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Visit-to-Visit Blood Pressure Variability and CSF Alzheimer Disease Biomarkers in Cognitively Unimpaired and Mildly Impaired Older Adults

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Abstract

Background and Objectives

Blood pressure variability is an emerging risk factor for cognitive decline and dementia, but mechanisms remain unclear. The current study examined whether visit-to-visit blood pressure variability is related to CSF Alzheimer disease biomarker levels over time and whether associations differed by *APOE* ε4 carrier status.

Methods

In this retrospective analysis of a prospective cohort study, cognitively unimpaired or mildly impaired older adults from the Alzheimer's Disease Neuroimaging Initiative underwent 3 to 4 blood pressure measurements over a 12-month period and ≥1 lumbar puncture for evaluation of CSF phosphorylated tau, total tau, and β-amyloid levels at follow-up (6–108 months later). *APOE* ε4 carriers were defined as having ≥1 ε4 allele. Visit-to-visit blood pressure variability was determined over 12 months as variability independent of mean. Only CSF samples collected after the final blood pressure measurement were analyzed. Bayesian linear growth modeling investigated the role of blood pressure variability, *APOE* ε4, and the passage of time on CSF biomarker levels after controlling for several variables, including average blood pressure and baseline hypertension.

Results

Four hundred sixty-six participants (mean 76.7 [SD 7.1] years of age) were included in the study. Elevated blood pressure variability was associated with increased CSF phosphorylated tau (β = 0.81 [95% CI 0.74, 0.97]), increased total tau (β = 0.98 [95% CI 0.71, 1.31]), and decreased β-amyloid levels (β = −1.52 [95% CI −3.55, −0.34]) at follow-up. *APOE* ε4 carriers with elevated blood pressure variability had the fastest increase in phosphorylated tau levels (β = 9.03 [95% CI 1.67, 16.36]). Blood pressure variability was not significantly related to total tau or β-amyloid levels over time according to *APOE* ε4 carrier status.

Discussion

Older adults with elevated blood pressure variability exhibit increased CSF phosphorylated tau, increased total tau, and decreased β-amyloid over time, suggesting that blood pressure variability may correlate with alterations in Alzheimer disease biomarkers. Findings warrant further study of the relationship between blood pressure variability and the development of Alzheimer disease. *APOE* ε4 carrier status moderated relationships between blood pressure variability and CSF phosphorylated tau but not total tau or β-amyloid, consistent with other studies relating hemodynamic factors to tau changes.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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 in the coinvestigators list at links.lww.com/WNL/B959.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **BMI** = body mass index; **BP** = blood pressure; **BPV** = BP variability; **CI** = credible interval; **CU** = cognitively unimpaired; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **Ptau** = phosphorylated tau; **SPRINT** = Systolic Blood Pressure Intervention Trial; **VIM** = variation independent of mean.

Vascular pathways to dementia have received increased attention[1] in part due to the potentially profound public health implications of modifiable vascular risk factors for dementia.[2] Blood pressure (BP) is a promising therapeutic target for the prevention of cognitive decline and dementia, including Alzheimer disease (AD).[3,4] The Systolic Blood Pressure Intervention Trial (SPRINT) in 2015 showed how aggressive BP lowering was related to decreased incidence of cognitive impairment.[5] More recent work has focused on BP variability (BPV) as another aspect of BP that may represent a modifiable risk factor for dementia.

BPV elevation over months to years (e.g., visit-to-visit BPV) and over shorter periods (e.g., day-to-day BPV) in older adults has been associated with cognitive impairment[6-8]; increased risk for vascular dementia, AD, and stroke[9-11]; and cerebrovascular disease severity,[12-14] above and beyond average BP levels.[15] Increased BPV also appears to occur before the onset of major neurocognitive dysfunction[16] and in the context of AD,[13,16-18] suggesting that BPV may be an early marker of vascular dysfunction in aging. Although 1 study on day-to-day BPV failed to detect any relationships with CSF AD biomarkers β-amyloid (Aβ), phosphorylated tau (Ptau), or total tau,[19] it is unclear whether visit-to-visit BPV may be related to these hallmark AD biomarkers. In addition, evidence suggests a joint effect of *APOE* ε4 and hypertension on CSF Ptau and total tau but not Aβ.[20] Less is known about relationships among BPV, *APOE* ε4, and CSF AD biomarker change over time. The present study investigated the longitudinal relationship between BPV and CSF Ptau, CSF total tau, and CSF Aβ levels over time, independently of average BP and baseline hypertension, in older adults who either were cognitively unimpaired (CU) or had mild cognitive impairment (MCI) and whether associations differed by *APOE* ε4 carrier status.

Methods

Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The ADNI is a multisite natural history study that has collected clinical, biomarker, and neuropsychological data since 2003 to measure the progression of typical aging, MCI, and AD. Volunteer adults (age 55–91 years) were enrolled if they met the following criteria: few depressive symptoms (Geriatric Depression Scale score <6), free of history of neurologic disease (other than suspected AD), no greater than mild dementia symptoms (Clinical Dementia Rating scale score ≤1), and low vascular risk (Hachinski Ischemic Score ≤4). Further study details can be found online.[21]

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by each institution, and all participants provided written informed consent before study enrollment.

The present study included participants who underwent clinical evaluation at study baseline and BP measurement at study screening, baseline, and the 6- and 12-month follow-up. Participants also underwent ≥1 lumbar puncture for the collection and evaluation of CSF AD biomarker levels after the final BP measurement at the 12-month follow-up.

Measures

Clinical Assessment

Baseline clinical evaluation identified participants to be CU or MCI using ADNI diagnostic criteria, as described elsewhere,[16,17] and all participants were confirmed to be without history of major neurocognitive disorder or stroke. Briefly, participants were determined to be CU by ADNI criteria if they had a Mini-Mental State Examination (MMSE) score >24 and Clinical Dementia Rating scale score of 0 and were without a history of major depressive disorder, MCI, or dementia. A clinical diagnosis of MCI was given if the following ADNI criteria were met[22]: subjective memory complaint; MMSE scores between 24 and 30 (inclusive); global Clinical Dementia Rating scale score of 0.5; scores on delayed recall of Story A of the Wechsler Memory Scale Revised Logical Memory II subtest that are below expected performance based on years of education; and did not meet clinical criteria for AD dementia. Alternative diagnostic criteria for MCI have been developed from the growing evidence of a high false-positive rate of MCI classification by ADNI criteria.[23-25] Therefore, participants were also categorized as either CU or MCI with these alternative criteria (see eAppendix 1, links.lww.com/WNL/B958), consistent with recent studies using ADNI data.[16] For the present investigation, main analyses combined CU and MCI participants into 1 group, while supplementary analyses explored groups separately using both ADNI and alternative diagnostic criteria.

BP Assessment

Seated BP measurements were obtained from participants 3 to 4 times between study screening and the 12-month follow-

up with a calibrated mercury sphygmomanometer, as previously described.[16-18] Intraindividual variation in BP over 12 months using 3 to 4 BP measurements was calculated as variation independent of mean (VIM). VIM is now a widely used index of visit-to-visit BPV that is uncorrelated with average BP across visits[13,15-18,26,27] and was recently shown to have stronger associations with all-cause mortality in the SPRINT dataset than coefficient of variation of BP.[28] VIM was calculated as VIM = SD/mean^x, where the power x was derived from nonlinear curve fitting of BP SD against average BP using the nls package in R (R Foundation for Statistical Computing, Vienna, Austria),[29] as described elsewhere.[26] Baseline hypertension was determined from the total sample average systolic BP taken at study baseline.

CSF AD Biomarker Assessment

Participants underwent ≥1 lumbar puncture after the final BP measurement at the 12-month follow-up. Details can be found on the ADNI site.[21] Briefly, lumbar puncture collected CSF samples for the assessment of Aβ, $Ptau_{181}$, and total tau levels with standardized methods described elsewhere.[30-33]

Other Measurements

The following were determined from baseline clinical evaluation: years of education, history of smoking, history of dyslipidemia, history of alcohol abuse, global cognition (i.e., MMSE score), body mass index (BMI, weight [kilograms]/height [meters] squared), use of antihypertensive medication, and use of antidementia agents. For baseline medication use, participants were categorized as those taking antihypertensive medication (all classes) vs those who were not and those taking antidementia agents vs those who were not. Baseline clinical evaluation also determined vascular risk, as described elsewhere,[16,18,34,35] and participants were categorized as having lower (≤1 vascular risk factor) or higher (≥2 vascular risk factors) vascular risk.[35] *APOE* ε4 carrier status was determined from baseline venipuncture as previously described.[36] Participants were categorized as those with at least 1 *APOE* ε4 allele vs those without.

Data Availability

Study data are available on the ADNI site.[21]

Statistical Analysis

Study data were collected prospectively, and all study questions and analyses were applied retrospectively. Bayesian linear growth modeling with the brms package[37] (eAppendix 1, links.lww.com/WNL/B958) in R[29] investigated the role of BPV, *APOE* ε4, and the passage of time on CSF AD biomarker levels. All models specified random intercepts for participant to account for individual variation in CSF AD biomarker change and fixed effects for BPV and *APOE* ε4 carrier status to test for differences in CSF AD biomarker change due to BPV and *APOE* ε4 carrier status, respectively. Only CSF samples acquired after the final BP measurement at the 12-month follow-up were used in analyses. Passage of time for lumbar puncture was calculated as months elapsed since BPV determination (range 6–108 months) and grand centered at 0. On the basis of the hypothesis that visit-to-visit BPV may be related to AD pathophysiology,[16-18] we first ran models examining a BPV by time interaction on CSF AD biomarker levels. Recent evidence suggests that BPV and *APOE* ε4 interact to predict medial temporal atrophy, a key region in AD, especially in older adults with abnormal levels of CSF Aβ and CSF Ptau.[18] In addition, *APOE* ε4 carriers with hypertension have been shown to have higher CSF Ptau and total tau levels than those who do not carry the ε4 allele.[20] Therefore, we additionally tested a 3-way interaction model of BPV by *APOE* ε4 carrier status by time predicting CSF AD biomarker levels. All models examined CSF AD biomarkers separately and controlled for age at CSF sample collection (years), sex (male vs female), *APOE* ε4 carrier status (for main effect models; carrier vs noncarrier), baseline MMSE score (out of 30), education (years), average BP (mm Hg), baseline hypertension (normotensive vs hypertensive), vascular risk (lower vs higher), and antihypertensive medication use (yes vs no). Sensitivity analyses included the following additional covariates: history of smoking (yes vs no), history of dyslipidemia (yes vs no), use of antidementia agents (yes vs no), clinical diagnosis (CU vs MCI, both criteria), history of alcohol abuse (yes vs no), and BMI. Model covariates reflect those commonly used in BPV research,[8] including those examining associations with CSF AD biomarkers.[19] Supplementary analyses explored CU and MCI groups separately using both ADNI and alternative diagnostic criteria (eAppendix 1, links.lww.com/WNL/B958). Effect estimates (β) represent unstandardized regression coefficients such that the amount of change in the dependent variable (CSF AD biomarker) is related to a 1-unit change in the independent variables (time [month]; BPV [SD]). All analyses were 2 tailed, and effect estimates with credible intervals (CIs) excluding 0 were considered significant.

Results

A total of 466 participants contributed to 757 CSF samples (median 2 CSF samples). The median time interval between BPV measurement and lumbar puncture/CSF sample collection was 12 months (interquartile range 24 months). Table 1 gives baseline demographic and clinical information. eTable 1, links.lww.com/WNL/B958, summarizes demographic and clinical information on excluded participants.

CSF AD Biomarker Levels

Elevated BPV was associated with increased Ptau levels (systolic β = 0.81 [95% CI 0.74, 0.97], diastolic β = 3.79 [95% CI 2.14, 5.41]) (Figure 1A), increased total tau levels (systolic β = 0.98 [95% CI 0.71, 1.31], diastolic β = 2.01 [95% CI 1.10, 2.90]) (Figure 1B), and decreased Aβ levels (systolic β = −1.52 [95% CI -3.55, −0.34], diastolic β = −3.46 [95% CI −7.02, −0.26]) at follow-up (Figure 1C).

APOE ε4

APOE ε4 carriers with elevated BPV had the fastest increase in Ptau levels (systolic β = 9.03 [95% CI 1.67, 16.36], diastolic β = 22.28 [95% CI 13.90, 30.52]) (Figure 2). BPV was not significantly related to total tau levels (systolic β = −0.33 [95%

Table 1 Baseline Clinical and Demographic Information

	Total sample (N = 466)
Age, y	76.6 (7.1)
Sex, n (% female)	203 (43.6)
Education, y	16.3 (2.6)
***APOE* ε4 carriers, n (%)**	148 (31.8)
ADNI MCI diagnosis, n (%)	313 (67.2)
MMSE score	28.3 (1.7)
BMI, kg/m^2	27.2 (4.9)
Vascular risk,[a] n (% low)	436 (93.6)
Vascular risk factors, n (%)	
Cardiovascular disease	42 (9.0)
Diabetes type 2	35 (7.5)
Atrial fibrillation	12 (2.6)
Carotid artery disease	4 (0.9)
TIA/subclinical stroke	9 (1.9)
Medication use, n (%)	
Antihypertensive agents	189 (40.6)
ACE inhibitors	72 (15.5)
ARBs	30 (6.4)
α-Blockers	10 (2.2)
Calcium channel blockers	34 (7.3)
Diuretics	39 (8.4)
Antidementia agents	57 (12.2)
Systolic BP, mm Hg	
Baseline	134.7 (16.4)
Average	133.6 (12.8)
VIM	5.4 (3.3)
Diastolic BP, mm Hg	
Baseline	74.2 (10.3)
Average	73.7 (7.9)
VIM	5.9 (1.2)

Abbreviations: ACE = angiotensin-converting enzyme; ADNI = Alzheimer's Disease Neuroimaging Initiative; ARB = angiotensin II receptor blocker; BMI = body mass index; BP = blood pressure; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; VIM = variability independent of mean.
Means and SDs are shown unless otherwise indicated.
[a] Baseline vascular risk level was determined from the presence/absence of individual risk factors (history of cardiovascular disease, history of diabetes type 2, history of atrial fibrillation, history of carotid artery disease, history of TIA/subclinical stroke). Risk level is lower (≤1 individual vascular risk factor) or higher (≥2 individual vascular risk factors), as described elsewhere.[16,34,35]

CI −1.21, 0.57], diastolic β = −0.24 [95% CI −1.18, 0.73]) or Aβ levels (systolic β = −1.07 [95% CI −2.31, 0.07], diastolic β = 1.95 [95% CI −1.11, 3.81]) over time according to *APOE* ε4 carrier status (data not shown).

Sensitivity Analyses

Primary findings of CSF change associated with BPV remained statistically significant (e.g., CI excluded 0) in sensitivity analyses controlling for history of smoking, history of dyslipidemia, use of antidementia agents, clinical diagnosis (CU vs MCI, both criteria), BMI, and history of alcohol abuse (eTables 2 and 3, links.lww.com/WNL/B958). Findings based on *APOE* ε4 carrier status remained statistically significant for CSF Ptau.

Supplementary Analyses

Supplementary analyses examining CU and MCI groups separately revealed similar associations in each group when both clinical diagnostic criteria were used (Results in the eAppendix, links.lww.com/WNL/B958).

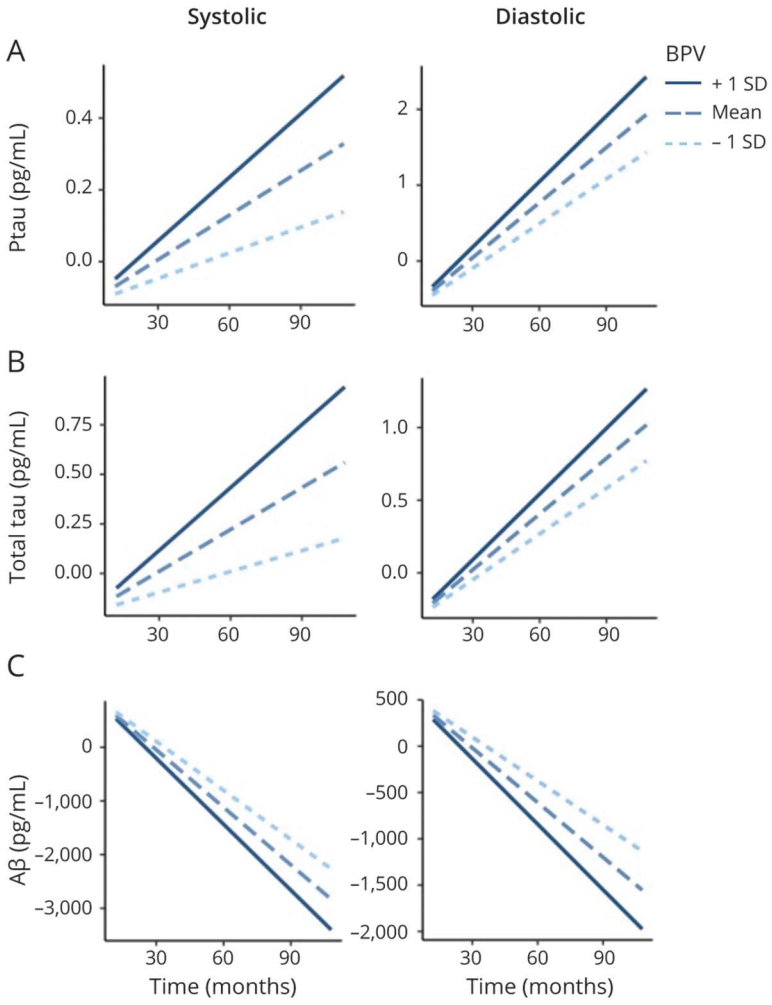
BPV was not significantly correlated with average BP levels (all $p > 0.05$), consistent with other studies suggesting that VIM is an index of BPV uncorrelated with average BP levels.[26]

Discussion

Study findings suggest that elevated visit-to-visit BPV is associated with increased CSF Ptau, increased CSF total tau, and decreased CSF Aβ levels over time in older adults who either were CU or had MCI independently of average BP levels. The current investigation adds to ongoing work detailing relationships between BPV and AD.[6,10,11,13,16-18,38] In addition, patterns of CSF change were observed predominantly in *APOE* ε4 carriers, consistent with recent work relating BPV and *APOE* ε4 to other important markers of AD (e.g., medial temporal volume loss).[18]

One recent study directly examined day-to-day BPV and CSF AD biomarkers in a sample of older adults without a history of major neurocognitive disorder and found no evidence of a relationship with CSF Ptau, CSF total tau, or CSF Aβ.[19] In contrast, the present study findings support the hypothesized association between visit-to-visit BPV and changing levels of all 3 CSF AD biomarkers in directions consistent with advancing AD pathophysiology (e.g., increasing Ptau levels, increasing total tau levels, and decreasing Aβ levels).[39] One possible explanation for this difference is that underlying mechanisms driving BPV elevation may differ for day-to-day BPV and visit-to-visit BPV.[40] Specifically, BPV measured over shorter intervals (e.g., beat to beat, day to day) is hypothesized to reflect CNS and reflex autonomic nervous system regulation, whereas longer intervals may be more related to arterial stiffness,[40] but more research is needed. Whether arterial stiffness is an index of BPV, a driver of BPV, or a consequence of BPV remains an open question.[38,40] However, growing evidence suggests a clear relationship between BPV and arterial health.[12] For example, several studies indicate that elevated BPV is predictive of cerebrovascular disease severity on

Figure 1 BPV and CSF AD Biomarker Level Change in Cognitively Unimpaired or Mildly Impaired Older Adults

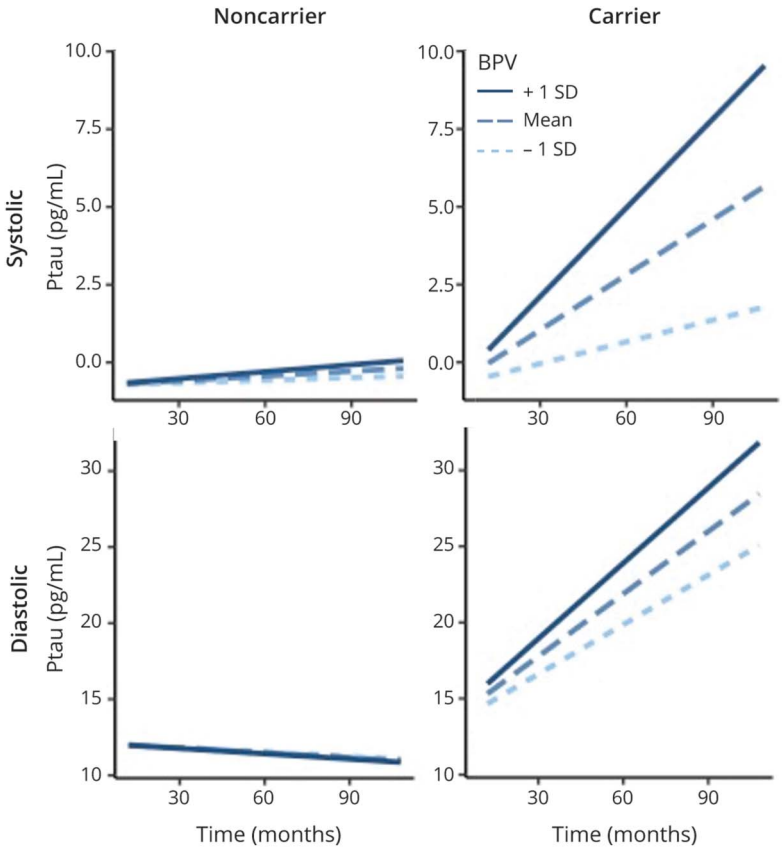


Conditional effects of the interaction of blood pressure (BP) variability (BPV) by time on (A) CSF phosphorylated tau (Ptau) levels, (B) CSF total tau levels, and (C) CSF β-amyloid (Aβ) levels in cognitively unimpaired or mildly impaired older adults. Model adjusted for age at CSF sample collection, sex, *APOE* ε4 carrier status, baseline Mini-Mental State Examination score, years of education, average BP, baseline hypertension, vascular risk, and antihypertensive medication use. AD = Alzheimer disease.

MRI[12] and postmortem evaluation.[13,14] Large fluctuations in BP are thought to cause mechanical stress to arterial walls by stretching tight neurovascular junctions[9] and establishing opportunities for cerebral hypoperfusion[17] and microvascular damage.[12] In addition, vascular clearance mechanisms of toxic proteins from the brain may be disrupted by high BPV,[9,15] which could be related to the present study findings relating BPV to abnormal levels of CSF Ptau, total tau, and Aβ. Alternatively, neurodegenerative effects on autonomic regulation centers in the brain could drive both BP fluctuations and AD pathophysiology.[38,41] While CSF samples were collected after BPV determination, it is difficult to discern whether BPV elevation is an upstream or downstream factor in changing CSF AD biomarker levels. Future studies should look to disentangle the temporal order of these relationships.

An interesting finding is that *APOE* ε4 appeared to modify the relationship between BPV and CSF Ptau, not CSF total tau or CSF Aβ, with effect sizes consistent with a prior cross-sectional study on hypertension, *APOE* ε4, and CSF AD biomarkers.[20] Growing evidence suggests that CSF Ptau is associated with neurofibrillary tangles, a neuropathologic marker of tau associated with AD, whereas CSF total tau may represent a less specific marker of neurodegeneration.[42] Some studies have also found that other BP measures such as average BP,[19] pulse pressure,[34,43] and mean arterial pressure[44] are more consistently related to CSF Ptau than to CSF Aβ. Other recent studies on average BP[45] and BPV[15] reported associations with neurofibrillary tangles but not with amyloid plaques. Beyond vascular factors, changes in cognition are more strongly associated with longitudinal changes in CSF tau than in CSF Aβ,[44] even over a short period of time.[46] In addition, a recent in vivo PET imaging study found that clinical phenotypes of AD are associated with differential patterns of tau but not Aβ pathology, especially in *APOE* ε4 carriers.[47] Together, these findings add to the growing evidence that hemodynamic factors may be particularly related to changes in tau, perhaps especially in individuals at increased genetic risk for AD due to the presence of the *APOE* ε4 allele, with potential therapeutic implications. While the majority of treatment studies of BP on cognition have focused on static levels of BP (e.g., average BP),[5,48] some evidence suggests

Figure 2 BPV and CSF AD Biomarker Level Change in Cognitively Unimpaired or Mildly Impaired Older Adults Based on APOE ε4 Carrier Status



Conditional effects of the interaction of blood pressure (BP) variability (BPV) by *APOE* ε4 carrier status by time on CSF phosphorylated tau (Ptau) levels in cognitively unimpaired or mildly impaired older adults. Model adjusted for age at CSF sample collection, sex, *APOE* ε4 carrier status, baseline Mini-Mental State Examination score, years of education, average BP, baseline hypertension, vascular risk, and antihypertensive medication use. AD = Alzheimer disease.

differential antihypertensive class effects on BPV in risk for stroke that are independent of average BP levels.[49] The present study did not directly address this point as it relates to CSF AD biomarker levels, but it remains an area of great interest in the current era of biomarker-guided precision medicine approaches to dementia care.[50]

Findings provide evidence that visit-to-visit BPV is related to change in CSF AD biomarkers. The study is strengthened by the longitudinal design and collection of CSF samples after BPV was determined. In addition, models examined CSF Ptau, CSF total tau, and CSF Aβ separately, which allowed us to appreciate individual contributions from these hallmark AD biomarkers. BPV was calculated from BP measurements collected in a way that is similar to routine clinical visits, further highlighting the utility of BPV as a marker related to AD pathophysiology in clinical practice.[40,51] The study is limited by certain characteristics of the ADNI dataset, including that some aspects of BP were not explicitly standardized across sites and the largely non-Hispanic White study sample with limited cerebrovascular disease included in the overall ADNI study precluded the investigation of more diverse samples and those with varying levels of cerebrovascular disease burden. Study findings are further limited by the retrospective nature of analyses. Last, while the present investigation did not directly examine associations with cognitive change, substantial evidence suggests that elevated BPV is related to cognitive impairment and progression to dementia beyond average BP levels,[15] suggesting BPV may be an understudied vascular risk factor for dementia.

Older adults with elevated BPV exhibit increased CSF Ptau, increased CSF total tau, and decreased CSF Aβ over time, suggesting that BPV may correlate with alterations in hallmark CSF AD biomarkers. These findings warrant further study of the relationship between BPV and the development of AD. *APOE* ε4 carrier status moderated the relationship between BPV and CSF Ptau but not CSF total tau or CSF Aβ, consistent with other studies relating hemodynamic factors to tau changes.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Contribution
Isabel J. Sible, MA	University of Southern California, Los Angeles	Design and conceptualized study; analyzed the data; interpreted the data; drafted the manuscript for intellectual content
Daniel A. Nation, PhD	University of California, Irvine	Design study; interpreted the data; revised the manuscript for intellectual content

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B959

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