Published in final edited form as:

Dement Geriatr Cogn Disord. 2018 ; 45(1-2): 66–78. doi:10.1159/000486955.

Associations of Pulse and Blood Pressure with Hippocampal Volume by APOE and Cognitive Phenotype: The Alzheimer's Disease Neuroimaging Initiative (ADNI)

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Abstract

Background: It is increasingly evident that high blood pressure can promote reduction in global and regional brain volumes. While these effects may preferentially affect the hippocampus, reports are inconsistent.

Methods: Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we examined the relationships of hippocampal volume to pulse pressure (PPR) and systolic (SBP) and diastolic (DBP) blood pressure according to apolipoprotein (APOE) ε4 positivity and cognitive status. The ADNI data included 1,308 participants: Alzheimer disease (AD = 237), late mild cognitive impairment (LMCI = 454), early mild cognitive impairment (EMCI = 254), and cognitively normal (CN = 365), with up to 24 months of follow-up.

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Author Contributions

J.S.N., R.F.G., and T.O.O. conceived the study. J.S.N. and T.O.O. cleaned and analyzed the data. All authors contributed to the study design and strategies for analyses. The manuscript was written by J.S.N, T.V.F, O.N., R.F.G., and T.O.O., and all authors participated in the review of the final paper. The ADNI collaborators were responsible for the collection and processing of the data.</author_notes>

Disclosure Statement

The authors have no commercial associations that might be a conflict of interest in relation to this article.

Results: Higher quartiles of PPR were significantly associated with lower hippocampal volumes (Q1 vs. Q4, $p = 0.034$) in the CN and AD groups, but with increasing hippocampal volume (Q1, $p = 0.008$; Q2, $p = 0.020$; Q3, $p = 0.017$; Q4 = reference) in the MCI groups. In adjusted stratified analyses among non-APOE $\epsilon 4$ carriers, the effects in the CN (Q1 vs. Q4, $p = 0.006$) and EMCI groups (Q1, $p = 0.002$; Q2, $p = 0.013$; Q3, $p = 0.002$; Q4 = reference) remained statistically significant. Also, higher DBP was significantly associated with higher hippocampal volume ($p = 0.002$) while higher SBP was significantly associated with decreasing hippocampal volume in the EMCI group ($p = 0.015$).

Conclusion: Changes in PPR, SBP, and DBP differentially influenced hippocampal volumes depending on the cognitive and APOE genotypic categories.

Keywords

Hippocampal volume; Pulse pressure; Blood pressure; Alzheimer disease; APOE $\epsilon 4$

Introduction

High blood pressure in midlife has been linked to memory loss and reduced cognitive skills in late life [1, 2]. Given that the brain requires a certain perfusion threshold for optimal function, hypertension-related vascular damage including widespread arteriolosclerosis can restrict blood flow to the brain, thereby causing neurodegeneration and consequent memory loss [3–5]. Together, this evidence suggests that hypertension is an important risk factor for cognitive decline and dementia [6–9].

Located in the brain's medial temporal lobe, the hippocampus is one of the most age-sensitive brain regions involved in cognition. While neurodegeneration and shrinkage of the hippocampus are common in cognitively impaired older adults, promoters of this shrinkage are poorly understood [10]. Because the hippocampus is responsible for long-term memory formation, damage or atrophy can result in anterograde and retrograde memory impairments [11].

Published reports have shown that elevated blood pressure can promote reduction in global and/or regional brain volumes [12–15], while low blood pressure may promote losses in the gray matter. Particularly, high blood pressure levels in midlife tend to correlate with regional brain atrophy, including the hippocampus, in late life [2, 16]. However, these results are inconsistent and structured studies on the relationship of blood pressure metrics to regional changes in brain volume and the hippocampus are limited. Interestingly, age-related arterial stiffening measured by brachial artery pulse pressure (PPR) has been linked to cerebral atrophy and cognitive deterioration [17]. While both systolic (SBP) and diastolic (DBP) blood pressure increase with age up to around the 6th decade in life [18], subsequent decreases in DBP alone result in widening of PPR [8]. Because increasing PPR can further endorse widespread atherosclerosis and increased arterial stiffness implicated in neurodegeneration, it may also influence brain volume in regions of interest. Therefore, because PPR is a composite measure of both DBP and SBP, it may inform the inconsistencies observed in the relationship of blood pressure to hippocampal volume.

The $\epsilon 4$ allele of the apolipoprotein (APOE) gene is an acknowledged genetic risk factor for Alzheimer disease (AD) [19–23]. Though the APOE gene regulates the levels of the multifunctional lipid transporter APOE, its relationships to levels of PPR, DBP, and SBP, and their combined effects on the hippocampus are unknown. Therefore, to test our primary hypothesis that PPR, DBP, and SBP influence changes in hippocampal volume, and to determine whether the effects are modified by APOE $\epsilon 4$ and cognitive status, especially in the mild cognitive impairment (MCI) prodromal stage of AD phenotype, we analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods

The ADNI was designed to improve methods for clinical trials by providing a large, publicly available database to inform cognitive deterioration leading to AD at an early stage, and mark its progress through biomarkers [24]. This landmark study, which began in October 2004, has made major contributions to AD research. In part, the goal of ADNI was to test whether neuroimaging, other biological markers, clinical measures, and neuropsychological assessments can be combined to inform cognitive deterioration from cognitively normal (CN) to MCI and AD. Participants in the ADNI study underwent baseline and periodic physical and neurological examinations and standardized neuropsychological assessments, and provided biological samples (blood, urine, and, in a subset, cerebrospinal fluid). The physical examinations included measurements of height, weight, SBP, and DBP. Seated brachial artery SBP and DBP were obtained using the standard of care approach, and PPR was calculated as SBP minus DBP [25].

The ADNI study also provided a rich set of magnetic resonance imaging (MRI), and several clinical and neuropsychological measures acquired from CN, MCI, and AD participants [26, 27]. The study followed participants over the course of 3 years with up to an additional 6 years of data acquired in the ADNI-GO and ADNI-2 projects [28]. Data obtained from the ADNI database (<http://adni.loni.usc.edu>) were downloaded around December 10, 2012, and 1,308 participants were isolated for these analyses: AD ($n = 237$), late MCI (LMCI; $n = 454$), early MCI (EMCI; $n = 254$), and CN ($n = 365$). We excluded MRI data for the 18-month visit from our analyses because of missing blood pressure values. Although blood pressure was assessed every 6 months for 24 months, and then yearly thereafter for 72 months, our analyses were limited to 24 months due to low numbers of AD participants with blood pressure data at the later follow-up times.

MCI participants had Mini-Mental State Examination (MMSE) [29] scores between 24 and 30 (inclusive), objective memory loss measured according to education-adjusted scores on the Wechsler Memory Scale Logical Memory II [30], Clinical Dementia Rating of 0.5 [31], absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and absence of dementia. Mild AD participants had MMSE scores between 20 and 26 (inclusive), Clinical Dementia Rating of 0.5 or 1.0, and met the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD.

Details of the ADNI study, including the acquisition of MRI, have been previously published [24, 26, 27]. For the current study, we selected participants who had brain MRI scans at baseline and at 12 and 24 months, as well as 2-year follow-up clinical evaluations. Because most of the participants in the ADNI study had MRI scans, the baseline visit for each participant was defined as the time of the first MRI scan. Prior to enrollment of participants, written informed consent forms approved by the participating Institutional Review Boards were used to inform and to obtain consent from prospective participants.

Statistical Analysis

We described baseline clinical and demographic characteristics of the participants by cognitive groups and quartiles of PPR (lowest = Q1 and highest = Q4), using means or proportions (Tables 1, 2). Initial analyses included a test of significance using analysis of variance (ANOVA) for continuous variables and a χ^2 test for categorical variables. To test our primary hypothesis that PPR influence changes in hippocampal volume and to determine whether the effects are modified by APOE ϵ 4 within baseline-defined phenotypic cognitive categories, we conducted a linear mixed effect model, using all available data. We then determined the least square means, estimates, and standard errors of the estimates for the association of hippocampal volume with PPR. To discount the effects of SBP, DBP, baseline hippocampal volume, education, gender, age, body mass index, and blood pressure, our final models included adjustments for these independent variables. To test the independent effects of SBP and DBP on hippocampal volume, we constructed additional independent linear mixed effects models using continuous blood pressure measures (SBP and DBP) stratified by cognitive status and APOE ϵ 4 carrier status. All p values were two-tailed, with $p < 0.05$ considered as statistically significant, and confidence intervals were computed at a 95% confidence level. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) [32] and Statistical Analysis and Graphics (NCSS 9.0.7, Kaysville, UT, USA) [33].

Results

Study Cohort

Using means for continuous measures and proportions for categories, the demographic characteristics of the participants by AD status at baseline and at 6, 12, and 24 months are presented in Table 1. Overall, AD and CN participants were similar in mean age, but significantly older than those in the EMCI group ($p < 0.001$). The sample consisted of more men except for the CN group, where the proportion of men equaled that of women. Both the EMCI and CN groups tended to be more educated (EMCI = 16.02 ± 2.63 years; CN = 16.20 ± 2.76 years). Both the MMSE and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) significantly correlated with cognitive diagnostic categories ($p < 0.001$), and hippocampal volume decreased across the cognitive spectrum – lowest in AD and highest in CN ($p < 0.001$). Whereas mean SBP and DBP were not statistically different across the groups at baseline, mean PPR showed significant differences across the cognitive groups, with the AD group having a higher mean PPR (60.90 ± 16.51) compared to the LMCI (58.80 ± 14.46), EMCI (58.70 ± 14.05), and CN (56.61 ± 14.74) groups, respectively. As anticipated, the mean hippocampal volume differed ($p < 0.001$) among cognitive groups

– lowest in the AD group ($5,726.54 \pm 1,003.26$) compared to the LMCI ($6,491.91 \pm 1,107.01$), EMCI ($7,308.37 \pm 1,027.11$), and CN ($7,361.12 \pm 920.69$) groups. Across cognitive groups, the trends in age, gender, MMSE and ADAS-Cog score, blood pressure, and hippocampal volume remained similar at 6, 12, and 24 months. Noticeably, the mean PPR remained significantly higher for AD (61.95 mm Hg) compared to LMCI (58.47 mm Hg), EMCI (52.00 mm Hg), and CN (58.69 mm Hg) groups at baseline. Notably, the increases observed with PPR paralleled the decreases in hippocampal volume among CN participants at 6, 12, and 24 months in the overall sample. Similar to baseline trends, mean hippocampal volume remained different at 24 months ($p < 0.001$) – significantly lower in the AD group ($5,186.46 \pm 1,121.39$) compared to the LMCI ($6,087.66 \pm 1,133.60$), EMCI ($7,101.87 \pm 1,093.24$), and CN ($7,033.94 \pm 959.11$) groups.

Hippocampal Volume and Quartiles of PPR

Table 3 shows the least square means, estimates, standard errors, and p values for the association between hippocampal volume and PPR (Q1 [lowest], Q2, Q3, Q4 [highest]) by cognitive status and APOE $\epsilon 4$ carrier status. In the combined sample, escalating quartiles of PPR were associated with decreasing hippocampal volume in the CN and AD groups, with Q1 being significantly higher than Q4 (reference) (both $p = 0.034$) (Table 3). However, in the EMCI group, increasing quartiles of PPR promoted statistically significant increases in hippocampal volume (Q1, $p = 0.008$; Q2, $p = 0.020$; Q3, $p = 0.017$; Q4 = reference). We did not observe a significant association of PPR with hippocampal volume in the LMCI group (all $p < 0.05$).

In stratified analyses restricted to APOE $\epsilon 4$ -negative participants, and adjusted for covariates, increasing PPR maintained a statistically significant association with decreasing hippocampal volume in the CN group (Q1 vs. Q4: estimate = 134.49 ± 48.73 , $p = 0.006$) but not in the AD group ($p = 0.246$). Consistent with our findings in the overall EMCI group, stratified analyses restricted to APOE $\epsilon 4$ -negative MCI participants showed that increasing quartiles of PPR was significantly associated with increasing hippocampal volume. These associations remained statistically significant after discounting the effects of SBP, DBP, baseline hippocampal volume, education, gender, age, BMI, and hypertension (least square means: Q1 = $7,271.78 \pm 31.36$, $p = 0.002$; Q2 = $7,350.28 \pm 28.35$, $p = 0.013$; Q3 = $7,347.58 \pm 25.05$, $p = 0.002$; Q4 = $7,487.27 \pm 40.55$, reference).

Hippocampal Volume and Blood Pressure

Figure 1 shows estimates and 95% confidence intervals for the differential effects of blood pressure on hippocampal volume by cognitive and APOE $\epsilon 4$ carrier status after adjusting for baseline hippocampal volume, education, gender, age, body mass index, and hypertension. Our results showed a U-shaped relationship between SBP and hippocampal volume. Strikingly, increasing SBP was associated with decreasing hippocampal volume in EMCI non-APOE $\epsilon 4$ carriers (estimate = 3.995 , SE = 1.614 , $p = 0.015$) but potentiated increased hippocampal volume (estimate = 2.901 , SE = 1.265 , $p = 0.022$) among CN non-APOE $\epsilon 4$ carriers. In similarly adjusted models (Fig. 2), DBP showed an inverse U-shaped relationship with hippocampal volume. Similar to PPR effects, increasing DBP promoted increasing hippocampal volume among EMCI non-APOE $\epsilon 4$ carriers (estimate = 6.916 , SE = 2.141 , p

= 0.002) and decreasing hippocampal volume in the CN group (estimate = -2.710, SE = 1.421, $p = 0.057$).

Discussion

The most significant findings from these analyses are that the relationship of blood pressure to hippocampal volume is not static, but rather dynamic across the cognitive spectrum, and is influenced by APOE $\epsilon 4$ genotype status. Remarkably, the MCI prodromal stage, an important transition point in cognitive trajectory, appeared vulnerable to changes in PPR, SBP, and DBP. Importantly, the PPR effects may more accurately reflect the dynamic relationships of blood pressure to hippocampal volume, especially given the opposing directionality of SBP and DBP effects on hippocampal volume.

Hypertension in midlife has been shown to increase dementia risk in late life [1, 2]. These effects can preferentially affect the temporal and frontal lobe brain volumes, and particularly the hippocampus [34]. A recent meta-analysis of data from four studies found that hypertension is associated with lower hippocampal volume [15]. However, these studies did not examine the blood pressure metrics most closely associated with brain volume reductions within cognitive categories or elucidate the differential effects of the APOE gene. Because DBP and SBP effects on cognitive phenotype and endophenotypes are inconsistent across multiple studies, other more relevant measures of their relationships to neurodegeneration warrants investigation.

Consistent with our a priori hypothesis for this study, increasing PPR promoted reduced hippocampal volume in CN non-APOE $\epsilon 4$ carriers. An additional important observation from our analyses is that increasing PPR conversely promoted increases in hippocampal volume in EMCI non-APOE $\epsilon 4$ carriers. One possible explanation for the latter effect is that increasing PPR at the EMCI prodromal stage may be an adaptive mechanism to increase brain perfusion and combat declining vascular compliance. Unfortunately, while this increase in PPR may transiently benefit hippocampal volume and the brain at the EMCI transitional stage, sustained increase is likely to further increase vascular resistance and compromise brain perfusion. Therefore, the decreasing hippocampal volume observed with increasing PPR in the CN and AD groups appears logical. Together, our results are significant in that they inform an important gap in the literature, using the robust ADNI data. Indeed, since widening PPR pressure represents either increased SBP and or decreased DBP, it may provide an insight into the inconsistency of the relationship of blood pressure to neurodegeneration.

Emerging evidence now suggests that the relationship of PPR to cognitive decline may be modified by APOE genotypes [35]. However, the explanations for these effects are unclear. Also, whether high blood pressure-related vascular disease is a cause of AD, merely coexists with AD, or worsens dementia needs clarity. Like SPB, PPR increases with age while changes in DBP increase less, or in fact decrease, resulting in isolated systolic hypertension in the aged. It is controversial whether blood pressure metrics are associated with hippocampal atrophy [36]. Because both high and low blood pressure may negatively affect cognition [37] and hippocampal volume, it is critical to identify a composite measure of both

DBP and SBP. Given the paucity of data on the relationship of PPR to hippocampal volume, our observation that the combined effects of PPR and APOE genotype status may better inform the relationship of vascular changes to neurodegeneration is an important addition to the literature.

Though the exact mechanism linking PPR to reduced hippocampal volume in the CN and AD groups needs more nuanced understanding, preferential global and regional effects of blood pressure on the brain, including the hippocampus, have been described [15]. These effects may be mediated, in part, by hypertension-related arteriolosclerosis, lower blood flow, and consequent hypoperfusion in the frontal and hippocampal brain regions [15]. Importantly, loss of vascular elasticity and increased vascular resistance, caused in part by increased vascular amyloid deposit and potentially microbleed [38–41], may mediate such effects. This view is supported by evidence showing that increased arterial stiffening predicts longitudinal change in cerebral amyloid retention [42, 43]. In fact, increasing evidence now suggests that arterial pulsatility contributes to the glymphatic system and waste clearance (including amyloid- β) from the central nervous system [44–48]. Therefore, disturbance of this system may also promote neurodegeneration [49, 50]. Independently, the presence of increased brain amyloid plaques in the hippocampus of decedents with premortem elevated SBP has also been observed [51]. Because both the prefrontal cortex and hippocampus receive afferent and send efferent projections to other brain regions, its sensitivity to blood pressure dynamics [52] may have downstream effects on other brain regions as well.

Both SBP and DBP likely contribute to CVD effects on neurodegeneration, but our results indicate that their effects may be conversely related across categories of cognition. In non- $\epsilon 4$ carrier MCI participants, increasing SBP and DBP are associated with decreasing and increasing hippocampal volumes, respectively. Consistent with our findings, den Heijer et al. [16] showed that global brain atrophy was associated with prior history of high and low DBP. In particular, high DBP obtained 5 years before brain MRI predicted more hippocampal atrophy, while low DBP in treated hypertensives was associated with more severe atrophy [16]. Also, men with untreated hypertension in midlife have been reported to have greater hippocampal atrophy than controls [1, 2], while higher CVD risks are associated with cortical thinning in hippocampal subregions CA2/3/dentate gyrus [36]. Given that AD pathology begins ~15 years before the clinical phenotype, the observed effects of SBP in the CN group may also be an adaptive mechanism prior to a yet undetermined blood pressure threshold. As in previous reports of a nonlinear (U-shaped) relationship of blood pressure to cognitive performance in older adults [53], a U-shaped relationship of SBP and DBP to hippocampal volume was also evident in our analyses. These findings are congruent with reports of inverse relationships of blood pressure to concentrations of hippocampal glutamate (a crucial prerequisite of memory formation) [54] and to AD diagnosis years after blood pressure became elevated [55]. However, our study is unique in that it has the advantage of a large sample size, longitudinal follow-up, and stratification into cognitive and APOE genotype categories.

In conclusion, our observations from these analyses suggest that PPR may differentially associate with hippocampal volume, depending on cognitive phenotypic category and APOE $\epsilon 4$ status. While CN brains may endure a temporally adaptive increase in SBP to increase

perfusion, sustained increase may eventually catalyze transition from CN to EMCI, and potentially to AD. Confirmation of these observations in future studies may enhance strategies to attenuate transition from MCI to AD [56, 57].

Strengths and Limitations

The prospective, longitudinal study design, large sample size, and MRI data are strengths of this study. Additional important strengths include the use of a multilevel approach conceptualized as regression models occurring at different levels [58] while accounting for dependencies in nested data. This approach enhanced the understanding of change over time and factors associated with change while accommodating both fixed and random effects.

Potential bias resulting from missing data, case selection factors, measurement errors, and inadequacy of model fit, as well as chance associations, must be considered. Because blood pressure was not an a priori outcome in the ADNI study, its assessment did not employ a unified procedure, but rather followed current clinical standards. While we considered previous history of hypertension in our analyses, we did not directly discount treatment effects. The lack of association in APOE $\epsilon 4$ carriers may relate to the significant effects of $\epsilon 4$ and the small sample size, and therefore requires further study.

Acknowledgments

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data, but did not participate in the analysis or writing of this report. Data collection and sharing for this project was funded by the ADNI (National Institutes of Health, NIH grant U01 AG024904). Details of the ADNI co-sponsors have been previously published [24, 26, 27].

Funding Sources

This work was supported by the National Institute on Aging at the NIH (grant U01 AG024904 to M.W. Weiner of the ADNI, and grants 5R01AG031517–2 and 5R01AG045058 to T.O. Obisesan) and, in part, by the National Center for Advancing Translational Sciences/NIH through the Clinical and Translational Science Award Program (CTSA; grant UL1TR000101). The funders had no role in the design, data collection, and interpretation of this study.

References

1. Korf ES, White LR, Scheltens P, Launer LJ: Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. *Hypertension* 2004; 44: 29–34. [PubMed: 15159381]
2. Korf ES, White LR, Scheltens P, Launer LJ: Midlife blood pressure and the risk of hippocampal atrophy. *Hypertension* 2004; 44: 29–34. [PubMed: 15159381]
3. Mercado JM, Hilsabeck R: Untreated hypertension can lead to memory loss by cutting down on blood flow to the brain. *Neurology* 2005; 64:E28–E29. [PubMed: 15851715]
4. Davis RN, Massman PJ, Doody RS: Effects of blood pressure on neuropsychological functioning in Alzheimer's disease. *Arch Clin Neuropsychol* 2003; 18: 19–32. [PubMed: 14591475]
5. Obisesan TO, Gillum RF, Johnson S, Umar N, Williams D, Bond V, et al.: Neuroprotection and neurodegeneration in Alzheimer's disease: role of cardiovascular disease risk factors, implications for dementia rates, and prevention with aerobic exercise in African Americans. *Int J Alzheimers Dis* 2012; 2012: 568382. [PubMed: 22577592]
6. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, et al.: Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol* 2014; 71: 1218–1227. [PubMed: 25090106]

7. Obisesan TO, Obisesan OA, Martins S, Alamgir L, Bond V, Maxwell C, et al.: High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: the Third National Health and Nutrition Examination Survey. *J Am Geriatr Soc* 2008; 56: 501–509. [PubMed: 18179496]
8. de Oliveira FF, Chen ES, Smith MC, Bertolucci PH: Associations of blood pressure with functional and cognitive changes in patients with Alzheimer's Disease. *Dement Geriatr Cogn Disord* 2016; 41: 314–323. [PubMed: 27398980]
9. Razay G, Williams J, King E, Smith AD, Wilcock G: Blood pressure, dementia and Alzheimer's disease: the OPTIMA longitudinal study. *Dement Geriatr Cogn Disord* 2009; 28: 70–74. [PubMed: 19648748]
10. Raz N, Daugherty AM, Bender AR, Dahle CL, Land S: Volume of the hippocampal subfields in healthy adults: differential associations with age and a pro-inflammatory genetic variant. *Brain Struct Funct* 2015; 220: 2663–2674. [PubMed: 24947882]
11. Rempel-Clower NL, Zola SM, Squire LR, Amaral DG: Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *J Neurosci* 1996; 16: 5233–5255. [PubMed: 8756452]
12. Fotuhi M, Do D, Jack C: Modifiable factors that alter the size of the hippocampus with ageing. *Nat Rev Neurol* 2012; 8: 189–202. [PubMed: 22410582]
13. Muller M, van der Graaf Y, Visseren FL, Vlek AL, Mali WP, Geerlings MI, et al.: Blood pressure, cerebral blood flow, and brain volumes. The SMART-MR study. *J Hypertens* 2010; 28: 1498–1505. [PubMed: 20453669]
14. Nagai M, Hoshida S, Ishikawa J, Shimada K, Kario K: Ambulatory blood pressure as an independent determinant of brain atrophy and cognitive function in elderly hypertension. *J Hypertens* 2008; 26: 1636–1641. [PubMed: 18622243]
15. Beauchet O, Celle S, Roche F, Bartha R, Montero-Odasso M, Allali G, et al.: Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. *J Hypertens* 2013; 31: 1502–1516. [PubMed: 23811995]
16. den Heijer T, Launer L, Prins N, Van Dijk E, Vermeer S, Hofman A, et al.: Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 2005; 64: 263–267. [PubMed: 15668423]
17. Nation DA, Preis SR, Beiser A, Bangen KJ, Delano-Wood L, Lamar M, et al.: Pulse pressure is associated with early brain atrophy and cognitive decline. *Alzheimer Dis Assoc Disord* 2016; 30: 210–215. [PubMed: 27556935]
18. Qiu C, Winblad B, Viitanen M, Fratiglioni L: Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older. *Stroke* 2003; 34: 594–599. [PubMed: 12624277]
19. Mahley RW: Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* 1988; 240: 622. [PubMed: 3283935]
20. Davignon J, Gregg RE, Sing CF: Apolipoprotein E polymorphism and atherosclerosis. *Arterioscler Thromb Vasc Biol* 1988; 8: 1–21.
21. Roses AD: Apolipoprotein E and Alzheimer's disease: a rapidly expanding field with medical and epidemiological consequences. *Ann NY Acad Sci* 1996; 802: 50–57. [PubMed: 8993484]
22. Bender AR, Raz N: Age-related differences in memory and executive functions in healthy APOE ϵ 4 carriers: the contribution of individual differences in prefrontal volumes and systolic blood pressure. *Neuropsychologia* 2012; 50: 704–714. [PubMed: 22245009]
23. Moffat S, Szekely C, Zonderman A, Kabani N, Resnick S: Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. *Neurology* 2000; 55: 134–136. [PubMed: 10891924]
24. Wyman BT, Harvey DJ, Crawford K, Bernstein MA, Carmichael O, Cole PE, et al.: Standardization of analysis sets for reporting results from ADNI MRI data. *Alzheimers Dement* 2013; 9: 332–337. [PubMed: 23110865]
25. Nation DA, Edmonds EC, Bangen KJ, Delano-Wood L, Scanlon BK, Han SD, 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. [PubMed: 25822631]

26. Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W, et al.: Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement* 2005; 1: 55–66. [PubMed: 17476317]
27. Weiner MW, Aisen PS, Jack CR, Jagust WJ, Trojanowski JQ, Shaw L, et al.: The Alzheimer's disease neuroimaging initiative: progress report and future plans. *Alzheimers Dement* 2010; 6: 202–211. e7. [PubMed: 20451868]
28. Jack CR, Bernstein MA, Borowski BJ, Gunter JL, Fox NC, Thompson PM, et al.: Update on the magnetic resonance imaging core of the Alzheimer's disease neuroimaging initiative. *Alzheimers Dement* 2010; 6: 212–220. [PubMed: 20451869]
29. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state:" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–198. [PubMed: 1202204]
30. Wechsler Memory Scale, ed 4 (WMS-IV). New York, Psychological Corporation, 2009.
31. Morris JC: Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr* 1997; 9: 173–176. [PubMed: 9447441]
32. SAS Institute: SAS/IML 9.3 User's Guide. SAS Institute, 2011.
33. Hintze J: NCSS 9 Statistical Software. Kaysville, NCSS, 2013.
34. Petrovitch H, White L, Izmirlian G, Ross G, Havlik R, Markesbery W, et al.: Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. *Neurobiol Aging* 2000; 21: 57–62. [PubMed: 10794849]
35. McFall GP, Wiebe SA, Vergote D, Westaway D, Jhamandas J, Bäckman L, et al.: ApoE and pulse pressure interactively influence level and change in the aging of episodic memory: protective effects among e2 carriers. *Neuropsychology* 2015; 29: 388. [PubMed: 25436424]
36. Donix M, Scharf M, Marschner K, Werner A, Sauer C, Gerner A, et al.: Cardiovascular risk and hippocampal thickness in Alzheimer's disease. *Int J Alzheimers Dis* 2013; 2013: 108021. [PubMed: 24228185]
37. Robertson AD, Messner MA, Shirzadi Z, Kleiner-Fisman G, Lee J, Hopyan J, et al.: Orthostatic hypotension, cerebral hypoperfusion, and visuospatial deficits in Lewy body disorders. *Parkinsonism Relat Disord* 2016; 22: 80–86. [PubMed: 26639982]
38. Schneider JA: High blood pressure and microinfarcts: a link between vascular risk factors, dementia, and clinical Alzheimer's disease. *J Am Geriatr Soc* 2009; 57: 2146–2147. [PubMed: 20121957]
39. Sepehry AA, Lang D, Hsiung GY, Rauscher A: Prevalence of brain microbleeds in Alzheimer disease: a systematic review and meta-analysis on the influence of neuroimaging techniques. *AJNR Am J Neuroradiol* 2016; 37: 215–222. [PubMed: 26635284]
40. Shams S, Granberg T, Martola J, Charidimou A, Li X, Shams M, et al.: Cerebral microbleeds topography and cerebrospinal fluid biomarkers in cognitive impairment. *J Cereb Blood Flow Metab* 2017; 37: 1006–1013. [PubMed: 27178426]
41. Maxwell SS, Jackson CA, Paternoster L, Cordonnier C, Thijs V, Al-Shahi Salman R, et al.: Genetic associations with brain microbleeds: systematic review and meta-analyses. *Neurology* 2011; 77: 158–167. [PubMed: 21715706]
42. Hughes TM, Kuller LH, Barinas-Mitchell EJ, McDade EM, Klunk WE, Cohen AD, et al.: Arterial stiffness and β -amyloid progression in nondemented elderly adults. *JAMA Neurol* 2014; 71: 562–568. [PubMed: 24687165]
43. Hughes TM, Kuller LH, Barinas-Mitchell EJ, Mackey RH, McDade EM, Klunk WE, et al.: Pulse wave velocity is associated with β -amyloid deposition in the brains of very elderly adults. *Neurology* 2013; 81: 1711–1718. [PubMed: 24132374]
44. Ueno M, Chiba Y, Murakami R, Matsumoto K, Kawauchi M, Fujihara R: Blood-brain barrier and blood-cerebrospinal fluid barrier in normal and pathological conditions. *Brain Tumor Pathol* 2016; 33: 89–96. [PubMed: 26920424]
45. Asgari M, de Zelicourt D, Kurtcuoglu V: Glymphatic solute transport does not require bulk flow. *Sci Rep* 2016; 6: 38635. [PubMed: 27929105]

46. Kiviniemi V, Wang X, Korhonen V, Keinänen T, Tuovinen T, Autio J, et al.: Ultra-fast magnetic resonance encephalography of physiological brain activity – glymphatic pulsation mechanisms? *J Cereb Blood Flow Metab* 2016; 36: 1033–1045. [PubMed: 26690495]
47. Rivera-Rivera LA, Turski P, Johnson KM, Hoffman C, Berman SE, Kilgas P, et al.: 4D flow MRI for intracranial hemodynamics assessment in Alzheimer's disease. *J Cereb Blood Flow Metab* 2016; 36: 1718–1730. [PubMed: 26661239]
48. Weller RO, Djuanda E, Yow HY, Carare RO: Lymphatic drainage of the brain and the pathophysiology of neurological disease. *Acta Neuropathol* 2009; 117: 1–14. [PubMed: 19002474]
49. Peng W, Achariyar TM, Li B, Liao Y, Mestre H, Hitomi E, et al.: Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. *Neurobiol Dis* 2016; 93: 215–225. [PubMed: 27234656]
50. Saito S, Ihara M: Interaction between cerebrovascular disease and Alzheimer pathology. *Curr Opin Psychiatry* 2016; 29: 168–173. [PubMed: 26779861]
51. Crawford F, Suo Z, Fang C, Mullan M: Characteristics of the in vitro vasoactivity of β -amyloid peptides. *Exp Neurol* 1998; 150: 159–168. [PubMed: 9514824]
52. Beauchet O, Herrmann FR, Annweiler C, Kerlerouch J, Gosse P, Pichot V, et al.: Association between ambulatory 24-h blood pressure levels and cognitive performance: a cross-sectional elderly population-based study. *Rejuvenation Res* 2010; 13: 39–46. [PubMed: 20230277]
53. Obisesan TO: Hypertension and cognitive function. *Clin Geriatr Med* 2009; 25: 259–288. [PubMed: 19555872]
54. Westhoff T, Schubert F, Wirth C, Joppke M, Klär A, Zidek W, et al.: The impact of blood pressure on hippocampal glutamate and mnemonic function. *J Hum Hypertens* 2011; 25: 256–261. [PubMed: 20463749]
55. Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA: Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. *Arch Neurol* 2001; 58: 1640–1646. [PubMed: 11594923]
56. Li J, Wang Y, Zhang M, Xu Z, Gao C, Fang C, et al.: Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology* 2011; 76: 1485–1491. [PubMed: 21490316]
57. Deschaintre Y, Richard F, Leys D, Pasquier F: Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* 2009; 73: 674–680. [PubMed: 19720973]
58. Bell BA, Smiley W, Ene M, Blue G, Smiley W, Ene M, et al. (eds): *An Intermediate Primer to Estimating Linear Multilevel Models Using SAS® PROC MIXED*. Washington, SAS Global Forum Proceedings, 2014.

Fig. 1. Linear mixed effects estimates and 95% CI for the association of hippocampal volume and diastolic blood pressure by Alzheimer disease and APOE ε4 carrier status. EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer disease.

Fig. 2. Linear mixed effects estimates and 95% CI for the association of hippocampal volume and diastolic blood pressure by Alzheimer disease and APOE ε4 carrier status. EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer disease.

Table 1.

Participant characteristics by categories of Alzheimer disease status

	AD	LMCI	EMCI	CN	P value
<i>Baseline</i>	(<i>n</i> =237)	(<i>n</i> =454)	(<i>n</i> =254)	(<i>n</i> =365)	
Age, years	74.57 (7.85)	73.28 (7.47)	70.78 (7.20)	74.38 (5.63)	<0.001
Female	109 (45.99%)	179 (39.43%)	113 (44.49%)	181 (49.59%)	0.032
Education, years	15.69 (2.86)	15.81 (2.99)	16.02 (2.63)	16.20 (2.76)	0.109
MMSE	23.11 (2.06)	27.14 (1.82)	28.38 (1.52)	29.03 (1.15)	<0.001
ADAS 13	30.22 (8.19)	18.67 (6.51)	12.53 (5.16)	9.27 (4.34)	<0.001
Pulse pressure	60.90 (16.51)	58.80 (14.46)	58.70 (14.05)	56.61 (14.74)	0.006
SBP, mm Hg	134.70 (17.63)	132.94 (16.68)	132.16 (16.59)	133.34 (16.13)	0.387
DBP, mm Hg	73.80 (9.00)	74.13 (9.49)	73.45 (9.65)	73.74 (9.92)	0.829
Hippocampal volume, mL	5,726.54 (1,003.26)	6,491.91 (1,107.01)	7,308.37 (1,027.11)	7,361.12 (920.69)	<0.001
<i>6 months</i>	(<i>n</i> =165)	(<i>n</i> =381)	(<i>n</i> =149)	(<i>n</i> =289)	
Age, years	74.60 (7.65)	73.65 (7.59)	69.93 (7.09)	74.88 (5.46)	<0.001
Female	81 (49.09%)	149 (39.11%)	60 (40.27%)	136 (47.06%)	0.066
Education, years	14.88 (3.17)	15.81 (2.94)	16.11 (2.69)	16.30 (2.81)	<0.001
MMSE	22.56 (3.45)	26.69 (2.62)	28.08 (1.77)	28.98 (1.12)	<0.001
ADAS 13	30.61 (9.24)	19.28 (7.69)	12.20 (5.99)	9.03 (4.37)	<0.001
Pulse pressure	61.13 (15.05)	58.85 (14.18)	57.88 (15.63)	59.95 (14.80)	0.188
SBP, mm Hg	135.01 (16.81)	133.03 (16.68)	131.68 (18.41)	133.19 (15.73)	0.361
DBP, mm Hg	73.88 (9.79)	74.17 (10.34)	73.81 (9.31)	73.24 (10.00)	0.697
Hippocampal volume, mL	5,589.68 (1,112.62)	6,360.33 (1,126.10)	7,391.75 (993.88)	7,237.55 (914.51)	<0.001
<i>12 months</i>	(<i>n</i> =120)	(<i>n</i> =318)	(<i>n</i> =119)	(<i>n</i> =255)	
Age, years	74.66 (7.48)	73.63 (7.50)	69.96 (7.41)	75.10 (5.53)	<0.001
Female	57 (47.50%)	116 (36.48%)	57 (47.90%)	116 (45.49%)	0.040
Education, years	14.89 (3.07)	16.05 (2.96)	16.37 (2.65)	16.27 (2.77)	<0.001
MMSE	20.94 (4.41)	26.45 (2.88)	28.44 (1.64)	29.04 (1.26)	<0.001
ADAS 13	32.98 (10.21)	19.71 (8.45)	10.92 (5.64)	8.36 (4.48)	<0.001
Pulse pressure	62.74 (16.34)	59.46 (13.75)	57.74 (15.42)	60.05 (14.71)	0.062

	AD	LMCI	EMCI	CN	P value
SBP, mm Hg	137.06 (17.36)	133.62 (16.88)	131.56 (19.28)	132.88 (16.33)	0.072
DBP, mm Hg	74.32 (9.81)	74.16 (9.78)	73.82 (10.54)	72.82 (9.87)	0.367
Hippocampal volume, mL	5,410.16 (1161.08)	6,324.52 (1182.00)	7,346.97 (1032.99)	7,191.89 (921.79)	<0.001
<i>24 months</i>					
	(n=83)	(n=184)	(n=38)	(n=155)	
Age, years	74.37 (7.50)	73.93 (7.14)	70.59 (7.57)	75.51 (5.07)	<0.001
Female	45 (54.22%)	63 (34.24%)	17 (44.74%)	71 (45.81%)	0.014
Education, years	15.10 (2.86)	15.72 (3.02)	16.26 (2.46)	16.05 (2.86)	0.072
MMSE	18.94 (5.71)	25.35 (4.06)	28.16 (1.85)	28.98 (1.22)	<0.001
ADAS 13	38.33 (12.29)	22.26 (9.53)	11.42 (6.15)	9.19 (4.99)	<0.001
Pulse pressure	61.95 (17.31)	58.47 (15.27)	52.00 (10.09)	58.69 (13.54)	0.008
SBP, mm Hg	135.57 (19.40)	132.58 (15.77)	129.75 (9.95)	132.39 (15.59)	0.265
DBP, mm Hg	73.62 (9.62)	74.12 (9.52)	77.75 (8.40)	73.71 (9.74)	0.113
Hippocampal volume, mL	5,186.46 (1,121.39)	6,087.66 (1,133.60)	7,101.87 (1,093.24)	7,033.94 (959.11)	<0.001

Values are mean ($\pm$ SD) when appropriate. AD, Alzheimer disease; LMCI, late mild cognitive impairment; EMCI, early mild cognitive impairment; CN, cognitively normal (control group); MMSE, Mini-Mental State Examination; ADAS 13, Alzheimer's Disease Assessment Scale-cognitive subscale; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2.

Participant characteristics by quartiles of pulse pressure

Characteristics	Q1	Q2	Q3	Q4	<i>p</i> value
<i>Baseline</i>	(<i>n</i> =366)	(<i>n</i> =247)	(<i>n</i> =298)	(<i>n</i> =312)	
Age, years	73.31 (5.04)	73.77 (4.70)	75.50 (5.14)	76.65 (5.91)	<0.001
Female	156 (42.62%)	107 (43.32%)	136 (45.64%)	146 (46.79%)	0.687
SBP, mm Hg	117.69 (10.21)	129.04 (11.34)	136.73 (10.13)	149.14 (13.23)	<0.001
DBP, mm Hg	75.71 (9.27)	74.68 (11.03)	73.28 (9.88)	70.77 (10.45)	<0.001
Hippocampal volume, mL	7,415.22 (921.34)	7,514.57 (872.90)	7,186.18 (1032.18)	7,417.09 (883.55)	<0.001
MMSE	28.96 (1.14)	29.23 (1.01)	29.18 (1.13)	28.75 (1.33)	<0.001
ADAS 13	8.72 (4.10)	8.73 (4.35)	9.65 (3.91)	10.04 (4.27)	<0.001
Education, years	16.53 (2.65)	15.96 (3.03)	16.25 (2.62)	16.37 (2.96)	0.095
<i>6 months</i>	(<i>n</i> =250)	(<i>n</i> =185)	(<i>n</i> =209)	(<i>n</i> =218)	
Age, years	73.71 (5.57)	75.26 (4.75)	75.65 (5.60)	77.49 (4.87)	<0.001
Female	105 (42.00%)	78 (42.16%)	81 (38.76%)	100 (45.87%)	0.528
SBP, mm Hg	121.46 (8.83)	127.34 (11.50)	131.58 (10.06)	151.94 (12.64)	<0.001
DBP, mm Hg	78.04 (8.92)	72.66 (10.66)	68.30 (9.88)	72.88 (8.84)	<0.001
Hippocampal volume, mL	7,468.25 (1045.52)	7,219.00(810.11)	7,187.98 (873.19)	7,210.44 (957.42)	0.003
MMSE	29.05 (1.10)	28.80 (1.32)	29.06 (1.08)	29.13 (0.76)	0.015
ADAS 13	8.33 (4.05)	8.77 (4.04)	8.94 (3.61)	9.44 (4.07)	0.025
Education, years	16.77 (2.81)	15.89 (2.73)	16.40 (2.94)	15.90 (2.86)	0.002
<i>12 months</i>	(<i>n</i> =187)	(<i>n</i> =135)	(<i>n</i> =166)	(<i>n</i> =158)	
Age, years	73.56 (4.58)	75.00 (4.80)	77.06 (5.28)	78.16 (5.87)	<0.001
Female	71 (37.97%)	53 (39.26%)	60 (36.14%)	82 (51.90%)	0.017
SBP, mm Hg	119.77 (9.92)	124.79 (7.17)	133.53 (9.06)	150.90 (14.55)	<0.001
DBP, mm Hg	75.74 (9.33)	69.61 (7.00)	70.96 (8.79)	71.59 (11.49)	<0.001
Hippocampal volume, mL	7,398.86 (1003.58)	7,181.04 (686.94)	7,103.47 (820.48)	7,004.59 (1074.90)	<0.001
MMSE	29.40 (0.76)	29.32 (0.90)	29.13 (1.18)	28.90 (1.57)	<0.001
ADAS 13	7.61 (4.18)	8.69 (4.52)	8.83 (4.52)	9.62 (4.03)	<0.001
Education, years	16.63 (2.87)	16.64 (2.42)	15.73 (3.18)	15.93 (2.45)	0.006
<i>24 months</i>	(<i>n</i> = 127)	(<i>n</i> = 83)	(<i>n</i> = 114)	(<i>n</i> = 98)	
Age, years	74.70 (5.14)	75.50 (4.49)	75.63 (4.54)	77.16 (5.10)	0.003
Female	56 (44.09%)	31 (37.35%)	47 (41.23%)	46 (46.94%)	0.595
SBP, mm Hg	116.23 (9.97)	128.65 (9.96)	136.17 (10.81)	147.04 (9.05)	<0.001
DBP, mm Hg	72.68 (10.09)	73.85 (11.08)	72.83 (10.30)	71.21 (8.41)	0.354
Hippocampal volume, mL	6,981.19 (1261.49)	7,019.10 (648.61)	7,016.23 (756.09)	7,364.14 (933.95)	0.014
MMSE	29.06 (1.09)	29.15 (1.14)	28.97 (1.38)	29.18 (1.06)	0.567
ADAS 13	8.55 (4.85)	9.00 (4.70)	7.78 (4.12)	8.67 (4.11)	0.250
Education, years	16.84 (2.19)	15.35 (3.44)	15.83 (2.83)	15.86 (2.97)	0.001

Values are mean ($\pm$ SD) when appropriate. SBP, systolic blood pressure; DBP, diastolic blood pressure; MMSE, Mini-Mental State Examination; ADAS 13, Alzheimer's Disease Assessment Scale-cognitive subscale.

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Table 3.

Association of hippocampal volume and pulse pressure by Alzheimer disease and APOE ε4 carrier status

Group	APOE ε4	Quartiles	LS mean	Effect	Estimate	SE	p value
CN	Combined (<i>n</i> = 354)	Q1	7,287.75	Q1 vs. Q4	92.21	43.25	0.034
		Q2	7,219.21	Q2 vs. Q4	23.66	33.07	0.475
		Q3	7,202.01	Q3 vs. Q4	6.46	25.03	0.797
		Q4	7,195.55	Q4 (Ref.)			
	Negative (<i>n</i> = 257)	Q1	7,343.35	Q1 vs. Q4	134.49	48.73	0.006
		Q2	7,271.57	Q2 vs. Q4	62.71	36.91	0.091
		Q3	7,243.25	Q3 vs. Q4	34.39	27.83	0.218
		Q4	7,208.87	Q4 (Ref.)			
	Positive (<i>n</i> = 97)	Q1	7,129.32	Q1 vs. Q4	-26.80	90.05	0.767
		Q2	7,059.34	Q2 vs. Q4	-96.78	71.33	0.180
		Q3	7,076.95	Q3 vs. Q4	-79.17	54.28	0.150
		Q4	7,156.12	Q4 (Ref.)			
EMCI	Combined (<i>n</i> = 235)	Q1	7,326.43	Q1 vs. Q4	-160.19	58.61	0.008
		Q2	7,375.47	Q2 vs. Q4	-111.15	46.74	0.020
		Q3	7,398.75	Q3 vs. Q4	-87.87	36.16	0.017
		Q4	7,486.62	Q4 (Ref.)			
	Negative (<i>n</i> = 135)	Q1	7,271.78	Q1 vs. Q4	-215.48	65.15	0.002
		Q2	7,350.28	Q2 vs. Q4	-136.98	53.30	0.013
		Q3	7,347.58	Q3 vs. Q4	-139.68	42.19	0.002
		Q4	7,487.27	Q4 (Ref.)			
	Positive (<i>n</i> = 100)	Q1	7,417.31	Q1 vs. Q4	-51.29	113.71	0.655
		Q2	7,471.94	Q2 vs. Q4	3.34	87.28	0.970
		Q3	7,458.52	Q3 vs. Q4	-10.08	64.62	0.877
		Q4	7,468.60	Q4 (Ref.)			
LMCI	Combined (<i>n</i> = 434)	Q1	6,353.06	Q1 vs. Q4	-17.47	44.68	0.696
		Q2	6,329.41	Q2 vs. Q4	-41.12	33.84	0.225
		Q3	6,336.13	Q3 vs. Q4	-34.41	26.32	0.192
		Q4	6,370.53	Q4 (Ref.)			
	Negative (<i>n</i> = 189)	Q1	6,631.34	Q1 vs. Q4	-56.39	57.04	0.325
		Q2	6,604.38	Q2 vs. Q4	-83.35	44.34	0.062
		Q3	6,649.69	Q3 vs. Q4	-38.04	35.08	0.280
		Q4	6,687.73	Q4 (Ref.)			
	Positive (<i>n</i> = 245)	Q1	6,142.06	Q1 vs. Q4	29.54	68.20	0.666
		Q2	6,116.51	Q2 vs. Q4	3.99	50.40	0.937

Group	APOE $\epsilon 4$	Quartiles	LS mean	Effect	Estimate	SE	<i>p</i> value
AD		Q3	6,090.43	Q3 vs. Q4	-22.09	38.45	0.566
		Q4	6,112.52	Q4 (Ref.)			
	Combined (<i>n</i> = 196)	Q1	5,580.87	Q1 vs. Q4	130.09	60.75	0.034
		Q2	5,519.20	Q2 vs. Q4	68.42	47.02	0.148
		Q3	5,497.06	Q3 vs. Q4	46.29	37.60	0.221
		Q4	5,450.78	Q4 (Ref.)			
	Negative (<i>n</i> = 55)	Q1	5,895.68	Q1 vs. Q4	140.19	118.74	0.246
		Q2	5,856.62	Q2 vs. Q4	101.13	92.21	0.281
		Q3	5,791.63	Q3 vs. Q4	36.14	76.92	0.642
		Q4	5,755.49	Q4 (Ref.)			
	Positive (<i>n</i> = 141)	Q1	5,453.66	Q1 vs. Q4	122.93	70.73	0.086
		Q2	5,395.61	Q2 vs. Q4	64.87	54.14	0.234
		Q3	5,389.29	Q3 vs. Q4	58.55	42.43	0.171
		Q4	5,330.74	Q4 (Ref.)			

A linear mixed effects model was used to obtain *p* values. Adjusted for systolic blood pressure, diastolic blood pressure, baseline hippocampal volume, education, gender, age, hypertension, and body mass index. CN, cognitively normal (control group); EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer disease; LS mean, least square mean.