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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'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 (ß: .81 [95% CI .74, .97]), increased total tau (ß: .98 [95% CI .71, 1.31]), and decreased amyloid-beta levels (ß: -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 (ß: 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 (Aβ), 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 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, 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,[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 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:[21] 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.[22–24] 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.[16] 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.[16–

[18] 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[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.[27] VIM was calculated as: VIM = SD/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,[28] as described elsewhere.[25] 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 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 Aβ, $Ptau_{181}$, and total tau levels, using standardized methods described elsewhere.[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,[16,18,33,34] and participants were categorized

as having lower (≤ 1 vascular risk factor) or higher (≥ 2 vascular risk factors) vascular risk.[34] APOE ϵ4 carrier status was determined from baseline venipuncture as previously described.[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[36] (see Supplementary Material in the Supplement for further details) in R[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,[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.[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.[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,[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 (see Supplementary Materials). Effect estimates (ß) 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: ß: .81 [95% CI .74, .97]; diastolic: ß: 3.79 [95% CI 2.14, 5.41]) (**Figure 1A**), increased total tau levels (systolic: ß: .98 [95% CI .71, 1.31]; diastolic: ß: 2.01 [95% CI 1.10, 2.90]) (**Figure 1B**), and decreased Aβ levels (systolic: ß: -1.52 [95% CI -3.55, -.34]; diastolic: ß: -3.46 [95% CI -7.02, -.26]) at follow-up (**Figure 1C**).

APOE ϵ4

APOE ϵ4 carriers with elevated BPV had the fastest increase in Ptau levels (systolic: ß: 9.03 [95% CI 1.67, 16.36]; diastolic: ß: 22.28 [95% CI 13.90, 30.52]) (**Figure 2**). BPV was not significantly related to total tau levels (systolic: ß: -.33 [95% CI -1.21, .57]; diastolic: ß: -.24 [95% CI -1.18, .73]) or Aβ levels (systolic: ß: -1.07 [95% CI -2.31, .07]; diastolic: ß: 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.[39] 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,[39] 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.[37,39] However, growing evidence suggests a clear relationship between BPV and arterial health.[12] For example, several studies indicate elevated BPV is predictive of cerebrovascular disease severity on 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] Additionally, 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.[37,40] 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.[20] 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.[41] Some studies

have also found that other BP measures, such as average BP,[19] pulse pressure,[33,42] and mean arterial pressure,[43] are more consistently related to CSF Ptau than to CSF Aβ. Other recent studies on average BP[44] and BPV[14] 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,[43] even over a short period of time.[45] 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.[46] 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),[5,47] some evidence suggests differential antihypertensive class effects on BPV in risk for stroke, independent of average BP levels.[48] 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.[49]

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.[39,50] 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,[15] 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

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, Irvine	Design study; interpreted the data; revised the manuscript for intellectual content

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REFERENCES

1. Zlokovic B V. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. Nature Publishing Group; 2011;12:723–738.
2. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011;10:819–828.
3. Yaffe K. Prevention of cognitive impairment with intensive systolic blood pressure control. JAMA. 2019;321:548–549.
4. Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. Lancet Neurol. 2020;19:61–70.
5. Wright JT, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103–2116.
6. Lattanzi S, Luzzi S, Provinciali L, Silvestrini M. Blood pressure variability predicts cognitive decline in Alzheimer's disease patients. Neurobiol Aging [online serial]. Elsevier Ltd; 2014;35:2282–2287. Accessed at: http://dx.doi.org/10.1016/j.neurobiolaging.2014.04.023.
7. Cho N, Hoshide S, Nishizawa M, Fujiwara T, Kario K. Relationship Between Blood Pressure Variability and Cognitive Function in Elderly Patients With Good Blood Pressure Control. Am J Hypertens. 2018;31:293–298.
8. Crichton GE, Elias MF, Dore GA, Torres R V, Robbins MA. Measurement-to-

measurement blood pressure variability is related to cognitive performance: the Maine Syracuse study. Hypertens (Dallas, Tex 1979) [online serial]. 2014/08/25. 2014;64:1094–1101. Accessed at: https://pubmed.ncbi.nlm.nih.gov/25156168.

9. Ma Y, Tully PJ, Hofman A, Tzourio C. Blood pressure variability and dementia: A state-of-the art review. Am J Hypertens. 2020;33:1059–1066.
10. Yoo JE, Shin DW, Han K, et al. Blood pressure variability and the risk of dementia: a nationwide cohort study. Hypertension. 2020;75:982–990.
11. Jia P, Lee HWY, Chan JYC, Yiu KKL, Tsoi KKF. Long-term blood pressure variability increases risks of dementia and cognitive decline: A meta-analysis of longitudinal studies. Hypertension [online serial]. American Heart Association; 2021;78:996–1004. Accessed at: https://doi.org/10.1161/HYPERTENSIONAHA.121.17788.
12. Ma Y, Song A, Viswanathan A, et al. Blood Pressure Variability and Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis of Population-Based Cohorts. Stroke. 2020;51:82–89.
13. Sible IJ, Bangen KJ, Blanken AE, Ho JK, Nation DA. Antemortem Visit-To-Visit Blood Pressure Variability Predicts Cerebrovascular Lesion Burden in Autopsy-Confirmed Alzheimer's Disease. Wharton W, editor. J Alzheimers Dis [online serial]. 2021;83:65–75. Accessed at: https://www.medra.org/servlet/aliasResolver?alias=iospress&doi=10.3233/JAD-210435.
14. Ma Y, Blacker D, Viswanathan A, et al. Visit-to-visit blood pressure variability, neuropathology, and cognitive decline. Neurology [online serial]. 2021;96:e2812 LP-e2823. Accessed at: http://n.neurology.org/content/96/23/e2812.abstract.
15. De Heus RAA, Tzourio C, Lee EJL, et al. Association between Blood Pressure Variability

with Dementia and Cognitive Impairment: A Systematic Review and Meta-Analysis. Hypertension. Epub 2021.:1478–1489.

16. Sible IJ, Nation DA, Alzheimer's Disease Neuroimaging Initiative. Long-term blood pressure variability across the clinical and biomarker spectrum of Alzheimer's disease. J Alzheimer's Dis [online serial]. 2020;77:1655–1669. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/32925032.

17. Sible IJ, Yew B, Dutt S, Bangen KJ, Li Y, Nation DA. Visit-to-visit blood pressure variability and regional cerebral perfusion decline in older adults. Neurobiol Aging [online serial]. Elsevier Inc.; 2021;105:57–63. Accessed at: https://doi.org/10.1016/j.neurobiolaging.2021.04.009.

18. Sible IJ, Nation DA. Blood pressure variability and medial temporal atrophy in apolipoprotein ϵ4 carriers. Brain Imaging Behav [online serial]. Epub 2021 Sep 28. Accessed at: https://link.springer.com/10.1007/s11682-021-00553-1.

19. Hu H, Meng L, Bi Y-L, et al. Tau pathologies mediate the association of blood pressure with cognitive impairment in adults without dementia: The CABLE study. Alzheimer's Dement [online serial]. United States; Epub 2021 May 25.:alz.12377. Accessed at: https://onlinelibrary.wiley.com/doi/10.1002/alz.12377.

20. Kester MI, van der Flier WM, Mandic G, Blankenstein MA, Scheltens P, Muller M. Joint Effect of Hypertension and APOE Genotype on CSF Biomarkers for Alzheimer's Disease. J Alzheimer's Dis [online serial]. Netherlands; 2010;20:1083–1090. Accessed at: https://www.medra.org/servlet/aliasResolver?alias=iospress&doi=10.3233/JAD-2010-091198.

21. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative

(ADNI): Clinical characterization. Neurology. 2010;74:201–209.

22. Bondi M, Edmonds EC, Jak AJ, et al. Neuropsychological criteria for Mild Cognitive Impairment improves diagnostic precision, biomarker associations, and progression rates. J Alzheimer's Assoc. 2014;42:275–289.

23. Edmonds EC, Delano-Wood L, Clark LR, et al. Susceptibility of the conventional criteria for mild cognitive impairment to false-positive diagnostic errors. Alzheimer's Dement. 2015;11:415–424.

24. Clark LR, Delano-Wood L, Libon DJ, et al. Are empirically-derived subtypes of mild cognitive impairment consistent with conventional subtypes? J Int Neuropsychol Soc. 2013;19:635–645.

25. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet [online serial]. Elsevier Ltd; 2010;375:895–905. Accessed at: http://dx.doi.org/10.1016/S0140-6736(10)60308-X.

26. Rouch L, Cestac P, Sallerin B, et al. Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: The S.AGES cohort. Hypertension. 2020;76:1280–1288.

27. Cheng Y, Li J, Ren X, et al. Visit-to-visit office blood pressure variability combined with Framingham risk score to predict all-cause mortality: A post hoc analysis of the systolic blood pressure intervention trial. J Clin Hypertens [online serial]. John Wiley & Sons, Ltd; 2021;23:1516–1525. Accessed at: https://doi.org/10.1111/jch.14314.

28. R Core Team. R: A language and environment for statistical computing. 2018.

29. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully

automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. Alzheimer's Dement. Epub 2016.

30. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's Dement. 2018;14:1470–1481.

31. Seibyl J, Shaw LM, Blennow K, et al. Amyloid-PET concordance of Elecsys® CSF biomarker immunoassays for Alzheimer's disease. Alzheimer's Dement [online serial]. Elsevier; 2017;13:P199–P200. Accessed at: http://dx.doi.org/10.1016/j.jalz.2017.07.062.

32. Shaw LM, Fields L, Korecka M, et al. Method comparison of AB(1-42) measured in human cerebrospinal fluid samples by liquid chromatography-tandem mass spectrometry, the INNO-BIA AlzBio3 assay, and the Elecsys® B-Amyloid(1-42) assay. Alzheimer's Dement. 2016;12:P668.

33. Nation DA, Edmonds EC, Bangen KJ, et al. Pulse pressure in relation to tau-mediated neurodegeneration, cerebral amyloidosis, and progression to dementia in very old adults. JAMA Neurol. 2015;72:546–553.

34. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: Adjustment for antihypertensive medication: The Framingham Study. Stroke. 1994;25:40–43.

35. Saykin AJ, Shen L, Foroud TM, et al. Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans. Alzheimer's Dement. 2010;6:265–273.

36. Bürkner PC. brms: An R package for Bayesian multilevel models using Stan. J Stat Softw. 2017;80.

37. Nagai M, Dote K, Kato M, et al. Visit-to-visit blood pressure variability and Alzheimer's disease: Links and risks. J Alzheimer's Dis. 2017;59:515–526.

38. Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA. American Medical Association; 2009;302:385–393.

39. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol. 2013;10:143–155.

40. Kitamura J, Nagai M, Ueno H, et al. The Insular Cortex, Alzheimer Disease Pathology, and Their Effects on Blood Pressure Variability. Alzheimer Dis Assoc Disord [online serial]. United States; 2020;34:282–291. Accessed at: https://journals.lww.com/10.1097/WAD.0000000000000340.

41. Jack CRJ, Bennett DA, Blennow K, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology. 2016;87:539–547.

42. Nation DA, Edland SD, Bondi MW, et al. Pulse pressure is associated with Alzheimer biomarkers in cognitively normal older adults. Neurology. 2013;81:2024–2027.

43. Glodzik L, Rusinek H, Pirraglia E, et al. Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly. Neurobiol Aging. 2014;35:64–71.

44. Arvanitakis Z, Capuano AW, Lamar M, et al. Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. Neurology. 2018;91:e517–e525.

45. Jack CR, Vemuri P, Wiste HJ, et al. Evidence for ordering of Alzheimer disease biomarkers. Arch Neurol [online serial]. 2011;68:1526–1535. Accessed at: https://doi.org/10.1001/archneurol.2011.183.

46. La Joie R, Visani A V, Lesman-Segev OH, et al. Association of APOE4 and Clinical

Variability in Alzheimer Disease With the Pattern of Tau- and Amyloid-PET. Neurology [online serial]. 2021;96:e650 LP-e661. Accessed at: http://n.neurology.org/content/96/5/e650.abstract.

47. Peters R, Yasar S, Anderson CS, et al. Investigation of antihypertensive class, dementia, and cognitive decline: A meta-analysis. Neurology. 2020;94:e267–e281.

48. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: A systematic review and meta-analysis. Lancet [online serial]. Elsevier Ltd; 2010;375:906–915. Accessed at: http://dx.doi.org/10.1016/S0140-6736(10)60235-8.

49. Hampel H, O'Bryant SE, Molinuevo JL, et al. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. Nat Rev Neurol [online serial]. 2018;14:639–652. Accessed at: https://pubmed.ncbi.nlm.nih.gov/30297701.

50. Kollias A, Stergiou GS, Kyriakoulis KG, Bilo G, Parati G. Treating Visit-to-Visit Blood Pressure Variability to Improve Prognosis. Hypertension [online serial]. American Heart Association; 2017;70:862–866. Accessed at: https://doi.org/10.1161/HYPERTENSIONAHA.117.10087.

Table 1.

Baseline clinical and demographic information.

	Total sample (*N* = 466)
Age (years)	76.6 (7.1)
Sex (*n*, % female)	203 (43.6%)
Education (years)	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* (*n*, % low)	436 (93.6%)
Vascular risk factors (*n*, %)	
Cardiovascular disease	42 (9.0%)
Diabetes mellitus 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%)
Alpha blockers	10 (2.2%)
Calcium channel blockers	34 (7.3%)

Diuretics	39 (8.4%)
Antidementia agents	57 (12.2%)
Systolic BP (mmHg)	
Baseline	134.7 (16.4)
Average	133.6 (12.8)
VIM	5.4 (3.3)
Diastolic BP (mmHg)	
Baseline	74.2 (10.3)
Average	73.7 (7.9)
VIM	5.9 (1.2)

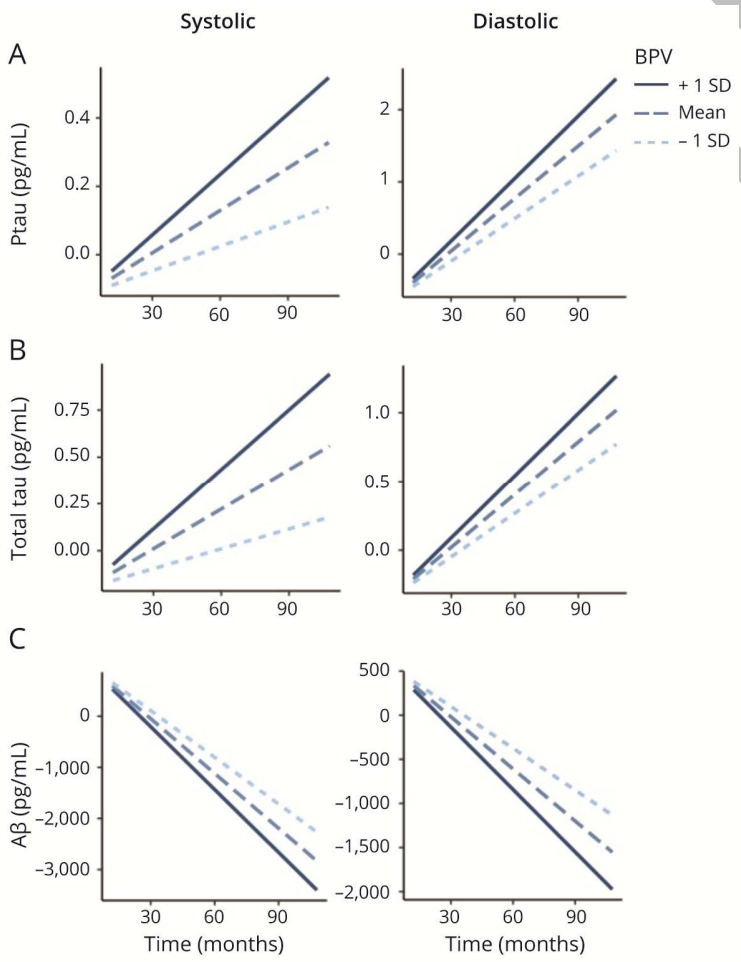
Means and SDs shown unless otherwise indicated.

*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

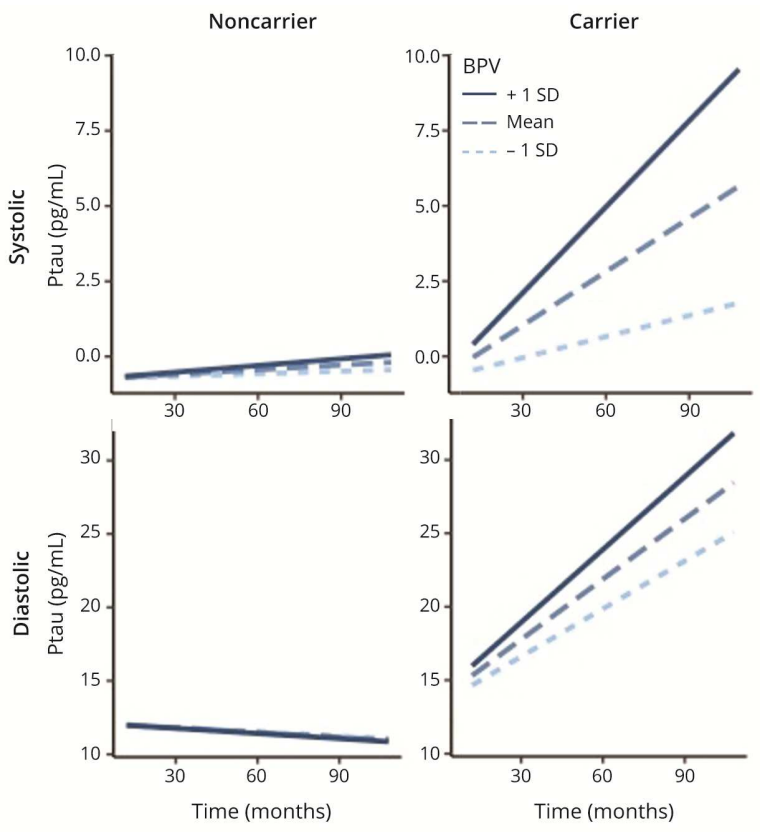
Conditional effects of the interaction of BPV by time on **A)** CSF Ptau levels, **B)** CSF total tau levels, and **C)** CSF Aβ levels in cognitively unimpaired or mildly impaired older adults. Model adjusted for age at CSF sample collection, sex, APOE ϵ4 carrier status, baseline MMSE score, years of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

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

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

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