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Exercise engagement as a moderator of *APOE* effects on amyloid deposition

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Abstract

Objective—*APOE* $\epsilon 4$ status has been associated with greater cortical amyloid deposition whereas exercise has been associated with less in cognitively normal adults. The primary objective here was to examine whether physical exercise moderates the association between *APOE* genotype and amyloid deposition in cognitively normal adults.

Method—*APOE* genotyping and a questionnaire on physical exercise engagement over the last decade were obtained in conjunction with cerebrospinal fluid (CSF) samples and amyloid imaging with PET-PIB. Participants were classified as either low or high exercisers based on exercise guidelines of the American Heart Association.

Subjects—201 cognitively normal adults (135 females) aged 45–88 were recruited from the Knight Alzheimer Disease Research Center at Washington University. CSF samples were collected from 165 participants. Amyloid imaging was performed on 163 participants.

Results—*APOE* $\epsilon 4$ carriers evidenced higher PIB binding ($p < .001$) and lower CSF $A\beta_{42}$ levels ($p < .001$) than non-carriers. Our previous findings of higher PIB binding ($p = .005$) and lower CSF $A\beta_{42}$ levels ($p = .009$) in more sedentary individuals were replicated. Most importantly, we observed a novel interaction between *APOE* status and exercise engagement for PIB binding ($p = .008$) such that a more sedentary lifestyle was significantly associated with higher PIB binding for $\epsilon 4$ carriers ($p = .013$) but not for $\epsilon 4$ non-carriers ($p = .208$). All findings remained significant after controlling for age, gender, education, hypertension, body mass index, diabetes, heart problems, history of depression and interval between assessments.

Conclusion—Collectively, these results suggest that cognitively normal sedentary *APOE* $\epsilon 4+$ individuals may be at augmented risk for cerebral amyloid deposition.

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INTRODUCTION

Presence of an *APOE* $\epsilon 4$ allele is the most established genetic risk factor for Alzheimer's disease (AD), with a greater percentage of AD individuals having an $\epsilon 4$ allele in comparison to the general population (1,2). In addition, age of dementia onset is earlier (2,3) and rate of cognitive decline may be greater in AD $\epsilon 4$ carriers compared to non-carriers (e.g., 4–6, but see 7,8). Even in cognitively normal middle-aged and older adults, *APOE* $\epsilon 4$ status has been associated with reduced cognitive performance (9) and greater cognitive decline (10,11). More recently, it has been demonstrated that cognitively normal adults with an *APOE* $\epsilon 4$ allele evidence greater cortical amyloid deposition as indicated by increased binding of the amyloid imaging agent, Pittsburgh Compound B (PIB), and lowered $A\beta_{42}$ in cerebrospinal fluid (CSF) (12–14).

Potentially modifiable lifestyle practices, such as engagement in physical exercise, may protect against cognitive decline. Mechanisms through which exercise may confer benefits include enhanced neurogenesis and angiogenesis, increased release of growth factors (e.g., brain-derived neurotrophic factor) that promote neuronal plasticity, and lowering of cardiovascular risk factors (16–18). An inverse association between physical activity and cognitive decline and dementia generally is supported, although there have been inconsistent findings (19,20). In addition, there have been mixed findings on the benefits of exercise in transgenic AD mouse models (21,22). We recently demonstrated, however, lower amyloid deposition, as estimated with PIB and CSF $A\beta_{42}$, in cognitively normal individuals who exercised regularly (12).

It has been suggested that *APOE* status may modify associations between lifestyle factors such as exercise engagement and risk of cognitive decline and dementia (23). Several examinations of potential interactive effects of *APOE* status and physical activity on cognitive decline have yielded mixed findings, with reports of greater beneficial effects of exercise for $\epsilon 4$ carriers (24–29), no difference between $\epsilon 4$ carriers and non-carriers in exercise effects (30–32), and greater benefits for $\epsilon 4$ non-carriers (33). By contrast, interactive effects of *APOE* status and physical exercise on amyloid deposition have not been fully investigated. The goal of the current study was to assess whether exercise moderates the effects of *APOE* status on amyloid deposition in a cohort of cognitively normal older adults. The primary hypotheses were that a) *APOE* $\epsilon 4$ status would be associated with greater amyloid deposition; b) exercise engagement would be associated with lower amyloid deposition; and c) a sedentary lifestyle would have a greater effect on amyloid deposition in *APOE* $\epsilon 4+$ individuals.

MATERIALS AND METHODS

Participants

Middle-aged and older adults, age 45–88 years, were recruited from the Knight Alzheimer Disease Research Center (ADRC) at Washington University. A subsample was recruited as part of an ongoing study at the ADRC on adult children with parents who were diagnosed with AD (34). Based on the Washington University Clinical Dementia Rating (CDR), a validated and reliable interview-based measurement sensitive in detecting the earliest stages of dementia, all participants were classified as cognitively normal (CDR=0) (35,36). Clinical assessment included a health history that determined the presence or history of diabetes, hypertension, neurological illness or injury, depression or cardiovascular compromise (e.g., history of angioplasty, atrial fibrillation). Height and weight were also obtained and used to calculate body mass index. Exclusionary criteria were major neurologic illnesses or injury (e.g., stroke, cerebrovascular disease, Parkinson disease).

Cerebrospinal fluid (CSF) samples were collected from 165 participants. Amyloid imaging with PIB was obtained in 163 participants. An exercise engagement questionnaire was administered to all participants. All participants consented to participation in accordance with guidelines of the Washington University Human Research Protection Office. Exercise and structural data (n=52; 37) and amyloid data (n=69; 12) from some of these participants have been published previously.

Measurement of physical exercise engagement

Validity—A validated questionnaire assessing history of walking, running and jogging (WRJ) activity for the past 10 years was used to estimate exercise engagement (38). The measure was significantly correlated with cardiorespiratory fitness measured via treadmill test in a sample of 5063 individuals aged 18–80 years. Stable correlations were observed between retrospective self-report of activity for a particular year and aerobic fitness for that year across 10 1-year assessment periods, suggesting participants across examined age range were capable of relatively accurate self-report over extended time span. Correlations were similar with and without controlling for age, suggesting age was not a significant contributor to observed associations.

Procedure—The questionnaire was administered by telephone, and participants reported number of months/year, number of workouts/week, average number of miles/workout, and average time/mile for each year in which they engaged in WRJ activity for the preceding 10 years. A physical exercise engagement score was derived for each participant by estimating metabolic equivalent (MET) values using the compendium of physical activities (38). The index of exercise engagement was average MET hours/week over the past 10 years.

The distribution of exercise engagement scores was zero-inflated and heavily skewed. Transformations (e.g. logarithmic) could not resolve these distributional issues. Therefore, rather than treating exercise engagement score as a continuous variable, participants were categorized into low and high exercise engagement groups based on whether reported exercise levels were at or above 7.5 MET-hours/week (30 minutes of moderate exercise 5 days/week) recommended by the American Heart Association (AHA) (12).

Cerebrospinal fluid collection, processing, and biomarker measurement

CSF free from blood contamination was collected by lumbar puncture in polypropylene tubes at 8:00 AM after overnight fasting as described previously (39). Samples were gently inverted to avoid gradient effects, briefly centrifuged at low speed to pellet any cellular elements, and aliquoted (500 μ l) into polypropylene tubes before freezing at -84°C . Analyses for A β_{42} were completed using commercial enzyme-linked immunosorbant assay (INNOTEST; Innogenetics, Ghent, Belgium). Samples were continuously kept on ice with only a single thaw after initial freezing before assaying.

PET-PIB imaging

In vivo amyloid imaging via positron emission tomography (PET) with PIB ([*N*-methyl- ^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole) was performed as described previously (40). Approximately 12 mCi of [^{11}C]PIB was administered intravenously simultaneous with initiation of a 60-minute dynamic PET scan in three-dimensional mode. Measured attenuation factors and a ramp filter were used to reconstruct dynamic PET images. Three-dimensional regions-of-interest were then created for each participant based on their individual MRI scans (T1-weighted $1\times 1\times 1.25\text{mm}$ MPRAGE). A binding potential (BP) for each region-of-interest was calculated to express regional binding values in a manner proportional to number of binding sites. BP values from prefrontal cortex, gyrus rectus, lateral temporal, and precuneus regions-of-interest were averaged to calculate a mean

cortical binding potential (MCBP) value based on brain regions known to have high PIB uptake among participants with AD (40). This derived MCBP value has been shown to correlate inversely with CSF A β ₄₂ (39) and exercise engagement (12), predict progression from cognitively normal status to symptomatic AD (41), and be associated with disrupted functional connectivity of the default mode (42).

APOE genotyping

TaqMan assays (Applied Biosystems, Foster City, USA) for both rs429358 (ABI#C_3084793_20) and rs7412 (ABI#C_904973_10) were used for *APOE* genotyping. Allele calling was performed using the allelic discrimination analysis module of ABI Sequence Detection Software. Positive controls for each of six possible *APOE* genotypes were included on the genotyping plate. Individuals were then classified as ϵ 4+ (44, 34, 24) or ϵ 4- (33, 23, 22).

Timing of assessments

Clinical assessment was within \pm 6.0 months (SD=12.4) of the PET scan and \pm 2.9 months (SD=3.9) of the CSF assessment. The interval between clinical and exercise assessments was \pm 3.4 months (SD=7.7) for PIB sample and \pm 3.3 months (SD=7.6) for CSF sample. Individuals were CDR 0 at all assessments.

Exercise assessment was within \pm 0.92 years (SD=1.3) of the PET scan. For 105/163 individuals, the exercise assessment was subsequent to the PET scan and thus captured exercise behavior during the time of the PET scan. For the remaining 58 individuals exercise assessment was prior to the PET scan by an average of $-$.33 years (SD=.33). Thus, for these individuals reported exercise behavior would have occurred almost exclusively during a time period prior to the PET scan.

Exercise assessment was within \pm 1.6 years (SD=2.2) of CSF assessment. For 113/165 individuals, exercise assessment was subsequent to CSF assessment and thus captured exercise behavior during the time of CSF assessment. For the other 52 individuals exercise assessment was prior to CSF assessment by an average of $-$.28 years (SD=.34). Thus, for these individuals reported exercise behavior would have occurred almost exclusively during a time period prior to CSF assessment.

Statistical analyses

All analyses were conducted using SPSS/PASW 17.0 (SPSS Inc., Chicago, Illinois). We first tested for group differences (i.e., Exercise Group, *APOE* status) in demographic and health variables using Student's t tests for continuous variables and Fisher's exact test for dichotomous variables (see Tables 1 and 2 for demographic and health data).

We used hierarchical multiple regression (using ordinary least squares (OLS)) to examine the unique variance accounted for by the Exercise Group \times *APOE* status interaction above and beyond the main effects (Exercise Group; *APOE* status) for each of the separate estimates of amyloid deposition. There were separate regression models for each complete cohort (i.e., MCBP and CSF A β ₄₂) with no missing data points. Exercise Group and *APOE* status main effects were entered in one step, and the Exercise Group \times *APOE* status interaction term was entered in the next step. Importantly, a significant interaction indicates that Exercise Group exerts a moderating effect on the influence of *APOE* status on amyloid deposition above and beyond the influence of either Exercise Group or *APOE* status alone. All statistical significance tests were 1-tailed as we had *a priori* directional hypotheses regarding main and interactive effects, and α =0.05.

RESULTS

MCBP cohort

There were significant *APOE* group differences in age ($p=.027$) and a non-significant trend for a group difference in hypertension ($p=.068$). In addition, there were significant Exercise group differences in education ($p=.043$) and hypertension ($p=.041$) and a non-significant trend for body mass index (BMI) ($p=.091$). Lastly, there was a significant correlation between MCBP and age ($p=.020$). No other associations with demographic or health variables reached or approached significance (all $ps>.145$). Thus, age, education, BMI and hypertension were included as covariates in the first step in the model examining MCBP. As there was evidence of mild-to-moderate heteroscedasticity in the initial OLS model (White's test=43.20, $p=.033$), robust regression was conducted and is reported below (results were equivalent for OLS and robust regression).

In the regression model examining MCBP (see Table 3), there were significant Exercise Group ($p<.001$) and *APOE* status ($p<.001$) differences. High exercise individuals evidenced lower MCBP compared to low exercise individuals (Mean difference=-.079; 95% CI=-.124; -.034) and $\epsilon 4+$ individuals evidenced higher MCBP compared to $\epsilon 4-$ individuals (Mean difference=.141; 95% CI=.071;.211). There was a significant Exercise Group \times *APOE* status interaction ($p=.002$; see Figure 1) that reflected a greater exercise effect on MCBP in $\epsilon 4+$ individuals (Mean difference between Exercise Groups=.183; 95% CI=-.308; -.059) compared to $\epsilon 4-$ individuals (Mean difference between Exercise Groups=-.019; 95% CI=-.052;.014). Notably, results were similar when other potentially confounding demographic and health variables (i.e., gender, diabetes, heart problems, history of depression), and the delay between the PET scan and exercise assessment, were additionally included as covariates (Exercise Group: $p<.001$; *APOE* status: $p<.001$; Exercise Group \times *APOE* status interaction: $p=.004$).

CSF $A\beta_{42}$ cohort

There were significant *APOE* group differences in age ($p=.015$), BMI ($p=.014$), and hypertension ($p=.012$) and significant Exercise group differences in BMI ($p<.001$) and hypertension ($p=.022$). No other associations approached or reached significance. Thus, age, BMI and hypertension were included as covariates in the first step in the model examining CSF $A\beta_{42}$. There was no evidence of heteroscedasticity (White's test=21.11, $p=.391$), so OLS regression results are reported.

In the regression model examining CSF $A\beta_{42}$ (see Table 4), there were significant Exercise Group ($p=.005$) and *APOE* status ($p<.001$) differences (see Figure 2). Low exercise individuals evidenced lower CSF $A\beta_{42}$ compared to high exercise individuals (Mean difference=96.08; 95% CI=17.21; 174.95) and $\epsilon 4+$ individuals also evidenced lower CSF $A\beta_{42}$ compared to $\epsilon 4-$ individuals (Mean difference=-159.18; 95% CI=-227.90; -90.45). However, the Exercise Group \times *APOE* status interaction was not significant ($p=.408$). Thus, the exercise effect on CSF $A\beta_{42}$ did not differ between $\epsilon 4+$ individuals (Mean difference between Exercise Groups=80.11; 95% CI=-41.368;201.577) and $\epsilon 4-$ individuals (Mean difference between Exercise Groups=102.48; 95% C =-2.354; 207.320). Notably, results were similar when other potentially confounding demographic and health variables (i.e., gender, education, diabetes, heart problems, history of depression), and the delay between the LP and exercise assessment, were included as covariates (Exercise Group: $p=.011$; *APOE* status: $p<.001$; Exercise Group \times *APOE* status interaction: $p=.365$).

DISCUSSION

APOE status is associated with increased risk of cognitive decline and elevated amyloid deposition (4–6,10–15). In contrast, exercise engagement has been associated with reduced risk of cognitive decline (19,20) and lower levels of amyloid deposition (12). In the current investigation we sought to replicate effects of *APOE* genotype and exercise engagement on amyloid deposition and further examine whether exercise moderates effects of *APOE* genotype on amyloid deposition.

Consistent with several past findings (12–15), the presence of an *APOE* $\epsilon 4$ allele was associated with elevated amyloid deposition as assessed with PET-PIB. In addition, we observed lower PIB binding for individuals who exercised at or above levels recommended by AHA, similar to our previous study of 69 individuals (12). However, here we report the novel finding of a significant interaction between *APOE* and exercise engagement for cerebral amyloid burden. Specifically, a significant effect of exercise engagement was present for *APOE* $\epsilon 4$ carriers but not for non-carriers, with sedentary $\epsilon 4+$ individuals evidencing greater MCBP compared to active $\epsilon 4+$ individuals. In fact, post-hoc analyses indicate that the magnitude of MCBP was equivalent between active $\epsilon 4+$ individuals and all $\epsilon 4-$ individuals ($t=.07$; $p=.414$), and between active $\epsilon 4+$ individuals and active $\epsilon 4-$ individuals ($t=-.722$; $p=.238$). Collectively, these findings suggest that the combination of $\epsilon 4+$ status and a sedentary lifestyle may place individuals at augmented risk for amyloid deposition, as assessed via PET-PIB. This result remained robust after controlling for significant group differences in demographic and health variables, and for additional health variables that did not differ between groups but may have potentially contributed to observed findings.

A greater effect of exercise engagement in *APOE* $\epsilon 4$ carriers is consistent with and extends existing data demonstrating increased risk of cognitive decline and dementia in sedentary $\epsilon 4+$ individuals (24–29; but see 30–33). Greater exercise-related improvements in cognitive performance and markers of hippocampal plasticity in *APOE* $\epsilon 4$ transgenic mice is also supportive of differential benefits for $\epsilon 4$ carriers (43). *APOE* $\epsilon 4$ appears to be associated with reduced neuronal plasticity (44,45), and it has been argued that this inherent neurophysiological disadvantage makes beneficial lifestyle factors, such as exercise, preferentially important for $\epsilon 4$ carriers (28,43). The MCBP findings support the idea that a physically active lifestyle may allow $\epsilon 4$ carriers to experience brain amyloid levels equivalent to $\epsilon 4-$ individuals. Although mechanisms through which exercise may influence amyloid deposition remain unclear, there may be both relatively direct effects on amyloid precursor protein metabolism (21,46,47) and indirect effects through influences on neurotrophic factors, neuroinflammation, cerebrovascular functioning or glucose metabolism (46–48).

In terms of CSF $A\beta_{42}$, we again observed that the *APOE* $\epsilon 4$ allele had a negative influence, with $\epsilon 4+$ individuals evidencing lower CSF $A\beta_{42}$, consistent with past reports (12–15). Exercise engagement was again associated with a more beneficial profile such that those who met AHA recommendations evidenced higher CSF $A\beta_{42}$. However, there was no interaction between *APOE* status and exercise engagement for CSF $A\beta_{42}$. Unlike for MCBP, sedentary $\epsilon 4+$ individuals did not evidence a significantly greater effect of exercise engagement on CSF $A\beta_{42}$ compared to active $\epsilon 4+$ individuals.

The reason for the discrepancy between MCBP and CSF $A\beta_{42}$ is uncertain. The two largely reflect complimentary estimates of the same process of amyloid plaque development in the brain and are strongly associated (e.g., 38,49). However, PET-PIB identifies only fibrillar $A\beta$ whereas CSF $A\beta_{42}$ levels may reflect nonfibrillar $A\beta$ species as well (50–52). In

addition, while CSF A β ₄₂ estimates could conceivably reflect amyloid deposition in various regions of the brain, the MCBP estimate represents select regions of high amyloid deposition, and this difference may contribute to our findings. It is also possible that the current sample size was insufficient to detect differences in exercise effects on *APOE* groups in terms of CSF A β ₄₂.

The current investigation provides support for an association between exercise engagement and amyloid deposition, with stronger associations in ϵ 4+ individuals in terms of MCBP. However, several limitations must be considered. It is conceivable that confounds not assessed here (e.g., socioeconomic status, ability to engage in physical exercise, personality) may have influenced our results, and are thus relevant to examine in future investigations. Inferences about causal flow between exercise and amyloid deposition are not possible given the cross-sectional design. While it is possible that subclinical dementia may have subtly influenced exercise engagement or reporting of exercise in ϵ 4+ individuals, neither the proportion of individuals meeting AHA-recommended levels nor mean exercise levels differed between *APOE* groups. Another potential concern is use of a self-report measure of exercise engagement and use of phone administration in contrast to the in-person interview used in the validation study (37). Furthermore, the measure is significantly, but not perfectly, correlated with cardiorespiratory fitness. Although the validation sample included older adults and the magnitude of association with cardiorespiratory fitness was similar with and without controlling for age, the measure may still be limited by older adults' ability to accurately recall and report their exercise behavior over an extended time span.

In summary, our findings suggest that exercise at levels recommended by the AHA may be particularly beneficial for cognitively normal ϵ 4+ individuals in reducing risk of brain amyloid deposition. Longitudinal investigations and intervention studies that incorporate measures through which exercise may influence amyloid deposition are warranted to address causality and mechanisms.

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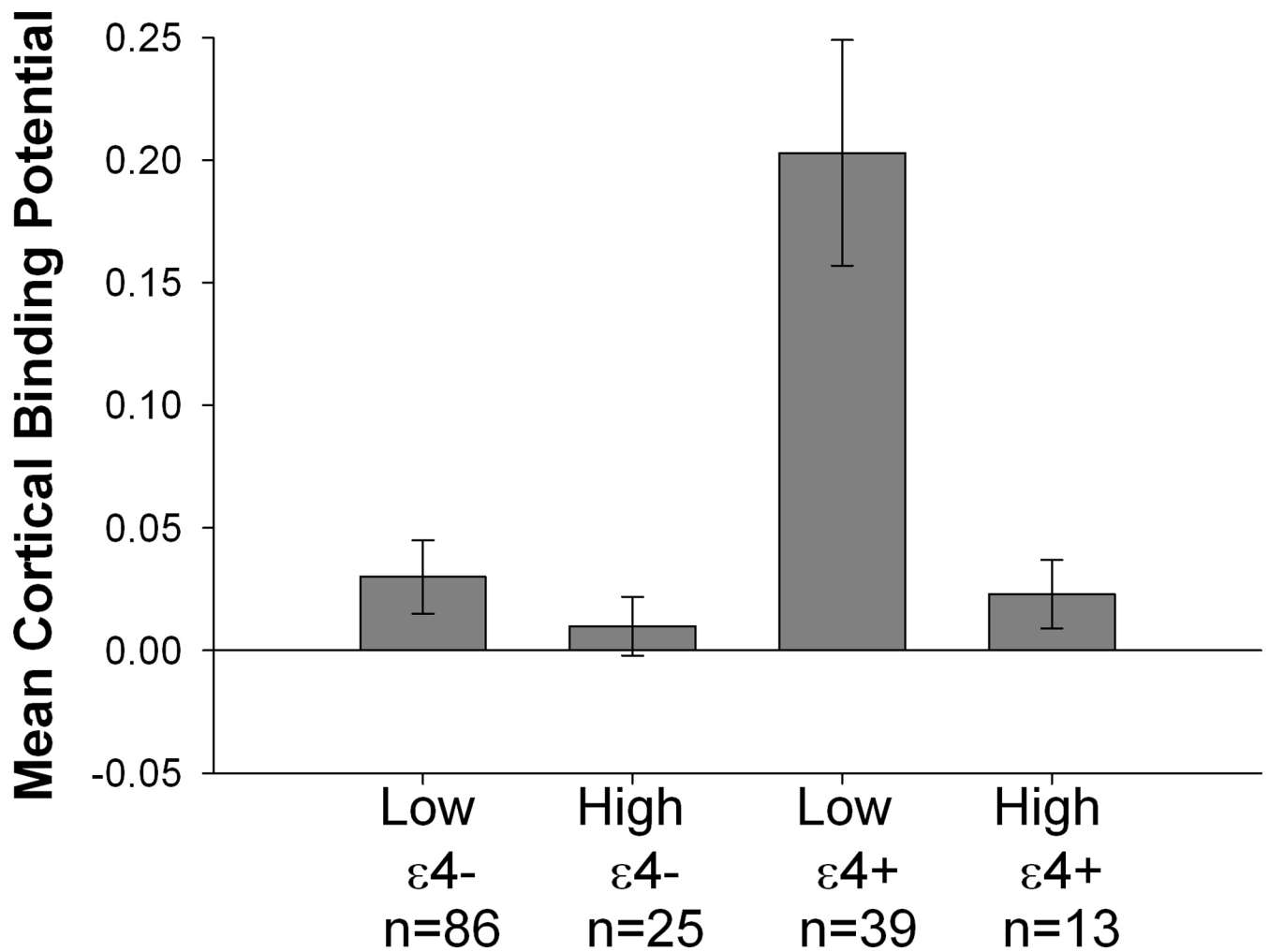


Figure 1.

Association between *APOE* status and exercise engagement for MCBP. There was a significant *APOE* status × exercise engagement interaction such that a more sedentary lifestyle was significantly associated with higher PIB for ε4 carriers but not for ε4 non-carriers. See text for details.

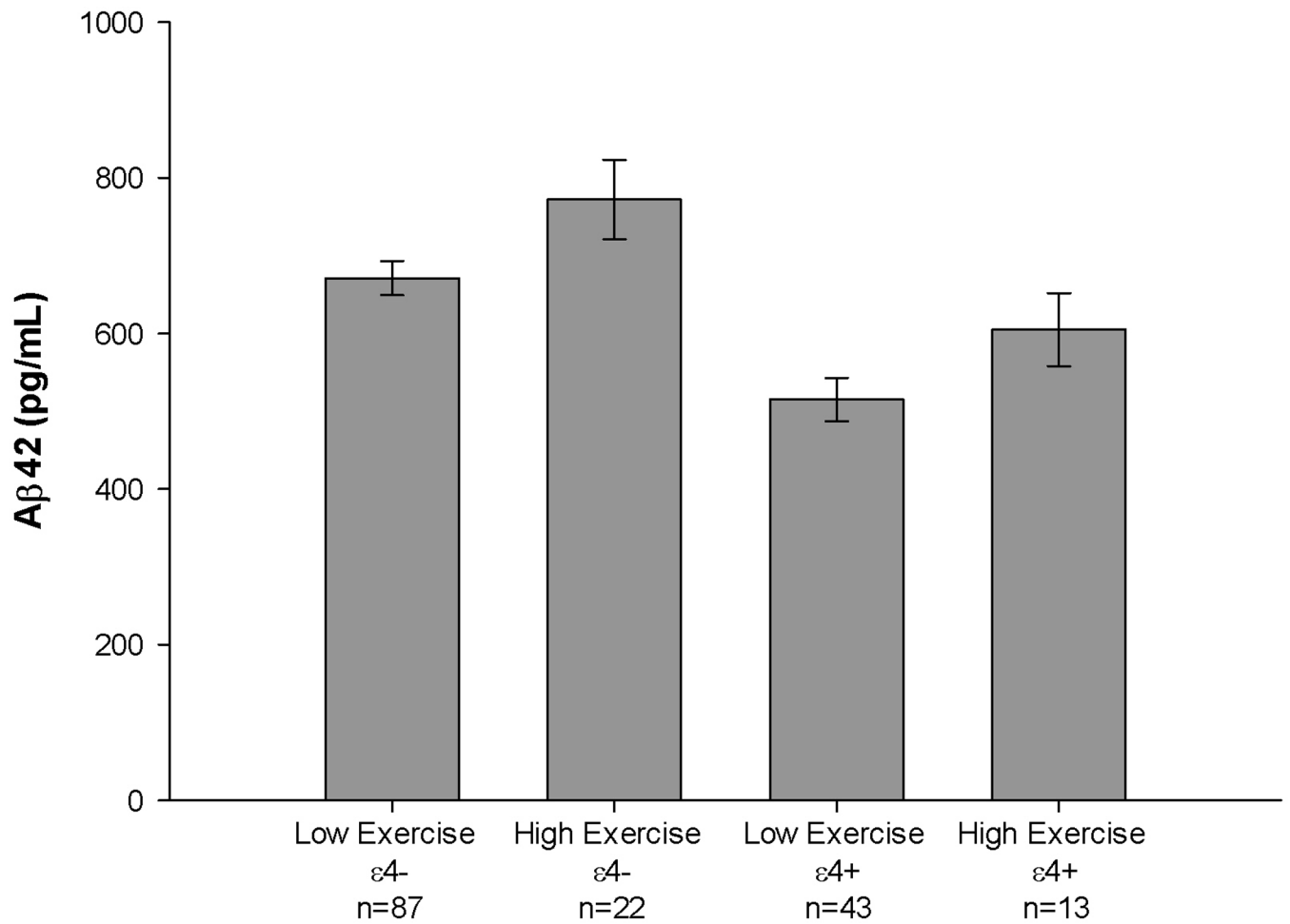


Figure 2.

Association between *APOE* status and exercise engagement for CSF Aβ₄₂. *APOE* ε₄ carriers evidenced lower CSF Aβ₄₂. Sedentary individuals evidenced lower CSF Aβ₄₂. The *APOE* status × exercise engagement interaction was not significant. See text for details.

Table 1Participant characteristics for *APOE* groups.

	PET Sample		CSF Sample	
	<i>APOE</i> ε4+	<i>APOE</i> ε4-	<i>APOE</i> ε4+	<i>APOE</i> ε4-
N	52	111	56	109
Mean age (SD), years	65 (10)	68 (10)*	64 (9)	68 (10)*
Gender (M/F)	14/38	38/73	16/40	37/72
Mean education (SD), years	16 (3)	16 (3)	16 (3)	16 (3)
Mean BMI (SD)	28 (6)	28 (6)	27 (5)	29 (6)*
Diabetes (-/+)	49/3	100/11	52/4	97/12
Mean MMSE (SD)	29.1 (1.5)	29.2 (.97)	29.3 (1.3)	29.1 (1.1)
Hypertension (-/+)	35/17	61/50	40/16	58/51*
Heart problems (-/+)	45/7	102/9	48/8	99/11
Depression (-/+)	43/9	97/14	47/9	96/13
Mean GDS (SD)	1.1 (1.4)	1.1 (1.6)	1.0 (1.4)	1.1 (1.5)
AHA exercise group (-/+)	39/13	86/25	43/13	87/22
Mean Exercise Score (SD), Met-hrs/wk	5.07 (7.06)	5.21 (7.46)	4.69 (6.45)	4.52 (6.13)
Mean MCBP (SD)	.16 (.26)	.03 (.10)**	--	--
Mean Aβ₄₂ (SD), pg/mL	--	--	536 (181)	692 (217)**

* $p < .05$;** $p < .01$.

MMSE=Mini-Mental State Exam; BMI=Body Mass Index; GDS=Geriatric Depression Scale. AHA exercise group represents whether individuals met the American Heart Association's recommended exercise levels (see text for details) with + indicating those who met recommendations.

Table 2

Participant characteristics for AHA exercise groups.

	PIB sample		CSF sample	
	<i>Exercisers</i>	<i>Non-exercisers</i>	<i>Exercisers</i>	<i>Non-exercisers</i>
N	38	125	35	130
Mean age (SD), years	65 (9)	67 (10)	66 (9)	67 (10)
Gender (M/F)	13/25	39/86	13/22	40/90
Mean education (SD), years	17 (3)	16 (3)*	16 (3)	16 (3)
Mean BMI (SD)	27 (5)	29 (6)	26 (4)	29 (6)**
Mean MMSE (SD)	29.4 (.94)	29.1 (1.2)	29.3 (.99)	29.2 (1.2)
Diabetes (-/+)	36/2	113/12	34/1	115/15
Hypertension (-/+)	27/11	69/56*	26/9	72/58*
Heart problems (-/+)	36/2	111/14	33/2	113/17
Depression (-/+)	34/4	106/19	30/5	113/17
Mean GDS score (SD)	1.1 (1.6)	1.1 (1.5)	1.3 (1.8)	1.0 (1.5)
APOE e4 (-/+)	25/13	86/39	22/13	87/43
Mean Exercise (SD), Met-hrs/wk	14.95 (8.83)	2.12 (2.28)**	13.88 (7.97)	2.14 (2.17)**
Mean MCBP (SD)	.01 (.06)	.09 (.20)**	--	--
Mean Aβ₄₂ (SD), pg/mL	--	--	710 (229)	620 (212)**

*
p < .05;**
p < .01.

MMSE=Mini-Mental Status Exam; BMI=Body Mass Index; GDS=Geriatric Depression Scale; Exercise groups are based on the American Heart Association's recommended exercise levels (see text for details).

Table 3

Regression results for MCBP cohort

Effect	ΔR^2	F-value (DF)	Unstd B (95%CI)	Std B	p-value
<i>Main Effects Step:</i>					
AHA Exercise Group	.167	16.707 (2, 156)	-.079 (-.124; -.034)	-.188	<.001
APOE status			.141 (.071; .211)	.371	<.001
<i>Interaction Step:</i>					
AHA Exercise Group \times APOE status	.029	6.021 (1, 155)	-.154 (-.257; -.050)	-.236	.002

Table 4

Regression results for CSF A β ₄₂ cohort

Effect	ΔR^2	F-value (DF)	Unstd B (95%CI)	Std B	p-
<i>Main Effects Step:</i>		13.460 (2, 158)			<.0001
AHA Exercise Group	.144		96.079 (17.208; 174.951)	.181	.008
APOE status			-159.175 (-227.903; -90.448)	-.346	<.0001
<i>Interaction Step:</i>		.055 (1, 157)			.408
AHA Exercise Group \times APOE status	.000		-19.078 (-179.724; 141.568)	-.024	.408