effect size ($\eta^2 = 0.07$) with lower global cognitive scores,

TABLE 2. Results of Multiple Regression Analyses: SBP and DBP as Predictors of Global Cognitive Scores (N = 101)

Dependent Variable: Global Cognitive Scores	Blood Pressure	Age	Sex	BP Medication	*ApoE* Genotype	Global FDDNP-PET Binding	Corrected Model
SBP	$F(1,95) = 2.83$ $p = 0.09$	$F(1,95) = 20.75$ **$p < 0.001$**	$F(1,95) < 0.01$ $p = 0.93$	$F(1,95) = 0.59$ $p = 0.44$	$F(1,95) = 0.05$ $p = 0.81$		$F(5,95) = 9.85$ **$p < 0.001$** $R^2 = 0.34$
SBP	$F(1,94) = 2.13$ $p = 0.14$	$F(1,94) = 16.33$ **$p < 0.001$**	$F(1,94) = 0.06$ $p = 0.79$	$F(1,94) = 0.48$ $p = 0.48$	$F(1,94) = 0.01$ $p = 0.90$	$F(1,94) = 9.22$ **$p = 0.003$**	$F(6,94) = 10.45$ **$p < 0.001$** $R^2 = 0.40$
DBP	$F(1,95) = 5.52$ **$p = 0.02$**	$F(1,95) = 30.51$ **$p < 0.001$**	$F(1,95) = 0.25$ $p = 0.61$	$F(1,95) = 0.98$ $p = 0.32$	$F(1,95) = 0.06$ $p = 0.79$		$F(5,95) = 10.64$ **$p < 0.001$** $R^2 = 0.35$
DBP	$F(1,94) = 2.59$ $p = 0.11$	$F(1,94) = 23.64$ **$p < 0.001$**	$F(1,94) = 0.02$ $p = 0.87$	$F(1,94) = 0.78$ $p = 0.37$	$F(1,94) = 0.02$ $p = 0.88$	$F(1,94) = 6.94$ **$p = 0.01$**	$F(6,94) = 10.58$ **$p < 0.001$** $R^2 = 0.40$

Notes: F-statistics are followed by degrees of freedom in parentheses. Significant *p*-values (at the Bonferroni-corrected level of $\alpha = 0.05/2$) are indicated in bold. Each row illustrates results of a separate general linear models using the following equations:

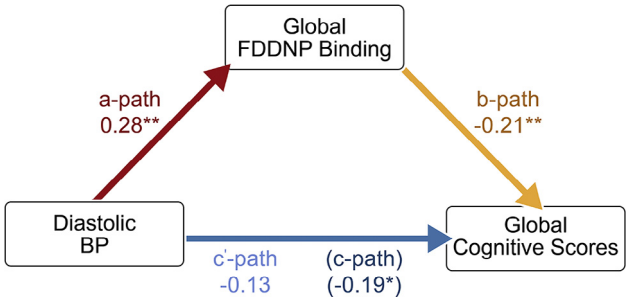
Row 1: Global cognitive scores = SBP + age + sex + *ApoE* status + intercept + error.

Row 2: Global cognitive scores = SBP + age + sex + *ApoE* status + global FDDNP-PET binding + intercept + error.

Row 3: Global cognitive scores = DBP + age + sex + *ApoE* status + intercept + error.

Row 4: Global cognitive scores = DBP + age + sex + *ApoE* status + global FDDNP-PET binding + intercept + error.

FIGURE 1. Global FDDNP-PET binding mediates the association between DBP and cognitive functioning.
Path coefficients (denoted by "*b*" in Table 3) are illustrated for all four paths in the mediation model. For all path coefficients, *t*- statistics followed by degrees of freedom in parentheses are provided in Table 3, along with *p* -values. In this Figure, path coefficients with *p*-values < 0.05 are followed by *, and those with *p*-values < 0.01 are followed by **. The c'-path and the c-path represent the associations between DBP and global cognitive performance (controlling for age, sex, blood pressure medication status, and *ApoE* genotype) with and without global FDDNP-PET binding included as a mediator, respectively. Here, the c'-path coefficient is not followed by either symbol, because the association between DBP and cognitive functioning with global FDDNP-PET binding included as a mediator is no longer significant.



suggesting that the relationship between higher DBP and poorer cognitive performance may be mediated by increased plaque and tangle load.

Mediation Analyses

Further analyses confirmed a statistical non-independence of effects. We observed a statistical mediation of the association between higher DBP and poorer cognitive functioning by increased *in vivo* plaque and tangle burden. Our results were consistent with a mediational model and revealed a significant indirect effect of DBP on global cognitive scores through global FDDNP-PET binding, with age, sex, blood pressure medication status, and *ApoE* genotype included as covariates ($a \times b = -0.06$). The association between DBP and cognitive functioning with global FDDNP-PET binding included as a mediator (i.e., the c'-path) was no longer significant. The mediator accounted for about 31% of the total effect (Figure 1, Table 3).

DISCUSSION

This report provides evidence that DBP (but not SBP) is significantly associated with global cognitive functioning, independently of age, sex, use of antihypertensive medications, and *ApoE* genotype in middle-aged and older adults without dementia. For the first time in this study, we also address a possible mechanism through which DBP affects cognitive decline in this population. Notably, our results suggest that increased *in vivo* plaque and tangle load may mediate the association between higher DBP and poorer cognitive performance, controlling for age, sex, blood pressure medication status, and *ApoE* genotype, in nondemented middle-aged and older adults.

Our findings that, unlike DBP, SBP is not significantly associated with general cognitive functioning in our study sample are consistent with those from three earlier reports[29–31] but are discordant with findings from two prior studies, which reported that higher SBP (and not DBP) were related to cognitive decline.[32,33] Demographic and clinical differences between study samples, varying measures of cognitive functioning, and a range of covariates included in the statistical models may account for these discrepant results. Although the relationships between blood pressure and cognitive outcomes are intricate and still debated,[34] two longitudinal studies in very large multiethnic samples support long-term associations between elevated DBP[35] and SBP in midlife[36] and cognitive impairment in old age.

Our analyses revealed a statistical mediation of the relationship between higher DBP and poorer cognitive performance by increased *in vivo* plaque and tangle burden in our study sample, consistent with published autopsy reports, which have provided strong evidence for an association between higher blood pressure and increased AD pathology. An early study showed that nondemented individuals with high blood pressure had increased incidence of both senile plaques and neurofibrillary tangles, suggesting that "hypertension may be a neuropathologic forerunner to AD." (p. 167)[37] Of particular relevance to the present study, another neuropathology report found that higher DBP in midlife was associated with greater numbers of tau tangles in the hippocampus at autopsy.[38]

Our findings of a significant association between higher DBP and increased *in vivo* plaque and tangle

TABLE 3. Global FDDNP-PET Binding (*m*) Mediates the Association Between DBP (*x*) and Global Cognitive Scores (*y*), with Age, Sex, Blood Pressure Medication Status, and *ApoE* Genotype as Covariates (N = 101)

Outcome	Model Summary	Path Coefficients	
		Path a	
Global FDDNP binding (*x* predicts *m*)	$F(5,95) = 3.42$ $p = 0.007$ $R^2 = 0.15$	$b = 0.28$ $t(95) = 2.77$ $p = 0.007$	
		Path b	**Path c'**
Global cognitive scores (*x* and *m* predict *y*)	$F(6,94) = 10.58$ $p < 0.0001$ $R^2 = 0.40$	$b = -0.21$ $t(94) = -2.63$ $p = 0.009$	$b = -0.13$ $t(94) = -1.61$ $p = 0.11$
		Path c	
Global cognitive scores total effect model (*x* predicts *y*)	$F(5,95) = 10.64$ $p < 0.0001$ $R^2 = 0.36$	$b = -0.19$ $t(95) = -2.35$ $p = 0.02$	
95% Bootstrapped Confidence Interval for a × b			**Percent Mediation**
[−0.12–−0.02]			0.31

Notes: In the "Model Summary" column, *F*-statistics are followed by degrees of freedom in parentheses. In the "Path Coefficient" column, *t*-statistics are followed by degrees of freedom in parentheses. Path coefficients (denoted by "*b*") are provided for all four paths in the simple mediation analysis using the PROCESS Procedure for SPSS.

The a-path represents the association between DBP and global FDDNP-PET binding (controlling for age, sex, blood pressure medication status, and *ApoE* genotype). The b-path denotes the relationship between global FDDNP-PET binding and global cognitive scores, while also controlling for DBP (in addition to age, sex, blood pressure medication status, and *ApoE* genotype). The c'-path and the c-path represent the associations between DBP and global cognitive performance (controlling for age, sex, blood pressure medication status, and *ApoE* genotype) with and without global FDDNP-PET binding included as a mediator, respectively. As a × b = c - c', the 95% confidence interval for a × b indicates that a significant medication has occurred when it does not include 0 and the c'-path is no longer significant. Percent mediation is a measure of effect size computed as (a × b)/(c' + a × b).

burden are consistent with some earlier reports but contradict other prior studies. One Pittsburgh Compound B–PET study (PIB-PET)– an imaging method that provides a measure of *in vivo* Aβburden – reported an association between higher DBP (but not SBP) and more pronounced Aβ deposition in elderly subjects.[39] On the other hand, another PIB-PET study found a positive correlation between SBP (but not DBP) and Aβ burden in healthy late middle-aged adults.[40] Likewise, while a study showed that DBP was correlated with plasma levels of Aβ in older adults,[41] other reports (which classified very elderly participants as Aβ-positive or Aβ-negative based on PIB-PET imaging) found that SBP (but not DBP) was associated with Aβ status at baseline,[42] and that neither measure was higher among Aβ-positive subjects at 2-year follow-up.[43] These discrepancies probably relate to the vast methodological differences between studies, including the demographic and clinical characteristics of the samples, the use of amyloid-specific or non-specific probes, continuous versus dichotomous measures of Aβ pathology, and the tissues examined (i.e., plasma or brain). Nonetheless, the extant literature illustrates the complexity and scope of existing knowledge in this area.

Despite the fact that we did not measure vascular pathology in this sample, the present findings suggest a direct relationship between DBP and the *in vivo* distribution of FDDNP in the brain, which, as we previously demonstrated, follows the patterns of plaque and tangle distribution seen at autopsy.[5] Prior studies have proposed that higher DBP may be associated with compromised vascular integrity, resulting in impaired Aβ clearance and increased phosphorylation of tau,[38,44] which may provide a possible explanation for our findings. Although the precise mechanisms underlying these associations remain unclear, some studies have elucidated a few of the mechanistic links between impaired vascular integrity and AD pathology. Notably, a review of the literature indicates that vascular injury reduces Aβ clearance at the blood–brain barrier and increases Aβ production from Aβ precursor protein, leading to Aβ accumulation. This accumulation in turn amplifies neuronal dysfunction, accelerates neurodegeneration, and can induce

hyperphosphorylation of tau, leading to neurofibrillary tangle formation.[45]

We found that DBP was significantly associated with cognitive functioning, controlling for blood pressure medication status. Nonetheless, the identification of global FDDNP-PET binding as a possible mediator of the relationship between higher DBP and poorer cognitive performance in nondemented middle-aged and older adults highlights the need for additional research into pharmacologic and behavioral interventions aimed at controlling blood pressure and/or reducing plaque and tangle burden early in life. Although some studies have shown that blood pressure control in middle-aged adults may help delay or stop the progression of cognitive decline in the elderly,[46] results from randomized trials of antihypertensive therapy for the prevention of dementia remain inconclusive.[16] Similar discrepancies exist in the postmortem literature, with conflicting reports about the effects of blood pressure medication status on plaque and tangle pathology.[37,47] This may be because key unmeasured genetic and/or physiologic factors may play important roles in the effect of antihypertensive therapy on AD pathology and cognitive functioning – future clinical trials should therefore benefit from stratifying participants accordingly. Moreover, because of its pluripotent effects on the vasculature, including the regulation of vascular tone, cerebral blood flow, endothelial function, microvascular recruitment, energy metabolism, and insulin actions on the vessel (all of which are important for brain health), physical exercise may be a promising behavioral intervention for mitigating the association between increased blood pressure and decreased cognitive performance.

Methodologic limitations should be noted. First, this is a cross-sectional, observational study, which cannot infer temporality and cannot exclude the role of residual confounding. These findings will thus need to be replicated in independent data sets, and using longitudinal designs to establish an association between the primary predictor and changes in the mediator, above and beyond the effect of prior mediator values and confounders. Moreover, we focused on systolic and diastolic values because they are generally obtained in standard clinical situations. In most cases, a single blood pressure measurement was recorded. In some instances, a second reading was obtained, and only the second measurement was reported, as detailed above. Therefore, it will be important for future studies to include more rigorous assessments of vital signs, such as evaluations of blood pressure measurement reproducibility. Future research should also examine how the pulsatile and steady components of blood pressure (i.e., pulse pressure and mean arterial pressure) relate to cognitive functioning and AD pathology, especially given the emerging evidence supporting an association between pulse pressure and Aβ deposition in the aging brain.[40,48] An additional limitation to this study may be that ambulatory blood pressure measurements were not recorded. Although some prior work showed that repeated ambulatory, but not clinic-based, SBP measures predicted cerebrovascular pathology, the authors did not seem to include DBP in their analyses.[49] Finally, while the current study focused on blood pressure, additional research will be necessary to determine how other vascular risk factors (such as diabetes, central obesity, and hyperhomocysteinemia) interact with each other and with plaque and tangle load to affect cognitive functioning in nondemented middle-aged and older adults.

Future investigations will also benefit from the use of innovative approaches derived from systems biology to incorporate the roles of multiple cell types that support the function of neural tissue, and the influence of various genetic factors into the science of vascular contributions to cognitive impairment and AD pathology, in order to develop more targeted and personalized treatment and prevention strategies. Nonetheless, by suggesting that *in vivo* plaque and tangle burden may mediate the association between higher DBP and poorer cognitive functioning, this study advances our understanding of some possible predictors of cognitive decline in nondemented middle-aged and older adults, and underscores the importance of devising early multimodal interventions (e.g., combining antihypertensive pharmacotherapy with Aβ or tau inhibition) to more effectively combat degenerative brain disorders.

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