GeroScience
https://doi.org/10.1007/s11357-025-02036-3

ORIGINAL ARTICLE

Longitudinal effects of cerebrovascular reactivity and cerebral pulsatility in cognitively intact older adults with APOE4: links with cognition

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Received: 2 September 2025 / Accepted: 2 December 2025

Abstract The apolipoprotein E4 (APOE4) allele is the strongest genetic risk factor for Alzheimer's disease (AD) and is linked to poorer cerebrovascular health. Cerebrovascular reactivity (CVR), an indicator of vascular reserve, and cerebral pulsatility (CP), a marker of vascular stiffness, are sensitive biomarkers of early vascular dysfunction associated with aging and AD. However, the relationship between APOE4 status and these cerebrovascular metrics remains unclear. This study investigated whether the APOE genotype influences longitudinal changes in CVR and CP, and their association with cognitive performance in cognitively unimpaired individuals. We utilized the PREVENT-AD cohort, including 101 APOE4 carriers (30 males and 71 females) and 152 non-APOE4 carriers (48 males and 104 females) aged 55 and older. Relative CVR and CP were derived from resting state functional magnetic resonance imaging data, with regional values extracted from cerebral arterial territories. Results indicated significant interactions between APOE4 status and relative CVR in the left middle cerebral artery and left posterior cerebral artery (PCA) territories. APOE4 status disaggregated analyses revealed that APOE4 carriers uniquely presented a significant decline in relative CVR within the left PCA. Furthermore, sex-specific effects were identified, with female APOE4 carriers having lower relative CVR in the right anterior cerebral artery

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11357-025-02036-3.

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Published online: 06 December 2025

territory compared to female non-carriers. Importantly, higher relative CVR was positively associated with better cognitive performance in APOE4 carriers. No significant effects of APOE4 status on CP were found. Together, these findings suggest that relative CVR may be an important early measure of cerebrovascular health and cognition in cognitively intact APOE4 carriers.

Keywords Cerebrovascular health · Cerebrovascular reactivity · Cerebral pulsatility · APOE4 · Cognition · Older adults

Introduction

Alzheimer's disease (AD) is the leading cause of dementia [1], with global cases of dementia projected to exceed 152 million by 2050 [2]. The apolipoprotein E4 (APOE4) gene is the leading genetic risk factor for AD [3]. Even in the absence of AD and dementia, the APOE4 genotype has been associated with poorer brain health, reflected by accelerated brain atrophy [4] and white matter hyperintensities progression [5]. These brain alterations have been proposed as potential mechanisms contributing to cognitive impairment in APOE4 carriers [6, 7].

Individuals with the APOE4 genotype demonstrate increased cerebrovascular vulnerability characterized by a steeper age-related decline in cerebral blood flow (CBF) compared to non-carriers [8]. While CBF is a well-established clinical measure of cerebrovascular health at rest [9], it reflects a homeostatic state and therefore does not capture the dynamic processes that allow the vascular system to meet transiently elevated demand. In contrast, cerebrovascular reactivity (CVR) [10], a measure of vascular reserve, and cerebral pulsatility (CP) [11], a marker of arterial stiffness, offer more comprehensive dynamic assessments of cerebrovascular function and are affected upstream of CBF [12].

CVR is an early vascular biomarker of aging [12, 13] and AD [14], reflecting CBF changes induced by dilation of cerebral arterioles in response to a vasodilatory stimulus, such as carbon dioxide (CO_2) [10]. Reduced CVR has been observed in individuals with AD compared to healthy controls, suggesting that impaired vascular reserve may contribute to disease pathology [14, 15]. Notably, in younger adults without any cognitive impairment, APOE4 carriers exhibit lower CVR compared to non-carriers [16]. However, the impact of APOE4 status on longitudinal changes in CVR remains unknown. Furthermore, whether there are sexual dimorphisms in the impact of APOE4 status on CVR has not been investigated, despite evidence demonstrating a higher risk for AD in females with the APOE4 genotype as compared to males [17].

CP is an important determinant of cerebrovascular health and an indicator of vascular stiffness [18], measuring the ability of cerebral arteries and arterioles to dampen the pressure and flow fluctuations of the cardiac cycle [11]. Greater pulsatility in brain vessels is thought to lead to microvascular damage and reduced CBF [19]. Increased pulsatility has been observed in individuals with AD [20–23], and is linked to cognitive decline [20]. Furthermore, elevated CP has been correlated to an increased risk of conversion to AD in individuals with cognitive impairment [24]. CP may be an important early biomarker of cerebrovascular dysfunction, as it has demonstrated greater sensitivity to cognitive function in older adults compared to CBF [25]. Despite these findings, the relationship between APOE4 status and CP in cognitively intact individuals remains poorly understood. Additionally, sex differences in the impact of APOE4 status on CP remain unknown, although recent evidence suggests that females exhibit higher pulsatility with age compared to males [26, 27].

The primary objective of this study was to evaluate the effect of APOE4 status on longitudinal changes in CVR and CP. A second objective was to investigate potential sex differences in these relationships. Finally, we explore whether APOE4 status influences the relationship between CVR, CP, and cognitive function. Together, quantification of CVR and CP may help detect early cerebrovascular dysfunction preceding cognitive impairment in populations genetically at risk of developing AD.

Methods

Participants

This longitudinal study included 101 APOE4 carriers (30 males and 71 females) and 152 non-APOE4

carriers (48 males and 104 females) aged 55 and older from the PRe-symptomatic EValuation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) dataset [28] at baseline. Longitudinal data—comprising repeated measures at a second time point—was available in 56 individuals with APOE4 (18 males and 38 females) and 100 subjects without APOE4 (30 males and 70 females). Detailed demographic information is presented in Table 1. Data for this study were obtained from PREVENT-AD Phase 2 (data release 8.0), as Phase 1 did not include functional magnetic resonance imaging (fMRI).

The PREVENT-AD program recruited individuals with a familial history of AD (father, mother, or multiple sibling). In this study, participants identified as having mild cognitive impairment (MCI) by a certified neuropsychologist were excluded at baseline. PREVENT-AD inclusion and exclusion criteria were based on the INTERPAD clinical trial [29] and a detailed description of the procedure can be found in [28]. In brief, participants needed to speak and write in French or English, did not present any history of inflammatory, chronic pain, liver, kidney, or cognitive disorders, and were not taking medications such as acetyl-cholinesterase inhibitors, corticosteroids, anti-coagulant, immunosuppressive, or anti-inflammatory drugs. Additionally, a study physician verified that participants did not present with neurological or physical conditions that would warrant exclusion.

The PREVENT-AD procedures were approved by McGill Institutional Review Board and/or Douglas

Table 1 Group differences between APOE4+ and APOE4− in demographic, relative CVR and CP

Demographic	Time Point 1	Time Point 2	Time Point 1	Time Point 2	Group comparisons
	APOE4+ (*n* = 101)	**APOE4+ (*n* = 56)**	**APOE4− (*n* = 152)**	**APOE4− (*n* = 100)**	***p*-values**
Age (years)*	67.94 ± 4.89	68.85 ± 4.24	69.07 ± 5.16	71.00 ± 5.26	**0.024**
Time point differences (years)	2.50 ± 0.61		2.61 ± 0.59		0.172
Sex (females/males)	71/30	38/18	104/48	70/30	0.904
Education (years)	15.16 ± 3.19	15.29 ± 3.46	15.91 ± 3.43	16.07 ± 3.55	0.045
RBANS (total scale index score)	99.95 ± 13.46	99.89 ± 10.37	101.48 ± 10.95	100.10 ± 9.35	0.583
Relative CVR	**APOE4+ (*n* = 99)**	**APOE4+ (*n* = 55)**	**APOE4− (*n* = 150)**	**APOE4− (*n* = 98)**	
Gray matter (a.u.)	1.22 ± 0.03	1.22 ± 0.03	1.23 ± 0.03	1.23 ± 0.03	0.254
Left ACA territory (a.u.)	1.29 ± 0.16	1.32 ± 0.19	1.33 ± 0.19	1.33 ± 0.19	0.073
Right ACA territory (a.u.)	1.23 ± 0.14	1.24 ± 0.14	1.27 ± 0.15	1.28 ± 0.17	0.212
Left MCA territory (a.u.)	1.20 ± 0.14	1.24 ± 0.15	1.24 ± 0.14	1.22 ± 0.12	0.031
Right MCA territory (a.u.)	1.31 ± 0.14	1.34 ± 0.14	1.34 ± 0.13	1.34 ± 0.15	0.250
Left PCA territory (a.u.)*	1.40 ± 0.25	1.29 ± 0.24	1.31 ± 0.21	1.31 ± 0.24	**0.020**
Right PCA territory (a.u.)*	1.45 ± 0.29	1.35 ± 0.24	1.35 ± 0.26	1.37 ± 0.25	**0.021**
Cerebral Pulsatility	**APOE4+ (*n* = 99)**	**APOE4+ (*n* = 55)**	**APOE4− (*n* = 148)**	**APOE4− (*n* = 98)**	
Gray matter (a.u.)	143.83 ± 39.71	147.11 ± 44.30	145.45 ± 40.69	159.16 ± 46.19	0.771
Left ACA territory (a.u.)	139.62 ± 42.67	143.43 ± 47.16	143.01 ± 42.97	154.49 ± 49.04	0.931
Right ACA territory (a.u.)	136.88 ± 43.14	141.84 ± 47.34	139.48 ± 42.33	152.75 ± 49.18	0.820
Left MCA territory (a.u.)	150.46 ± 45.45	154.07 ± 49.98	152.11 ± 44.67	166.23 ± 50.23	0.721
Right MCA territory (a.u.)	156.98 ± 47.53	161.12 ± 54.46	158.00 ± 47.28	176.52 ± 56.60	0.654
Left PCA territory (a.u.)	131.48 ± 34.30	133.88 ± 36.77	132.66 ± 35.76	143.54 ± 39.42	0.868
Right PCA territory (a.u.)	134.44 ± 33.27	137.55 ± 37.78	135.57 ± 36.10	146.90 ± 39.46	0.766

Group comparisons were evaluated only across time point 1; *APOE4+*, individuals with the APOE4 genotype; *APOE4−*, individuals without the APOE4 genotype; *RBANS*, Repeatable Battery for Assessment of Neuropsychological Status; *CVR*, cerebrovascular reactivity; *ACA*, anterior cerebral artery; *MCA*, middle cerebral artery; *PCA*, posterior cerebral artery; *significant *p*-values following Bonferroni-Hochberg correction

Mental Health University Institute Research Ethics Board. All participants from the PREVENT-AD study signed the informed consent forms in accordance with the declaration of Helsinki.

APOE genotyping

APOE genotyping was conducted to identify the allelic variants rs429358 and rs7412. Genomic DNA was extracted from 200 µl of whole blood using the QIASymphony apparatus and the DNA Blood Mini QIA Kit (Qiagen, Valencia, CA, USA). Detailed procedures for APOE genotyping can be found here [28]. In this study, individuals carrying at least one ε4 allele (either heterozygous or homozygous) were classified as APOE4 carriers (APOE4+). Those with only ε2 and ε3 alleles were categorized as non-carriers (APOE4−).

MRI acquisition

The MRI data were collected at the Douglas Research Center on a 3 Tesla Siemens PrismaFit scanner using a 32-channel head coil. Multi-echo resting state blood oxygenation level dependent (BOLD) fMRI were acquired using a 2D multiband gradient echo echo planar imaging sequence (voxel size = 3 mm isotropic, field of view (FOV) = 240 × 240 × 144 mm, repetition time = 1.0 s, echo times = 12.00/30.11/48.22 ms, flip angle = 48°, phase encoding direction = posterior to anterior, MB factor = 4, volumes = 512, scan duration = 604 s). For anatomical co-registration, T1-weighted data were obtained using a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (voxel size = 1 mm isotropic, FOV = 192 × 256 × 256 mm, repetition time = 2.3 s, echo time = 2.96 ms, inversion time = 0.9 s, flip angle = 9°, phase encoding direction = posterior to anterior).

Image processing

BOLD data at each echo time underwent motion correction with FSL *mcflirt*, followed by brain extraction with the *Brain Extraction Tool (BET)*. Temporal alignment of slices was then applied using FSL *slicetimer*. T1-weighted anatomical images were also skull stripped using *BET*, after which intensity non-uniformity was corrected using advanced normalization tool's (ANTs) *N4BiasFieldCorrection*. Co-registration of the BOLD data to the T1-weighted images was performed using a rigid body alignment of ANTs. After preprocessing of each echo, denoising of the multi-echo BOLD data was conducted with *tedana*. Lastly, spatial smoothing was applied to the denoised BOLD data using a Gaussian kernel with 6 mm full-width at half maximum (FWHM).

Image analysis

Relative CVR was obtained from the preprocessed resting state BOLD fMRI data, acquired without external CO_2 sampling [10]. Instead, spontaneous fluctuations in cerebral CO_2 were inferred from the lower frequencies of the BOLD signal, a technique which has been validated in previous work as a reliable proxy [30]. The BOLD time series were time domain-filtered (0–0.1164 Hz) using scipy, extracting a relative measure of resting CO_2 fluctuation. The filtered BOLD data was used as a regressor in a general linear model to compute voxel-wise CVR indices. Then, these CVR indices were normalized to the global brain average to yield a relative CVR map. Lastly, the relative CVR maps were normalised to MNI-152 space using ANTs.

CP was measured from the unprocessed first echo of the resting state BOLD fMRI data with the Hypersampling by Analytic Phase Projection -Yay (Happy) tool from Rapidtide program (https://doi.org/10.5281/zenodo.814990) [11]. The Happy algorithm computes pulsatility by analyzing the BOLD signal amplitude variations across a cardiac cycle. Notably, it does not require external plethysmography data, as the cardiac waveform is reconstructed directly from the BOLD signal, in which cardiac information is inherently embedded. Happy uses the highest signal-to-noise ratio (SNR) voxels to estimate the cardiac trace using a hypersampling technique to compensate for the long repetition time, which is then refined using a deep learning–based denoising filter. Since the BOLD signal originates from venous blood, Happy captures pulsatility through the passive expansion of veins in response to flow and pressure changes during the cardiac cycle relayed by both upstream and local vessels, providing a measure of local CP. The CP maps were generated from the Happy tool using the unprocessed first echo BOLD data, along with a binary brain mask (derived from the brain extraction step in the image

processing) and slice timing information. Unprocessed data is required because temporal filtering can distort or remove the high-frequency necessary for the cardiac waveform reconstruction. Motion correction was omitted since it could disrupt both acquisition timing and spatial alignment [11].

Data quality was assessed through both visual inspection of the CP and relative CVR maps, as well as by identifying outliers-participants with mean CP or relative CVR values within whole gray matter exceeding 3 standard deviations from the group mean. For relative CVR, 1 non-carrier participant was excluded due to poor data quality, and 3 participants (2 APOE4 carriers and 1 non-carrier) were identified as outliers. For CP, 2 participants (1 APOE4 carrier and 1 non-carrier) were excluded for poor data quality, and 4 participants (1 APOE4 carrier and 3 non-carriers) were considered outliers.

Region of interest (ROIs) analyses were conducted to extract CP and relative CVR from a 3D cerebral arterial atlas [31], including territories supplied by the left and right anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA). Gray matter segmentation of the MNI-152 template was performed using FSL *FAST*, and the resulting mask was applied to the ROIs to restrict the extraction of relative CVR and CP values to gray matter only.

Cognitive assessment

Cognitive function was evaluated using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) [32], a standardized tool designed to examine global cognitive functioning and detect deficits, particularly in older adults. The RBANS provides a total index score derived from five cognitive domains including immediate memory, delayed memory, language, attention, and visuospatial and constructional abilities. A detailed flowchart outlining the RBANS domains and their associated subtests is presented in Fig. S1.

Statistical analysis

Baseline group differences in age, sex, education, total scale index score (RBANS), relative CVR, and CP across the whole gray matter and ROIs were assessed using ANCOVA and binomial regression. The effects of age on relative CVR and CP within the whole gray matter in the whole sample were explored using multiple linear regressions. Linear mixed-effects models were performed to evaluate longitudinal changes in relative CVR and CP between APOE4 carriers and non-carriers across all participants. These models included random effects for relative CVR or CP, and fixed effects for age, time point, APOE4 status, sex, and an APOE4 status × time point interaction term. This interaction term was used to evaluate group-level differences over time. If significant interactions were observed, follow-up APOE disaggregated linear mixed-effects analyses were conducted to examine potential APOE4-specific longitudinal effects.

Sex-disaggregated linear mixed-effects analyses were also performed to explore sex-specific effects of APOE4 status on relative CVR and CP, adjusting for age and time point. Additionally, associations between relative CVR, CP, and the total index score from the RBANS were examined using linear mixed-effects models in the whole sample and by APOE4 status, controlling for age, sex, time point, and education. All statistical tests were corrected for multiple comparisons using the Bonferroni-Hochberg procedure ($p < 0.05$) [33].

Results

Demographic characteristics, group average values, and group differences in all parameters at Time Point 1, including CP and relative CVR, are presented in Table 1. Additionally, CP and relative CVR values stratified by APOE4 status, time point, and sex are shown in Table S1.

In baseline comparisons, APOE4 carriers (APOE4+) were significantly younger ($p = 0.024$; $\eta^2 p = 0.020$) than non-carriers (APOE4−), but we observed no other significant differences in demographic parameters. APOE4+ individuals also exhibited significantly higher relative CVR in the left ($p = 0.020$; $\eta^2 p = 0.022$) and right ($p = 0.021$; $\eta^2 p = 0.021$) PCA territories. No other significant group differences in relative CVR and CP were observed. In the whole sample, age was negatively associated with relative CVR ($p = 0.039$; t-stat $= -2.07$) and positively linked with CP ($p = 0.024$; t-stat $= 2.27$) in the whole gray matter, as displayed in Fig. S2.

Group differences in longitudinal relative CVR and CP

The effects of APOE4 status on longitudinal relative CVR are displayed in Fig. 1. Two distinct patterns were observed in the MCA and PCA territories. In the left MCA territory, while no longitudinal change in relative CVR was observed in the whole group, individuals with APOE4+ revealed a significant increase in relative CVR over time compared to individuals with APOE4− ($p = 0.016$; t-stat = 2.43), with males exhibiting higher relative CVR than females ($p < 0.001$; t-stat = −6.05). In the left PCA, a decline in relative CVR over time was observed in the whole sample ($p = 0.011$; t-stat = −2.55). Additionally, APOE4+ individuals showed a significant decrease in relative CVR over time in the left PCA, as compared to APOE4− individuals ($p = 0.012$; t-stat = −2.52), with females revealing higher relative CVR than males ($p < 0.001$; t-stat = 5.09). No significant APOE group interactions in longitudinal CP were detected.

Group-specific effects in longitudinal relative CVR

To investigate the presence of group-specific effects, we repeated the same models in data disaggregated for APOE4 status. In the APOE4 carrier group (APOE4+), the decrease in relative CVR over time in the left PCA remained significant ($p < 0.001$; t-stat = −3.63), with males demonstrating lower relative CVR than females ($p < 0.001$; t-stat = 3.64) (Fig. 2). No significant longitudinal changes in relative CVR were found among non-carriers (APOE4−).

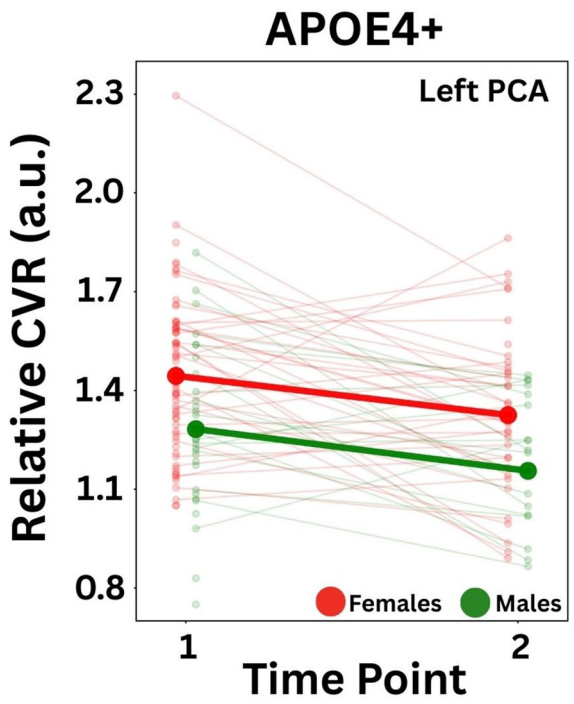

Fig. 2 APOE4-specific effects on relative CVR. Linear mixed-effects model revealing a significant decrease in relative CVR in individuals with the APOE4 genotype (APOE4+) within the left PCA territory. Sex differences are shown with lower relative CVR in males with APOE4+ compared to females with APOE4+

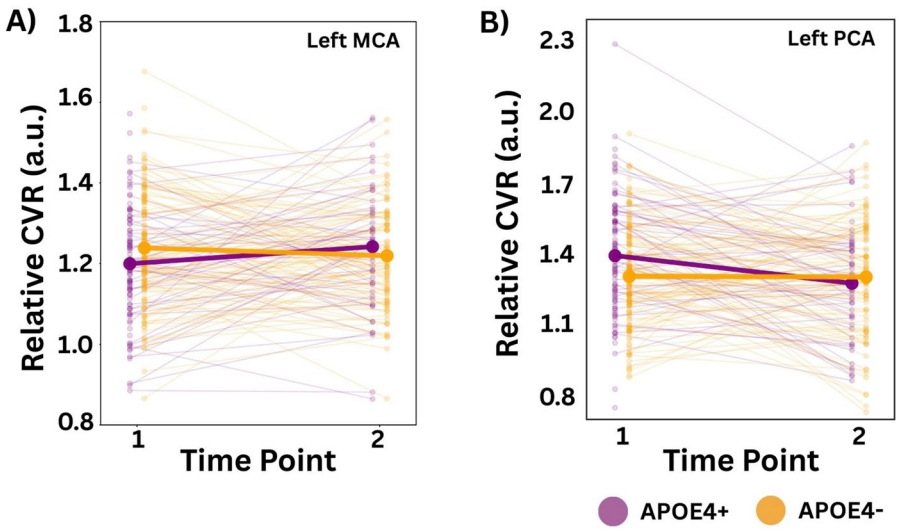

Fig. 1 Group differences in the longitudinal effects of relative CVR. Linear mixed-effects model results exhibiting significant group differences between individuals with the APOE4 genotype (APOE4+) and individuals without the APOE4 genotype (APOE4−) in **A** the left MCA and **B** the left PCA territories

APOE4 disaggregated analyses were not conducted for CP analyses, as no significant group-level differences were identified in the whole sample.

Sex-specific effects in relative CVR

Linear mixed-effects models were conducted using sex-disaggregated analyses to investigate potential sex-specific effects of APOE4 status on relative CVR. Females with APOE4+ revealed significantly lower relative CVR compared to females with APOE4− in the right ACA territory ($p = 0.007$; t-stat = −2.72) (Fig. 3). No significant group differences in relative CVR were observed in males and no significant effects were found in CP analyses.

Group differences in the relationship between relative CVR and cognition

In all participants, APOE4+ individuals showed significantly stronger positive associations between relative CVR and the RBANS total scale index score compared to APOE4− individuals, in both the whole gray matter ($p = 0.013$; t-stat = 2.48) and the right MCA territory ($p = 0.002$; t-stat = 3.19) (Fig. 4). In APOE4 status disaggregated analyses, these relationships remained significant in the whole gray matter ($p = 0.007$; t-stat = 2.74) and the right MCA territory ($p = 0.020$; t-stat = 2.36) within the APOE4+ group. No significant correlations were observed in the APOE4− group, and no effects were identified in CP analyses.

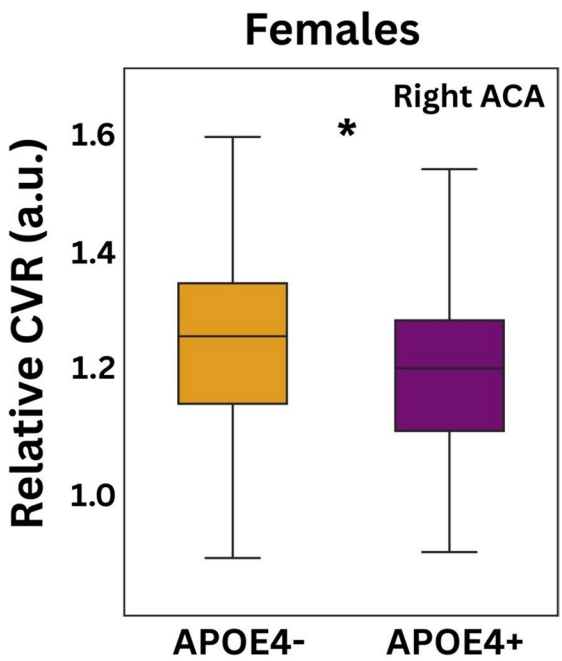

Fig. 3 Sex-specific effects of APOE4 status on relative CVR. Box plots of linear mixed-effects model analyses demonstrating lower relative CVR in females with the APOE4 genotype (APOE4+) compared to females without the APOE4 genotype (APOE4−) within the right ACA territory

Discussion

This study investigated the effects of APOE4 status on longitudinal CVR and CP in cognitively intact APOE4 carriers and non-carriers with a familial history of Alzheimer's disease. In cross-sectional group comparisons at baseline, APOE4 carriers had higher relative CVR in the bilateral PCA territory compared to non-carriers. Longitudinal analyses revealed that this higher PCA territory relative CVR was counteracted by a larger decline over two and a half years in APOE4 carriers, as compared to non-carriers. In contrast, relative CVR in the MCA territory was found to increase modestly over time in APOE4 carriers as compared to non-carriers, though this increase was not found to be significant in APOE4 status disaggregated analyses. Additionally, sex differences were identified in the left PCA of APOE4 carriers, with females exhibiting higher relative CVR than males across both time points, but lower relative CVR than non-carrier females in the right ACA. Importantly, these relative CVR effects carry functional significance as we also identified significant relationships between CVR and cognition. We observed both group-level and group-specific positive correlations among APOE4 carriers between relative CVR in the whole gray matter and right MCA and the RBANS total scale score index. No significant group differences were observed in measures of CP. Together, these findings suggest that cognitively intact APOE4 carriers exhibit a more pronounced decline in relative CVR compared to non-carriers, whereas APOE4 status appears to have no significant effects on CP in this population.

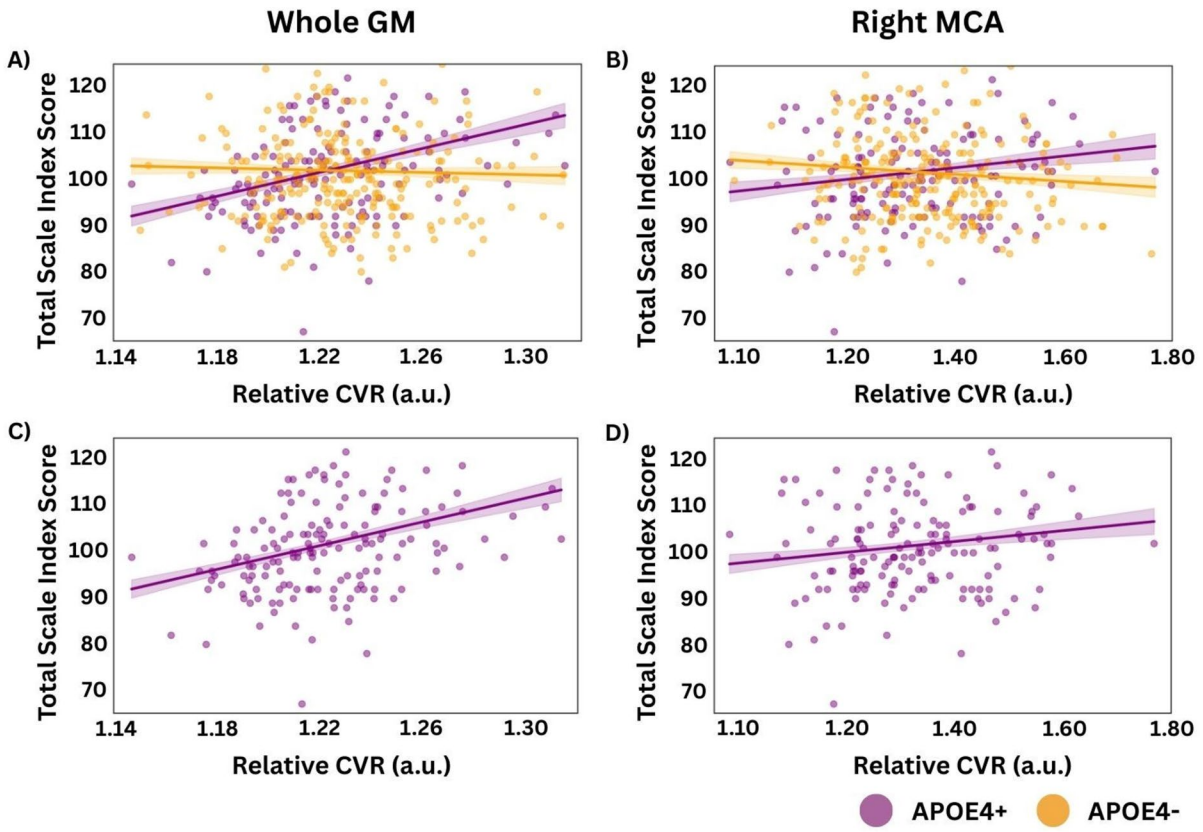

Fig. 4 Effects of relative CVR on cognition in APOE4 carriers. Linear mixed-effects model presenting significant group differences in the relationships between relative CVR and total scale index score in **A** the whole gray matter and **B** the right MCA territory. Among APOE4 carriers (APOE4+), significant associations between relative CVR and total scale index score are observed in **C** the whole gray matter and **D** the right MCA territory

Impact of APOE4 status on longitudinal relative CVR

APOE4 status had a significant impact on the trajectory of relative CVR over time across two AD-relevant cerebral arterial regions [34]. In post hoc analyses, APOE4 carriers showed decreasing relative CVR in the left PCA territory. To our knowledge, no other studies have assessed the longitudinal changes in CVR in this population. Interestingly, APOE4 carriers showed higher baseline relative CVR in the bilateral PCA compared to non-carriers. These findings contrast with cross-sectional studies in individuals without cognitive impairment where APOE4 carriers have shown reduced CVR compared to non-carriers [16, 35]. Nevertheless, our observation of a larger decline in relative CVR in the left PCA of APOE4 carriers suggests increased cerebrovascular vulnerability in this population. Reductions in CVR are well documented in individuals with MCI [36–38] and individuals with AD [14, 39–41]. These CVR deficits may have important downstream effects. Previous work has shown that cognitively intact APOE4 carriers with lower CVR have more white matter hyperintensities [42], and reduced CVR and the APOE4 genotype together have been linked to an increased risk of MCI conversion to AD [43].

Our findings revealed regional group differences, most prominently in the left PCA territory. Previous MRI-based research in a similar population reported lower CVR in APOE4 carriers across the whole brain and within the hippocampus [16], consistent with our longitudinal observations in the left PCA territory, which includes part of the hippocampus [44]. The hippocampus plays a critical role in cognitive functions such as memory and is among the first regions

affected in the early stages of AD [45]. Additionally, this region is particularly vulnerable to vascular injuries [44, 46]. Thus, the impaired vascular reserve of cognitively intact APOE4 carriers within this area may contribute to early cognitive decline. However, the specific regions of the cerebral vasculature involved in neurodegeneration remain unclear [47], likely due to the considerable variation in the underlying pathologies of these conditions [48]. Thus, our observation of greater decline in the PCA territory of APOE4 carriers aligns with prior evidence showing that APOE4 carriers are at a heightened risk for early cerebrovascular health decline [49–51]. Together, these findings support the hypothesis that APOE4 carriers are particularly vulnerable to early cerebrovascular changes associated with AD pathology, which is characterized by impaired CVR.

Sex-specific effects were revealed, with females carrying the APOE4 genotype demonstrating reduced relative CVR compared to female non-carriers. These findings highlight the importance of conducting sex-disaggregated analyses in assessing the impact of APOE4 status. Supporting our results, a previous study has shown that females with APOE4 show a steeper age-associated decrease in CBF compared to males with APOE4 [8]. Interestingly, they observed higher baseline perfusion in females with APOE4 compared to males with APOE4 [8]. This aligns with our results of lower relative CVR in male APOE4 carriers compared to female APOE4 carriers in the left PCA territory. Additionally, recent evidence reports reduced age-related CVR in older adult males compared to females [52, 53]. Although we did not identify sex differences in the rate of relative CVR decline, it may be that sex differences in rates of decline take longer to develop. Longer follow-up periods should be investigated in future studies to determine whether this is the case.

Impact of APOE4 status on longitudinal CP

Our findings revealed no significant effects of APOE4 status on local CP. This is consistent with previous studies showing null pulsatility differences between cognitively intact APOE4 carriers and non-carriers in large vessels using pulse wave velocity [54], pulse pressure [55] and pulsatility index [21, 56, 57]. Thus, individuals with APOE4 appear to follow a similar aging trajectory in terms of CP to individuals without APOE4. However, it is also possible that the effects of APOE4 on pulsatility may develop later in the course of disease, since a previous study [21] found that the APOE4 genotype and a familial history of AD were associated with higher pulse wave velocity compared to non-carriers without a familial history of AD, but only participants with an MCI or AD showed higher pulsatility [21]. Therefore, our findings suggest that APOE4 status does not significantly influence longitudinal effects of CP, though future studies with longer longitudinal follow-up are needed to determine whether this remains the case over the longer term and with advancing illness.

APOE4 status and cerebrovascular mechanisms

Cerebral amyloid angiopathy (CAA) may represent a potential underlying mechanism for the observed CVR decline in the left PCA territory. CAA is characterized by the accumulation of amyloid beta in the walls of blood vessels [51], predominantly affecting the posterior brain regions [58, 59], and increases the risk for dementia [60, 61]. Both a familial history of AD [62] and the presence of the APOE4 genotype [63, 64] heighten the risk of developing CAA. Prior work has demonstrated reduced CVR in individuals with CAA compared to healthy controls [65], including impaired CVR responses to visual stimulation [66]. Although our study was not designed to directly assess CAA-related pathology, these findings underscore the need for future studies to elucidate the role of CAA in cerebrovascular dysfunction in genetically predisposed individuals for AD.

Relative CVR appeared more sensitive than CP in detecting cerebrovascular decline in APOE4 carriers compared to non-carriers. Interestingly, these results may suggest a distinct pathophysiological cascade underlying cerebrovascular dysfunction in this population. CVR primarily reflects endothelial health and arteriole smooth muscle tone, capturing the vasodilatory capacity to enable increased blood flow and substrate delivery support to the surrounding tissues [67, 68]. Conversely, CP measures the transmission of pulsatile flow, indicative of mechanical stress within the vasculature [69]. Moreover, CP is greatly influenced by the attenuation of pulsatile waves from larger arteries [70], whereas CVR is more closely tied to microvascular endothelium regulation [71]. In postmortem analyses of AD brains, endothelial disruptions

indicative of microvascular injury are more pronounced than markers of macrovascular dysfunction [72]. In preclinical studies, the APOE4 allele has been associated with impaired endothelial nitric oxide release [73, 74]. This disruption of nitric oxide activity in mice has been proposed as a potential mechanism that may also be present in humans [75]. Furthermore, vasodilatory dysfunction has been shown to be an important contributor to AD pathology [76, 77]. Thus, our findings suggest that although APOE4 carriers may follow a similar aging trajectory regarding pulsatile dampening, they may experience a steeper decline in endothelial function, as evidenced by reduced vasodilatory capacity. Future studies should investigate targeted intervention aimed to improve CVR as a biomarker of endothelial health in APOE4 carriers.

Links with cognition

Individuals with the APOE4 genotype showed significant associations between relative CVR and cognitive performance within the whole gray matter and right MCA territory. Given that the RBANS total score index was designed to evaluate cognitive decline [32], reduced relative CVR in APOE4 carriers may indicate an elevated risk for cognitive impairment. To our knowledge, this is the first study to investigate how APOE4 status moderates the relationship between CVR and cognition in this population. These results are consistent with previous studies which have reported significant APOE4-related mediation effects of cerebral perfusion [6] and brain volumes [7] on cognition. Additionally, APOE4 is a well-established genetic risk for cognitive decline [78]. These findings suggest that cerebrovascular function may modulate the impact of APOE4 on cognitive outcomes [49]. Thus, CVR may be an important biomarker for early cerebrovascular deficits that impact global cognition in individuals carrying the APOE4 allele. While the RBANS total index score provides a standardized assessment of global cognition, it may be less sensitive to subtle cognitive deficits in cognitively intact individuals and to vascular-related changes. Future research should assess the role of APOE4 status in moderating the relationship between CVR and specific cognitive domains relevant to AD and dementia. Furthermore, identifying effective clinical interventions to improve CVR may serve as an important future direction for mitigating the risks associated with the APOE4 genotype on cognition.

Limitations

This study has several limitations, as both the relative CVR and CP methods are based solely on the resting state fMRI BOLD signals. The relative CVR approach, a gas-free technique, depends on natural fluctuations in participants' breathing to induce sufficient cerebral CO_2 changes to capture CVR. Furthermore, this method only provides relative measures of CVR since absolute values of CO_2 in millimeters of mercury were not acquired. The CP technique used in this study relies on the accurate measurement of the cardiac cycle without any plethysmography data. Additionally, the CP measurement is based on the BOLD signal, which reflects multiple vascular and metabolic processes and therefore lacks physiological specificity. Despite these limitations, both techniques have been validated against gold standards methods in previous research [10, 11]. Additionally, relative CVR and CP can be applied retrospectively to datasets [79] that include only resting state BOLD fMRI, making them practical tools in many research settings. Nevertheless, further validation is necessary before these methods can be reliably used in clinical populations. In the sex-specific subgroup analyses, the smaller male sample limited our ability to detect potential effects of APOE4 status on longitudinal relative CVR in males. Thus, while the observed effects in females support the importance of the right ACA, male-specific findings overall should be interpreted with caution. This study did not investigate the influence of cardiovascular risk profile or AD biomarkers (e.g., tau, amyloid beta) on relative CVR and CP. Future research is warranted to evaluate how these factors affect vascular function in APOE4 carriers. Lastly, longitudinal studies with extended follow-up periods (e.g., 5 to 10 years) are warranted, as the 2.5-year timeframe in this study may be too short to fully capture cerebrovascular changes associated with APOE4 status, particularly in a healthy and cognitively intact population.

Conclusions

In summary, our findings revealed that APOE4 carriers exhibit regional decline in relative CVR compared to non-carriers. Sex differences and sex-specific effects were observed in the relationship between APOE4 status and relative CVR. Additionally,

APOE4 status was positively associated with relative CVR and cognitive performance. In contrast, APOE4 status did not influence cross-sectional or longitudinal changes in CP. Thus, these results suggest that relative CVR could be an important and specific early biomarker of cerebrovascular health and cognitive function in individuals with the APOE4 genotype. Future research should investigate whether preventative interventions, such as cognitive and exercise training, can enhance cerebrovascular health in APOE4 carriers prior to the onset of cognitive decline and AD.

Acknowledgement We would like to acknowledge the PREVENT-AD research group for providing the dataset used in this study. The program was founded by Drs. John C. S. Breitner, Judes Poirier, and Pierre Etienne at the Douglas Hospital Research Center and McGill University, currently led by Dr. Sylvia Villeneuve (Director), Dr. Judes Poirier (Co-Director), and Jennifer Tremblay-Mercier (Study Coordinator). PREVENT-AD is the result of collaborative efforts from numerous co-investigators, staff, students, and postdoctoral fellows, with key contributions from authors affiliated with the project, including R. Nathan Spreng and Sylvia Villeneuve. We sincerely thank all participants for their involvement. We also thank Jennifer Tremblay-Mercier for data access, and acknowledge the contributions of Dr. Pedro Rosa-Neto, Dr. Poirier's laboratories, and the LORIS team at the Montreal Neurological Institute. For details on the PREVENT-AD project, see https://prevent-alzheimer.net/?page_id=42&lang=en. The CP pipeline used in this study came from Frederick, B, rapidtide [Computer Software] (2016–2024). Available from https://github.com/bbfrederick/rapidtide. https://doi.org/10.5281/zenodo.814990.

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Funding Funding for this project was supported by the Heart and Stroke Foundation of Canada (to Zacharie Potvin-Jutras) and Brain Canada (to Zacharie Potvin-Jutras). This study was also supported by the Canadian Natural Sciences and Engineering Research Council (RGPIN-2024-06455, to Claudine J. Gauthier), the Michal and Renata Hornstein Chair in Cardiovascular Imaging (to Claudine J. Gauthier) and Canadian Institutes of Health Research (468740, to Claudine J. Gauthier), the Alzheimer's Association (AARG-22-927100 to R. Nathan Spreng), and the National Institutes of Health (NIA R01 AG068563 to R. Nathan Spreng).

Declarations

Conflict of interest The authors declare no competing interests.

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