Journal of Alzheimer's Disease 93 (2023) 533–543
DOI 10.3233/JAD-221103
IOS Press

Visit-to-Visit Blood Pressure Variability and Cognitive Decline in Apolipoprotein ε4 Carriers versus Apolipoprotein ε3 Homozygotes

Isabel J. Sible[a], Daniel A. Nation[b,c,*] and for the Alzheimer's Disease Neuroimaging Initiative[1]
[a]*Department of Psychology, University of Southern California, Los Angeles, CA, USA*
[b]*Institute for Memory Impairments and Neurological Disorders, University of California Irvine, Irvine, CA, USA*
[c]*Department of Psychological Science, University of California Irvine, Irvine, CA, USA*

Accepted 8 March 2023
Pre-press 10 April 2023

Abstract.
Background: Blood pressure variability (BPV) is associated with cognitive decline and Alzheimer's disease (AD), but relationships with AD risk gene apolipoprotein (*APOE*) ε4 remain understudied.
Objective: Examined the longitudinal relationship between BPV and cognitive change in *APOE* ε4 carriers and *APOE* ε3 homozygotes.
Methods: 1,194 Alzheimer's Disease Neuroimaging Initiative participants (554 *APOE* ε4 carriers) underwent 3-4 blood pressure measurements between study baseline and 12-month follow-up. Visit-to-visit BPV was calculated as variability independent of mean over these 12 months. Participants subsequently underwent ≥1 neuropsychological exam at 12-month follow-up or later (up to 156 months later). Composite scores for the domains of memory, language, executive function, and visuospatial abilities were determined. Linear mixed models examined the 3-way interaction of BPV × *APOE* ε4 carrier status x time predicting change in composite scores.
Results: Higher systolic BPV predicted greater decline in memory (+1 SD increase of BPV: $\beta = -0.001$, $p < 0.001$) and language ($\beta = -0.002$, $p < 0.0001$) among APOE ε4 carriers, but not APOE ε3 homozygotes (memory: +1 SD increase of BPV: $\beta = 0.0001$, $p = 0.57$; language: $\beta = 0.0001$, $p = 0.72$). Systolic BPV was not significantly associated with change in executive function or visuospatial abilities in APOE ε4 carriers ($ps = 0.08$–0.16) or APOE ε3 homozygotes ($ps = 0.48$–0.12).
Conclusion: Cognitive decline associated with high BPV may be specifically accelerated among APOE ε4 carriers.

Keywords: Alzheimer's disease, APOE, blood pressure, cognitive dysfunction, neuropsychology

INTRODUCTION

Blood pressure (BP) management is regarded as a key prevention strategy for cognitive decline and dementia [1–4]. In addition to controlling mean BP levels, there is now an emerging interest in the poten-

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://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 at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Correspondence to: Daniel A. Nation, PhD, Associate Professor, University of California Irvine, Department of Psychological Science, 4201 Social and Behavioral Sciences Gateway, Irvine, CA 92697-7085, USA. Tel.: +1 949 824 9339; E-mail: dnation@uci.edu.

ISSN 1387-2877/$35.00

tial importance of variability in BP levels [5]—from beat-to-beat changes during a single recording to visit-to-visit variation across months and years. A growing number of studies suggest increased BP variability (BPV), independent of traditionally studied mean BP levels, is associated with cognitive impairment and decline, and increased risk and progression to dementia, including Alzheimer's disease (AD) and vascular dementia [6–9]. The majority of these studies on cognitive decline have relied on single tests of cognition (e.g., Mini-Mental State Examination) [9], but relationships with cognitive decline across different neuropsychological domains (e.g., memory, language, executive function, visuospatial abilities) are understudied. Apolipoprotein (*APOE*) ε4 remains the strongest genetic risk factor for late onset AD [10–13], and prior studies have suggested *APOE* ε4 may convey vulnerability to vascular factors [13, 14], raising the possibility of interactions with increased BPV. Consistent with this hypothesis, several recent studies indicate *APOE* ε4 modifies the relationship between high BPV and important markers of AD (e.g., cerebrospinal fluid (CSF) AD biomarker changes, temporal lobe tau accumulation, medial temporal lobe atrophy) [15–17]. However, less is known about the role of BPV in cognitive decline specific to *APOE* ε4 carriers at risk for AD relative to *APOE* ε3 homozygotes. To address this question, the present investigation examined the longitudinal relationship between BPV predicting cognitive decline in several neuropsychological domains over time in *APOE* ε4 carriers and *APOE* ε3 homozygotes, independent of mean BP levels, in a sample of cognitively unimpaired and mildly impaired older adults.

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, mild cognitive impairment (MCI), and AD. As previously described [18], volunteer adults (age 55–91), with or without memory complaints, were recruited from Alzheimer's Disease Research Centers and academic medical institutions across North America via newsletters, internet-based communications, direct mail, and news releases. Participants were enrolled if they met the following criteria: few

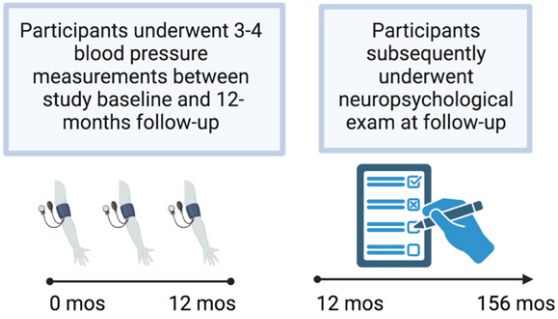

Fig. 1. Schematic of study design. Blood pressure was collected 3-4 times between study baseline and 12-month follow-up. Cognitive assessments took place at 12-month follow-up and later (up to 156 months later).

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 lower vascular risk (Hachinski Ischemic Score ≤4). Ethical approval was obtained for each institution involved and all participants provided written informed consent. Further study details can be found online (https://adni.loni.usc.edu).

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. Participant subsequently underwent ≥1 neuropsychological exam at 12-months follow-up or later (up to 156 months later) (Fig. 1).

Measures

Clinical assessment

Clinical diagnosis was determined at study baseline clinical evaluation, as previously described [15–21]. Participants were without history of major neurocognitive disorder or stroke and were identified as cognitively unimpaired or MCI based on established ADNI criteria [22]. Although alternative MCI criteria have demonstrated improved reliability and validity [23], ADNI criteria were utilized for the purposes of the present study which examined the cognitively unimpaired and MCI participants together. The ADNI criteria for cognitively unimpaired included: Mini-Mental State Exam (MMSE) score >24; Clinical Dementia Rating scale score of 0; without history of major depressive disorder, MCI, or dementia. Criteria for MCI were as follows [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; did not meet clinical criteria for AD dementia.

Cognitive assessment

Participants underwent extensive neuropsychological testing at different intervals depending on specific ADNI study enrollment (e.g., every 12 months, or every 6 months for the first year and then every 12 months, or another interval). The neuropsychological battery included Logical Memory, Rey Auditory Verbal Learning Test (RAVLT), Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog), MMSE, Wechsler Adult Intelligence Scale – Revised (WAIS-R), Trails Making Test, Montreal Cognitive Assessment (MoCA), Category Fluency, and Boston Naming Test (BNT). As recently described [24], individual test items from this battery were used to calculate cognitive composite scores for the domains of memory, language, executive function, and visuospatial abilities. Briefly, experts first assigned item-level data (e.g., MMSE: "What town or city are we in?"; Trail Making Test: Trails B time to complete) from each test to a cognitive domain and then used confirmatory factor analysis to reveal the four identified cognitive domains. Supplementary Tables 1–4 summarize the item-level data included in each cognitive composite score. Importantly, as part of the Alzheimer's Disease Sequencing Project (ADSP) (https://dss.niagads.org/studies/sa000001/) Phenotype Harmonization Consortium (PHC), these cognitive composite scores were harmonized across four large publicly available datasets (ADNI, Adult Changes in Thought [ACT], Religious Orders Study and Memory and Aging Project [ROS/MAP], National Alzheimer's Coordinating Center [NACC]) and standardized on the same metric to directly compare composite scores for participants across different studies using different neuropsychological batteries.

BP assessment

A calibrated mercury sphygmomanometer was used to obtain seated BP measurements from participants 3-4 times between study screening and 12-month follow-up, as described in detail elsewhere [15–20]. Briefly, participants were seated and resting, encouraged to refrain from talking during and shortly before BP measurement, and to remain as calm and undisturbed as possible. BP measurements were obtained from the dominant forearm arranged at the horizontal level of the fourth intercostal space at the sternum. BP was measured from the same arm, at a similar time of day, by the same person, and using the same device and cuff. We used the 3-4 BP measurements to calculate BPV over 12 months as variability independent of mean (VIM), an increasingly used index of BPV uncorrelated with mean BP levels across visits [6, 25]. We used bivariate correlation in our analysis to confirm VIM was not significantly correlated with mean BP ($r = 0.05$, $p = 0.11$). As previously described [25], VIM was calculated as: $\text{VIM} = \text{SD}/\text{mean}^x$, where the power x was derived from non-linear curve fitting of BP SD against mean BP using the nls package in R [26]. We also determined the SD, coefficient of variation (CV [100 × SD/mean]), and maximum minus minimum of BPV (see Supplementary Material). Mean BP over the 12-month period was also calculated.

Other measurements

APOE genotype was determined from participant blood samples using methods previously described [27]. Participants carrying an *APOE* ε2 allele (e.g., *APOE* ε2/ε2 [$n = 2$], *APOE* ε2/ε3 [$n = 114$], *APOE* ε2/ε4 [$n = 23$]) were excluded from the present analyses due to the lower frequency of *APOE* ε2 and the complexity of *APOE* ε2-associated risk/protection from vascular disease and AD [28]. In remaining participants, *APOE* ε4 carrier status was defined as having ≥1 *APOE* ε4 allele (e.g., *APOE* ε3/ε4, *APOE* ε4/ε4). Consistent with prior studies of aggregate vascular risk and AD [29], we calculated a traditional vascular risk factor composite score based on the presence (1) or absence (0) of the following: cardiovascular disease, diabetes, high total cholesterol, hypertension, atrial fibrillation, current smoking, and history of TIA/stroke (range 0–7). Antihypertensive (all classes) and antidementia medication use was determined at baseline clinical evaluation.

Statistical analysis

Linear mixed models examined the 3-way interaction of BPV × *APOE* ε4 carrier status (*APOE* ε3 homozygote versus *APOE* ε4 carrier) × time (months) on each of the four cognitive composite scores separately. Random intercepts for participant and site were included in the models. We only included cognitive data collected at 12-month follow-up (i.e., when BPV was determined) and later (range

0–156 months later) to help determine the temporal order and predictive value of any associations with BPV. We focused our investigation on systolic BPV based on the continued focus of randomized controlled trials on reducing systolic BP to improve cardiovascular and cognitive outcomes [30–32], and to reduce the likelihood of Type 1 error. However, we also report findings with diastolic BPV in the Supplementary Material. Analyses using the SD, CV, and maximum minus minimum indices of BPV are reported in the Supplementary Material. We also explored the 3-way interaction of mean BP × *APOE* ε4 carrier status × time in order to directly compare potential associations with BPV. Sensitivity analyses tested the robustness of findings after controlling for 1) number of antihypertensive medications, 2) antidementia agent use, 3) number of cognitive test administrations (median = 6, to assess for potential practice effects of repeated cognitive testing), 4) excluding participants with one cognitive assessment ($n = 188$), and 5) study wave (e.g., ADNI 1, ADNI 2, ADNI 3, ADNI GO). (see Supplementary Material). We also conducted an additional sensitivity analysis where participants were censored at their first missed visit. Exploratory analyses investigated associations in *APOE* ε3 homozygotes versus *APOE* ε3/ε4 versus *APOE* ε4/ε4 (see Supplementary Material). Model estimates (standardized beta [β]) are presented per +1 SD increase of BPV. All models included the following covariates: age at cognitive testing (years), sex (male versus female), race/ethnicity (white versus non-white due to limited number of non-white participants), education (years), mean systolic BP between study baseline and 12-month follow-up (mmHg), vascular risk composite score (0–7), and baseline clinical diagnosis (cognitively unimpaired versus MCI). All analyses were 2-tailed. Significance was set at $p < 0.10$ for 3-way interaction (BPV x APOE ε4 carrier status x time) and at $p < 0.05$ for *post-hoc* analyses and false-discovery rate (FDR)-correction. All analyses were carried out in R (version 4.1.2) [26] and used the lmer package.

RESULTS

A total of 1,194 participants (*APOE* ε3/ε3 [$n = 640$]; *APOE* ε3/ε4 [$n = 441$]; *APOE* ε4/ε4 [$n = 113$]) contributed to 5,240 cognitive assessments (median 6 cognitive assessments per participant) at 12-month follow-up and later. All participants completed cognitive testing at 12-month follow-up, $n = 300/1,194$ at 18-month follow-up, $n = 947/1,194$ at 24-month follow-up, $n = 709/1,194$ at 36-month follow-up, $n = 583/1,194$ at 48-months follow-up, $n = 361/1,194$ at 60-month follow-up, $n = 372/1,194$ at 72-month follow-up, $n = 302/1,194$ at 84-month follow-up, $n = 193/1,194$ at 96-month follow-up, $n = 100/1,194$ at 108-months follow-up, $n = 62/1,194$ at 120-month follow-up, $n = 48/1,194$ at 132-month follow-up, $n = 35/1,194$ at 144-month follow-up, $n = 29/1,194$ at 156-month follow-up, and $n = 5/1,194$ at 168-month follow-up. The median time interval between BPV determination and any cognitive assessment was 24 months (IQR: 30 months). Baseline clinical and demographic data are summarized in Table 1.

BPV

The 3-way interaction of systolic BPV × *APOE* ε4 carrier status x time was significant for all cognitive domain composite scores (memory: +1 SD increase of BPV: β = –0.04 [90% CI –0.06, –0.02], $p = 0.002$; language: +1 SD increase of BPV: β = –0.07 [90% CI –0.09, –0.04], $p < 0.001$; executive function: +1 SD increase of BPV: β = –0.03 [90% CI –0.06, –0.003], $p = 0.07$; visuospatial abilities: +1 SD increase of BPV: β = –0.08 [90% CI –0.13, –0.02], $p = 0.04$). *Post-hoc* analyses revealed that *APOE* ε4 carrier status significantly modified the relationship between systolic BPV and cognitive decline, such that higher systolic BPV was associated with declines in the domains of memory (+1 SD increase of BPV: β = –0.001, $p < 0.001$) and language (+1 SD increase of BPV: β = –0.002, $p < 0.0001$) among *APOE* ε4 carriers, but not *APOE* ε3 homozygotes (memory: +1 SD increase of BPV: β = 0.0001, $p = 0.57$; language: +1 SD increase of BPV: β = 0.0001, $p = 0.72$) (Fig. 2). Systolic BPV was not significantly associated with change in the domains of executive function or visuospatial abilities in *APOE* ε4 carriers (executive function: +1 SD increase of BPV: β = –0.0007, $p = 0.08$; visuospatial abilities: +1 SD increase of BPV: β = –0.001, $p = 0.16$) or *APOE* ε3 homozygotes (executive function: +1 SD increase of BPV: β = 0.0002, $p = 0.48$; visuospatial abilities: +1 SD increase of BPV: β = 0.001, $p = 0.12$) (data not shown). Findings were largely similar across systolic BPV indices, with VIM and CV showing the strongest associations (Supplementary Table 5). *Post-hoc* findings remained significant after FDR-correction. Diastolic BPV was associated with decline in memory, executive function, and visuospa-

Table 1
Baseline clinical and demographic information

	Total sample (N = 1,194)	*APOE* ε3 homozygotes (*n* = 640)	*APOE* ε4 carriers (*n* = 554)
Age (y)	73.3 (7.4)	74.4 (7.1)	72.2 (7.5)
Sex (*n*, % female)	522 (43.7%)	276 (43.1%)	246 (44.4%)
Race (*n*, %)			
American Indian/Alaskan	2 (0.2%)	2 (0.3%)	0 (0.0%)
Asian	20 (1.7%)	14 (2.2%)	6 (1.1%)
Black	38 (3.2%)	20 (3.1%)	18 (3.3%)
Hawaiian/Pacific Islander	1 (0.1%)	0 (0.0%)	1 (0.2%)
Multiracial	12 (1.0%)	5 (0.8%)	7 (1.3%)
Other	2 (0.2%)	1 (0.2%)	1 (0.2%)
White	1119 (93.7%)	598 (93.4%)	521 (94.0%)
Ethnicity (*n*, %)			
Hispanic/Latino	39 (3.3%)	21 (3.3%)	18 (3.3%)
Non-Hispanic/Latino	1155 (96.7%)	619 (96.7%)	536 (96.8%)
Education (y)	16.2 (2.7)	16.3 (2.7)	16.0 (2.8)
ADNI MCI diagnosis (*n*, %)	793 (66.4%)	378 (59.1%)	415 (74.9%)
Cognitive composite scores			
Memory	0.19 (0.9)	0.39 (0.8)	–0.04 (0.9)
Language	0.39 (0.7)	0.49 (0.6)	0.27 (0.7)
Executive function	0.34 (0.7)	0.45 (0.7)	0.21 (0.7)
Visuospatial abilities	–0.07 (0.5)	–0.02 (0.5)	–0.12 (0.5)
Vascular risk composite score*	1.5 (1.1)	1.6 (1.1)	1.4 (1.1)
Antihypertensive medication use (*n*, %)	493 (41.3%)	287 (44.8%)	206 (37.2%)
ACE inhibitors	174 (14.6%)	108 (16.9%)	66 (11.9%)
Alpha blockers	45 (3.8%)	26 (4.1%)	19 (3.4%)
ARBs	88 (7.4%)	50 (7.8%)	38 (6.9%)
Beta blockers	7 (0.6%)	5 (0.8%)	2 (0.4%)
Calcium channel blockers	88 (7.4%)	50 (7.8%)	38 (6.9%)
Central agonists	6 (0.5%)	5 (0.8%)	1 (0.2%)
Diuretics	85 (7.1%)	43 (6.7%)	42 (7.6%)
Number of antihypertensive agents (*n*, %)			
0	701 (58.7%)	353 (55.2%)	348 (62.8%)
1	334 (28.0%)	191 (29.8%)	143 (25.8%)
2	128 (10.7%)	75 (11.7%)	53 (9.6%)
3	27 (2.3%)	18 (2.8%)	9 (1.6%)
4	4 (0.4%)	3 (.5%)	1 (0.2%)
Antidementia agents (*n*, %)	196 (16.4%)	75 (11.7%)	121 (21.8%)
Systolic BP (mmHg)			
Baseline	133.1 (17.0)	133.9 (17.2)	132.3 (16.7)
Mean	133.7 (13.3)	134.3 (13.2)	132.9 (13.2)
VIM	14.7 (1.1)	14.7 (1.1)	14.7 (1.2)
Diastolic BP (mmHg)			
Baseline	74.0 (9.5)	74.0 (9.7)	74.0 (9.2)
Mean	74.1 (7.6)	73.9 (7.7)	74.3 (7.4)
VIM	8.5 (1.5)	8.6 (1.6)	8.5 (1.4)

Means and SDs shown unless otherwise indicated. *Baseline vascular risk composite score (range 0–7) determined from presence (1) or absence (0) of individual vascular risk factors: cardiovascular disease, diabetes, high total cholesterol, hypertension, atrial fibrillation, current smoking, history of transient ischemic attack/stroke, as previously described [29]. BP, blood pressure; VIM, variability independent of mean; MCI, mild cognitive impairment; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ADNI, Alzheimer's Disease Neuroimaging Initiative.

tial abilities in *APOE* ε4 carriers but not *APOE* ε3 homozygotes (Supplementary Table 6).

Mean BP

The 3-way interaction of mean systolic BP × *APOE* ε4 carrier status × time was not significant for any cognitive domain composite score (memory: +1 SD increase of BPV: β = 0.007 [90% CI –0.01, 0.03], $p = 0.57$; language: +1 SD increase of BPV: β = 0.008 [90% CI –0.02, 0.04], $p = 0.61$; executive function: +1 SD increase of BPV: β = –0.01 [90% CI –0.04, 0.02], $p = 0.47$; visuospatial abilities: +1 SD increase of BPV: β = –0.04 [90% CI –0.10,

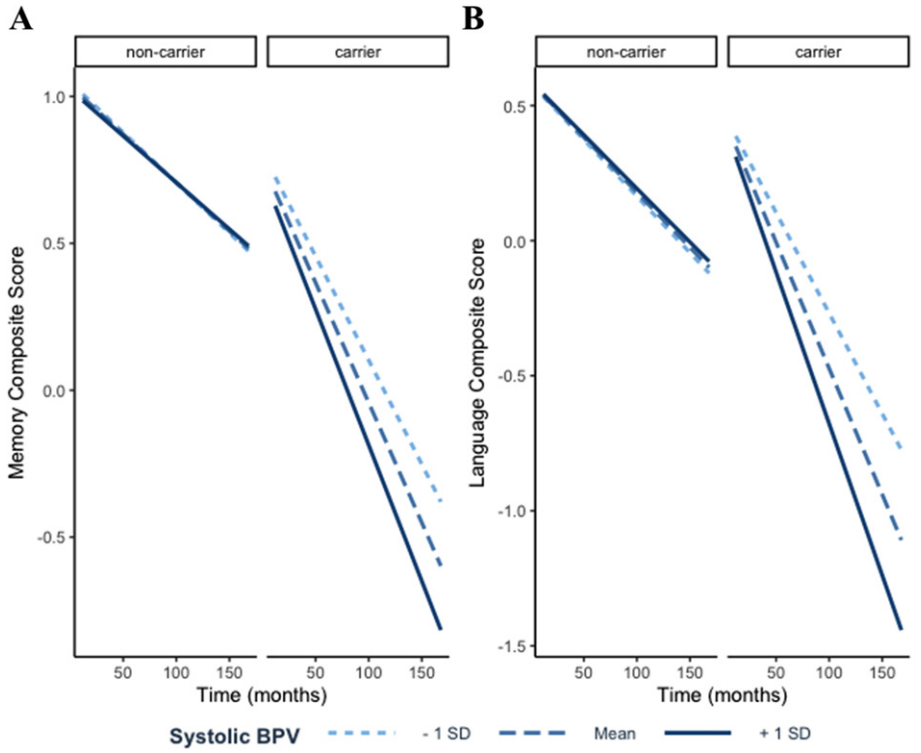

Fig. 2. *APOE* ε4 carrier status and systolic BPV interact to predict cognitive decline. Conditional effects of systolic BPV by *APOE* ε4 carrier status by time on A) memory composite score and B) language composite score. Models adjusted for age at cognitive testing, sex, race/ethnicity, years of education, mean systolic BP, vascular risk composite score, and baseline clinical diagnosis. BPV, blood pressure variability

0.02], $p = 0.31$) (data not shown). Associations with mean diastolic BP were consistent (Supplementary Table 7).

Sensitivity analyses

Systolic BPV findings remained largely unchanged in sensitivity analyses controlling for 1) number of antihypertensive medications, 2) antidementia agent use, 3) number of cognitive test administrations, 4) excluding participants with one cognitive assessment, and 5) study wave (Supplementary Table 8). Findings were consistent in an additional sensitivity analysis where participants were censored at their first missed visit (Supplementary Table 8).

Exploratory analyses

In exploratory analyses across *APOE* genotype (*APOE* ε3 homozygote versus *APOE* ε3/ε4 versus *APOE* ε4/ε4) (Supplementary Table 9), elevated systolic BPV was associated with declines in language (+1 SD increase of BPV: $\beta = -0.002, p < 0.001$) and executive function (+1 SD increase of BPV: $\beta = -0.001, p = 0.04$) in *APOE* ε3/ε4 carriers, but not *APOE* ε3 homozygotes (language: +1 SD increase of BPV: $\beta = 0.0001, p = 0.72$; executive function: +1 SD increase of BPV: $\beta = 0.0002, p = 0.49$). Higher systolic BPV was associated with significant decline in language (+1 SD increase of BPV: $\beta = -0.002$, $p = 0.03$) and a trend for decline in executive function (+1 SD increase of BPV: $\beta = -0.002, p = 0.06$) in *APOE* ε4/ε4 carriers. Higher systolic BPV was associated with memory decline in *APOE* ε3/ε4 carriers (+1 SD increase of BPV: $\beta = -0.002, p < 0.001$), but not *APOE* ε4/ε4 carriers (+1 SD increase of BPV: $\beta = -0.0004, p = 0.58$) or *APOE* ε3 homozygotes (+1 SD increase of BPV: $\beta = 0.0001, p = 0.57$). Systolic BPV was not associated with change in visuospatial abilities in *APOE* ε3 homozygotes (+1 SD increase of BPV: $\beta = 0.001, p = 0.12$), *APOE* ε3/ε4 (+1 SD increase of BPV: $\beta = -0.002, p = 0.12$), or *APOE* ε4/ε4 (+1 SD increase of BPV: $\beta = -0.002$, $p = 0.22$).

DISCUSSION

Findings suggest *APOE* ε4 modifies the relationship between visit-to-visit BPV and cognitive decline, independent of mean BP levels, in a sample of cognitively unimpaired and mildly impaired older adults. Specifically, higher systolic BPV was predictive of decline in memory and language among *APOE* ε4 carriers, but systolic BPV showed no relationship with cognitive decline in any cognitive domain among *APOE* ε3 homozygotes. There was also a trend for decline in executive function among *APOE* ε4 carriers with elevated systolic BPV in exploratory analyses. Additional declines in visuospatial ability were observed in *APOE* ε4 carriers with elevated diastolic BPV. The current study findings are consistent with prior studies linking BPV to cognitive decline and dementia risk [9], and further suggest that BPV-associated risk may be specific to *APOE* ε4 carriers at risk for AD. Additional findings from the present study identify BPV-associated decline specific to neuropsychological domains impacted in early-stage AD, including memory, language, and executive function [33]. Together these results are consistent with prior work linking BPV elevation to other AD marker abnormalities on CSF, PET, and MRI. Based on these findings, further studies of BPV as a potential risk factor for AD are warranted, and may have implications for risk assessment, prevention, and treatment.

Prior work suggests traditional vascular risk factor (e.g., hypertension, pulse pressure, cardiovascular disease, diabetes, atherosclerosis) burden is more strongly associated with cognitive decline in *APOE* ε4 carriers than in non-carriers [14, 34–36], suggesting *APOE* ε4 may convey vulnerability to vascular factors. This is consistent with studies demonstrating cerebrovascular dysfunction in *APOE* ε4 carriers, including increased blood-brain barrier permeability [13] and decreased cerebral blood flow [37]. The present study highlights BPV as a newer aspect of BP that is increasingly associated with poor brain health outcomes, independent of traditionally studied/targeted mean BP levels. Moreover, high BPV appears to be more consistently related to poor outcomes than other BP measures. For example, while both high and low mean BP, and high and low pulse pressure, have been associated with increased dementia risk [1, 38–41], no studies to date have observed low BPV in association with cognitive decline. Additionally, in our analysis, mean BP was not significantly associated with cognitive decline based on *APOE* ε4 carrier status.

It has been hypothesized that arterial stiffness may underlie the relationship between BPV and cognitive decline [5]. Recent work also suggests a strong association between BPV and cerebrovascular health as evidenced on MRI (e.g., white matter hyperintensities) [42–44] and postmortem evaluation (e.g., atherosclerosis in the Circle of Willis) [45, 46]. Chronic large fluctuations in BP are thought to have a "tsunami effect" [47] on arterial walls and promote arterial remodeling, blood-brain barrier breakdown, and endothelial dysfunction, all of which are critical to neurovascular unit functioning and cognition [48]. It was also recently shown that *APOE* ε4 carriers exhibit blood-brain-barrier breakdown in the hippocampus and medial temporal lobe, regions especially vulnerable to AD, and cognitive impairment [13]. Additionally, recent studies suggest *APOE* ε4 modifies the relationship between BPV and other important markers of AD, such as medial temporal brain volume loss [15], tau accumulation in the temporal lobe [17], and alterations in CSF AD biomarkers in directions consistent with advancing AD [16]. Interestingly, higher BPV in *APOE* ε4 carriers in the present study was associated with declines in memory and language, neuropsychological domains that largely rely on medial temporal regions vulnerable to AD pathology (and especially in *APOE* ε4 carriers) [13]. Elevated BPV in *APOE* ε4 carriers was also related to decline in executive function, which is often impacted by cerebrovascular disease burden [43]. The present findings with memory, language, and executive function decline are largely consistent with prior work investigating the role of *APOE* ε4 in cognitive decline and more well-studied vascular risk factors, such as hypertension, pulse pressure, cardiovascular disease, and diabetes [14, 35]. Elevated diastolic BPV was associated with decline in visuospatial abilities in *APOE* ε4 carriers. These studies also showed links between vascular factors and visuospatial abilities in *APOE* ε4 carriers. It is possible that *APOE* ε4 may drive vascular dysfunction, including elevated BPV, and associated cognitive decline. Alternatively, elevated BPV may accelerate vascular contributions to cognitive impairment and AD, especially in individuals at increased genetic risk for AD. Finally, it is possible that AD changes such as neurodegenerative effects on brain regions critical to autonomic regulation (perhaps more pronounced in *APOE* ε4 carriers), may drive BPV and cognitive impairment [49]. Cognitive

composite scores were from neuropsychological testing after BPV was determined, suggesting that high BPV may predate and predict cognitive decline, but additional longitudinal studies are needed.

Our study provides new information about the role of *APOE* ε4 carrier status in the increasingly studied relationship between BPV and cognitive decline and dementia risk [9]. Additionally, our findings across multiple neuropsychological domains add to prior work largely reporting on declines in single tests of cognitive function [9]. Findings were robust even in a sample of older adults with no detectible cognitive impairment or mild impairments, further highlighting the possibility that elevated BPV may be an important but understudied early vascular risk factor for cognitive decline and AD [19]. The present investigation is strengthened by the longitudinal design with up to 14 years of follow-up from study baseline, and the use of cognitive composite scores easily comparable across other large datasets. There are several limitations worth noting. First, the study sample was largely comprised of non-Hispanic white individuals. Important advances in obtaining more diverse samples are underway and future datasets with more racial and ethnic heterogeneity will add to the present study findings. Additionally, participants were recruited from Alzheimer's Disease Research Centers and academic medical institutions, which may have biased sample selection for those with cognitive impairment (especially cognitive impairment in those at increased genetic risk for AD through the *APOE* ε4 allele) more than studies relying solely on community-based recruitment efforts. Furthermore, 46.4% of the present sample (comparing *APOE* ε3 homozygotes versus *APOE* ε4 carriers) were *APOE* ε4 carriers, which is higher than community-based studies and may limit generalizability of findings. However, our finding that elevated BPV is associated with cognitive decline is consistent with other BPV studies utilizing different datasets from around the world, including those with similar and different study samples and recruitment methods (e.g., SPRINT, Ohasama, Rotterdam, JPAD2, S.AGES, Three-City, Ohasama) [9]. Although BPV was determined from BP measurements obtained in ways similar to routine clinical visits, some aspects of BP collection were not standardized across sites (e.g., stimulant intake/exercise/hydration day of BP measurement, etc.) and the auscultation method has the added weakness of introducing the possibility of observer error (versus automated devices). Furthermore, other aspects of the ADNI BP collection protocol were not standardized or optimized, such as whether/how technicians were trained, specific duration of rest period, if proper arm support was used, or if cuff size was based upon measured arm circumference. Findings remained in sensitivity analyses controlling for number of antihypertensive medications used, but we did not directly explore potential antihypertensive class treatment effects (mono therapy or combination therapy) on BPV and cognitive decline due to the relatively limited sample size needed for this type of analysis. Some studies suggest differential class effects of BPV on risk for stroke [50, 51]. This remains an active area of investigation with the potential to update guidelines on BP control in older adults [52, 53]. Similarly, this is a retrospective study and prospective and/or interventional studies on BPV and cognition have the potential to further our knowledge about the nuances of BP management for dementia prevention.

APOE ε4 modifies the relationship between BPV and cognitive decline, independent of mean BP levels, in a sample of older adults without major neurocognitive dysfunction. Findings add to ongoing work detailing relationships between BPV and AD [7, 15–19, 45] and support the hypothesized link between *APOE* ε4 and vascular contributions to dementia risk [13].

ACKNOWLEDGMENTS

We would like to thank the participants and their families, investigators, and researchers from the ADNI study.

FUNDING

The study data analysis was supported by NIH/NIA grants (R01AG064228, R01AG060049, P30AG066519, P01AG052350) and Alzheimer's Association grant AARG-17-532905.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-

Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Cognitive composite scores were prepared, archived, and distributed by the National Institute on Aging Alzheimer's Disease Data Storage Site (NIAGADS) at the University of Pennsylvania (U24-AG041689), funded by the National Institute on Aging.

CONFLICT OF INTEREST

Daniel Nation is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review.

DATA AVAILABILITY

These data were derived from the following resources available in the public domain: ADNI; https://adni.loni.usc.edu/.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-221103.

REFERENCES

[1] Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, Gulati M, Kamel H, Knopman DS, Launer LJ, Saczynski JS, Seshadri S, Zeki Al Hazzouri A (2016) Impact of hypertension on cognitive function: A scientific statement from the American Heart Association. *Hypertension* **68**, e67-e94.

[2] Yaffe K (2019) Prevention of cognitive impairment with intensive systolic blood pressure control. *JAMA* **321**, 548-549.

[3] Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* **10**, 819-828.

[4] Iadecola C (2014) Hypertension in dementia. *Hypertension* **64**, 3-5.

[5] Nagai M, Dote K, Kato M, Sasaki S, Oda N, Kagawa E, Nakano Y, Yamane A, Higashihara T, Miyauchi S, Tsuchiya A (2017) Visit-to-visit blood pressure variability and Alzheimer's disease: Links and risks. *J Alzheimers Dis* **59**, 515-526.

[6] Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, Berrut G, Corruble E, Derumeaux G, Falissard B, Forette F, Pasquier F, Pinget M, Ourabah R, Danchin N, Hanon O, Vidal JS (2020) Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: The S.AGES cohort. *Hypertension* **76**, 1280-1288.

[7] Lattanzi S, Viticchi G, Falsetti L, Buratti L, Luzzi S, Provinciali L, Silvestrini M (2014) Visit-to-visit blood pressure variability in Alzheimer disease. *Alzheimer Dis Assoc Disord* **28**, 347-351.

[8] Lattanzi S, Luzzi S, Provinciali L, Silvestrini M (2014) Blood pressure variability predicts cognitive decline in Alzheimer's disease patients. *Neurobiol Aging* **35**, 2282-2287.

[9] Ma Y, Tully PJ, Hofman A, Tzourio C (2020) Blood pressure variability and dementia: A state-of-the art review. *Am J Hypertens* **33**, 1059-1066.

[10] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.

[11] Serrano-Pozo A, Das S, Hyman BT (2021) APOE and Alzheimer's disease: Advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol* **20**, 68-80.

[12] Jak AJ, Houston WS, Nagel BJ, Corey-Bloom J, Bondi MW (2007) Differential cross-sectional and longitudinal impact of APOE genotype on hippocampal volumes in nondemented older adults. *Dement Geriatr Cogn Disord* **23**, 382-389.

[13] Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, Pachicano M, Joe E, Nelson R, Orazio LMD, Buennagel DP, Harrington MG, Tammie LS, Fagan AM, Ringman JM, Schneider LS, John C (2020) APOE4 leads to early blood-brain barrier dysfunction predicting human cognitive decline. *Nature* **581**, 71-76.

[14] Bangen KJ, Beiser A, Delano-Wood L, Nation DA, Lamar M, Libon DJ, Bondi MW, Seshadri S, Wolf PA, Au R (2013) APOE genotype modifies the relationship between midlife vascular risk factors and later cognitive decline. *J Stroke Cerebrovasc Dis* **22**, 1361-1369.

[15] Sible IJ, Nation DA (2021) Blood pressure variability and medial temporal atrophy in apolipoprotein ∈4 carriers. *Brain Imaging Behav* **16**, 792-801.

[16] Sible IJ, Nation DA (2022) Visit-to-visit blood pressure variability and CSF Alzheimer's disease biomarkers in cognitively unimpaired and mildly impaired older adults. *Neurology* **98**, E2446-E2453.

[17] Sible IJ, Nation DA, Weiner M, Aisen P, Petersen R, Jack CR, Jagust W, Trojanowki JQ, Toga AW, Beckett L, Green RC, Saykin AJ, Morris J, Shaw LM (2022) Visit-to-visit blood pressure variability and longitudinal tau accumulation in older adults. *Hypertension* **79**, 629-637.

[18] Sible IJ, Yew B, Dutt S, Bangen KJ, Li Y, Nation DA (2021) Visit-to-visit blood pressure variability and regional cerebral perfusion decline in older adults. *Neurobiol Aging* **105**, 57-63.

[19] Sible IJ, Nation DA (2020) Long-term blood pressure variability across the clinical and biomarker spectrum of Alzheimer's disease. *J Alzheimers Dis* **77**, 1655-1669.

[20] Sible IJ, Jang JY, Sultzer DL, Nation DA (2022) Visit-to-visit blood pressure variability and subthreshold depressive symptoms in older adults. *Am J Geriatr Psychiatry* **30**, 1110-1119.

[21] Kapoor A, Gaubert A, Marshall A, Meier IB, Yew B, Ho JK, Blanken AE, Dutt S, Sible IJ, Li Y, Jang JY, Brickman AM, Rodgers K, Nation DA (2021) Increased levels of circulating angiogenic cells and signaling proteins in older adults with cerebral small vessel disease. *Front Aging Neurosci* **13**, 711784.

[22] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR, Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW (2010) Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. *Neurology* **74**, 201-209.

[23] Bondi M, Edmonds EC, Jak AJ, Clark LR, Delano-Wood L, McDonald CR, Nation DA, Libon DJ, Au R, Galasko DR, Salmon DP (2014) Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *J Alzheimers Dis* **42**, 275-289.

[24] Mukherjee S, Choi S-E, Lee ML, Scollard P, Trittschuh EH, Mez J, Saykin AJ, Gibbons LE, Sanders RE, Zaman AF, Teylan MA, Kukull WA, Barnes LL, Bennett DA, Lacroix AZ, Larson EB, Cuccaro M, Mercado S, Dumitrescu L, Hohman TJ, Crane PK (2022) Cognitive domain harmonization and cocalibration in studies of older adults. *Neuropsychology*. doi: 10.1037/neu0000835.

[25] Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR (2010) Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* **375**, 895-905.

[26] R Core Team (2020) *R: A language and environment for statistical computing*.

[27] Saykin AJ, Shen L, Foroud TM, Potkin SG, Swaminathan S, Kim S, Risacher SL, Nho K, Huentelman MJ, Craig DW, Thompson PM, Stein JL, Moore JH, Farrer LA, Green RC, Bertram L, Jack CR, Weiner MW; Alzheimer's Disease Neuroimaging Initiative (2010) Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans. *Alzheimers Dement* **6**, 265-273.

[28] Li Z, Shue F, Zhao N, Shinohara M, Bu G (2020) APOE2: Protective mechanism and therapeutic implications for Alzheimer's disease. *Mol Neurodegener* **15**, 63.

[29] Bangen KJ, Nation DA, Delano-Wood L, Weissberger GH, Hansen LA, Galasko DR, Salmon DP, Bondi MW (2015) Aggregate effects of vascular risk factors on cerebrovascular changes in autopsy-confirmed Alzheimer's disease. *Alzheimers Dement* **11**, 394-403.e1.

[30] Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, Davatzikos C, Desiderio L, Erus G, Fine LJ, Gaussoin SA, Harris D, Hsieh M-K, Johnson KC, Kimmel PL, Tamura MK, Launer LJ, Lerner AJ, Lewis CE, Martindale-Adams J, Moy CS, Nasrallah IM, Nichols LO, Oparil S, Ogrocki PK, Rahman M, Rapp SR, Reboussin DM, Rocco M V, Sachs BC, Sink KM, Still CH, Supiano MA, Snyder JK, Wadley VG, Walker J, Weiner DE, Whelton PK, Wilson VM, Woolard N, Wright JTJ, Wright CB (2019) Effect of intensive vs standard blood pressure control on probable dementia: A randomized clinical trial. *JAMA* **321**, 553-561.

[31] Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, Fine LJ, Goff DC, Johnson KC, Killeen AA, Lewis CE, Oparil S, Reboussin DM, Rocco M V, Snyder JK, Williamson JD, Wright JT, Whelton PK (2014) The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: The Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials* **11**, 532-546.

[32] Nasrallah IM, Pajewski NM, Auchus AP, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, Davatzikos C, Desiderio L, Doshi J, Erus G, Fine LJ, Gaussoin SA, Harris D, Johnson KC, Kimmel PL, Kurella Tamura M, Launer LJ, Lerner AJ, Lewis CE, Martindale-Adams J, Moy CS, Nichols LO, Oparil S, Ogrocki PK, Rahman M, Rapp SR, Reboussin DM, Rocco M V., Sachs BC, Sink KM, Still CH, Supiano MA, Snyder JK, Wadley VG, Walker J, Weiner DE, Whelton PK, Wilson VM, Woolard N, Wright JT, Wright CB, Williamson JD, Bryan RN (2019) Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA* **322**, 524.

[33] Guarino A, Favieri F, Boncompagni I, Agostini F, Cantone M, Casagrande M (2019) Executive functions in Alzheimer disease: A systematic review. *Front Aging Neurosci* **10**, 437.

[34] Lee W-J, Liao Y-C, Wang Y-F, Lin Y-S, Wang S-J, Fuh J-L (2020) Summative effects of vascular risk factors on the progression of Alzheimer disease. *J Am Geriatr Soc* **68**, 129-136.

[35] Nation DA, Preis SR, Beiser A, Bangen KJ, Delano-wood L, Lamar M, Libon DJ, Seshadri S, Wolf PA, Au R (2016) Pulse pressure is associated with early brain atrophy and cognitive decline modifying effects of APOE-ε4. *Alzheimer Dis Assoc Disord* **30**, 210-215.

[36] Oberlin LE, Manuck SB, Gianaros PJ, Ferrell RE, Muldoon MF, Jennings JR, Flory JD, Erickson KI (2015) Blood pressure interacts with APOE ε4 to predict memory performance in a midlife sample. *Neuropsychology* **29**, 693-702.

[37] Thambisetty M, Beason-Held L, An Y, Kraut MA, Resnick SM (2010) APOE ε4 genotype and longitudinal changes in cerebral blood flow in normal aging. *Arch Neurol* **67**, 93-98.

[38] McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, Seshadri S (2017) Blood pressure from mid- to late life and risk of incident dementia. *Neurology* **89**, 2447-2454.

[39] Glodzik L, Rusinek H, Pirraglia E, McHugh P, Tsui W, Williams S, Cummings M, Li Y, Rich K, Randall C, Mosconi L, Osorio R, Murray J, Zetterberg H, Blennow K, de Leon M

(2014) Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly. *Neurobiol Aging* **35**, 64-71.

[40] Qiu C, Winblad B, Fratiglioni L (2005) The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* **4**, 487-499.

[41] Nation DA, Edmonds EC, Bangen KJ, Delano-Wood L, Scanlon BK, Han SD, Edland SD, Salmon DP, Galasko DR, Bondi MW (2015) Pulse pressure in relation to tau-mediated neurodegeneration, cerebral amyloidosis, and progression to dementia in very old adults. *JAMA Neurol* **72**, 546-553.

[42] Ma Y, Song A, Viswanathan A, Blacker D, Vernooij MW, Hofman A, Papatheodorou S (2020) Blood pressure variability and cerebral small vessel disease: A systematic review and meta-analysis of population-based cohorts. *Stroke* **51**, 82-89.

[43] Tully PJ, Yano Y, Launer LJ, Kario K, Nagai M, Mooijaart SP, Claassen JAHR, Lattanzi S, Vincent AD, Tzourio C, Variability in Blood Pressure and Brain Health Consortium (2020) Association between blood pressure variability and cerebral small-vessel disease: A systematic review and meta-analysis. *J Am Heart Assoc* **9**, e013841.

[44] Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, DeCarli C, Brown TR, Mayeux R (2010) Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol* **67**, 564-569.

[45] Sible IJ, Bangen KJ, Blanken AE, Ho JK, Nation DA (2021) Antemortem visit-to-visit blood pressure variability predicts cerebrovascular lesion burden in autopsy-confirmed Alzheimer's disease. *J Alzheimers Dis* **83**, 65-75.

[46] Ma Y, Blacker D, Viswanathan A, van Veluw SJ, Bos D, Vernooij MW, Hyman BT, Tzourio C, Das S, Hofman A (2021) Visit-to-visit blood pressure variability, neuropathology, and cognitive decline. *Neurology* **96**, e2812 LP-e2823.

[47] Saji N, Toba K, Sakurai T (2016) Cerebral small vessel disease and arterial stiffness: Tsunami effect in the brain? *Pulse* **3**, 182-189.

[48] Nagai M, Hoshide S, Nishikawa M, Masahisa S, Kario K (2014) Visit-to-visit blood pressure variability in the elderly: Associations with cognitive impairment and carotid artery remodeling. *Atherosclerosis* **233**, 19-26.

[49] Kitamura J, Nagai M, Ueno H, Ohshita T, Kikumoto M, Toko M, Kato M, Dote K, Yamashita H, Kario K (2020) The insular cortex, alzheimer disease pathology, and their effects on blood pressure variability. *Alzheimer Dis Assoc Disord* **34**, 282-291.

[50] Rothwell PM, Howard SC, Dolan E, Brien EO, Dobson JE, Dahlöf B, Poulter NR, Sever PS (2010) Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* **9**, 469-480.

[51] Webb AJ, Fischer U, Mehta Z, Rothwell PM (2010) Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: A systematic review and meta-analysis. *Lancet* **375**, 906-915.

[52] Nagai M, Kario K (2021) Visit-to-visit office blood pressure variability revisited in SPRINT. *J Clin Hypertens* **23**, 1526-1528.

[53] Nagai M, Kato M, Dote K (2021) Visit-to-visit blood pressure variability in mild cognitive impairment: A possible marker of Alzheimer's disease in the SPRINT study? *J Clin Hypertens* **23**, 2129-2132.