Title

Pulse pressure and APOE ε4 dose interact to affect cerebral blood flow in older adults without dementia.

Authors

Edwards, Lauren

Thomas, Kelsey

Weigand, Alexandra

et al.

Publication Date

2024

DOI

10.1016/j.cccb.2024.100206

Peer reviewed

Cerebral Circulation - Cognition and Behavior 6 (2024) 100206

Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

journal homepage: www.sciencedirect.com/journal/cerebral-circulation-cognition-and-behavior

Pulse pressure and APOE ε4 dose interact to affect cerebral blood flow in older adults without dementia

Lauren Edwards [a], Kelsey R. Thomas [b,c], Alexandra J. Weigand [a], Emily C. Edmonds [d,e], Alexandra L. Clark [f], Einat K. Brenner [c], Sarah J. Banks [g], Paul E. Gilbert [a,h], Daniel A. Nation [i], Lisa Delano-Wood [c,j], Mark W. Bondi [c,j], Katherine J. Bangen [b,c,*], for the Alzheimer's Disease Neuroimaging Initiative[1]

[a] San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[b] Research Service, VA San Diego Healthcare System, San Diego, CA, USA
[c] Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA
[d] Banner Alzheimer's Institute, Tucson, AZ, USA
[e] Departments of Neurology and Psychology, University of Arizona, Tucson, AZ, USA
[f] Department of Psychology, University of Texas at Austin, Austin, TX, USA
[g] Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA
[h] Department of Psychology, San Diego State University, San Diego, CA, USA
[i] Department of Psychology, University of California Irvine, Irvine, CA, USA
[j] Psychology Service, VA San Diego Healthcare System, San Diego, CA, USA

ARTICLE INFO

Keywords:
Alzheimer's disease
Apolipoprotein E
Arterial spin labeling
Cerebral blood flow
Pulse pressure

ABSTRACT

This study assessed whether the effect of vascular risk on cerebral blood flow (CBF) varies by gene dose of apolipoprotein (APOE) ε4 alleles. 144 older adults without dementia from the Alzheimer's Disease Neuroimaging Initiative underwent arterial spin labeling and T1-weighted MRI, APOE genotyping, fluorodeoxyglucose positron emission tomography (FDG-PET), lumbar puncture, and blood pressure (BP) assessment. Vascular risk was assessed using pulse pressure (systolic BP – diastolic BP). CBF was examined in six AD-vulnerable regions: entorhinal cortex, hippocampus, inferior temporal cortex, inferior parietal cortex, rostral middle frontal gyrus, and medial orbitofrontal cortex. Linear regressions tested the interaction between APOE ε4 dose and pulse pressure on CBF in each region, adjusting for age, sex, cognitive classification, antihypertensive medication use, FDG-PET, reference CBF region, and AD biomarker positivity. There was a significant interaction between pulse pressure and APOE ε4 dose on CBF in the entorhinal cortex, hippocampus, and inferior parietal cortex, such that higher pulse pressure was associated with lower CBF only among ε4 homozygous participants. These findings demonstrate that the association between pulse pressure and regional CBF differs by APOE ε4 dose, suggesting that targeting modifiable vascular risk factors may be particularly important for those genetically at risk for AD.

Introduction

Growing evidence suggests that early cerebrovascular dysfunction is implicated in Alzheimer's disease (AD) [1–3]. Cerebral blood flow (CBF) measured via arterial spin labeling (ASL) magnetic resonance imaging (MRI) is one method by which cerebrovascular dysfunction may be assessed using magnetically labeled arterial water to quantify the rate of delivery of arterial blood to brain tissue. ASL imaging has been identified as a promising biomarker for AD [4]. Studies of ASL MRI in older adults have detected that individuals with AD demonstrate hypoperfusion compared to controls [5], consistent with studies showing associations between perfusion and cross-sectional cognition [6] as well as AD pathology [7]. In contrast, hyperperfusion has been reported in individuals with subtle cognitive impairment compared to controls,

* Corresponding author at: 9500 Gilman Drive, Mail Code 151B, San Diego, CA 92093-9151, USA.
E-mail address: kbangen@ucsd.edu (K.J. Bangen).

[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

https://doi.org/10.1016/j.cccb.2024.100206
Received 26 October 2023; Received in revised form 20 December 2023; Accepted 14 January 2024
Available online 28 January 2024

potentially indicative of a compensatory response to maintain baseline cognitive abilities [8]. Thus, there may exist an "inverted U" such that hyperperfusion underlies early stages of cognitive dysfunction, which later transitions to hypoperfusion as cognition further declines to mild cognitive impairment or dementia. As a predictive tool, alterations in CBF have been associated with longitudinal cognitive decline, neurodegeneration, and progression of cerebrovascular lesions [9] as well as decline in everyday functioning [10].

Given the increasing recognition of cerebrovascular dysfunction in AD, it is unsurprising that vascular risk factors such as pulse pressure, a proxy measure of arterial stiffness [11], have also been shown to play a role in AD. Studies have found that elevated pulse pressure is associated with increased AD biomarkers [11–13], cerebrovascular pathology at autopsy [14], and risk of dementia [12,15]. Elevated pulse pressure may exert detrimental effects by contributing to blood-brain barrier dysfunction and inducing microvascular damage [16]. Furthermore, several studies have found that elevated pulse pressure is associated with a reduction in CBF [17,18], although other studies have reported no such relationship [19,20]. Discrepancies in findings across studies may be a result of differing sample characteristics. Taken together, the extant literature suggests that, while hypoperfusion may be another avenue by which neuronal damage occurs due to elevated pulse pressure, a more refined understanding of the context in which this effect is observed is warranted.

In addition to modifiable risk factors, the apolipoprotein E (APOE) ε4 allele is a well-characterized susceptibility gene for AD. Possession of the APOE ε4 allele has been associated with a number of AD-related outcomes, including greater accumulation of amyloid, a hallmark biomarker of AD [21], as well as neurodegeneration, [22] and risk of dementia [23,24]. Furthermore, APOE ε4 has been implicated in cardiovascular disease, such that APOE ε4 carriers are at greater risk for coronary disease and heart attack [25,26]. Unsurprisingly, associations with cerebrovascular dysfunction have also been reported, including reports of greater microvascular pathology [27,28], blood-brain barrier dysfunction [29], and reductions [30,31] or increases [32] in CBF in APOE ε4 carriers.

Given the independent effects that pulse pressure and APOE ε4 exert on brain health in older adults, examination of a possible interactive effect of these variables on CBF may have implications for understanding the mechanism behind how these risk factors impact brain and cognitive function. Therefore, we sought to determine whether the effect of pulse pressure on CBF varies by APOE ε4 genotype. In particular, we examined whether gene dose of APOE ε4 alleles (i.e., number of ε4 alleles) modifies the association between pulse pressure and regional CBF in older adults without dementia.

Material and methods

The ADNI dataset

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see www.adni-info.org. This study was reviewed by the University of California, San Diego institutional review board and accepted as Exempt (Protocol #801817). The ADNI study has been approved by the institutional review boards at each of the participating sites. All participants, or authorized representatives, gave written informed consent at each site. All procedures were done in accordance with Good Clinical Practice guidelines, US 21CFR Part 50 – Protection of Human Subjects and Park 56 – Institutional Review Boards (IRBs)/Research Ethics Boards (REBs).

Participants

As previously described [33], ADNI participants are 55–90 years old, fluent in English or Spanish with at least 6 years of education, have a Geriatric Depression Scale score of less than 6 and a modified Hachinski Ischemic Scale score of less than 5 at enrollment. The present study included 144 older adult participants from ADNI GO/ADNI 2 when ASL data were collected on a subset of the larger ADNI sample. Participants were included if they had ASL data (including reference region data) that was collected within 12 months of their baseline visit and passed quality control standards; did not have dementia at their baseline study visit; and had APOE genotyping, demographic characeristics, fluorodeoxyglucose positron emission tomography (FDG-PET), cerebrospinal fluid, and blood pressure data available at baseline.

Imaging and cerebrospinal fluid

Detailed information describing the imaging data acquisition and processing is available online at www.loni.usc.edu. Briefly, all MR imaging was collected on a 3.0 Tesla scanner, and ASL and structural MRI scans were collected in the same session. T1-weighted 3D MPRAGE sequence parameters included field of view = 256 mm, repetition time = 2300 ms, echo time = 2.98 ms, flip angle = 9°, and resolution = 1.1 × 1.1 × 1.2 mm^3. Structural scans were skull stripped, segmented, and parcellated using FreeSurfer.

Pulsed ASL scans were collected using QUIPSS II with thin-slice TI1 periodic saturation with echo-planar imaging [34]. The following scan parameters were used: inversion time of arterial spins (TI1) = 700 ms, total transit time of spins (TI2) = 1900 ms, tag thickness = 100 mm, tag to proximal slice gap = 25.4 mm, repetition time = 3400 ms, echo time = 12 ms, field of view = 256 mm, matrix = 64×64, 24 4-mm thick axial slices [52 tag + control image pairs], time lag between slices = 22.5 ms.

ASL data processing was largely automated as previously described [9], including motion correction, alignment of each ASL frame to the first frame using a rigid body transformation and least squares fitting using SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/). Perfusion-weighted images were computed as the difference of the mean-tagged and mean-untagged ASL images and were intensity scaled both to account for signal decay during acquisition and to generate intensities in meaningful physiological units. After geometric distortion correction, ASL images were aligned to structural T1 images using FSL. Partial volume correction that assumed that CBF in gray matter is 2.5 times greater than in white matter was performed in order to minimize the effects of lower perfusion in white matter on CBF estimates. The partial volume corrected perfusion-weighted images were normalized by the reference image (i.e., an estimate of blood water magnetization) to convert the signal into units of mL/100 g tissue/min. Participants that failed to pass quality control for ASL images were excluded from the present study.

FreeSurfer-derived anatomical regions of interest (ROIs) were applied to extract regional CBF estimates for each participant. Six *a priori* ROIs were examined: (1) entorhinal cortex, (2) hippocampus, (3) inferior parietal lobe, (4) inferior temporal gyrus, (5) medial orbitofrontal cortex, and (6) rostral middle frontal gyrus. These regions were chosen due to previous research showing these regions are vulnerable to subtle changes in preclinical AD [35]. These regions were also chosen to maintain consistency with our previous studies examining CBF in ADNI [8,36]. CBF estimates were also extracted from the precentral gyrus as a reference region, as this region is not thought to be impacted in early AD. Mean CBF corrected for partial volume effects was extracted for each of the ROIs for each hemisphere separately and then averaged to obtain bilateral CBF estimates for each ROI. If participants were missing baseline ASL but had ASL within the first year of their baseline visit, the first occasion of ASL data was used in analyses.

Brain glucose metabolism was measured by FDG PET. Detailed information describing the FDG PET data acquisition, processing, and analysis is available online at http://adni.loni.usc.edu/. Briefly, FDG scanning began 30 min after intravenous injection of an approximately 5 mCi dose of tracer. PET images were spatially normalized to a Montreal Neurological Institute (MNI) PET template. Consistent with prior work in ADNI [8,9], a composite meta-ROI that is comprised of the standardized uptake value ratios (SUVRs) of the angular gyri, middle/inferior temporal gyri, and posterior cingulate gyrus was calculated. Metabolic changes in these brain regions are associated with cognitive performance in patients with MCI and AD [37,38]. The meta-ROI was normalized using the pons and cerebellum as a reference region. The meta-ROI FDG PET was included as a covariate in the present analyses as a measure of global brain metabolism to allow for interpretation of effects on CBF independent of glucose metabolism.

Alzheimer's disease CSF biomarkers were processed using Elecsys® immunoassays. Alzheimer's disease biomarker positivity was defined using the previously determined CSF p-tau/Aβ ratio cut-score of >0.0251 pg/ml, which was optimized for the ADNI sample [39]. This was included as a covariate in these analyses to facilitate interpretation of the interactive effects of pulse pressure and APOE ε4 allele dose on CBF independent of AD biomarkers, which have been shown to be associated with cerebral blood flow [7,40].

Clinical and cognitive data

Demographic variables included as covariates were age and sex. Cardiovascular risk was assessed using pulse pressure (systolic blood pressure – diastolic blood pressure) as a proxy for arterial stiffness [14]. *APOE* ε4 frequency was determined by the number of ε4 alleles (0, 1, 2). Participant self-reported use of antihypertensive medications (present or absent) at their baseline visit was included as an additional covariate to account for the effects of blood pressure management on the results.

Cognitive status (MCI or cognitively unimpaired [CU]) was determined using actuarial neuropsychological criteria as described previously [41,42]. Briefly, among participants without dementia per ADNI criteria [33], raw scores on six neuropsychological tests were converted to age-, sex-, and education-adjusted z-scores based on normative data from a 'robust normal' control group of participants who remained cognitively normal throughout their participation in ADNI ($n = 525$). If participants demonstrated impairment on two z-scores in one cognitive domain, or on one z-score across all three cognitive domains (memory, language, attention/executive function), they were classified as MCI ($n = 49$). Participants that did not demonstrate these impairments were classified as CU ($n = 97$).

Statistical analysis

Six linear regression models tested the interaction between categorical APOE ε4 dose (0, 1, or 2 alleles) and continuous pulse pressure on CBF in each ROI. Covariates included age, sex, cognitive classification, antihypertensive medication use, cerebral metabolism (FDG-PET composite), reference region CBF (precentral gyrus), and AD biomarker positivity. All continuous variables were z-scored for each analysis. All categorical variables were dummy coded. Results were considered statistically significant at $p<.05$. An omnibus test for the pulse pressure by categorical APOE ε4 dose was first examined. If the interaction omnibus test was significant, simple effects were assessed to describe the directionality of the effect.

In addition, two sets of secondary analyses were run. First, we ran the same linear regressions described above, but replaced standard pulse pressure with the pulse pressure index [43]. The pulse pressure index is calculated by dividing pulse pressure by systolic blood pressure, and has been purported to account for the effect of varying blood pressure on pulse pressure and may more specifically reflect arterial stiffness [43,44]. Therefore, we ran secondary analyses to determine whether results still held when using this alternative measure of arterial stiffness rather than pulse pressure. Second, we ran the same linear regressions described initially but with the addition of the modified Hachinski Ischemic Scale as a covariate to determine whether the interactive effects of pulse pressure and APOE ε4 dose persisted when additionally adjusting for general vascular risk burden. For all models, we assessed for influential values using the deleted fit statistic, and models were tested with and without cases which exceeded an absolute value of $2\sqrt{(p/n)}$, where p represents number of model parameters and n is sample size [45]. If significant omnibus interaction test results were attenuated when these cases were removed, we ensured that significant results were not driven by a single participant. All significant omnibus interaction effects reported in this paper remained significant when the single most influential participant was excluded.

Some participants were missing CBF data for some of the individual regions. These individuals failed to pass ADNI Free Surfer QC relevant to the effected region of interest. All 144 participants had CBF data available for the hippocampus, entorhinal cortex, medial orbitofrontal cortex, and rostral middle frontal cortex; 142 participants had CBF data for the inferior parietal cortex; and 136 participants had CBF data for the inferior temporal cortex.

Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 27 (SPSS IBM, New York, USA) and R version 4.3.1. Figures were created in RStudio version 2023.06.0 + 421.

Results

Demographic, clinical, and imaging characteristics are reported in Table 1. The mean age was 71.3 years, and 48.6 % of the sample was female. The sample was predominantly White (94.4 %) and non-Hispanic (95.8 %) and was highly educated (mean education of 16.7 years). There was a significant association between APOE ε4 dose and

Table 1
Participant demographics.

	Overall ($N = 144$)
Age (years)	
Mean (SD)	71.3 (6.78)
Sex	
Male	74 (51.4 %)
Female	70 (48.6 %)
Education (years)	
Mean (SD)	16.7 (2.60)
Race	
Asian	1 (0.7 %)
Black	4 (2.8 %)
More than one	3 (2.1 %)
White	136 (94.4 %)
Ethnicity	
Hispanic/Latino	6 (4.2 %)
Not Hispanic/Latino	138 (95.8 %)
APOE ε4 Alleles	
0	87 (60.4 %)
1	46 (31.9 %)
2	11 (7.6 %)
Diagnosis	
Cognitively Unimpaired	96 (66.7 %)
Mild Cognitive Impairment	48 (33.3 %)
CSF p-tau/Aβ Biomarker Status	
Negative	85 (59.0 %)
Positive	59 (41.0 %)
FDG PET (SUVR)	
Mean (SD)	1.24 (0.142)
Pulse Pressure (mm HG)	
Mean (SD)	56.9 (14.7)
Modified Hachinski Ischemic Scale	
Mean (SD)	0.542 (0.708)
Antihypertensive Use	
No antihypertensive use	76 (52.8 %)
Antihypertensive use	68 (47.2 %)

cognitive status such that there was a greater number of individuals without any ε4 alleles in the cognitively unimpaired group relative to the MCI group ($X^2 = 10.33$, $p = 0.006$). There was no significant association between cognitive group and pulse pressure ($r = -0.088$, $p = 0.289$).

A significant omnibus interaction between pulse pressure and APOE ε4 dose was found on CBF in the hippocampus ($F_{2,\ 131} = 5.56$, $p = 0.005$), entorhinal cortex ($F_{2,\ 131} = 5.99$, $p = 0.003$), and inferior parietal cortex ($F_{2,\ 129} = 6.30$, $p = 0.002$) (Fig. 1). Simple slope analyses demonstrated that among participants with two ε4 alleles, higher pulse pressure was significantly associated with lower CBF in the hippocampus (simple slope [SS] $= -0.92$, $p = 0.001$), entorhinal cortex (SS $= -1.11$, $p = 0.001$), and inferior parietal cortex (SS $= -0.78$, $p = 0.001$). However, among participants with zero or one ε4 allele, there was no significant association between pulse pressure and CBF in these regions ($|SSs| \leq 0.15$, ps ≥ 0.237). No significant interaction between pulse pressure and APOE ε4 dose was found in the inferior temporal cortex ($F_{2,\ 123} = 2.17$, $p = 0.119$), rostral middle frontal gyrus ($F_{2,\ 131} = 0.04$, $p = 0.958$), or medial orbitofrontal cortex ($F_{2,\ 131} = 0.90$, $p = 0.408$) (Fig. 1).

Results remained qualitatively and statistically similar when using pulse pressure index as a predictor instead of pulse pressure. A significant interaction between pulse pressure and APOE ε4 dose was found in the hippocampus ($F_{2,\ 131} = 5.00$, $p = 0.008$), entorhinal cortex ($F_{2,\ 131} = 5.71$, $p = 0.004$), and inferior parietal cortex ($F_{2,\ 129} = 4.71$, $p = 0.011$), but not the inferior temporal cortex ($F_{2,\ 123} = 2.16$, $p = 0.119$), rostral middle frontal gyrus ($F_{2,\ 131} = 0.13$, $p = 0.881$), or medial orbitofrontal cortex ($F_{2,\ 131} = 0.71$, $p = 0.500$).

Results also remained qualitatively and statistically similar when additionally adjusting for general vascular risk assessed via the modified Hachinski Ischemic Scale. A significant interaction between pulse pressure and APOE ε4 dose was found in the hippocampus ($F_{2,\ 130} = 5.00$, $p = 0.008$), entorhinal cortex ($F_{2,\ 130} = 5.37$, $p = 0.006$), and inferior parietal cortex ($F_{2,\ 128} = 5.93$, $p = 0.003$), but not the inferior temporal cortex ($F_{2,\ 122} = 1.90$, $p = 0.154$), rostral middle frontal gyrus ($F_{2,\ 130} = 0.05$, $p = 0.949$), or medial orbitofrontal cortex ($F_{2,\ 130} = 0.99$, $p = 0.374$).

Discussion

In our well-characterized sample of older adults without dementia, the effect of pulse pressure on CBF in the hippocampus, entorhinal cortex, and inferior parietal cortex was dependent upon APOE ε4 dose. In particular, higher pulse pressure was associated with lower CBF only among those with two APOE ε4 alleles. However, there was no interaction between APOE ε4 dose and pulse pressure on CBF in the medial orbitofrontal cortex, rostral middle frontal cortex, or inferior temporal cortex. Furthermore, results were independent of general ischemic vascular risk and AD biomarker status and were replicated using an alternative proxy measure of arterial stiffness, the pulse pressure index.

Although no study to our knowledge has previously examined whether pulse pressure and APOE ε4 interact to predict cerebrovascular dysfunction measured by CBF, our findings are consistent with several studies that have reported a similar interactive effect on other AD-related outcomes. In particular, elevated pulse pressure has been

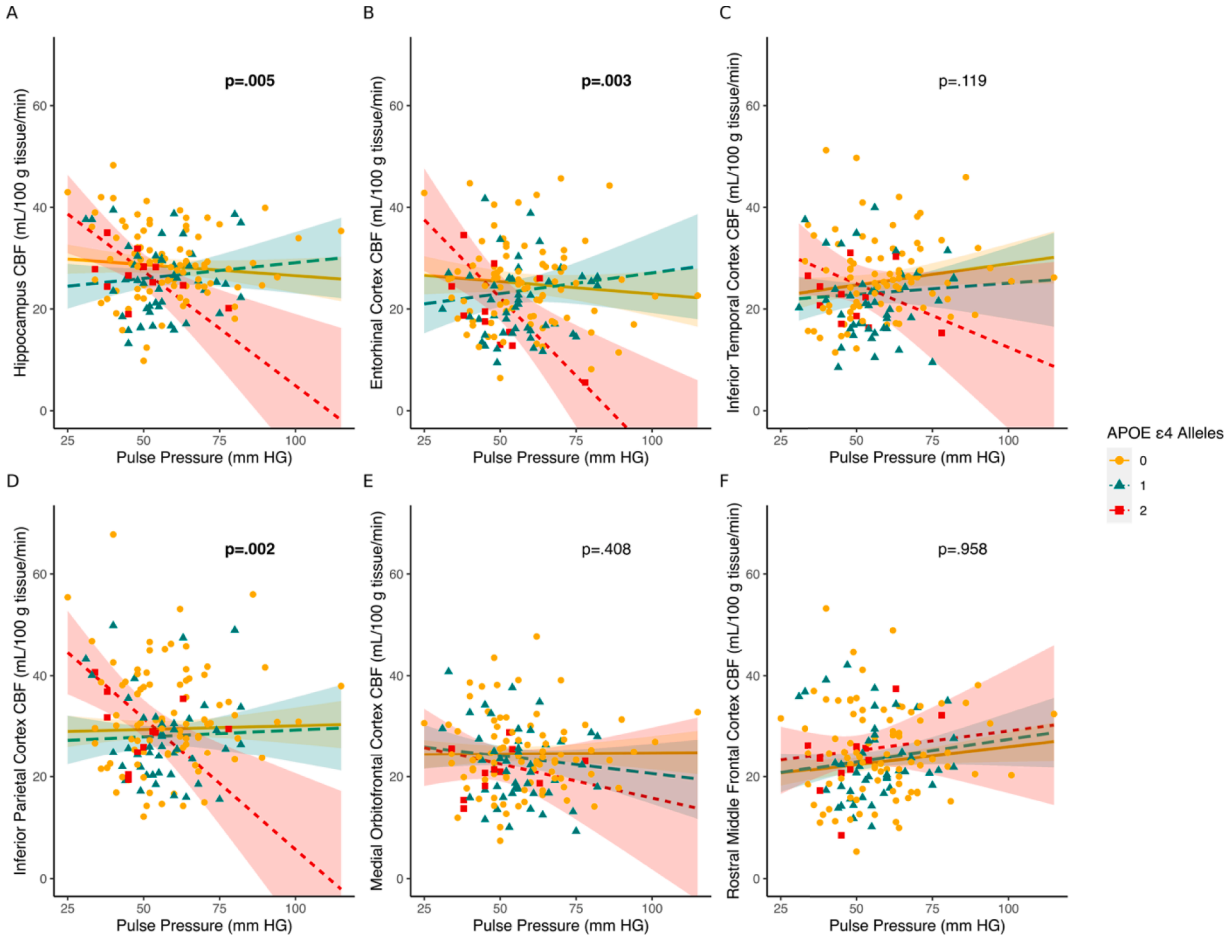

Fig. 1. Interaction between pulse pressure and APOE ε4 allele dose on CBF in A) hippocampus, B) entorhinal cortex, C) inferior temporal cortex, D) inferior parietal cortex, E) medial orbitofrontal cortex, and F) rostral middle frontal cortex. Predicted slopes and raw data points are shown. Omnibus interaction p values are included and bolded where significant ($p < 0.05$).

shown to be associated with greater visuospatial decline [46] and episodic memory impairment [47] as well as microstructural abnormalities [48] in APOE ε4 carriers compared to non-carriers. However, one study showed no cross-sectional interactive effects between pulse pressure and APOE ε4 on functional status [49]. Findings of this study also suggested that, while high pulse pressure predicted greater longitudinal functional decline than low pulse pressure among non-ε4-carriers, the rate of longitudinal functional decline in ε4 carriers did not vary by pulse pressure. Future work is warranted to better understand how interactive effects of pulse pressure and APOE ε4 dose may differentially effect CBF and cognitive and functional outcomes, both cross-sectionally and longitudinally.

Our study adds to a limited and mixed literature on the interactive effects of vascular risk factors and APOE ε4 genotype on CBF. For example, consistent with our findings, another study showed that arterial stiffening as measured via pulse wave velocity was previously found to be more strongly negatively associated with region-specific CBF among ε4 carriers than noncarriers, both in participants with MCI and normal cognition [50]. In contrast, in another study, pulse wave velocity was found to interact with APOE ε4 carrier status to affect CBF in participants with diagnoses ranging from cognitively unimpaired to dementia [51]. However, the associations were not significant in either the carrier or non-carrier group. Importantly, neither of these studies examined the dose effect of the APOE ε4 allele; such a lack of consistent findings may be because the lack of distinction between one and two APOE ε4 alleles obfuscates or blurs important distinct relationships.

We found that the effect of pulse pressure on CBF was dependent on APOE ε4 dose in the hippocampus, entorhinal cortex, and inferior parietal cortex, but not the inferior temporal cortex, rostral middle frontal gyrus, or medial orbitofrontal cortex. The medial temporal lobe (MTL) is known to be an area of early pathological changes in AD [52], and a MTL pattern of tau pathology and neurodegeneration has been particularly associated with APOE ε4 carriers [53,54]. Furthermore, MTL tau PET has been negatively associated with cerebral blood flow in APOE ε4 carriers only [40]. Therefore, our regional findings suggest that cerebrovascular dysfunction (i.e., hypoperfusion) related to vascular risk (i.e., pulse pressure) may play a mechanistic role in the development of AD pathology in those homozygous for the APOE ε4 allele. Indeed, the MTL has also been shown to be a site of early blood-brain barrier breakdown in APOE ε4 carriers [29]. Similarly, researchers have observed vascular dysfunction as measured by increased parietal white matter hyperintensities in presymptomatic individuals with autosomal-dominant AD [55] and in APOE ε4 carriers [56]. Such findings appear to reflect another manifestation of AD-related cerebrovascular changes. The localization of our findings to medial temporal and parietal regions therefore seems to suggest that neurovascular unit dysfunction may be involved in the development of AD pathology as proposed by the two-hit vascular model of AD [57]. Future work should seek to interrogate the etiology of this selective vulnerability of specific regions to the effects of pulse pressure and APOE ε4 genotype, in particular though investigation of these interactive effects in the context of different biomarker profiles (e.g., under the ATN framework).

Strengths of our study include examining APOE ε4 dose rather than modeling a binary measure of APOE ε4 carrier vs. non-carrier status. Although this results in a small sample size of homozygous ε4 carriers, it also allows for more detailed examination of APOE genotypes. Additionally, the inclusion of multiple regions of interest allowed us to examine region-specific effects on CBF. Furthermore, the ADNI sample is well-characterized, and the analyses adjusted for AD biomarkers (CSF p-tau/Aβ ratio) that may affect CBF. Finally, our analyses adjusted for FDG-PET SUVR to account for neuronal metabolism, which is known to affect hypoperfusion [58].

It is important to note limitations of the current study. First, the sample was made up of primarily White individuals with high educational attainment, as well as those with overall low vascular risk burden. Further research is needed in more ethnoracially diverse groups, especially given their increased risk for AD. Ongoing efforts to increase representation in the ADNI4 sample will make this possible in the near future. Second, the present study does not capture all measures of vascular dysfunction, including white matter hyperintensity burden, microbleeds, lacunes, cerebral amyloid angiopathy, and other features that are not currently readily assessed via MRI. Future work examining other modalities of cerebrovascular dysfunction would expand upon the current findings. Additionally, due to a low ε4 sample in each cognitive status group (i.e., MCI and normal cognition), we were unable to perform analyses in each group separately. Future work should seek to uncover the clinical ramifications of these associations, including impact on cognition. Lastly, we examined the effect of the number of APOE ε4 alleles, without consideration of APOE ε2 or ε3 alleles due to sample constraints (e.g., only 4 ε2/ε4 participants were present in this sample) and our present aim. Given that APOE ε2 has been shown to be protective in older adults [59], it will be important to examine all APOE allelic combinations in future analyses where larger samples are available.

Overall, our findings demonstrate that the negative effect of high pulse pressure on reduced CBF is most impactful among individuals with two APOE ε4 alleles. Compatible with a precision medicine approach, these results suggest that targeting modifiable and easily detectable vascular risk factors, such as pulse pressure, may be particularly important for prevention and treatment in those at high genetic risk for AD. Future research is needed in order to better understand the role that pulse pressure plays in cerebrovascular pathological processes for genetically at-risk individuals and to clarify the downstream effects of changes in CBF across the aging spectrum.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the U.S. Department of Veterans Affairs Clinical Sciences Research and Development Service [Career Development Award-2 1IK2CX001865 to K.R.T. and Merit Award 1I01CX001842 to K.J.B], NIH grants [R01 AG063782 to K.J.B., R03 AG070435 to K.R.T., R01 AG049810 to M.W.B.].

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 (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.

Data availability

Publicly available datasets were analyzed in this study. This data can be found here: http://adni.loni.usc.edu/.

CRediT authorship contribution statement

Lauren Edwards: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Kelsey R. Thomas:** Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Alexandra J. Weigand:** Data curation, Writing – review & editing. **Emily C. Edmonds:** Writing – review & editing. **Alexandra L. Clark:** Writing – review & editing. **Einat K. Brenner:** Writing – review & editing. **Sarah J. Banks:** Writing – review & editing. **Paul E. Gilbert:** Writing – review & editing. **Daniel A. Nation:** Methodology, Writing – review & editing. **Lisa Delano-Wood:** Writing – review & editing. **Mark W. Bondi:** Writing – review & editing. **Katherine J. Bangen:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

Dr. Bondi receives royalties from Oxford University Press. No other authors have competing interests to declare.

Acknowledgment

The authors have no acknowledgments to report.

References

[1] M.D. Sweeney, K. Kisler, A. Montagne, et al., The role of brain vasculature in neurodegenerative disorders, Nat. Neurosci. 21 (2018) 1318–1331.
[2] A.C. Yang, R.T. Vest, F. Kern, et al., A human brain vascular atlas reveals diverse mediators of Alzheimer's risk, Nature 603 (2022) 885–892.
[3] B.V. Zlokovic, Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders, Nat. Rev. Neurosci. 12 (2011) 723–738.
[4] C.E. Wierenga, C.C. Hays, Z.Z. Zlatar, Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease, J. Alzheimer. Dis. 42 (2014) S411–S419.
[5] I. Asllani, C. Habeck, N. Scarmeas, et al., Multivariate and univariate analysis of continuous arterial spin labeling perfusion MRI in Alzheimer's disease, J. Cereb. Blood Flow Metab. 28 (2008) 725–736.
[6] A.E. Leeuwis, M.R. Benedictus, J.P.A. Kuijer, et al., Lower cerebral blood flow is associated with impairment in multiple cognitive domains in Alzheimer's disease, Alzheimer. Dement. 13 (2017) 531–540.
[7] A. Rubinski, D. Tosun, N. Franzmeier, et al., Lower cerebral perfusion is associated with tau-PET in the entorhinal cortex across the Alzheimer's continuum, Neurobiol. Aging 102 (2021) 111–118.
[8] K.R. Thomas, J.R. Osuna, A.J. Weigand, et al., Regional hyperperfusion in older adults with objectively-defined subtle cognitive decline, J. Cereb. Blood Flow Metab. (2020), 0271678×20935171.
[9] K.J. Bangen, K.R. Thomas, D.L. Sanchez, et al., Entorhinal perfusion predicts future memory decline, neurodegeneration, and white matter hyperintensity progression in older adults, J. Alzheimer. Dis. 81 (2021) 1711–1725.
[10] D.L. Sanchez, K.R. Thomas, E.C. Edmonds, et al., Regional hypoperfusion predicts decline in everyday functioning at three-year follow-up in older adults without dementia, J. Alzheimer. Dis. 77 (2020) 1291–1304.
[11] D.A. Nation, S.D. Edland, M.W. Bondi, et al., Pulse pressure is associated with Alzheimer biomarkers in cognitively normal older adults, Neurology. 81 (2013) 2024–2027.
[12] D.A. Nation, E.C. Edmonds, K.J. Bangen, et al., Pulse Pressure in Relation to Tau-Mediated Neurodegeneration, Cerebral Amyloidosis, and Progression to Dementia in Very Old Adults, JAMA Neurol. 72 (2015) 546–553.
[13] A.J. Weigand, A.J. Macomber, K.S. Walker, et al., Interactive effects of pulse pressure and tau imaging on longitudinal cognition, J. Alzheimer. Dis. 89 (2022) 633–640.
[14] D.A. Nation, L. Delano-Wood, K.J. Bangen, et al., Antemortem pulse pressure elevation predicts cerebrovascular disease in autopsy-confirmed Alzheimer's disease, J. Alzheimer. Dis. 30 (2012) 595–603.
[15] C. Qiu, B. Winblad, M. Viitanen, et al., Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older, Stroke 34 (2003) 594–599.
[16] R.A. Levin, M.H. Carnegie, D.S. Celermajer, Pulse Pressure: an Emerging Therapeutic Target for Dementia, Front. Neurosci. 14 (2020). https://www.frontiersin.org/articles/10.3389/fnins.2020.00669. accessed 15 December 2022.
[17] L.L. Beason-Held, A. Moghekar, A.B. Zonderman, et al., Longitudinal changes in cerebral blood flow in the older hypertensive brain, Stroke 38 (2007) 1766–1773.
[18] L. Glodzik, H. Rusinek, W. Tsui, et al., Different relationship between systolic blood pressure and cerebral perfusion in subjects with and without hypertension, Hypertension 73 (2019) 197–205.
[19] J.C. Foster-Dingley, J.E.F. Moonen, A.J.M. de Craen, et al., Blood pressure is not associated with cerebral blood flow in older persons, Hypertension 66 (2015) 954–960.
[20] J.W. van Dalen, H.J. Mutsaerts, J. Petr, et al., Longitudinal relation between blood pressure, antihypertensive use and cerebral blood flow, using arterial spin labelling MRI, J. Cereb. Blood Flow Metab. 41 (2021) 1756–1766.
[21] A.S. Fleisher, K. Chen, X. Liu, et al., Apolipoprotein E ε4 and age effects on florbetapir positron emission tomography in healthy aging and Alzheimer disease, Neurobiol. Aging 34 (2013) 1–12.
[22] A.J. Jak, W.S. Houston, B.J. Nagel, et al., Differential Cross-Sectional and Longitudinal Impact of APOE Genotype on Hippocampal Volumes in Nondemented Older Adults, DEM 23 (2007) 382–389.
[23] E.H. Corder, A.M. Saunders, W.J. Strittmatter, et al., Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families, Science (1979) 261 (1993) 921–923.
[24] L.A. Farrer, L.A. Cupples, J.L. Haines, et al., Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease meta analysis consortium, JAMA 278 (1997) 1349–1356.
[25] S.S. Anand, C. Xie, G. Paré, et al., Genetic variants associated with myocardial infarction risk factors in over 8000 individuals from five ethnic groups: the INTERHEART Genetics Study, Circ. Cardiovasc. Genet. 2 (2009) 16–25.
[26] A.M. Bennet, E. Di Angelantonio, Z. Ye, et al., Association of apolipoprotein E genotypes with lipid levels and coronary risk, JAMA 298 (2007) 1300–1311.
[27] E.G. Stopa, P. Butala, S. Salloway, et al., Cerebral cortical arteriolar angiopathy, vascular beta-amyloid, smooth muscle actin, braak stage, and APOE genotype, Stroke 39 (2008) 814–821.
[28] A.G. Yip, A.C. McKee, R.C. Green, et al., APOE, vascular pathology, and the AD brain, Neurology. 65 (2005) 259–265.
[29] A. Montagne, D.A. Nation, A.P. Sagare, et al., APOE4 leads to blood–brain barrier dysfunction predicting cognitive decline, Nature 581 (2020) 71–76.
[30] N. Filippini, K.P. Ebmeier, B.J. MacIntosh, et al., Differential effects of the APOE genotype on brain function across the lifespan, Neuroimage 54 (2011) 602–610.
[31] L. Michels, G. Warnock, A. Buck, et al., Arterial spin labeling imaging reveals widespread and Aβ-independent reductions in cerebral blood flow in elderly apolipoprotein epsilon-4 carriers, J. Cereb. Blood Flow Metab. 36 (2016) 581–595.
[32] K.J. Bangen, K. Restom, T.T. Liu, et al., Assessment of Alzheimer's disease risk with functional magnetic resonance imaging: an arterial spin labeling study, J. Alzheimer. Dis. 31 (Suppl 3) (2012) S59–S74.
[33] R.C. Petersen, P.S. Aisen, L.A. Beckett, et al., Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization, Neurology. 74 (2010) 201–209.
[34] W.M. Luh, E.C. Wong, P.A. Bandettini, et al., QUIPSS II with thin-slice TI1 periodic saturation: a method for improving accuracy of quantitative perfusion imaging using pulsed arterial spin labeling, Magn. Reson. Med. 41 (1999) 1246–1254.
[35] B.C. Dickerson, T.R. Stoub, R.C. Shah, et al., Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults, Neurology. 76 (2011) 1395–1402.
[36] S.L. Holmqvist, K.R. Thomas, E.C. Edmonds, et al., Cognitive dispersion is elevated in amyloid-positive older adults and associated with regional hypoperfusion, J. Int. Neuropsycholog. Soc. (2022) 1–11.
[37] W.J. Jagust, D. Bandy, K. Chen, et al., The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core, Alzheimer. Dement. 6 (2010) 221–229.
[38] S.M. Landau, D. Harvey, C.M. Madison, et al., Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI, Neurobiol. Aging 32 (2011) 1207–1218.
[39] O. Hansson, J. Seibyl, E. Stomrud, et al., CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts, Alzheimer. Dement. 14 (2018) 1470–1481.
[40] C.G. Swinford, S.L. Risacher, A. Vosmeier, et al., Amyloid and tau pathology are associated with cerebral blood flow in a mixed sample of nondemented older adults with and without vascular risk factors for Alzheimer's disease, Neurobiol. Aging 130 (2023) 103–113.
[41] M.W. Bondi, E.C. Edmonds, A.J. Jak, et al., Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates, J. Alzheimer. Dis. 42 (2014) 275–289.
[42] A.J. Weigand, K.R. Thomas, K.J. Bangen, et al., APOE interacts with tau PET to influence memory independently of amyloid PET in older adults without dementia, Alzheimer. Dement. 17 (2021) 61–69.
[43] Y. Peng-Lin, L. Yue-Chun, Pulse pressure index (pulse pressure/systolic pressure) may be better than pulse pressure for assessment of cardiovascular outcomes, Med. Hypoth. 72 (2009) 729–731.
[44] M.L. Werhane, K.R. Thomas, K.J. Bangen, et al., Arterial stiffening moderates the relationship between type-2 diabetes mellitus and white matter hyperintensity burden in older adults with mild cognitive impairment, Front. Aging Neurosci. 13 (2021) 716638.
[45] D.A. Belsley, E. Kuh, R.E. Welsch, Regression Diagnostics: Identifying Influential Data and Sources of Collinearity, John Wiley & Sons, Inc., 1980.

[46] D.A. Nation, S.R. Preis, A. Beiser, et al., Pulse pressure is associated with early brain atrophy and cognitive decline: modifying effects of APOE4, Alzheimer Dis. Assoc. Disord. 30 (2016) 210–215.
[47] A.R. Bender, N. Raz, Age-related differences in episodic memory: a synergistic contribution of genetic and physiological vascular risk factors, Neuropsychology. 26 (2012) 442–450.
[48] Parada H., Bergstrom J., Bangen K.J., et al. Pulse pressure trajectories predict brain microstructure in community-dwelling older adults: associations with executive function and modification by APOE. *Alzheimer. Dement.*. Epub ahead of print 1 November 2022. DOI: 10.1002/alz.12844.
[49] M.L. Werhane, K.R. Thomas, E.C. Edmonds, et al., Differential effect of APOE ε4 status and elevated pulse pressure on functional decline in cognitively normal older adults, J. Alzheimer. Dis. 62 (2018) 1567–1578.
[50] A.L. Jefferson, F.E. Cambronero, D. Liu, et al., Higher aortic stiffness is related to lower cerebral blood flow and preserved cerebrovascular reactivity in older adults, Circulation 138 (2018) 1951–1962.
[51] C. Coffin, C.K. Suerken, J.R. Bateman, et al., Vascular and microstructural markers of cognitive pathology, Alzheimer. Dement.: Diagn. Assessm. Dis. Monitor. 14 (2022) e12332.
[52] H. Braak, E. Braak, J. Bohl, Staging of Alzheimer-related cortical destruction, Eur. Neurol. 33 (1993) 403–408.
[53] C. Geroldi, M. Pihlajamäki, M.P. Laakso, et al., APOE-ε4 is associated with less frontal and more medial temporal lobe atrophy in AD, Neurology. 53 (1999) 1825–1832.
[54] R. La Joie, A.V. Visani, O.H. Lesman-Segev, et al., Association of APOE4 and clinical variability in Alzheimer disease with the pattern of tau- and amyloid-PET, Neurology. (2020), https://doi.org/10.1212/WNL.0000000000011270.
[55] S. Lee, F. Viqar, M.E. Zimmerman, et al., White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network, Ann. Neurol. 79 (2016) 929–939.
[56] A.M. Brickman, N. Schupf, J.J. Manly, et al., APOE ε4 and risk for Alzheimer's disease: do regionally distributed white matter hyperintensities play a role? Alzheimer. Dement. 10 (2014) 619–629.
[57] C. Iadecola, Neurovascular regulation in the normal brain and in Alzheimer's disease, Nat. Rev. Neurosci. 5 (2004) 347–360.
[58] E.S. Musiek, Y. Chen, M. Korczykowski, et al., Direct comparison of fluorodeoxyglucose positron emission tomography and arterial spin labeling magnetic resonance imaging in Alzheimer's disease, Alzheimer. Dement. 8 (2012) 51–59.
[59] C.R Martins, A. Oulhaj, C.A. de Jager, et al., APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model, Neurology. 65 (2005) 1888–1893.