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Increased hippocampal blood flow in sedentary older adults at genetic risk for Alzheimer's disease

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Abstract

Resting cerebral blood flow (CBF) decreases with age; however regulatory increases in hippocampal CBF have been associated with genetic risk (Apolipoprotein E [APOE] $\epsilon 4$ carriers) for Alzheimer's disease (AD). Although physical activity (PA) exerts beneficial effects on CBF in healthy elders, the effects of sedentary behaviors on CBF remain unknown. We measured resting hippocampal CBF (via arterial spin labeling magnetic resonance imaging) and sedentary time/PA (via accelerometry) on 33 cognitively healthy adults (ages 52–81), 9 of which were APOE $\epsilon 4$ carriers. Results indicate that the relationship between sedentary time and CBF in the left hippocampus differs by APOE status, whereby APOE $\epsilon 4$ carriers show higher CBF as a function of longer sedentary time ($B=10.8$, $SE=3.17$, $\beta=.74$, $t=3.41$, $p<.01$) compared to noncarriers ($B=1.4$, $SE=2.7$, $\beta=.096$, $t=.51$, $p=.61$), possibly suggesting a CBF regulatory response to compensate for metabolic alterations in dementia risk. These preliminary data suggest that the relationship between CBF and sedentary time is different in APOE $\epsilon 4$ carriers and noncarriers and that sedentary time may act as a behavioral risk factor for CBF dysregulation in those at genetic risk for developing AD. More research is needed to further understand the role of sedentary behaviors and physical activity on CBF, especially in individuals at genetic risk of developing AD.

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Keywords

Apolipoprotein E; sedentary behavior; physical activity; magnetic resonance imaging; arterial spin labeling; cerebral blood flow; hippocampus; biological aging

1. Introduction

Adequate blood flow to the brain is crucial to meet the metabolic demands necessitated by cognitive activity; however, resting cerebral blood flow (CBF) progressively declines with age after the third decade of life [1–3]. Moreover, vascular dysregulation has been implicated in the pathogenesis of Alzheimer's disease (AD) as evidenced by alterations in cerebral capillaries, white matter lesions, and reductions in CBF and glucose utilization [4]. Using arterial spin labeling (ASL), a non-invasive magnetic resonance imaging (MRI) technique which provides a measure of CBF in humans, Alsop and colleagues found lower CBF in older adults with probable AD when compared to age-matched controls in temporal, parietal, frontal, and posterior cingulate cortex [5]. However, the mechanisms underlying these vascular changes, and modifying effects of behavior, such as physical activity and sedentary time, are not well understood.

Cardiovascular fitness and physical activity have been consistently associated with improved cognitive function [6–8], strengthened and/or more efficient functional brain activity [9–17], and increased brain volume in older adults [18–22]. More recently, studies have shown that exercise also exerts positive changes on the cerebral vasculature [1, 7, 23–28], including preserved CBF in areas associated with aging and AD using ASL [29], higher middle cerebral artery blood flow velocity in young and older adults using transcranial doppler ultrasound [23, 24, 27, 29], and associations between physical fitness, vascular function and cognitive performance in older women [24]. Studies investigating differences in CBF between fit and sedentary individuals have revealed that CBF was 17% higher in highly fit men when compared to sedentary adults [23], and that the systemic circulation benefits of exercise seem to extend to the brain in fit postmenopausal women compared to their sedentary counterparts [24]. Furthermore, using ASL fMRI, acute increases in CBF were revealed immediately following 30 minutes of moderate exercise in young adults [30]. No data are available however, regarding the possible effects of sedentary behavior as a risk factor on CBF regulation.

Sedentary behavior, or prolonged time spent sitting or reclining, during which little energy expenditure occurs above rest (e. g., watching television, using the computer, driving), has been found to predict negative outcomes, such as mortality and cardiometabolic disease, independently of time spent in exercise [31]. That is, sedentary behavior is an independent predictor of poor health outcomes above and beyond the contribution of exercise. Sedentary behaviors in older adults have been associated with accelerated secondary aging [32], lower functional fitness [33], lower rates of successful aging [34], poorer cognitive performance [35], and increased risk for all-cause mortality, independent of physical activity [36]. Moreover, no studies have yet reported on the relationship between physical activity and sedentary behaviors on CBF in those at risk for developing AD by virtue of the

apolipoprotein (APOE) $\epsilon 4$ allele. Therefore, the current study used ASL to non-invasively assess the relationship between objectively measured physical activity, sedentary behaviors, and resting hippocampal CBF in cognitively normal individuals and to preliminarily examine whether this relationship differs in individuals at genetic risk for AD (APOE $\epsilon 4$ carriers). We also explored whether CBF in the hippocampus was associated with memory performance.

The hippocampus was targeted in this investigation given its important role in memory functions and the dynamic CBF changes associated with this area in individuals at genetic risk for AD [37, 38]. Left and right hippocampi were studied separately due to previously reported asymmetrical atrophy rates in APOE $\epsilon 4$ carriers and individuals with AD [39]. We hypothesized that physical activity would be associated with higher CBF and sedentary time with lower CBF in cognitively intact non-APOE $\epsilon 4$ carriers. For those at genetic risk for AD, we predicted increased CBF in the hippocampus compared to noncarriers due to early regulatory compensation, as has been previously reported [37]. To our knowledge, this is the first study to investigate the relationship between physical activity, sedentary behavior, and CBF in cognitively intact individuals at genetic risk for developing AD.

2. Materials and Methods

2.1. Participants

Thirty-three community-dwelling older adults between the ages of 52 and 81 were included in the current analyses. These participants were recruited from an ongoing longitudinal research study of normal aging at the University of California, San Diego. Recruitment for the current investigation was not based on APOE genotype, but rather on willingness to participate in the physical activity measurement protocol. As a result, genotype data were examined *ex post facto*, resulting in 9 APOE $\epsilon 4$ allele carriers (2 $\epsilon 4/\epsilon 4$ and 7 $\epsilon 3/\epsilon 4$) and 24 non- $\epsilon 4$ carriers (21 $\epsilon 3/\epsilon 3$, 2 $\epsilon 2/\epsilon 3$, and 1 $\epsilon 2/\epsilon 2$). Due to the small sample size, exploring genotype effects of all APOE allele variants beyond $\epsilon 4$ carriers and noncarriers was not possible in the current analyses. As part of the larger study, all participants underwent neurological and medical examinations, buccal swab DNA extraction for APOE genotyping, laboratory testing, and neuropsychological evaluation. Exclusion criteria included: history of dementia, neurological disorders, significant cerebrovascular disease, major psychiatric diagnoses, and contraindications to undergo MRI (e.g., ferrous implants, pacemaker, claustrophobia, etc). Based on the comprehensive neuropsychological assessment, all individuals included in this sample were deemed to have current normal cognitive function based on consensus by two neuropsychologists (A.J.J., C.E.W.), using the empirically-derived criteria for normal cognition versus mild cognitive impairment (MCI) developed by Jak and colleagues (see Table 2 in Jak and colleagues for a full list of the neuropsychological tests used to derive a diagnosis) [40]. Signed informed consent was obtained from all participants in accordance with the University of California, San Diego's Institutional Review Board and the Declaration of Helsinki.

2.2. Apolipoprotein E genotyping

Genotyping for APOE alleles was performed using PCR Restriction Fragment Length Polymorphism analysis [For details, see 38, 41].

2.3. Physical activity monitoring period

To measure physical activity levels, all participants were asked to wear an accelerometer for seven days and to not modify their regular, everyday activities. Minutes of sedentary time, light, moderate, and vigorous physical activity were measured with the Actigraph accelerometer (model GT1M). Participants were instructed to wear the Actigraph on their right hip from the time they awoke in the morning until they went to sleep at night, only removing the monitor to avoid getting it wet (e.g., during showering, swimming, etc.). The Actigraph has been shown to be valid for quantifying activity levels in laboratory and field settings [42]. A monitored hour was not considered valid if the number of consecutive minutes of 0 counts exceeded 30 minutes. Data from the monitors were considered valid if the monitor was worn for at least 3 of the 7 days and for at least 10 hours each day. A range of 3 to 7 days of monitoring has been found to give reliable estimates of physical activity [43, 44]. Daily hours of sedentary behavior were estimated by summing minutes with acceleration counts between 0 and 100 for valid hours of monitoring. Acceleration counts were translated into minutes of light, moderate, and vigorous physical activity using accepted cut points of 1952 and 5725, respectively [45]. The average number of minutes spent in light, moderate, and vigorous physical activity was summed for each participant to create a composite of all physical activities per hour.

2.4. Cerebral blood flow assessment (ASL): Image acquisition

MRI scanning for ASL acquisition was performed using a 3.0 Tesla General Electric EXCITE whole body scanner with an 8-channel receive-only head coil (General Electric Medical Systems, Milwaukee, WI, USA). A structural T1-weighted high resolution Fast Spoiled Gradient–Recalled–Echo image was acquired to provide anatomic reference with 172 1-mm thick sagittal slices, FOV=25 cm, TR=8 ms, TE=3.1 ms, flip angle=12°, T1=450, 256×192 matrix, Bandwidth=31.25 kHz [46]. Resting-state CBF data were acquired in one run (4 min 20 sec), using a pulsed ASL sequence (QUantitative Imaging of Perfusion with a Single Subtraction, version II; PICORE QUIPSS II), with a dual-echo, single-shot spiral acquisition [47]. Parameters included: 5 6-mm thick contiguous oblique slices acquired at the level of the hippocampus, FOV=24 cm, TR=3000 ms, TE1=2.4, TE2=24 ms, flip angle=90°, T11=700 ms, T12=1400 ms, 64×64 matrix, tag thickness 20 cm, tag to proximal slice gap 1cm. Additionally, one cerebrospinal fluid (CSF) reference scan was acquired for use in CBF quantification. The CSF scan consisted of a single-echo, single repetition scan acquired at full relaxation and echo time equal to 2.4 ms. This scan used the same in-plane parameters as the resting ASL scan, but the number of slices was increased to cover the lateral ventricles.

2.5. Neuropsychological testing

An extensive neuropsychological test battery was administered to all participants as part of the larger longitudinal aging study. However, given the hippocampi's early and prominent

role in the development of AD, the positive impact of exercise on the hippocampus specifically, and its involvement in memory functions, we limited this preliminary investigation to the relationship between hippocampal CBF and cognitive tests of memory performance. Memory tests included: The Wechsler Memory Scale-Revised [WMS-R]: Logical Memory [LM] I and II and Visual Reproductions [VR] I and II [48] and The California Verbal Learning Test-II [CVLT-II] total learning trials 1–5 [49]. All neuropsychological tests were demographically-corrected using available normative data.

Since vascular risk has been implicated in the pathogenesis of dementia, we calculated body mass index (BMI) using the standard formula [weight in lbs/(height in inches)² * 703] and used the Framingham Stroke Risk Profile [50] to estimate the 10-year probability for risk of stroke using gender-corrected scores based on the following risk factors: age, systolic blood pressure, diabetes mellitus, cigarette smoking, history of cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, and use of antihypertensive medications.

2.6. Structural and ASL image processing

All imaging data were processed using Analysis of Functional NeuroImages [AFNI] [51], FMRIB Software Library [FSL] [52], and in-house MATLAB scripts. For processing details, please refer to [37, 46]; but briefly, anatomical images were skull-stripped and later segmented into gray matter, white matter, and CSF. An automated hippocampal region of interest (ROI) was created using Freesurfer [Freesurfer ASEG], which was inspected and manually edited as needed. For volumetric analysis, all tissue compartments and the hippocampal ROI were normalized by dividing each value by total brain volume.

ASL data were motion-corrected by co-registering the ASL time series to the middle time point. For each participant, a mean ASL image was formed from the average difference of the control and tag images using surround subtraction to create an uncorrected perfusion time series, and slice time delays were accounted for, making the inversion time TI2 slice specific [53]. This mean ASL image was converted to absolute units of CBF (mL/100 g tissue/minute) using the CSF signal to estimate the equilibrium magnetization of blood [54]. The high-resolution T1-weighted images and partial volume segmentations were registered to ASL space, and partial volume segmentations were down-sampled to the resolution of the ASL data. Mean CBF restricted to gray matter for the left and right hippocampi were extracted separately and served as the dependent variables.

2.7. Data analyses

Once the left and right hippocampal CBF values were extracted, all statistical analyses were carried out using IBM SPSS Statistics (version 21). All variables entered into the regression models were normally distributed as assessed by a combination of histogram/Q-Q/P-P plot inspection and Shapiro-Wilk tests of normality. There were no univariate or multivariate outliers based on regression diagnostics. To compare demographics and variables of interest between dementia risk groups (APOE ε4 carriers vs. noncarriers), we conducted independent samples T-tests for continuous variables or chi square analyses for categorical variables (Table 1). Hierarchical linear regressions were conducted to investigate whether the relationship between physical activity/sedentary behavior and CBF changed as a

function of genetic risk, after controlling for age (Table 2). All variables entered into the regression models were centered (or demeaned) and regressions were conducted for sedentary time and physical activity separately for the right and left hippocampi. Left or right hippocampal CBF was the dependent variable and predictors included: age (block1), sedentary or physically active time (block 2), genetic risk (APOE ϵ 4 carrier/noncarrier) (block3), and the interaction term between genetic risk and either sedentary or physically active time (block 4). Pearson bivariate correlations were carried out to investigate the relationship between CBF in the hippocampus and tests of memory function.

3. Results

APOE ϵ 4 carriers and noncarriers did not differ significantly on age, gender, education, number of sedentary or physically active hours per day, accelerometer wear time, body mass index (BMI), vascular risk (Framingham Stroke Risk Profile), left and right hippocampal CBF, left and right hippocampal volume, or memory performance (Table 1). Similarly, there was no association between left and right hippocampal volume (corrected for total brain size) and left and right hippocampal CBF (all $p > .05$), ruling out possible CBF effects due to gray matter atrophy.

When *sedentary time* was entered as a predictor of left hippocampal CBF, the overall model was significant and explained 44% of the variance on CBF, $F(4,28)=5.5$, $R^2=.44$, Adjusted $R^2=.36$, $R^2=.25$ (from block1), $p < .01$ (Table 2). Age and the interaction term between sedentary time and genetic risk were significant contributors to the model, with APOE ϵ 4 carriers exhibiting higher levels of CBF as sedentary time increased (Figure 1). Follow-up regression analyses indicated that the relationship between CBF and sedentary time in the left hippocampus was only significant for APOE ϵ 4 carriers ($B = 10.8$, $SE = 3.17$, $\beta = .74$, $t = 3.41$, $p = .002$) and not for noncarriers ($B = 1.4$, $SE = 2.7$, $\beta = .096$, $t = .51$, $p = .61$). Results did not change when adjusting for accelerometer wear time in the model. For the right hippocampus, the overall model was significant as well, explaining 36% of the variance on CBF, $F(4,28)=3.9$, $R^2=.36$, Adjusted $R^2=.27$, $R^2=.14$ (from block1), $p < .05$. Only age predicted CBF in the right hippocampus.

When *physical activity* was entered as a predictor of left hippocampal CBF, the overall model was significant, $F(4,28)=3.6$, $R^2=.34$, Adjusted $R^2=.25$, $R^2=.15$ (from block1), $p < .05$. Only age was a significant predictor of left hippocampal CBF, although the interaction term between physical activity and genetic risk approached significance ($p = .066$), with those at genetic risk displaying lower CBF compared to noncarriers of the APOE ϵ 4 allele. For the right hippocampus, the overall model was significant, explaining 32% of the variance, $F(4,28)=3.3$, $R^2=.32$, Adjusted $R^2=.23$, $R^2=.1$ (from block1), $p < .05$. Only age was a significant predictor of right hippocampal CBF, although the interaction between physically active time and genetic risk approached significance ($p = .067$), with APOE ϵ 4 carriers showing lower levels of CBF with increased physical activity and noncarriers displaying higher CBF with higher physical activity levels. There were no significant associations between hippocampal CBF and memory performance measures.

4. Discussion

Sedentary behavior has emerged in the literature as an important contributor to all-cause mortality and increased risk of metabolic disease in children and adults, independent of physical activity levels [55, 56]. Those with metabolic syndrome are at increased risk of diabetes and cardiovascular disease, both of which have been associated with AD risk. Hence, the role of sedentary behavior on cerebral perfusion deserves further attention, especially in preclinical AD, given that Americans over the age of 60 spend approximately 60% of waking hours performing sedentary activities [57]. The purpose of the current study was to characterize the relationship between resting hippocampal CBF, physical activity, and sedentary behavior in cognitively normal individuals and to preliminarily examine whether this relationship differs in individuals at genetic risk for developing AD by virtue of the APOE $\epsilon 4$ allele.

In this cross-sectional study, we found that the relationship between CBF and sedentary time changed as a function of APOE $\epsilon 4$ status in the left hippocampus, whereby APOE $\epsilon 4$ carriers showed increased CBF with longer sedentary time, whereas this relationship was not significant in noncarriers. Although these results may seem counterintuitive, adults at risk for dementia (APOE $\epsilon 4$ carriers) have previously demonstrated elevated CBF in the medial temporal lobes compared to noncarriers [37, 38]. This elevation of CBF in AD risk has been previously interpreted as a possible regulatory compensation mechanism for metabolic alterations in preclinical AD and/or an increased demand for glucose and oxygen to support neuronal activity [37, 58]. Thus, the current results may suggest a possible regulatory CBF response in APOE $\epsilon 4$ carriers as a function of increased sedentary time. Although the interaction between sedentary time and APOE $\epsilon 4$ carrier status was only significant for CBF in the left hippocampus, the pattern of results was very similar for the right hippocampus and may not have reached statistical significance due to our small sample size. Future studies should include larger samples to investigate whether changes in CBF as a function of exercise are asymmetrical in the hippocampus. In the current study however, hippocampal volume was not associated with CBF in the right and left hippocampi, thus our findings seem to be independent of hippocampal volume or atrophy rates.

Although the role of the APOE $\epsilon 4$ genotype on CBF remains unclear, there is ample literature suggesting a link between cerebrovascular dysregulation and/or disease and AD [5, 59–61]. Cerebrovascular dysregulation alters the brain's control mechanisms that ensure nutrient delivery and control homeostasis for efficient brain functioning, [4] and there is evidence that cerebrovascular dysregulation is present in AD [5] and in individuals at genetic risk for developing AD [37, 38, 41]. Aerobic fitness has been found to improve cerebral hemodynamics (e.g., maximal oxygen consumption, middle cerebral artery velocity, cerebrovascular resistance/conductance) in older adult males [28], increase the change in vasodilator response to hypercapnia in older adults [62], and reduce age-related declines in CBF [23]. Hence, there is compelling evidence for a link between the pathogenesis of AD and vascular health [63], and that cerebrovascular processes can be modified by exercise, possibly due to increased CBF resulting from the acute effects of autonomic modulation of endothelial function [60] and chronic changes associated with angiogenesis [25, 64]. Since this is the first study to investigate sedentary time as a possible

risk factor for CBF dysregulation, the mechanisms associated with the observed increases in CBF deserve further scrutiny, although disruptions in vascular mechanisms should be considered in future studies.

One limitation of the current study is its small sample size, which did not allow us to study all APOE allele variants independently. However, even with a small sample, we were able to find statistically significant large effects of sedentary behavior on CBF for APOE $\epsilon 4$ carriers after controlling for age. Furthermore, the current sample size is larger than that reported in other published studies investigating exercise and CBF using ASL in humans [29, 30]. Thus, we believe the current findings to be of importance in advancing the investigation of the effects of sedentary behaviors and physical activity on CBF using non-invasive imaging methods such as ASL. Future studies should include larger samples and study all APOE allele variants, as well as investigate the relationship between sedentary behavior/physical activity and CBF in individuals diagnosed with MCI, who are at high risk for developing AD. Another limitation of the current study is its cross-sectional nature, which does not allow us to attest to causation. Longitudinal intervention studies should investigate how changes in physical activity levels and sedentary behaviors affect CBF and cognitive function and whether they are associated with conversion to MCI or AD. Several strengths of the current study should also be highlighted. Accelerometers were used to measure physical activity, which are considered a more reliable tool for the assessment of physical activity than self-report questionnaires [65]. This is the first study, to our knowledge, to investigate the relationship between sedentary behavior, physical activity, and CBF in individuals at increased risk for AD using ASL. Furthermore, ASL is a safe and non-invasive MRI technique able to measure CBF in-vivo, and has been shown to be sensitive to perfusion changes immediately following exercise [30].

In conclusion, this is the first study to find that the relationship between CBF and sedentary time differed as a function of AD risk, whereby APOE $\epsilon 4$ carriers showed increased CBF in the left hippocampus compared to noncarriers with longer sedentary time. The current preliminary findings suggest that sedentary time may act as a behavioral risk factor for alterations in resting CBF that have previously been interpreted as reflecting a regulatory compensation response in those at genetic risk for AD; and that the combination of genetic vulnerability and increased sedentary time may exacerbate this regulatory response. More research is warranted to better understand how sedentary behavior and physical activity affect CBF and cognitive function in older adults at risk for AD.

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--- B = 1.4, SE = 2.7, β = .096, t = .51, p = .61

— B = 10.8, SE = 3.17, β = .74, t = 3.41, p = .002

Figure 1.

Notes: Scatter plot depicts the relationship between age-adjusted left hippocampal CBF and sedentary time, which is modified by APOE status. β -values represent the main effect of sedentary time for each APOE group separately. Higher sedentary time is associated with greater CBF in APOE ϵ 4 carriers only.

Table 1

Participant descriptive characteristics by APOE group

	e4 carrier (N=9)	e4 noncarrier (N=24)	Statistics	
	Mean (SD)	Mean (SD)	t or χ^2	df p
Age	71 (6.9)	68.21 (9.1)	-0.8	31 0.41
Gender	6 w/3 m	16 w/8 m	0.0	1 1.00
Years of education	16.89 (1.5)	16.42 (2.4)	-0.5	31 0.59
Sedentary time (hrs/day)	8.64 (1.8)	8.78 (1.2)	0.3	31 0.80
Physically active time (hrs/day)	4.7 (1.5)	4.5 (1.3)	-0.3	31 0.76
Accelerometer wear time (hours)	78.9 (25.1)	92.6 (22.7)	1.5	31 0.14
BMI	26.21 (5.2)	25.38 (5.4)	-0.4	28 0.70
Vascular risk %	9.12 (7.9)	6.91 (4.6)	-1.0	29 0.34
Left hc CBF (mL/100g tissue/min)	69.29 (21.1)	68.20 (19.5)	-0.1	31 0.89
Right hc CBF (mL/100g tissue/min)	52.36 (18.2)	52.81 (19)	0.1	31 0.95
Left hc volume (mm ³)	2907.11 (390.4)	2992.95 (424.2)	0.5	31 0.60
Right hc volume (mm ³)	3105.66 (320.5)	3234 (425.5)	0.8	31 0.42
Left hc volume/whole brain	0.23 (0.04)	0.22 (0.02)	-0.2	31 0.87
Right hc volume/whole brain	0.24 (0.03)	0.24 (0.02)	0.1	31 0.94
WMS-R LM I (SS)	13.22 (4.1)	12.88 (2.8)	-0.3	31 0.78
WMS-R LM II (SS)	13.44 (3.1)	13.25 (2.9)	-0.2	31 0.87
WMS-R VR I (SS)	14 (2.6)	14 (2.1)	0.0	30 1.00
WMS-R VR II (SS)	14.88 (1.4)	13.46 (2.6)	-2.0	24 0.06
CVLT 1-5 (T)	55.11 (10.6)	55.83 (8.8)	0.2	31 0.84

Notes: BMI = body mass index; Vascular risk = Framingham % Stroke Risk Profile; Left and Right hc CBF (mL/100g tissue/min) = left and right hippocampal cerebral blood flow measured via arterial spin labeling; Left and Right hc volume (mm³) = left and right hippocampal volume and proportion of hc volume/whole brain volume; WMS-R = Wechsler Memory Scale-revised; LM = Logical Memory I and II total score; VR = Visual Reproduction I and II total score; CVLT-II = California Verbal Learning Test-II; SS = standard score; T = T score.

Table 2

Hierarchical linear regressions results (N=33)

	Left hippocampal CBF					Right hippocampal CBF					
	B	SE	β	t	p	B	SE	β	t	p	
Physical Activity	(Constant)	67.2	3.5	--	19.2	0.00	52.0	3.3	--	15.6	0.00
	Age	-1.3	0.4	-0.6	-3.1	0.00	-1.1	0.4	-0.5	-2.7	0.01
	Physical Activity (PA)	-0.9	3.1	-0.1	-0.3	0.77	1.4	3.0	0.1	0.5	0.65
	Genetic Risk	6.0	6.8	0.1	0.9	0.39	3.5	6.5	0.1	0.5	0.60
	PA * Genetic Risk	-9.5	5.0	-0.4	-1.9	0.07	-9.1	4.8	-0.4	-1.9	0.07
Sedentary Behavior	(Constant)	67.4	3.2	--	20.9	0.00	52.0	3.2	--	16.0	0.00
	Age	-1.0	0.3	-0.4	-3.0	0.01	-1.0	0.3	-0.5	-3.0	0.01
	Sedentary Time (ST)	1.4	2.7	0.1	0.5	0.61	1.5	2.7	0.1	0.6	0.58
	Genetic Risk	5.0	6.2	0.1	0.8	0.43	3.2	6.3	0.1	0.5	0.62
	ST * Genetic Risk	9.4	4.2	0.4	2.3	0.03	6.0	4.2	0.3	1.4	0.17

2 Notes: Hierarchical regression results for step 4 (including all variables) of the models. **Bold** font represents statistically significant coefficients, $p < .05$. CBF = Cerebral blood flow measured via arterial spin labeling; B=Unstandardized coefficient; SE = Standard Error; β =Standardized coefficient. All variables were centered prior to regression analyses. Regression coefficients above are for APOE $\epsilon 4$ noncarriers as the reference group. See Figure 1 for APOE $\epsilon 4$ carriers' coefficients.