Cerebrovascular response to exercise interacts with individual genotype and amyloid-beta deposition to influence response inhibition with aging

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Abstract

The etiology of cognitive dysfunction associated with Alzheimer's disease (AD) and dementia is multifactorial. Yet, mechanistic interactions among key neurobiological factors linked to AD pathology are unclear. This study tested the effect of interactions between cerebrovascular function, individual genotype, and structural brain pathology on response inhibition performance, an early and sensitive indicator of cognitive executive dysfunction with aging.

We quantified cerebrovascular response (CVR) to moderate-intensity aerobic exercise using transcranial doppler ultrasound and global amyloid-beta (Aβ) deposition using positron emission tomography in a group of cognitively normal older adults genotyped as *APOE4* carriers and noncarriers. We quantified response inhibition during a cognitive Stroop test.

Individuals with blunted CVR possessed greater Aβ deposition. There was CVR-by-carrier status-by-Aβ interaction on response inhibition. Blunted CVR was associated with impaired response inhibition specifically in carriers. Despite having greater Aβ deposition, carriers with higher CVR demonstrated better response inhibition.

Cerebrovascular interactions with individual genotype and structural brain pathology may provide a physiologically-informed target for precision-medicine approaches for early treatment and prevention of cognitive dysfunction with aging.

Keywords

cardiovascular; cognition; executive function; Stroop; Alzheimer's disease; transcranial Doppler; amyloid plaque; *APOE*

1. Introduction

Among a growing older adult population, the development of cognitive dysfunction is common but poorly understood. Profound individual differences in aging trajectories allow some older adults to maintain cognitive performance to the end of life while others suffer the debilitating loss of cognitive function associated with Alzheimer's disease (AD) and related dementias (ADRD). The field of aging neurobiology increasingly recognizes cognitive decline with aging as having a mixed pathology and multifactorial etiology (Iturria-Medina et al., 2016, 2017); thus, a trans-disciplinary approach is imperative to enhance our understanding of the diverse and interacting mechanisms leading to ADRD. In the present study, we provide an initial characterization of interactions among key neurobiological factors that have been identified as significant contributors to the development of cognitive dysfunction and AD, including cerebrovascular function (Iadecola, 2004; Xie et al., 2016; Ouellette and Lacoste, 2021), structural brain pathology (Jack et al., 2010; Hampel, 2013), and individual genotype (Heffernan et al., 2016). Further, we investigate the behavioral relevance of these interactions on response inhibition performance in cognitively normal older adults.

Early detection of pathologic disease processes is imperative as a first step towards the development of effective prevention strategies and interventions for age-related neuropathologies, in particular those involving vascular aging (e.g. AD, vascular dementia, endothelial dysfunction, vascular Parkinsonism) (Pantsiou et al., 2018). One of the earliest behavioral manifestations of mild cognitive impairment (MCI) that can progress to dementia has been identified as impaired cognitive executive function (Hutchison et al., 2010; Kirova et al., 2015). Specifically, the ability to suppress an undesired default or automatic response in the presence of interfering stimuli, or *response inhibition*, can distinguish between older adults who are cognitively normal versus MCI (Hutchison et al., 2010). Additionally, cortical activity dysfunction during response inhibition may underpin cognitive interference in motor behavior (Palmer et al., 2021), a common observation in older adults with MCI and early-stage AD (Coelho et al., 2012; Kirova et al., 2015), and older adults at high genetic risk for AD (Whitson et al., 2018). Yet the neurobiologic and physiologic mechanisms that contribute to the early-stage development of impaired response inhibition behavior remain elusive. Such knowledge could be leveraged towards the development of prevention strategies for clinical syndromes in the early stages of MCI, AD and related dementias.

Cerebrovascular pathology is commonly detected in older adults who present with behavioral deficits associated with clinical AD syndrome (Lorius et al., 2015; Wolters Frank J. et al., 2017; Sweeney et al., 2018; Bracko et al., 2021) and is linked to biomarkers of brain pathology, particularly the deposition of amyloid-beta (Zlokovic et al., 2005; Sisante et al., 2019; Solis et al., 2020). The dynamic characterization of cerebral blood flow response

under conditions of physiologic stress enables the assessment of the cerebrovascular regulatory response to a wide variety of physiological inputs common in daily activities (Ferguson, 2014), including altered perfusion pressure, arterial blood gas, neural activity, and brain metabolism (Smith and Ainslie, 2017). Indeed, cerebrovascular response under such conditions of *physiologic stress* (e.g. sit-to-stand positional changes, aerobic exercise, heat stress, hypoxia) appear to play an important role in maintaining brain metabolism and function with aging (Bundo et al., 2002; Ogoh and Ainslie, 2009a, 2009b; Sato et al., 2011; Ogoh et al., 2013; Steinback and Poulin, 2016), as the effects of repeated transient disruption of blood, glucose, and oxygen supply to brain tissue accumulate over time (Tarumi and Zhang, 2018). Impaired cerebral blood flow can promote ischemic microlesions (Iadecola, 2004), and alter blood-brain barrier trafficking of amyloid-beta (Aβ) (Zlokovic et al., 2005), slowing the clearance of Aβ and promoting its accumulation in the brain.

Using transcranial Doppler ultrasound (TCD) to assess cerebral artery blood flow velocity, our group previously found that older adults demonstrate a blunted cerebrovascular response (CVR) during an acute bout of moderate-intensity aerobic exercise (Sisante et al., 2019; Alwatban et al., 2020), which may serve as an early indicator of cerebrovascular dysfunction in preclinical older adult populations (Alwatban et al., 2020). Further, CVR was associated with elevated levels of Aβ deposition, a hallmark of AD, in the brains of cognitively normal older adults (Sisante et al., 2019). Interestingly, cerebrovascular assessments performed at rest have not been able to discriminate cognitive status (Xie et al., 2016) or Aβ levels (Sisante et al., 2019) in these preclinical older adult populations, suggesting that *acute aerobic exercise assessment paradigms may enhance the detection of subtle impairments in vascular function in the early stages of disease*. Consistent with this theory, dysfunctional cerebral blood flow has been detected in older adults with MCI (Xie et al., 2016) and precedes the onset of dementia, implicating its early mechanistic role in cognitive decline with aging (Iadecola, 2004). However, despite the apparent role of CVR dysfunction in the preclinical stages of brain pathology, the interactions between CVR and other key neurobiological factors linked to early-stage cognitive impairments and AD pathology remain unknown.

Possession of *Apolipoprotein E4* (*APOE4*), the strongest known genetic risk factor for sporadic Alzheimer's disease (Heffernan et al., 2016), is strongly linked to cerebrovascular dysfunction (Montagne et al., 2020). Cognitively normal older adults with an *APOE4* allele demonstrate a greater decline in cerebral blood flow with aging compared to noncarriers (Thambisetty et al., 2010), and an earlier blood-brain barrier breakdown that precipitates subsequent cognitive decline (Montagne et al., 2020). Recently, our group found that *APOE4* carriers with lowest resting conductance in middle cerebral artery blood flow had the greatest Aβ deposition, a relationship that was not present in noncarriers (Kaufman et al., 2021b). Yet, in the context of early-stage cognitive impairments, the behavioral relevance of APOE4 genotype in the presence of multifactorial aging pathologies among a heterogenous older adult population is poorly understood.

In this study, we aimed to 1) investigate the interactive effect of *APOE4* carrier status on the relationship between CVR to exercise and Aβ deposition and 2) test whether interactions between *APOE4* carrier status, CVR, and Aβ deposition affect cognitive performance

involving response inhibition in a group of cognitively normal older adults. We hypothesized that 1) older adults with the most robust CVR to a bout of moderate-intensity aerobic exercise would have the lowest levels of Aβ deposition, with the strongest effect in *APOE4* carriers, and 2) higher CVR would attenuate the negative effect of Aβ deposition on response inhibition performance, particularly in *APOE4* carriers.

2. Materials and Methods

2.1. Participants

We selected a subset of 70 older adults from a well-characterized data registry of 125 cognitively normal older adults from the University of Kansas Alzheimer's Disease Research Center (AHA 16GRNT30450008 (SB)) (Alwatban et al., 2020; Perdomo et al., 2020; Liu et al.). Our recruitment efforts within this cohort included those individuals with complete datasets for cerebrovascular function assessment, genetic *APOE* profiling, and structural neuroimaging for Aβ deposition. Inclusion criteria were (1) between 65 and 90 years old, (2) normal cognition with the absence of clinical dementia or cognitive impairment and (3) physical ability to exercise. Exclusion criteria were (1) insulin-dependent diabetes; (2) peripheral neuropathy; (3) active coronary artery disease (angina, myocardial infarction) within 2 years that, in the investigator's opinion, could pose a safety risk with exercise, unless cleared by the participant's physician; (4) congestive heart failure; (5) the presence of 1 or 2 *APOE2* alleles. The experimental protocol was approved by the University of Kansas Institutional Review Board (IRB#: STUDY00001444) and all participants provided written informed consent.

2.2. Acute bout of aerobic exercise on a recumbent stepper

Participants underwent a bout of moderate-intensity aerobic exercise on a recumbent stepper in an experimental protocol previously described in detail (Billinger et al., 2017; Ward et al., 2018; Witte et al., 2019). Briefly, participants arrived to the laboratory between 7:30–9:00am after abstaining from caffeine for 12 hours, physical activity for 24 hours, and consuming a large meal for 2 hours. The exercise testing room was quiet, dimly lit, and temperature controlled between 22 and 24 degrees Celsius. Following 8 minutes of quiet rest seated on the recumbent stepper (NuStep T5XR), participants began an exercise familiarization bout to determine target power. Following an 8-minute seated rest recording, participants began exercising on the recumbent stepper, maintaining a step rate of 120 steps-per-minute and beginning at a resistance of 40W. The work resistance was increased until the participant reached the target heart rage range of 40–60% of age-predicted heart rate reserve and maintained this target heart rate for one continuous minute (Billinger et al., 2017; Sisante et al., 2019). The participant then maintained exercise at this moderate-intensity hear rate zone for 8 minutes.

2.3. Cerebro- and cardiovascular assessment and analyses

During rest and exercise bouts, we measured left cerebral blood flow velocity using transcranial Doppler ultrasound (TCD) with a 2-MHz probe (RobotoC2MD, Multigon Industries) placed over the temporal window. If the left MCA signal was not obtainable, the right MCA was used. We used a 5-lead electrocardiogram for continuous heart rate

monitoring. All data were sampled at 500 Hz and acquired through an analog to digital data acquisition unit (NI-USB-6212, National Instruments) and custom written software operating in MATLAB (The Mathworks Inc). MCAv, MAP and end tidal CO_2 were synchronized across the cardiac cycle (Billinger et al., 2017; Ward et al., 2018; Sisante et al., 2019; Perdomo et al., 2020). Data with R-to-R intervals greater than 5 Hz or changes in peak blood flow velocity greater than 10 cm/s in a single cardiac cycle were considered not physiologically real and censored. Acquisitions with more than 15% of data points censored were discarded. Experimenters were blinded to Aβ deposition level, cognitive function, and *APOE* carrier status.

The mean MCA blood flow velocity was calculated during the 8-minute baseline rest and 8-minute moderate-intensity exercise bout. We calculated cerebrovascular response (CVR) as the difference between mean MCA blood flow velocity during exercise and mean MCA blood flow velocity at rest (Sisante et al., 2019). Across all participants (n=70), we calculated an average intra-trial coefficient of variation for mean MCAv under resting conditions of 8.0% and the moderate-intensity aerobic exercise condition of 9.1%.

2.4. Structural neuroimaging of amyloid-beta (Aβ) deposition

Participants underwent Florbetapir PET scans on a GE Discovery ST-16 PET/CT scanner at approximately 50 minutes after administration of intravenous florbetapir 18F-AV45 (370 MBq). Continuous acquisition of two 5-minute PET brain frames were summed and attenuation corrected (Vidoni et al., 2021). The global standardized update value ratio (SUVR) was calculated using standard procedures described previously (Liu et al.) to determine global Aβ deposition for each participant. Individuals were classified as having elevated Aβ deposition with global Aβ levels > 1.1, a threshold previously identified as a sensitive detector of neural plaques (Clark et al., 2012; Joshi et al., 2012) and that is associated cerebrovascular dysfunction in older adults (Sisante et al., 2019).

2.5. *APOE* genotyping

Whole blood was drawn and stored frozen at −80 degrees Celsius prior to genetic analyses using a Taqman single nucleotide polymorphism (SNP) allelic discrimination assay (ThermoFisher) to determine *APOE* genotype. Taqman probes were used to determine *APOE4, APOE3,* and *APOE2* alleles to the two *APOE*-defining SNPs, rs429358 (C_3084793_20) and rs7412 (C_904973_10) (Kaufman et al., 2021c; Vidoni et al., 2021). Individuals were classified as *APOE4* carrier in the presence of 1 or 2 *APOE4* alleles (e.g. E3/E4, E4/E4). Individuals with homozygous E3 (e.g. E3/E3) were classified as a noncarriers. Because *APOE2* is associated with reduced risk for Alzheimer's disease, all *APOE2* carriers, whether homozygous or paired with a different *APOE* allele), were excluded from analyses in the present study (Whitson et al., 2018; Kaufman et al., 2021a).

2.6. Cognitive behavior assessment

2.6.1.   Clinical neuropsychological test battery—The Uniform Data Set (UDS) neuropsychological test battery and the Clinical Dementia Rating (CDR) scale employed by the United States Alzheimer's Disease Research Center network (Morris, 1993; Monsell et al., 2016) were performed for all participants on a separate day. All participants completed a

standard in-person clinical and cognitive evaluation, during which the clinical CDR was performed by a trained clinician and the neuropsychological test battery by a trained psychometrist. Clinical and cognitive data were reviewed and finalized at a consensus diagnostic conference (Graves et al., 2015). All participants in the present analysis were rated as CDR = 0 and cognitively normal. Participant also completed a Mini-Mental State Exam (MMSE) (Folstein et al., 1975) (Table 1).

2.6.2. Response Inhibition Performance—Participants completed a Stroop test during which they were presented with three conditions: 1) Stroop word reading, where color words were printed in black ink, 2) Stroop color naming, in which rectangular color patches were shown, and 3) Stroop interference, in which color words were printed in an incongruent ink color and participants were instructed to ignore the word and state the color of the ink. Each of the three conditions was presented individually in a 45-second trial. The raw number of correct responses was recorded within the time limit for each condition.

The difference in the time for naming the colors in which the words are printed and the same colors printed in rectangles is the measure of the interference of conflicting word stimuli upon naming colors, standardized for speed differences between people (raw number of word interference on color /raw number of control color squares read) (Stroop, J, 1935).

We calculated response inhibition performance as the Stroop ratio, where:

$$Stroop \quad Ratio = \frac{\text{Stroop interference condition raw score}}{\text{Stroop color condition raw score}}$$

A Stroop ratio = 1.0 reflects perfect response inhibition performance and no interference of conflicting word stimuli. Here, the participant perfectly inhibited interfering word stimuli during the Stroop interference condition, with no slowing of response time relative to the control Stroop color condition. A Stroop ratio = 0.0 reflects poor response inhibition performance and complete failure to inhibit conflicting word stimuli on a color naming task. Here, the participant was unable to state any correct responses during the Stroop interference condition. Additionally, in the absence of response inhibition, we quantified a cognitive processing speed control condition as the Stroop color naming score normalized to the test time duration of 45 seconds.

2.7. Statistical analyses

We tested for normality and heterogeneity of variance of all data used for analyses using Kolmogorov-Smirnov and Levene's tests, respectively. To test the effect of *APOE4* carrier status on the relationship between CVR and Aβ, we performed two-way moderated multiple linear regression analysis after controlling for participant age and workload at moderate intensity exercise normalized to participant body weight. In an exploratory analyses, we tested whether individuals classified as possessing elevated global Aβ levels (>1.1 SUVR) displayed differential relationships between CVR and Aβ deposition in each *APOE4* carriers and noncarriers.

To test for interactions between *APOE4* carrier status, CVR, and Aβ deposition on response inhibition performance, we performed a three-way multiple linear regression analyses after controlling for participant age. Specifically included in the three-way model were CVR, *APOE4* carrier status, Aβ deposition, and the interaction CVR × carrier status × Aβ deposition. The relationship between Aβ deposition and response inhibition performance was compared for participants across the range of CVR to aerobic exercise. Additionally, we tested the behavioral specificity for the predictive ability of interactions between CVR, *APOE4* carrier status, and Aβ deposition by testing the three-way multiple regression model against the cognitive processing speed control condition.

In an exploratory analysis, we tested response inhibition performance in *APOE4* carriers and noncarriers as a function of CVR classification. Here, we dichotomized participants by the group median CVR value and performed a two-way analysis of variance (ANOVA). All analyses were performed using SPSS version 25 with an a priori level of significance set to 0.05.

3. Results

Among the 70 total participants included in analyses (67% female, 29% *APOE4* carriers, 71±5 yo) (Table 1), there were no significant differences between *APOE4* carriers and noncarriers in response inhibition performance (p=.301), age (p=.94), normalized workload (p=.966), gender distribution (p=.723), MMSE (p=.916), or CVR to aerobic exercise (p=.716) in carriers and noncarriers. *APOE4* carriers had greater levels of Aβ deposition compared to noncarriers (p=.02).

3.1. Relationship between cerebrovascular function and amyloid beta and effect of *APOE4*

After controlling for age and normalized workload, the two-way multiple regression model significantly predicted Aβ deposition, $F_{5,69}$=4.05, p=0.003, R^2=0.24, adjusted R^2=0.18. Regression coefficients and standard errors are detailed in Table 2. A higher CVR predicted lower Aβ deposition across all participants (p=.018) (Figure 1). Though *APOE4* carriers showed a stronger effect of CVR on Aβ deposition compared to noncarriers, the difference of this relationship was not significant (t=−0.50, p=.618). There was a main effect of *APOE* carrier status on Aβ deposition in the model, with *APOE4* carriers having greater Aβ deposition than noncarriers (p=.041) (Table 2).

Exploratory analyses revealed that the negative association between CVR and Aβ deposition was driven by individuals classified as having elevated Aβ levels (>1.1), with the strongest effect in *APOE4* carriers (Figure 1 B&C). We found differential relationships between CVR and Aβ deposition in *APOE4* carriers with elevated versus nonelevated Aβ levels(CVR- by-Aβ interaction, t=−2.39, p=.032) (Figure 1B), in which *APOE4* carriers classified as having elevated Aβ demonstrated a stronger negative effect of CVR on Aβ deposition compared to *APOE4* carriers classified as nonelevated Aβ (Figure 1B). In *APOE4* noncarriers, individuals with elevated Aβ levels also showed a stronger negative association between CVR and Aβ deposition compared to those with nonelevated Aβ levels (Figure 1C), but differences in this effect were not significant (CVR- by- Aβ interaction, t=−1.11, p=.272).

3.2. Interactions between cerebrovascular function, amyloid-beta, and APOE genotype as predictors of response inhibition behavior

After controlling for age and normalized workload, the multiple regression model significantly predicted response inhibition performance, $F_{6,69}$=2.92, p=.014, R^2=0.22, adjusted R^2=0.14. Regression coefficients and standard errors are detailed in Table 3. There was a significant three-way interaction between CVR, *APOE* carrier status, and Aβ deposition (t=2.68, p=.010), indicating differences in the predictive value of Aβ deposition and CVR on response inhibition performance for *APOE4* carriers and noncarriers. Specifically, *APOE4* carriers with higher CVR demonstrated better response inhibition performance (p<.001), while noncarriers showed no significant effect of CVR (p=.112) (Figure 2). As illustrated in Figure 3A & B, *APOE4* carrier status moderated the interactive effect of CVR and Aβ deposition on response inhibition.The model predicted that *APOE4* carriers who achieved a high CVR would show a positive relationship between Aβ deposition and response inhibition, where carriers with a robust CVR to an acute bout of aerobic exercise were predicted to perform better on the response inhibition task despite having high levels of Aβ deposition. In contrast, the model predicted that Aβ deposition would have no effect on response inhibition performance in *APOE4* carriers who had lower CVR (Figure 3A). Noncarriers showed a lower effect of CVR on the relationship between Aβ deposition and response inhibition, where older adult noncarrier performance was independent of their CVR to the exercise bout (Figure 3B).

When participants were dichotomized by the group median CVR value (5.7 cm/s), there was a significant *APOE4* carrier group × CVR interaction (($F_{3,69}$)=12.84, p=.001) on response inhibition performance (Figure 3C). Post-hoc analyses revealed that *APOE4* carriers with a high CVR (5.7cm/s) demonstrated higher response inhibition performance compared to *APOE4* carriers with low CVR (< 5.7cm/s) (t= −3.19, p=.005) and noncarriers with high CVR (t=−2.51, p=.017). Among participants with low CVR, *APOE4* carriers had poorer response inhibition performance compared to noncarriers (t=2.64, p=.013). Within the noncarrier group, noncarriers with low CVR had higher response inhibition performance compared to those with high CVR (t=2.18, p=.034) (Figure 3C).

3.3. Specificity of physiologic interactions for response inhibition

Controlling for age and normalized workload, the three-way multiple regression model (factors: CVR, *APOE4* carrier status, and Aβ deposition) failed to predict cognitive processing speed ($F_{6,69}$=1.825, p=.108, R^2=0.148, adjusted R^2=0.067). Specifically, the main effect of CVR remained the only significant predictor in this three-way model (t= 2.230, p=.029), while no interactive effects (p=.159), effects of Aβ deposition (p=.949), or effects of *APOE4* carrier status (p=.758) were observed (Supplementary Figure S1).

4. Discussion

Findings of the present study shed light on the complex neurobiological interactions of factors known to influence the development of cognitive dysfunction with aging. Our results provide novel evidence for the behavioral significance of interactions between cerebrovascular function, individual genotype, and structural brain pathology. Despite

having higher Aβ deposition, we found that *APOE4* carriers who had a more robust CVR to exercise had higher response inhibition performance, an effect that was not present in noncarriers. These findings imply higher cerebrovascular function may serve a neuroprotective role for the preservation of cognitive executive function specifically in *APOE4* carriers, possibly through increased resiliency to Aβ deposition with aging. Building upon previous research, our findings support an individualized framework gleaned from a multifactorial approach for detection of subtle impairments in cognitive behavior prior to the onset of clinical syndrome associated with AD and age-related neurodegenerative disorders. Together, these results may be informative for targeted precision-medicine approaches for early intervention and prevention of declines in cognitive executive function with aging.

4.1. Cerebrovascular response (CVR) to exercise is linked to amyloid beta (Aβ) deposition in the absence of clinical cognitive dysfunction

Our findings support the assessment of CVR to acute aerobic exercise as a useful functional biomarker of structural brain pathology in the absence of clinically detectible impairments in cognitive function. In the present study, we found that cognitively normal older adults with blunted CVR to aerobic exercise demonstrated greater Aβ deposition (Figure 1A), a finding consistent with previous work from our laboratory (Sisante et al., 2019) across a larger cohort of older adults. This finding also supports previous research implicating cerebrovascular assessments performed under conditions of physiologic stress may be sensitive enough to detect the first signs of dysfunction in the modulation of cerebral blood flow that may be salient to subtle changes in cognitive function in preclinical older adult populations. When Aβ was viewed as a continuous variable, no group differences in the association between CVR and Aβ deposition were detected (Figure 1A). Interestingly, when participants were classified by the presence of clinically relevant levels of elevated Aβ (>1.1 SUVR) (Clark et al., 2012; Joshi et al., 2012), we observed an interactive effect in the relationship between CVR and AB deposition in APOE4 carriers (Figure 1B). Here, *APOE4* carriers with elevated Aβ deposition were unable to achieve a robust CVR to exercise, an effect that was not present in noncarriers. Together, these findings provide evidence that the strongest physiologic interactions between CVR and Aβ deposition are present in a subgroup of individuals who carry the *APOE4* allele and possess elevated levels of Aβ deposition. The identification of this subgroup of individuals may provide a useful target for precision medicine approaches aimed at modulating cerebrovascular or structural brain metrics to influence brain health and function with aging.

Our findings implicate common neurobiological mechanisms that contribute to cerebrovascular dysfunction and structural brain pathology in the early stages of brain aging. In particular, *APOE4* carriers demonstrate the strongest negative relationship between CVR to exercise and Aβ deposition (Figure 1A&B) that is consistent with a mechanistic link between CV dysfunction and deposition of Aβ in the aging brain. However, the causal nature of this relationship remains to be tested. For example, the presence of Aβ may blunt the CVR to exercise through increased resistance of blood flow and perfusion to cortical tissues as blood flow velocity increases during aerobic exercise (Niwa et al., 2002; Iadecola, 2004). Consistent with this theory, increasing Aβ levels in the brains of rodents can reduce cerebral blood flow (i.e. elevated Aβ led to reduced blood flow to the brain) (Suo et al.,

1998). Conversely, poor cerebrovascular function may alter blood-brain barrier trafficking of Aβ, slowing the clearance of Aβ and promoting its accumulation in the brain (Zlokovic et al., 2005). This theory is also supported by animal research, where bilateral carotid artery stenosis significantly increased Aβ levels (i.e. blunting cerebral blood flow led to increased Aβ deposition) (Yamada et al., 2011). The later may also be supported by evidence that habitual aerobic exercise appears to have no effect on Aβ deposition in older adults (Vidoni et al., 2021), yet can improve cerebrovascular health (Thomas et al., 2013; Whitaker et al., 2020) and slow or, in some cases, reverse the development of cognitive impairment in older adults (Zhang et al., 2020). These observations may explain the neuroprotective effect of aerobic exercise against AD and related dementias (Tarumi and Zhang, 2018). Future research aimed at modulating each of these variables (e.g. aerobic exercise interventions that improve CVR) will provide insight into the directionality of the relationship between cerebrovascular function and structural brain pathology.

4.2. Behavioral significance of interactions between individual genotype, cerebrovascular function, and brain structure

Importantly, our findings provide evidence for the *behavioral significance* of interactions between individual genotype, cerebrovascular function, and brain structure. We found that cerebrovascular function interacts with individual *APOE* genotype and Aβ deposition to influence an individual older adult's ability to inhibit a default and undesired response (Figure 2 and Figure 3A&B). Our results are consistent with accumulating evidence within the field of aging neurobiology and the increasing recognition of the mixed pathology and multifactorial etiology that contributes to cognitive decline with aging (Iturria-Medina et al., 2016, 2017). Clinically, it is well known that an individual who has structural brain biomarker evidence of AD pathology (e.g. high levels of Aβ deposition) may paradoxically present with the absence of any behavioral indicator associated with AD clinical syndrome. Notably, vascular pathology and individual genotype (e.g. possession of the *APOE4* allele) are frequently detected in the typical clinical presentation of AD (Iadecola, 2004; Xie et al., 2016; Ouellette and Lacoste, 2021), and can significantly increase an individual's risk for developing dementias (Heffernan et al., 2016). Building upon our current knowledge of each of these factors individually, our present results provide unique insight into interactions between these key neurobiological factors that can be gleaned from an interdisciplinary and multifactorial assessment of AD and related dementia risk factors. This rich multifactorial approach offers a powerful characterization of factors potentially influencing the early development of cognitive behavioral impairment that could have clinically meaningful implications for intervention, treatment, and prevention of AD and related dementia in preclinical older adult populations.

4.3. Role of cerebrovascular health as a function of individual genotype in the preservation of brain behavioral function with aging

Our results suggest cerebrovascular function plays a key role in the early behavioral manifestations of cognitive executive dysfunction in older adults who carry the *APOE4* allele. The three-way interaction model found that older adult *APOE4* carriers with blunted CVR to exercise demonstrated poorer response inhibition performance, while CVR did not predict behavioral performance in noncarriers (Figure 2). The characterization

of these interactions builds upon previous findings from our laboratory, in which we demonstrated measures poor cardiovascular health negatively influenced the CVR to exercise preferentially in *APOE4* carriers (Kaufman et al., 2021c). Our findings are also consistent with previous evidence demonstrating a stronger effect of cardiovascular health on cognitive performance metrics in *APOE4* carriers (Zade et al., 2010; Caselli et al., 2011; Shaaban et al., 2019). Specifically within a behavioral context, a key novel finding of the present study identifies the unique relationship between cerebrovascular response and response inhibition performance in *APOE4* carriers compared to noncarriers. The positive relationship between CVR and response inhibition performance supports that *higher cerebrovascular regulatory function may serve a unique neuroprotective function in early brain aging processes affecting cognition in APOE4 carriers*, while playing less of a role in noncarriers. Interestingly, Kaufman et al. (2021a) revealed that cerebrovascular dysfunction in *APOE4* carriers was *differentially modifiable* through an aerobic exercise intervention compared to noncarriers, with older adult *APOE4* carriers showing greater improvements in cerebral blood flow following a year-long exercise intervention (Kaufman et al., 2021a). Despite the strong ties between physical fitness and cerebrovascular health, we found that these physiologic interactions were able to predict cognitive behavior even when controlling for normalized workload at a matched heart rate range, a proxy metric for physical fitness (Table 3). Interestingly, previous research by Ward et al (Ward et al., 2018) found that older and younger adults who were matched to identical workloads during moderate intensity exercise demonstrated differences in cardiovascular responsiveness to the acute exercise bout, suggesting an influence of aging on these physiologic interactions. Together, these findings support that cerebrovascular response during aerobic exercise provides unique insight into mechanisms of brain health and behavior that are not available from physical fitness assessments alone and may be useful to guide approaches aimed at preventing and reversing cognitive decline in aging populations.

4.4. Genetic mechanisms influencing interactions between cerebrovascular function and structural brain pathology in the context of cognitive behavior

Possession of an *APOE4* allele may reveal unique genetic mechanisms that influence interactions between cerebrovascular response and structural brain pathology to influence cognitive behavior in older adults. Specifically, we found differential effects of CVR on the relationship between Aβ and response inhibition in *APOE4* carriers and noncarriers (Figure 3A&B). In *APOE4* carriers, individuals with a higher CVR and greater Aβ deposition had higher response inhibition performance, an effect not observed in *APOE4* carriers with low CVR or noncarriers (Figure 3A&B). Further, *APOE4* carriers with high CVR outperformed both carriers with low CVR and noncarriers on the response inhibition task (Figure 3C). In the face of age-related neuropathology, some individuals appear to utilize a neurologic "reserve" that enables behavioral compensation and attenuates cognitive decline (Stern et al., 2019). Findings in the present study provide preliminary evidence that the neuroprotective effect of high CVR in *APOE4* carriers may act mechanistically through increased resilience to age-related structural pathology reflected in Aβ deposition, potentially supporting a functional neurologic "reserve" in the aging brains of these individuals. We also found that, among participants with low CVR, *APOE4* carriers had poorer response inhibition compared to noncarriers (Figure 3C). This suggests that cerebrovascular health not only

serves a specialized protective effect to *maintain* cognitive function, but may additionally attenuate the rate of cognitive decline that is accelerated in *APOE4* carriers (Caselli et al., 2004, 2007). It is conceivable that such differences in the resiliency effect of cerebrovascular function between *APOE4* carriers and noncarriers may overlap with the neurobiological mechanisms that predispose *APOE4* carriers to a higher genetic risk for the development of AD in the later stages of aging (Farrer et al., 1997; Heffernan et al., 2016). Further, our findings that CVR has a greater effect on cognitive function in *APOE4* carriers compared to noncarriers supports the notion of different etiologies and pathologic disease processes leading to the development of AD for each *APOE4* carriers and noncarriers (Emrani et al., 2020), particularly that cerebrovascular dysfunction may play a preferential role in dementia pathogenesis for *APOE4* carriers (Høgh et al., 2001; Montagne et al., 2020). These preliminary findings motivate future research in a larger cohort of heterogeneous older adults that may additionally include *APOE2* carriers, for whom the effect of resiliency to aging processes has been most consistently observed and reported (Farrer et al., 1997; James et al., 2017).

In the present study, the limited range of participants who possessed high levels of Aβ deposition (e.g. >1.1 SUVR) may limit the generalization of these findings to older adults with the more advanced signatures of structural brain pathology. For example, the low representation of participants with both high Aβ deposition and high CVR (as illustrated in Figure 3 A&B), could be explained by the fact that high Aβ deposition in these individuals may lead to cerebrovascular dysfunction, impeding their ability to achieve robust CVR during exercise. As such, a plausible alternative theory would be that individuals in this cohort of cognitively normal older adults with high Aβ deposition (and low CVR) may possess a neuroprotective resilience against the development of MCI in the presence of high levels of Aβ deposition, enabling their inclusion in the present study. Indeed, the expansion of the range of cognitive abilities to include those older adults with MCI may increase the upper range of AB deposition particularly in *APOE4* carriers. Expansion of the range of cognitive ability among participants could potentially equalize the differences in levels of Aβ deposition between groups (see Table 1) and even lead to an *inverse* relationship between Aβ deposition and response inhibition performance, in contrast to the positive relationship observed in Figure 3A. Future studies that include older adults with MCI may expand and equalize the range of Aβ deposition across groups and elucidate the presence of these interactive relationships and salience to cognitive behavior.

While high cerebrovascular function demonstrated a neuroprotective effect for *APOE4* carriers, an interesting pattern in our data suggests that noncarriers may possess greater resiliency to potential negative effects of low CVR and high Aβ deposition. While *APOE4* carriers with high CVR had higher response inhibition performance, noncarriers with *low* CVR tended to have higher response inhibition performance than noncarriers with high CVR, though the relationship of this effect did not meet our a priori adopted level of significance (Figure 2) and showed a lower magnitude of effect compared to the contrasting effect observed in *APOE4* carriers (Figure 3C). Previous studies found that, compared to cognitively normal *APOE4* carriers, noncarriers showed differences in cortical neural function (Leuthold et al., 2013) and had greater adaptive processes to repeated trauma (James et al., 2017). Although the mechanisms are not yet fully understood, these interactive

functional and structural processes appear to increase neuroprotection and promote brain resilience to specific disease processes in noncarriers, including the development of MCI (Pa et al., 2009), posttraumatic stress disorder (Peterson et al., 2015), and recovery from traumatic brain injury (Zhou et al., 2008). A greater ability to repair and protect against neuronal damage offered by the noncarrier-specific genotypic interaction (Mahley and Rall, 2000) may similarly increase noncarriers' resilience to the chronic neurotoxic effects poor cerebrovascular function on both the accumulation of Aβ in the brain (Figure 1) and cognitive performance (Figure 2 and Figure 3) compared to *APOE4* carriers in the present study. This notion of increased resilience to low cerebrovascular function in noncarriers may be further supported by the larger range of CVR, particularly in the lower range of response, present in noncarriers compared to *APOE4* carriers in the present study (Table 1), Notably, our exclusion of older adults with MCI would have biased the selection of only individuals with such genotypic resiliency (i.e. excluding those with low CVR and high Aβ without this protective adaptive characteristic, which could have effectively narrowed the range of CVR in *APOE4* carriers in the present study). The present participant selection criteria may explain poorer response inhibition performance in noncarriers with low Aβ and high CVR (Figure 3B & C). Future research in animal models may elucidate our mechanistic understanding of risk and resilience associated with individual *APOE* genotype and further identify epigenetic pathways underpinning individual-specific physiologic stress responses for neuronal repair and protection in the context of cerebrovascular health and cognitive dysfunction with aging.

4.5   Cerebrovascular dysfunction affects neural networks involved in response inhibition in the early stages of cognitive dysfunction with aging

Our hypothesis-driven analyses in the present study focused on the neurobiological factors influencing a highly specific aspect of cognition involving inhibition of a default and undesired response (Stroop, J, 1935; Hutchison et al., 2010). While interactions between CVR, *APOE4* genotype, and Aβ deposition were predictive of response inhibition performance (Table 2), the failure of these physiologic interactions to predict general cognitive processing speed implicates their functional neural specificity (Wessel and Aron, 2017; Wessel et al., 2019). The present findings are in line with previous research supporting the specificity of cerebrovascular function and individual *APOE* genotype (Whitson et al., 2018) effects on response inhibition behavior that engages inhibitory neural networks within the prefrontal cortex (PFC) (Wessel and Aron, 2017; Wessel et al., 2019). In neurologically-intact young adults, differences in acute cerebrovascular changes within the frontal cortical regions could be dissociated during a challenging Stroop task; here, participants with a greater frontal cortical hemodynamic response demonstrated higher response inhibition performance (Gratton et al., 2020). In aging populations, previous studies have demonstrated n that cortical inhibitory function is one of the earliest neural mechanisms affected by aging processes in cognitively normal older adults (Nielson et al., 2002; Heise et al., 2013; Levin et al., 2014; Rossiter et al., 2014; Legon et al., 2016), which may explain the presence of impaired response inhibition in older adults with absent clinical cognitive syndrome in the present study. Interestingly, PFC brain regions may preferentially benefit from the therapeutic effects of aerobic exercise interventions on cognition (Duchesne et al., 2015; Levin and Netz, 2015), supporting the robust interactive effect of cerebrovascular function

on response inhibition performance in the present study. Taken together, these findings may inform the development of individualized approaches for therapeutic noninvasive brain stimulation (e.g. neuromodulation of PFC brain regions in preclinical *APOE4* carriers) for the treatment and prevention of cognitive dysfunction with aging (Hsu et al., 2015).

4.6 Limitations

When no signal in the left MCA could be detected, we used the right MCA response to aerobic exercise in the present study, as previous results from our laboratory found no systematic differences in cerebrovascular kinetic responses to aerobic exercise between left and right MCA (Billinger et al., 2017). However, others have reported differences between left versus right sided hemisphere pulsatility (Atwi et al., 2020). Whether measurements of cerebrovascular function between left and right MCA can be substituted interchangeably remains to be tested in a larger study across more diverse aging populations, and should be considered carefully in the interpretation of the results of the present study.

Assessment of CVR during a validated acute moderate-intensity aerobic exercise paradigm (Billinger et al., 2008, 2017) is behaviorally relevant to activities commonly faced by older adults in the community (e.g. ascending a flight of stairs). It remains to be seen how the CVR to other types of acute physiologic stressors compare to an aerobic exercise paradigm. It is possible that the high demand of the cerebrovascular regulatory response required for brain blood flow during a bout of moderate-intensity aerobic exercise is an earlier and more sensitive detector for autonomic nervous system dysfunction with aging, and could provide unique physiologic information independent of gravity-dependent activities. Alternatively, the temporal demand required for rapid cerebrovascular response during a behavior such as a sit-to-stand positional transfer may reveal insight into autonomic nervous system dysfunction with aging not available during activities with prolonged duration responses such as aerobic exercise. Future research is warranted to compare paradigms involving physiologic stressors that are behaviorally relevant to older adults.

It is important to consider the limitations of the statistical modeling approach used in the present study within the context of the relatively modest sample size. In particular, the higher levels of AB deposition in the *APOE4* carrier group compared to the noncarrier group (difference magnitude of 0.07 SUVR, see Table 1) could influence the present results; future studies that increase the heterogeneity of cognitive inclusion criteria and in a larger cohort of older adults could help to mitigate these limitations. Given the novelty of the present dataset, our dichotomization of CVR using the group median provides a first step towards better understanding the influence of CVR on other physiologic and behavioral metrics. While providing an interesting illustration of the relationship between Aβ deposition and response inhibition performance in individuals with high versus low CVR to exercise (Figure 3 A&B), this sample-based classification method is likely sub-optimal in comparison to a physiologically-informed CVR classification method. Notably, given the significant interaction of CVR as a *continuous* variable with *APOE4* carrier status and Aβ deposition for the prediction of response inhibition performance, we cannot rule out the possibility that CVR may not possess a behaviorally salient threshold. As such, we expect that these results will guide future studies with larger sample sizes that will be more

adequately powered to determine whether the presence of a physiologically-based threshold for CVR classification exists for the detection of interactive physiologic effects on cognitive behavior. The speed dependence of the Stroop task in the present study could influence results compared to other methods of assessing response inhibitory control (e.g. The Tower of Hanoi task, the WCST, and the Iowa Gambling task). Thus, results of the present study may not be generalizable to generalized inhibitory control outside of this temporal context.

In the present study, we do not account for individual chronotype, which can have an effect on physical and cognitive performance (Facer-Childs et al., 2018). While all participants performed CVR assessment in the morning, diurnal variation and sleep pattern could have influenced cognitive performance (Song et al., 2019), as the time of cognitive testing was not controlled in the present study.

Sex as a biological variable has been shown to have complex interactions with each *APOE* genotype and cardiovascular function with aging (Farrer et al., 1997; Riedel et al., 2016; Ward et al., 2018; Vermunt et al., 2019). In the present study, there were no differences in gender distribution between *APOE4* carrier groups (Table 1). However, these findings together with previous research motivate an in-depth exploration of the effect of sex and interactions with key physiologic factors known to influence the development of structural brain pathology and early cognitive impairment with aging.

5. Conclusions

Interactions between cerebrovascular function, individual genotype, and structural brain pathology may offer a useful and sensitive biomarker for early preclinical behavioral manifestations of cognitive impairment in older adults. Additionally, cerebrovascular response to aerobic exercise may provide a physiologically-informed target for precision-medicine approaches aimed at attenuating negative effects of structural brain pathology and preventing age-related declines in cognitive executive function. Future research may reveal that individuals with *APOE4* carrier genotype show the highest therapeutic benefit for such intervention approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Data Availability Statement

The datasets generated and analyzed supporting the conclusions of this article will be made available by the authors upon request, without undue reservation.

Abbreviations:

CVR	cerebrovascular response
Aβ	amyloid-beta
APOE4	Apolipoprotein E allele 4
AD	Alzheimer's Disease
MCI	mild cognitive impairment
ANOVA	analysis of variance
SD	standard deviation

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Highlights

- Interactions between CVR, *APOE* genotype, and Aβ are relevant to cognitive behavior.

- Blunted CVR to exercise is associated with impaired response inhibition specifically in *APOE4* carriers.

- *APOE4* carriers with more robust CVR have higher response inhibition performance, despite having greater Aβ deposition.

- Assessment of multifactorial neurobiological variables offers an early and sensitive biomarker of cognitive behavioral dysfunction with aging.
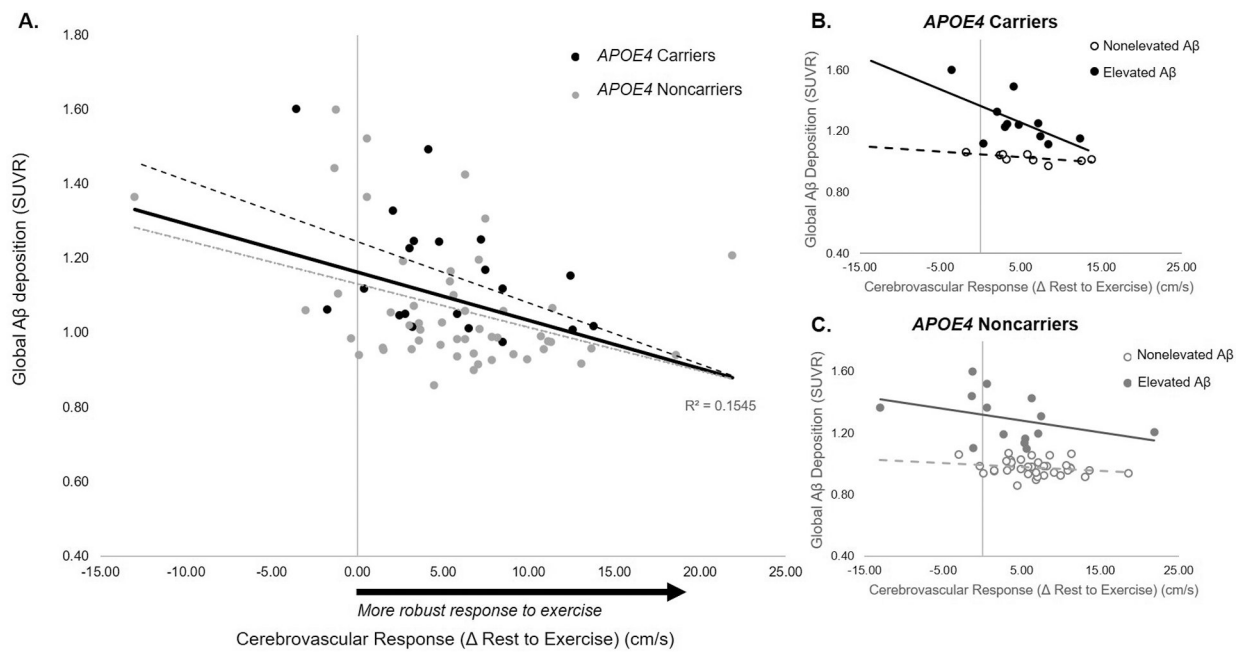
Figure 1.

Relationship between cerebrovascular response to moderate-intensity exercise and global amyloid-beta (Aβ) burden. A higher CVR predicted lower Aβ deposition across all participants (p=.013) (**A**). In *APOE4* carriers, individuals classified as having elevated Aβ (solid line) demonstrated a stronger negative effect of CVR on Aβ deposition compared to *APOE4* carriers classified as nonelevated Aβ (broken line) (p=.032) (**B**). In *APOE4* noncarriers, there were no significant differences in the effect of CVR on Aβ deposition between individuals with elevated versus nonelevated Aβ deposition (p=.272) (**C**).
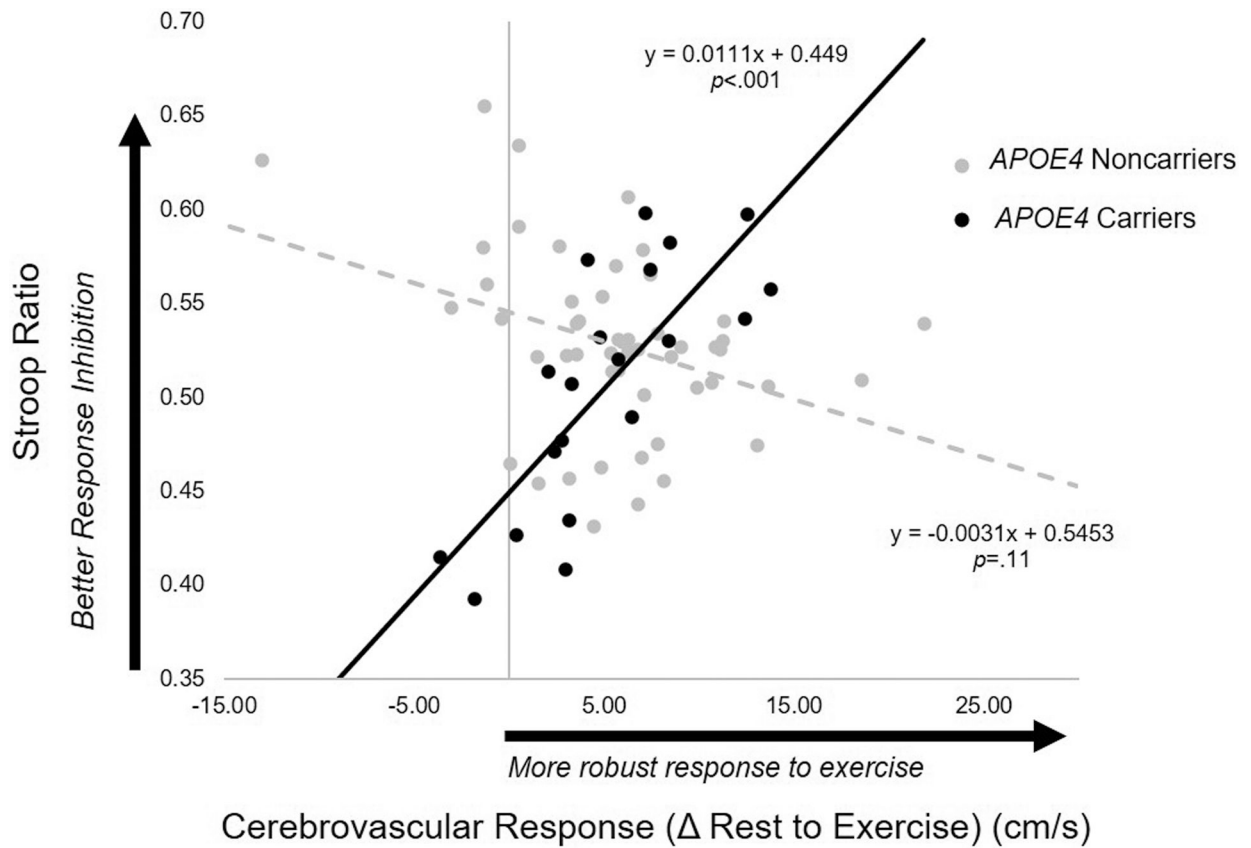
Figure 2.
Association between cerebrovascular response to moderate-intensity aerobic exercise and
response inhibition performance predicted from the regression model in *APOE4* carriers
(n=20) (solid line) and noncarriers (n=50) (broken line). In *APOE4* carriers, greater
cerebrovascular response to exercise was associated with better performance on the Stroop
response inhibition task (p<.001). In noncarriers, no relationship was observed (p=.112).
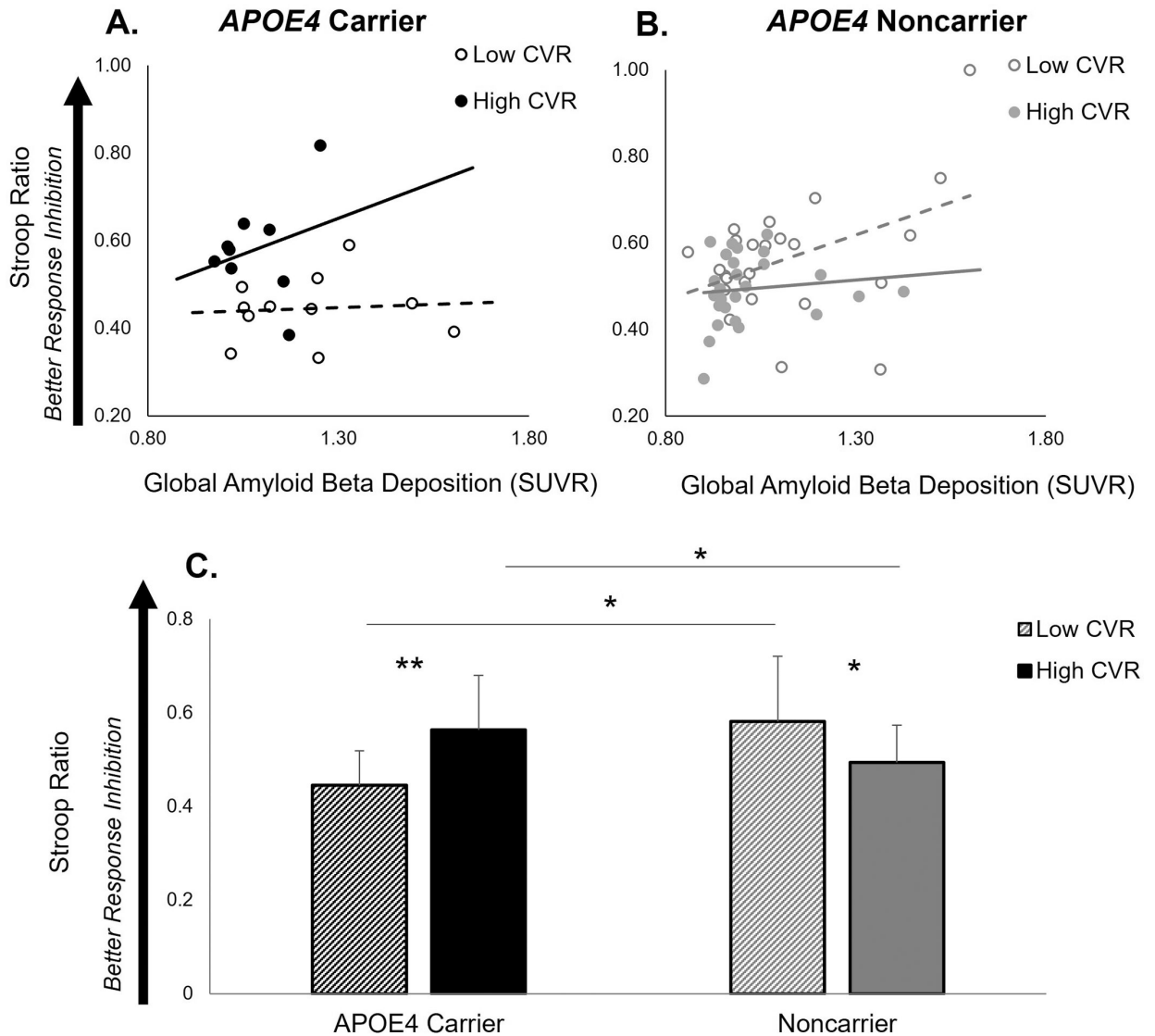Results for this regression model are detailed in Table 3.

Figure 3.
Association between Aβ deposition and response inhibition performance illustrated as a function of cerebrovascular response (CVR) to moderate-intensity aerobic exercise in *APOE4* carriers (black color) (n=20) **(A)** and noncarriers (grey color) (n=50) **(B)**. *APOE4* carriers with high CVR (5.7cm/s) (solid line) showed a positive relationship between Aβ deposition and response inhibition performance, while *APOE4* carriers with low CVR (< 5.7cm/s) (broken line) showed no positive effect. CVR also showed a lower effect on response inhibition in noncarriers. Results for this regression model are detailed in Table 3. **(C)** Response inhibition performance in *APOE4* carriers and noncarriers with low and high CVR. There was a significant *APOE4* carrier group × CVR interaction. *APOE4* carriers with high CVR had higher response inhibition performance compared to *APOE4* carriers with low CVR (*p*=.005) and noncarriers (p=.017). Among individuals with low CVR, *APOE4* carriers had lower response inhibition performance compared to noncarriers

(p=.013). Within the noncarrier group, noncarriers with low CVR had higher response inhibition performance compared to those with high CVR (p=.034). *p<.05, **p<.01. CVR is illustrated as a median (5.7cm/s) split of the group, where High CVR 5.7cm/s; Low CVR < 5.7cm/s.

Table 1.

Participant characteristics.

	All (n=70)	**APOE4 (+) (n=20)**	**APOE4 (−) (n=50)**
Age (years)	71±5 [65–87]	71±7 [65–87]	71±5 [65–81]
Workload (W/kg BW)	0.80±.0.27 [0.20–1.46]	0.81±.0.39 [0.20–1.46]	0.80±.0.21 [0.24–1.17]
Gender	F=47 M=23	F=13 M=7	F=34 M=16
MMSE	28.6±1.8 [22.0–30.0]	28.6±1.4 [25.0–30.0]	28.7±2.0 [22.0–30.0]
Aβ Deposition	1.09±.17 [0.86 to 1.6]	1.16±.17 [0.98 to 1.6]	1.07±.17 [0.86 to 1.6]
CVR	5.55±5.29 [−13.00 to 21.88]	5.18±4.58 [−3.57 to 13.78]	5.69±5.58 [−13.00 to 21.88]
Stroop ratio	0.52±.12 [0.29 to 1.0]	0.51±.12 [0.33 to 0.82]	0.53±.17 [0.29 to 1.00]

MMSE = Mini-Mental State Exam; Aβ = amyloid-beta; CVR = cerebrovascular response to moderate-intensity aerobic exercise; Aβ = amyloid-beta; [Range]; W= Watts at moderate intensity exercise workload; kg BW = kilograms of body weight. Values are depicted as mean ± SD.

Table 2.

Two-way moderated multiple regression analysis testing the effect of *APOE4* carrier status on the relationship between CVR and Aβ deposition after controlling for age, N = 70; Regression model predicting Aβ deposition, *p*=.003.

Variable	*B*	SE*B*	β	p-value
Intercept	0.794	0.278		.006 *
Age	0.004	0.004	0.138	.227
Workload (W/ kg BW)	−0.054	0.075	−0.084	.474
CVR	−0.056	0.023	−0.308	.018 *
APOE4 carrier status (+)	0.087	0.042	0.227	.041 *
Interaction *APOE4* carrier status (+) × CVR	−0.025	0.050	−0.063	.618

Aβ = amyloid-beta; CVR = cerebrovascular response to moderate-intensity aerobic exercise; SE*B* = standard error of the coefficient; *B* = unstandardized regression coefficient; β = standardized coefficient;

*
p<.05

Table 3.

Three-way multiple regression analysis results to predict response inhibition performance after controlling for age, N = 70; Regression Model, p=.014.

Variable	B	SE_B	β	p-value
Intercept	0.674	0.207		.002*
Age	−0.006	0.003	−0.257	.033*
Workload (W/kg BW)	0.004	0.52	0.009	.942
CVR	−0.002	0.003	−0.080	.557
APOE4 carrier status (+)	−0.130	0.044	−0.509	.004*
Aβ deposition	0.236	0.085	0.356	.007*
Interaction *APOE4* carrier status (+) *Aβ *CVR	0.015	0.005	0.485	.001*

Aβ = amyloid-beta; CVR = cerebrovascular response to moderate-intensity aerobic exercise; SE_B = standard error of the coefficient; B = unstandardized regression coefficient; β = standardized coefficient;

*
p<.05