Radiology

Brain Oxygen Extraction by Using MRI in Older Individuals: Relationship to Apolipoprotein E Genotype and Amyloid Burden

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Background: Apolipoprotein E4 (APOE4) is a major genetic risk factor for late-onset Alzheimer disease. However, the mechanisms by which APOE4 affects the brain, underpinning this risk, have not been fully elucidated.

Purpose: To investigate the influence of APOE4 on global cerebral oxygen extraction fraction (OEF) and possible mediation through amyloid burden by using MRI-based brain oxygen extraction technique.

Materials and Methods: Participants were enrolled from a longitudinal prospective study, the Biomarkers for Older Controls at Risk for Dementia study (data collected from January 2015 to December 2017), of whom 35% (50 of 143 participants) were APOE4 carriers. OEF was measured by using a T2-relaxation-under-spin-tagging MRI technique with a 3.0-T MRI system. PET acquired with carbon 11–labeled Pittsburgh compound B tracer was available in 119 participants to measure amyloid burden. Cognitive performance was assessed by using domain-specific composite scores including executive function, episodic memory, visual-spatial processing, and language. Linear regression analysis was performed to investigate the relationship between APOE4, OEF, and amyloid burden. The association between OEF and cognitive function was studied for the entire study cohort and separately for the APOE4 carriers and noncarriers.

Results: A total of 143 cognitively healthy individuals (mean age ± standard deviation, 69.1 years ± 8.2; 57 men and 86 women) were studied. APOE4 genetic status was associated with lower OEF (noncarriers, 41.1% ± 5.8; one E4 allele, 40.1% ± 4.9; two E4 alleles, 36.7% ± 4.5; $P = .03$). Furthermore, among APOE4 carriers, lower OEF correlated with lower executive function scores ($\beta = 0.079$ *z* score for each percent change in OEF; $P = .03$). Amyloid burden and OEF were independently associated with APOE4 but were not associated with one another, suggesting that the effect of APOE4 on OEF is not mediated by amyloid.

Conclusion: MRI-based brain oxygen extraction shows that cognitively healthy carriers of the apolipoprotein E4 gene manifest diminished brain oxygen extraction capacity independent of amyloid burden.

Online supplemental material is available for this article.

Apolipoprotein E allele 4 (APOE4) is a major genetic risk factor for late-onset Alzheimer disease (1). Caucasian carriers of the APOE4 gene have 10–30 times the risk of developing Alzheimer disease compared with noncarriers (2). Therefore, identification of imaging hallmarks of APOE4 carriers, especially at a stage when their cognitive function is still intact, may help to identify individuals for early intervention trials.

Differences in glucose metabolism between APOE carriers versus noncarriers have been consistently observed in posterior temporal and parietal regions (3). Anatomic differences in the brain of APOE4 carriers have also been reported in cognitively healthy APOE4 carriers compared with noncarriers, most often in brain regions susceptible to pathologic processes of Alzheimer disease such as hippocampus (4–6), although findings have been mixed (7,8). In addition, many studies have indicated that APOE4 carriers have higher amyloid deposition in the cerebral cortex (9–11).

Oxygen extraction fraction (OEF) is a physiologic marker reflecting percentage of oxygen extracted from the blood supply of the brain, which is directly associated with brain oxygen metabolism. Recent studies suggest that OEF may be a sensitive marker in differentiating healthy aging from Alzheimer disease. For example, OEF shows a pronounced increase with age in cognitively healthy individuals (12) but is lower in patients with mild cognitive impairment compared with age-matched control participants. Additionally, these changes in OEF are evident before detectable differences in global brain volume (13) (although local structural changes in Alzheimer disease–vulnerable regions may be present among individuals with

Abbreviations

APOE4 = apolipoprotein E4, OEF = oxygen extraction fraction

Summary

MRI-based brain oxygen extraction shows that cognitively healthy older individuals who carry the apolipoprotein E4 gene have diminished oxygen extraction capacity independent of amyloid burden, which may represent an early sign of brain dysfunction associated with lower executive function.

Key Points

- Brain oxygen extraction in older individuals who have one copy of the apolipoprotein E4 (APOE4) gene is 1% lower than in noncarriers, whereas it is 4% lower in individuals with two copies of the APOE4 gene.
- Among the APOE4 carriers, a lower oxygen extraction corresponds to poorer executive cognitive function.

mild cognitive impairment [14]). However, to our knowledge, to date no study has investigated the effect of APOE4 on OEF. Furthermore, given evidence of a relationship between APOE4 and amyloid accumulation (9–11), it is important to examine whether the association between OEF and APOE4, if any, is mediated by level of amyloid burden.

In this study, we hypothesized that cerebral oxygen extraction is altered in cognitively healthy individuals carrying the APOE4 gene. T2-relaxation-under-spin-tagging (or TRUST) MRI (15,16) was used to quantify global OEF. Compared with previous techniques, TRUST MRI has excellent test-retest reproducibility, shorter imaging time (1.2 min), and does not require injection of exogenous agent. In this study, we measured OEF in 143 cognitively healthy participants, 50 of whom were APOE4 carriers, and examined the effect of APOE4 on OEF. We also examined the potential role of amyloid accumulation (measured by using PET) in mediating the OEF and APOE4 relationship, as well as the relationship between OEF and cognitive function in the context of APOE genotype.

Materials and Methods

Study Participants

The participants were part of the cohort of a longitudinal, prospective, Health Insurance Portability and Accountability Act–compliant, institutional review board–approved study titled Biomarkers for Older Controls at Risk for Dementia (or BIOCARD) (17–19). The data reported here were collected between January 2015 and December 2017, when we first began to perform OEF MRI. Details of participant recruitment, clinical evaluation, and annual cognitive assessment have been described in Albert et al (17). Briefly, the participants included in this study consisted of 143 cognitively healthy individuals (mean age ± standard deviation, 69.1 years ± 8.2; 57 men and 86 women). All participants signed institutional review board–approved written informed consent forms prior to participation.

Clinical and Cognitive Assessments

A consensus diagnosis procedure was implemented by the staff of BIOCARD Clinical Core at Johns Hopkins University (Baltimore, Md), led by an experienced neuropsychologist (M.A., with more than 40 years of experience) (see Appendix E1 [online] for details).

As described previously, participants underwent a comprehensive battery of standardized neuropsychological tests, assessing multiple domains of cognition (17,20). The tests scores were used to create four composite scores, reflecting verbal episodic memory, executive function, visual-spatial processing, and language. The raw scores of each test were converted to *z* scores by using mean and standard deviation of test scores of the entire BIOCARD cohort from an earlier visit, and the *z* scores were summed to yield a standardized domain score (see Figure E1 in Appendix E1 [online] for details). The range and median values of each domain score are provided in Tables 1 and 2.

APOE Genotyping

The APOE4 carrier status was determined and coded as follows: individuals with two E4 alleles were coded as 2, individuals with one E4 allele were coded as 1, and individuals with no E4 alleles were coded as 0. The staff performing the genotyping was blinded to the participant's cognitive status.

Vascular Risk Assessment

Vascular risk score was calculated based on history of hypertension, hypercholesterolemia, diabetes, smoking, and body mass index, ranging from 0 to 5 (5 is worst) (21). Use of medication was obtained by using questionnaires. The numbers of participants who were taking antihypertensive, hyperlipidemia, hypercholesterolemia, or diabetes drugs were calculated.

MRI Image Acquisition and Processing

All MRI examinations were conducted with a 3.0-T MRI system (Achieva; Philips Healthcare, Best, the Netherlands). OEF was calculated by using the following equation:

$$\mathrm{OEF} = (Y_a - Y_v)/Y_a,$$

where Y_a is arterial oxygenation (assumed to be 98%) and Y_v is venous oxygenation. Global venous oxygenation was measured from the superior sagittal sinus with a pulse-sequence TRUST technique (15) (Fig 1) (see Appendix E1 [online] for sequence details). 95% confidence interval of transverse relaxation rate (or 1/T2) (delta R2), representing the uncertainty of OEF measurement, was calculated for all participants. TRUST data that had a delta R2 greater than 5 Hz were excluded from further analysis.

White matter hyperintensities were assessed by a board-certified neuroradiologist at fluid-attenuated inversion recovery MRI to obtain a Fazekas score indicating its severity. A T1-weighted magnetization-prepared rapid gradient-echo (or MPRAGE) examination was also acquired for brain volume quantification by using an automatic processing tool, MRICloud (*https://www.MRICloud.org*; Johns Hopkins University, Baltimore, Md) (22). Details are described in Appendix E1 (online).

The staff who performed the image analysis (Z.L., with 3 years of experience) was blinded to the participant's cognitive status.

Table 1: Demographic Information of All Participants

Variable	All Participants	Apolipoprotein E Subgroups		
		No E4 Allele	One E4 Allele	Two E4 Alleles
No. of participants	143	93	40	10
Age (y)	69.1 ± 8.2	69.4 ± 8.7	69.0 ± 7.7	67.0 ± 4.5
Sex*				
Female	86 (60.1)	56 (60.2)	26 (65.0)	4 (40)
Male	57 (39.9)	37 (39.8)	14 (35.0)	6 (60)
Education (y)	17.4 ± 2.2	17.3 ± 2.2	17.4 ± 2.3	18.7 ± 1.6
Episodic memory†	1.57 ± 1.37	1.52 ± 1.41	1.71 ± 1.25	1.47 ± 1.58
Executive function‡	0.64 ± 1.27	0.59 ± 1.25	0.86 ± 1.26	0.21 ± 1.42
Visual-spatial function§	0.76 ± 1.39	0.70 ± 1.42	0.95 ± 1.32	0.57 ± 1.38
Language‖	0.61 ± 1.16	0.62 ± 1.15	0.66 ± 1.20	0.28 ± 1.24
Oxygen extraction fraction (%)	40.5 ± 5.6	40.96 ± 5.80	40.20 ± 4.90	36.73 ± 4.49
Fazekas score	1.40 ± 0.75	1.42 ± 0.75	1.38 ± 0.75	1.35 ± 0.75
Vascular risk score	1.59 ± 1.20	1.62 ± 1.18	1.58 ± 1.27	1.40 ± 1.26
No. of participants on vascular medication	76	52	19	5

Note.—Unless otherwise specified, data are means ± standard deviation.

* Data in parentheses are percentages.

† Range of episodic memory score: −2.93 to 4.73 (median, 1.56).

‡ Range of executive function score: −5.41 to 3.48 (median, 0.79).

§ Range of visual-spatial function score: −3.50 to 3.50 (median, 1.03).

‖ Range of language function score: −2.54 to 3.85 (median, 0.40).

Table 2: Demographic Information of Participants with Carbon 11–labeled Pittsburgh Compound B Tracer PET Measures

Variable	All Participants	Apolipoprotein E Subgroups		
		No E4 Allele	One E4 Allele	Two E4 Alleles
No. of participants	119	77	33	9
Age (y)	68.7 ± 8.6	68.94 ± 9.11	68.79 ± 8.36	66.89 ± 4.48
Sex*				
Female	72 (60.5)	47 (61.0)	21 (63.6)	4 (44.4)
Male	47 (39.5)	30 (39.0)	12 (36.4)	5 (55.6)
Education (y)	17.5 ± 2.2	17.32 ± 2.15	17.55 ± 2.40	18.78 ± 1.72
Episodic memory†	1.66 ± 1.37	1.61 ± 1.40	1.81 ± 1.25	1.61 ± 1.61
Executive function‡	0.70 ± 1.30	0.68 ± 1.29	0.85 ± 1.30	0.35 ± 1.44
Visual-spatial function§	0.79 ± 1.37	0.70 ± 1.43	1.05 ± 1.19	0.62 ± 1.45
Language‖	0.64 ± 1.21	0.63 ± 1.18	0.74 ± 1.28	0.35 ± 1.30
Oxygen extraction fraction (%)	40.66 ± 5.48	41.35 ± 5.64	40.01 ± 5.02	37.19 ± 4.51
Cortical distribution volume ratio	1.04 ± 0.15	1.01 ± 0.12	1.12 ± 0.18	1.07 ± 0.16
Fazekas score	1.42 ± 0.75	1.44 ± 0.75	1.36 ± 0.78	1.44 ± 0.73
Vascular risk score	1.50 ± 1.16	1.54 ± 1.14	1.45 ± 1.21	1.44 ± 1.33
No. of participants on vascular medication	61	41	16	4

Note.—Unless otherwise specified, data are means ± standard deviation.

* Data in parentheses are percentages.

† Range of episodic memory score: −2.93 to 4.73 (median: 1.62).

‡ Range of executive function score: −5.41 to 3.48 (median, 0.91).

§ Range of visual-spatial function score: −3.50 to 3.50 (median, 1.03).

‖ Range of language function score: −2.54 to 3.85 (median, 0.73).

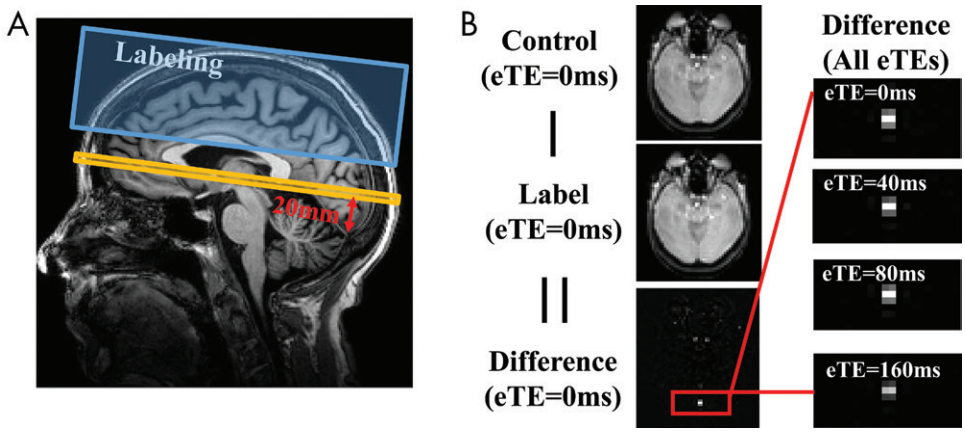

Figure 1: Images show typical results of T2-relaxation-under-spin-tagging (or TRUST) MRI. *A*, Position of image plane for TRUST MRI. Yellow bar indicates imaging slice. Blue box indicates labeling slab. *B*, Representative images of TRUST MRI for quantification of cerebral venous oxygenation. Paired subtraction between control and label images results in a different image, in which superior sagittal sinus (red box) is prominent. Fitting of signal as function of effective echo time (eTE) results in estimation of venous blood T2. Blood T2 can then be converted to oxygenation level by using calibration plot established in literature.

PET with Pittsburgh Compound B Image Acquisition and Processing

PET scans with carbon 11 (^{11}C)–labeled Pittsburgh compound B were performed by using a GE scanner (Advance PET; GE Healthcare, Milwaukee, Wis) in a subset of 119 study participants (Table 2). Distribution volume ratio images were generated by using a method reported by Bilgel et al (23). Mean cortical distribution volume ratio was calculated as an index of cortical ^{11}C Pittsburgh compound B retention to quantify amyloid accumulation (see Appendix E1 [online]).

Statistical Analysis

All statistical analyses were performed by using in-house Matlab (version R2016a; Mathworks, Natick, Mass) scripts. Potential group differences in demographic and cognitive variables between APOE4 carriers versus noncarriers were assessed by using Kruskal-Wallis rank sum test.

The relationship between OEF and APOE4 status was examined with linear regression analysis, in which OEF was the dependent variable and APOE4 carrier status (0, 1, or 2) was the independent variable, with age as a covariate. Post hoc analyses were performed to compare OEF between each pair of the groups, after adjusting for age. We also repeated the regression analyses by adding Fazekas score, vascular risk score, and vascular medication status as covariates.

To further investigate whether the association between APOE4 and OEF is mediated by amyloid burden, we performed a multivariable linear regression analysis in which OEF was the dependent variable, whereas Pittsburgh compound B to cortical distribution volume ratio, APOE4, the cortical distribution volume ratio and APOE4 interaction, and age were the independent variables.

We also examined the association between OEF level and cognitive performance by using the four cognitive composite scores as dependent variables in separate linear regression analyses, with the following predictors: age, education, OEF, APOE4 status, and APOE4 and OEF interaction. When the interaction was found to be significant, separate post hoc analyses were conducted for APOE4 carriers and noncarriers.

In all analyses, a two-tailed *P* value of .05 or less was considered to indicate statistical significance. Bonferroni correction was performed to account for multiple cognitive domains.

Results

Demographic Information and APOE Genotypes

Demographic information of the participants is shown in Table 1. The participants (mean age, 69.1 years ± 8.2; 57 men and 86 women) included 93 APOE4 noncarriers, 40 carriers with one E4 allele (ie, heterozygotes), and 10 carriers with two E4 alleles (ie, homozygotes).

We found no significant differences across APOE groups in terms of age (P = .27), sex (P = .35), education (P = .15), or use of vascular medication (P = .65). There was not a relationship between APOE4 genotype and domain-specific cognitive scores (executive function, P = .57; episodic memory, P = .33; visual-spatial processing, P = .54; language, P = .81).

Effect of APOE4 on OEF

Figure 2 shows representative TRUST MRI data in participants with different numbers of APOE4 alleles. Five of the 143 participants had a delta R2 greater than 5 Hz and were excluded from regression analyses. The remaining participants (n = 138) had an OEF of 40.5% ± 5.6 and mean delta R2 of 2.13 Hz. The results of the linear regression models are shown in Table 3. We found a negative association between OEF and APOE genotype (β = −1.6% per allele; P = .03 (Table 3, model 1). APOE4 carriers had a lower OEF compared with noncarriers (Fig 3) (noncarriers, 41.1% ± 5.8; one E4 allele, 40.1% ± 4.9; two E4 alleles, 36.7% ± 4.5). Post hoc analysis showed that there was a difference in OEF between noncarriers and participants with two E4 alleles (P = .03), and a trend of difference between participants with one E4 allele and those with two E4 alleles (P = .07). However, no difference was found

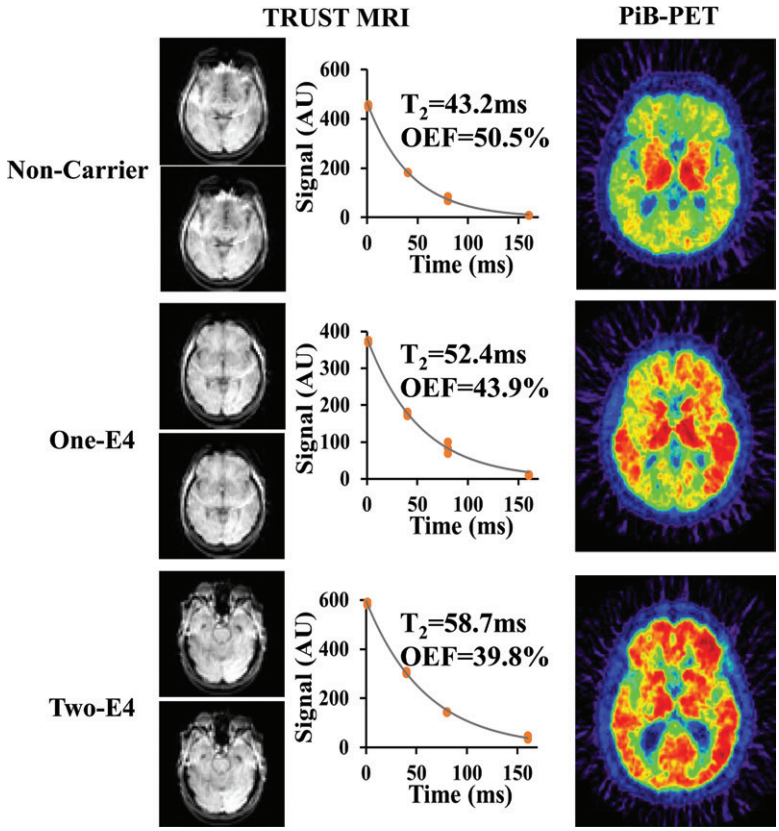

Figure 2: Representative images of T2-relaxation-under-spin-tagging (or TRUST) MRI and PET acquired with carbon 11–labeled Pittsburgh compound B tracer (or PiB-PET) in participants with different numbers of apolipoprotein E4 alleles. OEF = oxygen extraction fraction.

when comparing noncarriers and participants with one E4 allele (P = .35).

Fazekas scores of the participants are summarized in Table 1. There was no difference in Fazekas score across APOE groups (P = .81). When including the Fazekas score in the regression model, the relationship between OEF and APOE genotype remained significant (β = −1.7% per allele; P = .03), whereas Fazekas score did not have an effect on OEF (P = .34). Similarly, there was no difference in vascular risk score across APOE groups (P = .77). When including vascular risk score as a covariate, the relationship between OEF and APOE4 remained significant (β = −1.6% per allele; P = .04), whereas OEF was not associated with vascular risk score (P = .39). When including both Fazekas score and vascular risk score as covariates, the association between OEF and APOE4 remained (β = −1.6% per allele; P = .04). Vascular medications did not alter the relationship between OEF and APOE4. After adjusting for use of vascular medication, APOE4 genotype still revealed a significant effect on OEF (β = −1.6% per allele; P = .03).

Relationship between APOE4, Amyloid Burden, and OEF

We reanalyzed the data by using the subset of participants who had undergone PET scans with Pittsburgh compound B (n = 116; mean age, 68.7 years ± 8.6; 45 men and 71 women). Linear regression analysis revealed an association between OEF and APOE4 status (β = −1.8% per allele; P = .02 (Table 3, model 6) (see Figure E2 [online]), but none between OEF and cortical distribution volume ratio (P = .29) and no cortical distribution volume ratio and APOE4 interaction (P = .19) (Table 3, model 7). APOE4 showed a positive association with cortical distribution volume ratio (β = 0.066 unit per allele; P = .002) (Table 3, model 8) (see Figure E3 [online]).

Relationship between OEF and Cognitive Function

To examine whether differences in OEF between APOE4 carriers and noncarriers were associated with cognitive performance, we tested the association between OEF and each of the domain-specific cognitive scores. We found no association between OEF and any of the cognitive composite scores (P > .05) (Table 3, model 9). However, we found a significant APOE and OEF interaction for executive function (P = .009; corrected P = .04) (Table 3, model 10). Post hoc models showed a positive association between OEF and executive function in the APOE4 carriers (β = 0.079 z score for each percent change in OEF; P = .03) (Table 3, model 11), but no association between OEF and executive function for noncarriers (P > .05). Figure 4 shows the scatter plot between OEF and the executive function score in APOE4 carriers (n = 49, partialing out education).

Relationship between APOE4 Gene and Brain Volumes

In linear regression analyses (with brain volume as the dependent variable, and APOE4 and age as the independent variables), we did not observe an association between APOE4 and brain volume measures, including gray matter volume (P = .31), white matter volume (P = .52), frontal lobe volume (P = .95), parietal lobe volume (P = .57), temporal lobe volume (P = .25), occipital lobe volume (P = .25), hippocampal volume (P = .75), amygdala volume (P = .94), and entorhinal cortex volume (P = .93).

Discussion

We examined the relationship between apolipoprotein E4 (APOE4) carrier status and cerebral oxygen extraction in a group of cognitively healthy older individuals. We found that APOE4 was significantly associated with oxygen extraction fraction (OEF). Individuals carrying the APOE4 gene manifested significantly lower OEF (noncarriers, 41.1% ± 5.8; one E4 allele, 40.1% ± 4.9; two E4 alleles, 36.7% ± 4.5). Moreover, this reduction was associated with lower scores on a composite measure of executive function.

To the best of our knowledge, this study is the first to investigate cerebral oxygen extraction in cognitively healthy APOE4 carriers compared with noncarriers. Our results suggest that, compared with noncarriers, older individuals with one APOE4 allele showed a reduction in OEF of approximately 1%, whereas

Table 3: Linear Regression Models and Results

Model No.	Coefficient (unit)	Standard Error (unit)	*P* Value
Model 1			
Participant group			
All (*n* = 138)			
Dependent variable			
OEF			
Independent variables			
APOE4	−1.64 (per allele)	0.75 (per allele)	.03
Age	0.10 (per year)	0.057 (per year)	.07
Model 2			
Participant group			
All (*n* = 138)			
Dependent variable			
OEF			
Independent variables			
APOE4	−1.65 (per allele)	0.75 (per allele)	.03
Age	0.13 (per year)	0.063 (per year)	.04
Fazekas score	−0.66 (per unit)	0.69 (per unit)	.34
Model 3			
Participant group			
VRS subset (*n* = 134)			
Dependent variable			
OEF			
Independent variables			
APOE4	−1.57 (per allele)	0.76 (per allele)	.04
Age	0.095 (per year)	0.058 (per year)	.10
VRS	0.35 (per unit)	0.40 (per unit)	.39
Model 4			
Participant group			
VRS subset (*n* = 134)			
Dependent variable			
OEF			
Independent variables			
APOE4	−1.58 (per allele)	0.76 (per allele)	.04
Age	0.11 (per year)	0.064 (per year)	.07
Fazekas score	−0.64 (per unit)	0.73 (per unit)	.38
VRS	0.40 (per unit)	0.41 (per unit)	.33
Model 5			
Participant group			
All (*n* = 138)			
Dependent variable			
OEF			
Independent variables			
APOE4	−1.62 (per allele)	0.75 (per allele)	.03
Age	0.10 (per year)	0.057 (per year)	0.08
Medication	0.32 (if medicated)	0.94 (if medicated)	0.73
Model 6			
Participant group			
PET subset (*n* = 116)			
Dependent variable			
OEF			
Independent variables			
APOE4	−1.80 (per allele)	0.78 (per allele)	.02
Age	0.15 (per year)	0.057 (per year)	.009

Table 3 *(continues)*

Table 3 *(continued)*: Linear Regression Models and Results

Model No.	Coefficient (unit)	Standard Error (unit)	*P* Value
Model 7			
Participant group			
PET subset (n = 116)			
Dependent variable			
OEF			
Independent variables			
APOE4	−1.68 (per allele)	0.80 (per allele)	.04
cDVR	−3.92 (per unit)	3.67 (per unit)	.29
cDVR and APOE4	7.18	5.46	.19
Age	0.16 (per year)	0.058 (per year)	.007
Model 8			
Participant group			
PET subset (n = 116)			
Dependent variable			
cDVR			
Independent variables			
APOE4	0.066 (per allele)	0.021 (per allele)	.002
Age	0.0036 (per year)	0.0015 (per year)	.02
Model 9			
Participant group			
All (n = 138)			
Dependent variable			
Executive function			
Independent variables			
OEF	0.020 (z score per unit)	0.019 (z score per unit)	.29
Age	−0.041 (z score per year)	0.013 (z score per year)	.002
Education	0.13 (z score per year)	0.047 (z score per year)	.006
Model 10			
Participant group			
All (n = 138)			
Dependent variable			
Executive function			
Independent variables			
APOE4	0.076 (z score per allele)	0.18 (z score per allele)	.67
OEF	0.027 (z score per unit)	0.019 (z score per unit)	.17
APOE4 and OEF	0.084	0.032	.009
Age	−0.040 (z score per year)	0.012 (z score per year)	.002
Education	0.13 (z score per year)	0.047 (z score per year)	.005
Model 11			
Participant group			
APOE4 carriers (n = 49)			
Dependent variable			
Executive function			
Independent variables			
OEF	0.079 (z score per unit)	0.022 (z score per unit)	.03
Age	0.011 (z score per year)	0.024 (z score per year)	.66
Education	0.17 (z score per year)	0.078 (z score per year)	.04

Note.—APOE4 = apolipoprotein E4, cDVR = cortical distribution volume ratio, OEF = oxygen extraction fraction, VRS = vascular risk score.

those with two APOE4 alleles quadrupled this amount. In fact, this level of OEF reduction is comparable to those observed in patients with mild cognitive impairment (reduction of 3.8%) (13). Physiologic alterations in cognitively healthy APOE4 carriers have two possible mechanisms. They may reflect early signs of brain dysfunction due to preclinical pathologic processes of Alzheimer disease, or they may reflect a compensatory response of the brain to other insults induced by the APOE4 gene or preclinical pathologic processes of Alzheimer disease, including amyloid. The positive correlation between OEF and executive

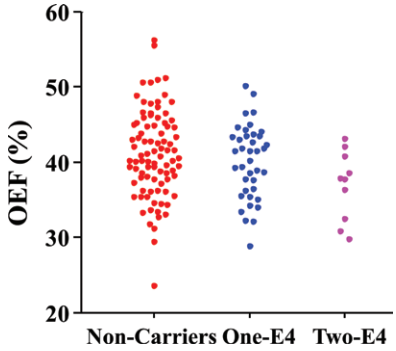

Figure 3: Image shows oxygen extraction fraction (OEF) in apolipoprotein E4 carriers and noncarriers.

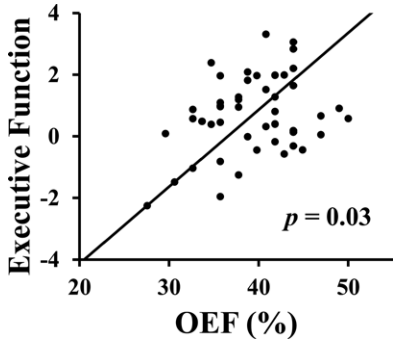

Figure 4: Scatter plot shows oxygen extraction fraction (OEF) and executive function (*z* score) in apolipoprotein E4 carriers (n = 49).

function suggested that reduced OEF in APOE4 carriers represents a sign of brain dysfunction rather than a compensatory response. Taken together, these observations suggest that brains of APOE4 carriers extract less oxygen from the incoming bloodstream, leaving a higher amount of oxygen in the venous blood, thereby leading to subtle changes in cognition. It is also worth noting that the brain volume analysis did not show significant differences between APOE4 carriers and noncarriers, which is consistent with many reports in the literature that have examined cognitively healthy individuals (7,8,24). Thus, functional brain changes, including oxygen extraction, may begin prior to structural changes or cognitive impairment. This raises the possibility that OEF may be an early marker of impending cognitive decline, although additional longitudinal studies are needed to test this hypothesis.

A strength of our study is that 119 (83%) of the participants also underwent a PET scan with Pittsburgh compound B, which enabled us to examine the interrelationship among APOE4, OEF, and amyloid burden. Although OEF and amyloid burden were each independently associated with APOE4, we found no association between OEF and amyloid burden. Thus, our results suggest that the effect of APOE4 on oxygen extraction is independent of amyloid accumulation, and may instead be driven by other mechanisms by which APOE4 affects the brain.

The effects of APOE4 on other cerebrovascular parameters have been reported previously. For example, Suri and colleagues (25) suggested that APOE4 carriers have preserved basal cerebral blood flow but reduced metabolism, which would indicate a lower OEF as observed in the present study. Those authors also used a carbon dioxide physiologic challenge to measure cerebrovascular reactivity of the participants and observed that APOE4 carriers manifested a diminished cerebrovascular reactivity compared with noncarriers. This finding suggested that vascular function in APOE4 carriers is also diminished. Poor vascular function could result in an impairment in cognitive function, as previous literature in cognitive aging has suggested that lower cerebral blood flow, in particularly in the frontal lobe, is predictive of cognitive decline (26). However, reductions in cerebral blood flow and in OEF in the context of cognitive function likely reflect different pathophysiologic processes, in that lower cerebral blood flow indicates impaired vascular function and oxygen supply, whereas lower OEF is attributed to impairment in oxygen consumption.

Advances in MRI technology allow noninvasive measurement of cerebral oxygen consumption (15,27,28). The TRUST MRI technique used in our study allowed us to measure venous oxygenation, and therefore OEF, within 1.2 minutes of MRI examination time without injection of any exogenous agent or blood sampling. The technique used in this study has previously been tested for reproducibility and revealed an intrasession coefficient of variation of 2.0% ± 0.3, an intersession coefficient of variation of 2.6% ± 0.4 (29), and an interscanner coefficient of variation of 3.3% ± 0.6 (30).

Our study had several limitations. First, the MRI measure we used is global in nature and has no spatial information. Additionally, the OEF measurement was made without restriction of caffeine consumption, which could alter brain perfusion and oxygenation (31). We did not ask our participants to refrain from caffeine consumption because of concerns of potential withdrawal effects, which will affect the scores of cognitive assessment. Finally, because our cohort is enriched for family history of dementia, a relatively high fraction of our participants are APOE4 carriers. Therefore, caution should be used when extending the findings in the present study to a general population, which is expected to have a lower APOE4 carrier fraction.

In conclusion, we examined the relationship between oxygen extraction fraction (OEF), apolipoprotein E4 (APOE4), and amyloid burden. Our results suggest that OEF is lower in APOE4 carriers and the extent of its reduction is associated with performance in executive function.

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References

1. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261(5123):921–923.
2. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997;278(16):1349–1356.
3. Reiman EM, Chen K, Alexander GE, et al. Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. Proc Natl Acad Sci U S A 2005;102(23):8299–8302.
4. Fouquet M, Besson FL, Gonneaud J, La Joie R, Chételat G. Imaging brain effects of APOE4 in cognitively normal individuals across the lifespan. Neuropsychol Rev 2014;24(3):290–299.
5. Honea RA, Vidoni E, Harsha A, Burns JM. Impact of APOE on the healthy aging brain: a voxel-based MRI and DTI study. J Alzheimers Dis 2009;18(3):553–564.
6. Wishart HA, Saykin AJ, McAllister TW, et al. Regional brain atrophy in cognitively intact adults with a single APOE epsilon4 allele. Neurology 2006;67(7):1221–1224.
7. Filippini N, Ebmeier KP, MacIntosh BJ, et al. Differential effects of the APOE genotype on brain function across the lifespan. Neuroimage 2011;54(1):602–610.
8. Reiman EM, Uecker A, Caselli RJ, et al. Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Ann Neurol 1998;44(2):288–291.
9. Ma J, Yee A, Brewer HB Jr, Das S, Potter H. Amyloid-associated proteins alpha 1-antichymotrypsin and apolipoprotein E promote assembly of Alzheimer beta-protein into filaments. Nature 1994;372(6501):92–94.
10. Pletnikova O, Rudow GL, Hyde TM, et al. Alzheimer lesions in the autopsied brains of people 30 to 50 years of age. Cogn Behav Neurol 2015;28(3):144–152.
11. Resnick SM, Bilgel M, Moghekar A, et al. Changes in Aβ biomarkers and associations with APOE genotype in 2 longitudinal cohorts. Neurobiol Aging 2015;36(8):2333–2339.
12. Peng SL, Dumas JA, Park DC, et al. Age-related increase of resting metabolic rate in the human brain. Neuroimage 2014;98:176–183.
13. Thomas BP, Sheng M, Tseng BY, et al. Reduced global brain metabolism but maintained vascular function in amnestic mild cognitive impairment. J Cereb Blood Flow Metab 2017;37(4):1508–1516.
14. Jack CR Jr, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 1999;52(7):1397–1403.
15. Lu H, Ge Y. Quantitative evaluation of oxygenation in venous vessels using T2-relaxation-under-spin-tagging MRI. Magn Reson Med 2008;60(2):357–363.
16. Xu F, Uh J, Liu P, Lu H. On improving the speed and reliability of T2-relaxation-under-spin-tagging (TRUST) MRI. Magn Reson Med 2012;68(1):198–204.
17. Albert M, Soldan A, Gottesman R, et al. Cognitive changes preceding clinical symptom onset of mild cognitive impairment and relationship to ApoE genotype. Curr Alzheimer Res 2014;11(8):773–784.
18. Soldan A, Pettigrew C, Cai Q, et al. Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease. Neurobiol Aging 2017;60:164–172.
19. Pettigrew C, Soldan A, Zhu Y, et al. Cognitive reserve and cortical thickness in preclinical Alzheimer's disease. Brain Imaging Behav 2017;11(2):357–367.
20. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. Alzheimer Dis Assoc Disord 2009;23(2):91–101.
21. Gottesman RF, Schneider AL, Zhou Y, et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. JAMA 2017;317(14):1443–1450.
22. Mori S, Wu D, Ceritoglu C, et al. MRICloud: delivering high-throughput MRI neuroinformatics as cloud-based software as a service. Comput Sci Eng 2016;18(5):21–35.
23. Bilgel M, An Y, Zhou Y, et al. Individual estimates of age at detectable amyloid onset for risk factor assessment. Alzheimers Dement 2016;12(4):373–379.
24. Fleisher AS, Podraza KM, Bangen KJ, et al. Cerebral perfusion and oxygenation differences in Alzheimer's disease risk. Neurobiol Aging 2009;30(11):1737–1748.
25. Suri S, Mackay CE, Kelly ME, et al. Reduced cerebrovascular reactivity in young adults carrying the APOE epsilon4 allele. Alzheimers Dement. 2015;11(6):648-57 e1.
26. De Vis JB, Peng SL, Chen X, et al. Arterial-spin-labeling (ASL) perfusion MRI predicts cognitive function in elderly individuals: a 4-year longitudinal study. J Magn Reson Imaging 2018;48(2):449–458.
27. Wehrli FW, Fan AP, Rodgers ZB, Englund EK, Langham MC. Susceptibility-based time-resolved whole-organ and regional tissue oximetry. NMR Biomed 2017;30(4):e3495.
28. Chen JJ, Pike GB. Human whole blood T2 relaxometry at 3 Tesla. Magn Reson Med 2009;61(2):249–254.
29. Liu P, Dimitrov I, Andrews T, et al. Multisite evaluations of a T2 -relaxation-under-spin-tagging (TRUST) MRI technique to measure brain oxygenation. Magn Reson Med 2016;75(2):680–687.
30. Jiang D, Liu P, Li Y, Mao D, Xu C, Lu H. Cross-vendor harmonization of T_2 -relaxation-under-spin-tagging (TRUST) MRI for the assessment of cerebral venous oxygenation. Magn Reson Med 2018;80(3):1125–1131.
31. Xu F, Liu P, Pekar JJ, Lu H. Does acute caffeine ingestion alter brain metabolism in young adults? Neuroimage 2015;110:39–47.