



## Pulse pressure and APOE $\epsilon$ 4 dose interact to affect cerebral blood flow in older adults without dementia

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### ABSTRACT

This study assessed whether the effect of vascular risk on cerebral blood flow (CBF) varies by gene dose of apolipoprotein (APOE)  $\epsilon$ 4 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  $\epsilon$ 4 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  $\epsilon$ 4 dose on CBF in the entorhinal cortex, hippocampus, and inferior parietal cortex, such that higher pulse pressure was associated with lower CBF only among  $\epsilon$ 4 homozygous participants. These findings demonstrate that the association between pulse pressure and regional CBF differs by APOE  $\epsilon$ 4 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,

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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)  $\epsilon 4$  allele is a well-characterized susceptibility gene for AD. Possession of the APOE  $\epsilon 4$  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  $\epsilon 4$  has been implicated in cardiovascular disease, such that APOE  $\epsilon 4$  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  $\epsilon 4$  carriers.

Given the independent effects that pulse pressure and APOE  $\epsilon 4$  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  $\epsilon 4$  genotype. In particular, we examined whether gene dose of APOE  $\epsilon 4$  alleles (i.e., number of  $\epsilon 4$  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](http://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 characteristics, 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](http://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 =  $1.1 \times 1.1 \times 1.2 \text{ mm}^3$ . Structural scans were skull stripped, segmented, and parcellated using FreeSurfer.

Pulsed ASL scans were collected using QUIPSS II with thin-slice T11 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 =  $64 \times 64$ , 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 (SUVs) 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)
<b>Age (years)</b>	
Mean (SD)	71.3 (6.78)
<b>Sex</b>	
Male	74 (51.4 %)
Female	70 (48.6 %)
<b>Education (years)</b>	
Mean (SD)	16.7 (2.60)
<b>Race</b>	
Asian	1 (0.7 %)
Black	4 (2.8 %)
More than one	3 (2.1 %)
White	136 (94.4 %)
<b>Ethnicity</b>	
Hispanic/Latino	6 (4.2 %)
Not Hispanic/Latino	138 (95.8 %)
<b>APOE ε4 Alleles</b>	
0	87 (60.4 %)
1	46 (31.9 %)
2	11 (7.6 %)
<b>Diagnosis</b>	
Cognitively Unimpaired	96 (66.7 %)
Mild Cognitive Impairment	48 (33.3 %)
<b>CSF p-tau/Aβ Biomarker Status</b>	
Negative	85 (59.0 %)
Positive	59 (41.0 %)
<b>FDG PET (SUVr)</b>	
Mean (SD)	1.24 (0.142)
<b>Pulse Pressure (mm HG)</b>	
Mean (SD)	56.9 (14.7)
<b>Modified Hachinski Ischemic Scale</b>	
Mean (SD)	0.542 (0.708)
<b>Antihypertensive Use</b>	
No antihypertensive use	76 (52.8 %)
Antihypertensive use	68 (47.2 %)

cognitive status such that there was a greater number of individuals without any  $\epsilon 4$  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  $\epsilon 4$  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  $\epsilon 4$  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  $\epsilon 4$  allele, there was no significant association between pulse pressure and CBF in these regions ( $|SSs| \leq 0.15$ ,  $p \geq 0.237$ ). No significant interaction between pulse pressure and APOE  $\epsilon 4$  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).

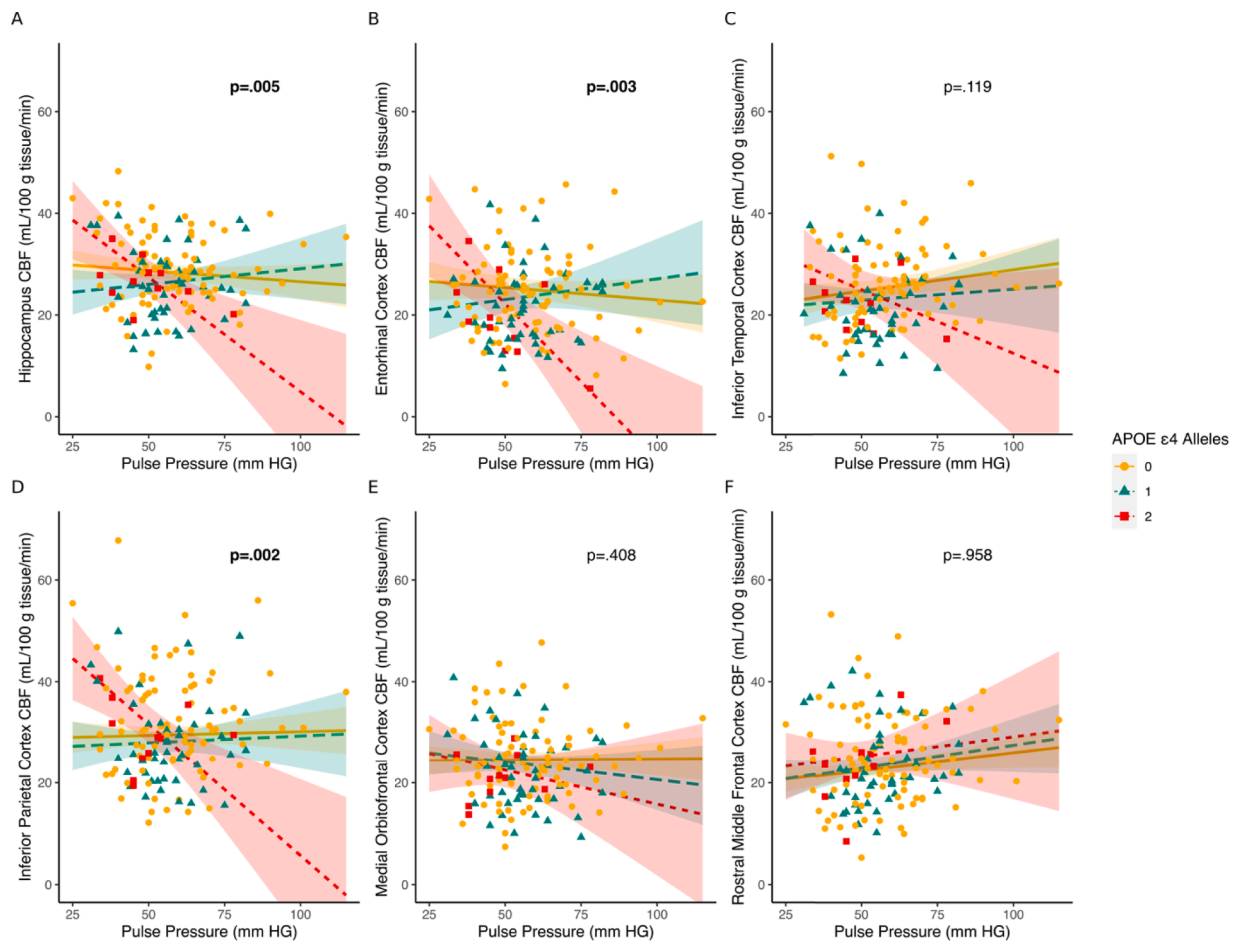
Results remained qualitatively and statistically similar when using pulse pressure index as a predictor instead of pulse pressure. A significant interaction between pulse pressure and APOE  $\epsilon 4$  dose was found in the hippocampus ( $F_{2, 131} = 5.00$ ,  $p = 0.008$ ), entorhinal cortex ( $F_{2, 131} = 5.71$ ,  $p = 0.004$ ), 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  $\epsilon 4$  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  $\epsilon 4$  dose. In particular, higher pulse pressure was associated with lower CBF only among those with two APOE  $\epsilon 4$  alleles. However, there was no interaction between APOE  $\epsilon 4$  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  $\epsilon 4$  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  $\epsilon 4$  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  $\epsilon 4$  carriers compared to non-carriers. However, one study showed no cross-sectional interactive effects between pulse pressure and APOE  $\epsilon 4$  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- $\epsilon 4$ -carriers, the rate of longitudinal functional decline in  $\epsilon 4$  carriers did not vary by pulse pressure. Future work is warranted to better understand how interactive effects of pulse pressure and APOE  $\epsilon 4$  dose may differentially affect 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  $\epsilon 4$  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  $\epsilon 4$  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  $\epsilon 4$  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  $\epsilon 4$  allele; such a lack of consistent findings may be because the lack of distinction between one and two APOE  $\epsilon 4$  alleles obfuscates or blurs important distinct relationships.

We found that the effect of pulse pressure on CBF was dependent on APOE  $\epsilon 4$  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  $\epsilon 4$  carriers [53,54]. Furthermore, MTL tau PET has been negatively associated with cerebral blood flow in APOE  $\epsilon 4$  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  $\epsilon 4$  allele. Indeed, the MTL has also been shown to be a site of early blood-brain barrier breakdown in APOE  $\epsilon 4$  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  $\epsilon 4$  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  $\epsilon 4$  genotype, in particular through 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  $\epsilon 4$  dose rather than modeling a binary measure of APOE  $\epsilon 4$  carrier vs. non-carrier status. Although this results in a small sample size of homozygous  $\epsilon 4$  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/A $\beta$  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 ethnographically 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  $\epsilon 4$  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  $\epsilon 4$  alleles, without consideration of APOE  $\epsilon 2$  or  $\epsilon 3$  alleles due to sample constraints (e.g., only 4  $\epsilon 2/\epsilon 4$  participants were present in this sample) and our present aim. Given that APOE  $\epsilon 2$  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  $\epsilon 4$  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.

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## 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.

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