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

Author(s):
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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’s 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 3-4 blood pressure measurements over a 12-month period and ≥ 1 lumbar puncture for the evaluation of CSF phosphorylated tau, total tau, and amyloid-beta 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:** 466 participants (mean 76.7 (7.1 SD) years of age) were included in the study. Elevated blood pressure variability was associated with increased CSF phosphorylated tau (β: .81 [95% CI .74, .97]), increased total tau (β: .98 [95% CI .71, 1.31]), and decreased amyloid-beta levels (β: -1.52 [95% CI -3.55, -.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 amyloid-beta levels over time based on APOE ε4 carrier status.

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

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’s disease (AD).\(^3,4\) The SPRINT trial in 2015 showed how aggressive BP lowering was related to decreased incidence of cognitive impairment.\(^5\) More recent work has focused on the variability in BP as another aspect of BP that may represent a modifiable risk factor for dementia.

Blood pressure variability (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 BPV may be an early marker of vascular dysfunction in aging. Although one study on day-to-day BPV failed to detect any relationships with CSF AD biomarkers amyloid-beta (A\(\beta\)), phosphorylated tau (Ptau), or total tau,\(^19\) it is unclear whether visit-to-visit BPV may be related to these hallmark AD biomarkers. Additionally, evidence suggests a joint effect of APOE \(\epsilon4\) and hypertension on CSF Ptau and total tau, but not A\(\beta\).\(^20\) Less is known about relationships among BPV, APOE \(\epsilon4\), and CSF AD biomarker change over time. The present study investigated the longitudinal relationship between BPV and CSF Ptau, CSF total tau, and CSF A\(\beta\) levels over time, independent of average BP and baseline hypertension, in older adults who were either
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) were enrolled if they met the following criteria: few depressive symptoms (Geriatric Depression Scale < 6), free of history of neurological disease (other than suspected AD), no greater than mild dementia symptoms (Clinical Dementia Rating scale ≤ 1), and low vascular risk (Hachinski Ischemic Score ≤ 4). Further study details can be found online (https://adni.loni.usc.edu/).

Standard Protocol Approvals, Registrations, and Patient Consents

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

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

Clinical assessment

Baseline clinical evaluation identified participants to be CU or MCI using ADNI diagnostic criteria, as described elsewhere, 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 Exam (MMSE) score > 24; Clinical Dementia Rating scale score of 0; without history of major depressive disorder, MCI, or dementia. A clinical diagnosis of MCI was given if the following ADNI criteria were met: subjective memory complaint; Mini Mental State Exam (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; did not meet clinical criteria for AD dementia.

Alternative diagnostic criteria for MCI have been developed based on growing evidence of a high false positive rate of MCI classification by ADNI criteria. As such, participants were also categorized as either CU or MCI using these alternative criteria (see Supplementary Materials in the Supplement for further details), consistent with recent studies using ADNI data. For the present investigation, main analyses combined CU and MCI participants into one group, while supplementary analyses explored groups separately using both ADNI and alternative diagnostic criteria.

BP assessment

Seated BP measurements were obtained from participants 3-4 times between study screening and 12-months follow-up using a calibrated mercury sphygmomanometer, as previously described.
Intraindividual variation in BP over 12 months using 3-4 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\textsuperscript{13,15–18,25,26} and was recently shown to have stronger associations with all-cause mortality in the SPRINT dataset than coefficient of variation of BP.\textsuperscript{27} VIM was calculated as: \( VIM = \frac{SD}{\text{mean}}^x \), where the power \( x \) was derived from non-linear curve fitting of BP SD against average BP using the nls package in R,\textsuperscript{28} as described elsewhere.\textsuperscript{25} Baseline hypertension was determined from the total sample average systolic BP taken at study baseline.

CSF AD biomarker assessment
Participants underwent \( \geq 1 \) lumbar puncture after the final BP measurement at 12-months follow-up. Details can be found on the ADNI site: http://adni.loni.usc.edu/methods/. Briefly, lumbar puncture collected CSF samples for the assessment of A\( \beta \), Ptau\textsubscript{181}, and total tau levels, using standardized methods described elsewhere.\textsuperscript{29–32}

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 (kg) / height (meters) squared), use of antihypertensive medication, use of antidementia agents. For baseline medication use, participants were categorized as those taking antihypertensive medication (all classes) versus those who were not, and those taking antidementia agents versus those who were not. Baseline clinical evaluation also determined vascular risk, as described elsewhere,\textsuperscript{16,18,33,34} and participants were categorized
as having lower (≤ 1 vascular risk factor) or higher (≥ 2 vascular risk factors) vascular risk.\textsuperscript{34} APOE ε4 carrier status was determined from baseline venipuncture as previously described.\textsuperscript{35} Participants were categorized as those with at least one APOE ε4 allele versus those without.

**Data Availability**

Study data is available on the ADNI site: https://adni.loni.usc.edu/.

**STATISTICAL ANALYSIS**

Study data were collected prospectively, and all study questions and analyses were applied retrospectively. Bayesian linear growth modelling using the brms package\textsuperscript{36} (see Supplementary Material in the Supplement for further details) in R\textsuperscript{28} 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 12-months 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. Based on the hypothesis that visit-to-visit BPV may be related to AD pathophysiology,\textsuperscript{16–18} we first ran models examining a BPV by time interaction on CSF AD biomarker levels. Recent evidence suggests 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.\textsuperscript{18} Additionally, APOE ε4 carriers with hypertension have been shown to have higher CSF Ptau and CSF total tau levels than those who do not carry the ε4 allele.\textsuperscript{20} As such, 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 non-carrier), baseline MMSE score (out of 30), education (years), average BP (mmHg), 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), BMI (weight (kg) / height (meters) squared). Model covariates reflect those commonly used in BPV research, including those examining associations with CSF AD biomarkers. Supplementary analyses explored CU and MCI groups separately using both ADNI and alternative diagnostic criteria (see Supplementary Materials). Effect estimates (β) represent unstandardized regression coefficients, such that the amount of change in the dependent variable (CSF AD biomarker) is related to a one-unit change in the independent variables (time [month]; BPV [SD]). All analyses were 2-tailed and effect estimates with credible intervals (CI) 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 (IQR: 24 months). See Table 1 for baseline demographic and clinical information. eTable 1 summarizes demographic and clinical information on excluded participants.
**CSF AD biomarker levels**

Elevated BPV was associated with increased Ptau levels (systolic: β: .81 [95% CI .74, .97]; diastolic: β: 3.79 [95% CI 2.14, 5.41]) (Figure 1A), increased total tau levels (systolic: β: .98 [95% CI .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, -.34]; diastolic: β: -3.46 [95% CI -7.02, -2.6]) 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: -.33 [95% CI -1.21, .57]; diastolic: β: -.24 [95% CI -1.18, .73]) or Aβ levels (systolic: β: -1.07 [95% CI -2.31, .07]; diastolic: β: 1.95 [95% CI 1.11, 3.81]) over time based on 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 (see eTables 2-3). 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 using both clinical diagnostic criteria (see Supplementary Results in the Supplement).

BPV was not significantly correlated with average BP levels (all $p$’s > .05), consistent with other studies suggesting VIM is an index of BPV uncorrelated with average BP levels.²⁵

DISCUSSION

Study findings suggest 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 were either CU or had MCI, independent of average BP levels. The current investigation adds to ongoing work detailing relationships between BPV and AD.⁶,¹⁰,¹¹,¹³,¹⁶–¹⁸,³⁷ Additionally, patterns of CSF change were predominantly observed 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 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 three CSF AD biomarkers in directions consistent with advancing AD pathophysiology (e.g., increasing Ptau levels, increasing total tau levels, and decreasing Aβ levels).³⁸ 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. Specifically, BPV measured over shorter intervals (e.g., beat-to-beat, day-to-day) is hypothesized to reflect central and reflex autonomic nervous system regulation, whereas longer intervals may be more related to arterial stiffness, 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. However, growing evidence suggests a clear relationship between BPV and arterial health. For example, several studies indicate elevated BPV is predictive of cerebrovascular disease severity on MRI and postmortem evaluation. Large fluctuations in BP are thought to cause mechanical stress to arterial walls by stretching tight neurovascular junctions and establishing opportunities for cerebral hypoperfusion and microvascular damage. Additionally, vascular clearance mechanisms of toxic proteins from the brain may be disrupted by high BPV, 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. 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.

Interestingly, APOE ε4 appeared to modify the relationship between BPV and CSF Ptau, and 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. Growing evidence suggests CSF Ptau is associated with neurofibrillary tangles, a neuropathological marker of tau associated with AD, whereas CSF total tau may represent a less specific marker of neurodegeneration. Some studies
have also found that other BP measures, such as average BP, pulse pressure, and mean arterial pressure, are more consistently related to CSF Ptau than to CSF Aβ. Other recent studies on average BP and BPV 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, even over a short period of time. Additionally, 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. Together these findings add to the growing evidence that hemodynamic factors may be particularly related to changes in tau, and 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), some evidence suggests differential antihypertensive class effects on BPV in risk for stroke, independent of average BP levels. 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.

Findings provide novel 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. Additionally, 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. The study is limited by certain characteristics of the
ADNI dataset, including 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. Finally, while the present investigation did not directly examine associations with cognitive change, substantial evidence suggests elevated BPV is related to cognitive impairment and progression to dementia, beyond average BP levels, suggesting BPV may be an understudied vascular risk factor for dementia.

CONCLUSION
Older adults with elevated BPV exhibit increased CSF Ptau, increased CSF total tau, and decreased CSF Aβ over time, suggesting BPV may correlate with alterations in hallmark CSF AD biomarkers. 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.
# APPENDIX 1: Authors

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<thead>
<tr>
<th>Name</th>
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<th>Contribution</th>
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<tr>
<td>Isabel J. Sible, MA</td>
<td>University of Southern California, Los Angeles</td>
<td>Design and conceptualized study; analyzed the data; interpreted the data; drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>Daniel A. Nation, PhD</td>
<td>University of California, Irvine, Irvine</td>
<td>Design study; interpreted the data; revised the manuscript for intellectual content</td>
</tr>
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</table>
REFERENCES


8. Crichton GE, Elias MF, Dore GA, Torres R V, Robbins MA. Measurement-to-


with Dementia and Cognitive Impairment: A Systematic Review and Meta-Analysis.


### Table 1.

Baseline clinical and demographic information.

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Means and SDs shown unless otherwise indicated.

*Baseline vascular risk level determined from presence/absence of individual risk factors (history of cardiovascular disease, history of diabetes mellitus 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.¹⁶,³³,³⁴

Abbreviations: MMSE = Mini Mental State Exam; BP = blood pressure; BMI = body mass index; VIM = variability independent of mean; MCI = mild cognitive impairment; CDR-sb = Clinical Dementia Rating Scale sum of box score; ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; ADNI = Alzheimer’s Disease Neuroimaging Initiative; TIA = transient ischemic attack
Figure 1. BPV and CSF AD biomarker level change in cognitively unimpaired or mildly impaired older adults

Conditional effects of the interaction of BPV by time on A) CSF Ptau levels, B) CSF total tau levels, and C) CSF Aβ levels in cognitively unimpaired or mildly impaired older adults. Model adjusted for age at CSF sample collection, sex, APOE ε4 carrier status, baseline MMSE score, years of education, average BP, baseline hypertension, vascular risk, and antihypertensive medication use.

Abbreviations: BPV = blood pressure variability; AD = Alzheimer’s disease; Ptau = phosphorylated tau; Aβ = amyloid-beta; CSF = cerebrospinal fluid; MMSE = Mini Mental State Exam

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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 BPV by APOE ε4 carrier status by time on CSF Ptau levels in cognitively unimpaired or mildly impaired older adults. Model adjusted for age at CSF sample collection, sex, APOE ε4 carrier status, baseline MMSE score, years of education, average BP, baseline hypertension, vascular risk, and antihypertensive medication use.

Abbreviations: BPV = blood pressure variability; AD = Alzheimer’s disease; Ptau = phosphorylated tau; CSF = cerebrospinal fluid; MMSE = Mini Mental State Exam
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