Published in final edited form as:
Arch Neurol. 2012 May ; 69(5): 636–643. doi:10.1001/archneurol.2011.845.

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

Denise Head, PhD[1,2,6], **Julie M. Bugg, PhD**[1], **Alison M. Goate, PhD**[3,4,5,6,7], **Anne M. Fagan, PhD**[3,6,7], **Mark A. Mintun, MD**[2,6], **Tammie Benzinger, MD, PhD**[2,6], **David M. Holtzman, MD**[3,6,7], and **John C. Morris, MD**[3,6]

[1]Department of Psychology, Washington University, St. Louis, MO

[2]Department of Radiology, Washington University, St. Louis, MO

[3]Department of Neurology, Washington University, St. Louis, MO

[4]Department of Psychiatry, Washington University, St. Louis, MO

[5]Department of Genetics, Washington University, St. Louis, MO

[6]The Knight Alzheimer's Disease Research Center, Washington University, St. Louis, MO

[7]Hope Center for Neurological Disorders, Washington University, St. Louis, MO

Abstract

Objective—*APOE* ε4 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* ε4 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 ε4 carriers ($p=.013$) but not for ε4 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* ε4+ individuals may be at augmented risk for cerebral amyloid deposition.

Address correspondence to: Denise Head, PhD, Washington University, Department of Psychology, Campus Box 1125, One Brookings Dr., St. Louis, MO 63130, ph: +1 (314) 935-8732, fax: +1 (314) 935-4711, dhead@wustl.edu.

The authors and their institution have no conflicts of interest related to this work.

INTRODUCTION

Presence of an *APOE* ε4 allele is the most established genetic risk factor for Alzheimer's disease (AD), with a greater percentage of AD individuals having an ε4 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 ε4 carriers compared to non-carriers (e.g., 4–6, but see 7,8). Even in cognitively normal middle-aged and older adults, *APOE* ε4 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* ε4 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 ε4 carriers (24–29), no difference between ε4 carriers and non-carriers in exercise effects (30–32), and greater benefits for ε4 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* ε4 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* ε4+ 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 (500μl) into polypropylene tubes before freezing at −84°C. Analyses for $A\beta_{42}$ 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 1×1×1.25mm 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 $A\beta_{42}$ (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 ε4+ (44, 34, 24) or ε4− (33, 23, 22).

Timing of assessments

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

Exercise assessment was within ±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 ±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×*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 $A\beta_{42}$) with no missing data points. Exercise Group and *APOE* status main effects were entered in one step, and the Exercise Group×*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 ε4+ individuals evidenced higher MCBP compared to ε4− individuals (Mean difference=.141; 95%CI=.071;.211). There was a significant Exercise Group×*APOE* status interaction (p=.002; see Figure 1) that reflected a greater exercise effect on MCBP in ε4+ individuals (Mean difference between Exercise Groups=.183; 95%CI=−.308; −.059) compared to ε4− 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×*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 ε4+ individuals also evidenced lower CSF $A\beta_{42}$ compared to ε4− individuals (Mean difference=−159.18; 95% CI=− 227.90; −90.45). However, the Exercise Group×*APOE* status interaction was not significant (p=.408). Thus, the exercise effect on CSF $A\beta_{42}$ did not differ between ε4+ individuals (Mean difference between Exercise Groups=80.11; 95%CI=−−41.368;201.577) and ε4− 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×*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* ε4 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* ε4 carriers but not for non-carriers, with sedentary ε4+ individuals evidencing greater MCBP compared to active ε4+ individuals. In fact, post-hoc analyses indicate that the magnitude of MCBP was equivalent between active ε4+ individuals and all ε4− individuals (t=.07; p=.414), and between active ε4+ individuals and active ε4− individuals (t=−.722; p=.238). Collectively, these findings suggest that the combination of ε4+ 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* ε4 carriers is consistent with and extends existing data demonstrating increased risk of cognitive decline and dementia in sedentary ε4+ individuals (24–29; but see 30–33). Greater exercise-related improvements in cognitive performance and markers of hippocampal plasticity in *APOE* ε4 transgenic mice is also supportive of differential benefits for ε4 carriers (43). *APOE* ε4 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 ε4 carriers (28,43). The MCBP findings support the idea that a physically active lifestyle may allow ε4 carriers to experience brain amyloid levels equivalent to ε4− 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* ε4 allele had a negative influence, with ε4+ 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 ε4+ individuals did not evidence a significantly greater effect of exercise engagement on CSF $A\beta_{42}$ compared to active ε4+ 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 Aβ whereas CSF $A\beta_{42}$ levels may reflect nonfibrillar Aβ species as well (50–52). In

addition, while CSF $A\beta_{42}$ 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 $A\beta_{42}$.

The current investigation provides support for an association between exercise engagement and amyloid deposition, with stronger associations in ε4+ 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 ε4+ 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 ε4+ 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.

Acknowledgments

We thank our lumbar puncture physicians for obtaining CSF samples, Ms. Aarti Shah and Mr. Matt Amos for processing and analyzing the CSF samples, and Ms. Sushila Sathyan for scheduling the lumbar punctures. We thank the Knight Alzheimer Disease Research Center Genetics Core for *APOE* genotyping. This work was supported by NIH grants P50 AG05861, P01 AG03991 and P01 AG026276. J.M.B. was supported by NIA 5T32AG00030.

REFERENCES

1. 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; 278:1349–1356. [PubMed: 9343467]
2. 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; 261:921–923. [PubMed: 8346443]
3. Blacker D, Haines JL, Rodes L, et al. ApoE-4 and age at onset of Alzheimer's disease: the NIMH genetics initiative. Neurology. 1997; 48:139–417. [PubMed: 9008509]
4. Brayne C, Harrington CR, Wischik CM, et al. Apolipoprotein E genotype in the prediction of cognitive decline and dementia in a prospectively studied elderly population. Dementia. 1996; 7:169–174. [PubMed: 8740632]
5. Craft S, Teri L, Edland SD, et al. Accelerated decline in apolipoprotein E-epsilon4 homozygotes with Alzheimer's disease. Neurology. 1998; 51:149–153. [PubMed: 9674794]
6. Martins CA, Oulhaj A, de Jager CA, Williams JH. APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. Neurology. 2005; 65:1888–1893. [PubMed: 16380608]

7. Hoyt BD, Massman PJ, Schatschneider C, Cooke N, Doody RS. Individual growth curve analysis of APOE epsilon 4-associated cognitive decline in Alzheimer disease. Arch Neurol. 2005; 62:454–459. [PubMed: 15767511]
8. Kleiman T, Zdanys K, Black B, et al. Apolipoprotein E epsilon4 allele is unrelated to cognitive or functional decline in Alzheimer's disease: retrospective and prospective analysis. Dement Geriatr Cogn Disord. 2006; 22:73–82. [PubMed: 16699282]
9. Small BJ, Rosnick CB, Fratiglioni L, Bäckman L. Apolipoprotein E and cognitive performance: a meta-analysis. Psychol Aging. 2004; 19:592–600. [PubMed: 15584785]
10. Caselli RJ, Dueck AC, Osborne D, et al. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. N Engl J Med. 2009; 361:255–263. [PubMed: 19605830]
11. Knopman DS, Mosley TH, Catellier DJ, Coker LH. Atherosclerosis Risk in Communities Study Brain MRI Study. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimers Dement. 2009:207–214. [PubMed: 19362884]
12. Liang KY, Mintun MA, Fagan AM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. Ann Neurol. 2010; 68:311–318. [PubMed: 20818789]
13. Morris JC, Roe CM, Xiong C, et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol. 2010; 67:122–131. [PubMed: 20186853]
14. Sunderland T, Mirza N, Putnam KT, et al. Cerebrospinal fluid beta-amyloid1–42 and tau in control subjects at risk for Alzheimer's disease: the effect of APOE epsilon4 allele. Biol Psychiatry. 2004; 56:670–676. [PubMed: 15522251]
15. Vemuri P, Wiste HJ, Weigand SD, et al. Alzheimer's Disease Neuroimaging Initiative. Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. Ann Neurol. 2010; 67:308–316. [PubMed: 20373342]
16. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007; 30:464–472. [PubMed: 17765329]
17. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007; 39:1423–1434. [PubMed: 17762377]
18. van Praag H. Neurogenesis and exercise: past and future directions. Neuromolecular Med. 2008; 10:128–140. [PubMed: 18286389]
19. Lee Y, Back JH, Kim J, et al. Systematic review of health behavioral risks and cognitive health in older adults. Int Psychogeriatr. 2010; 22:174–187. [PubMed: 19883522]
20. Plassman BL, Williams JW Jr, Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann Intern Med. 2010; 153:182–193. [PubMed: 20547887]
21. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J Neurosci. 2005; 25:4217–4221. [PubMed: 15858047]
22. Pietropaolo S, Sun Y, Li R, Brana C, Feldon J, Yee BK. The impact of voluntary exercise on mental health in rodents: a neuroplasticity perspective. Behav Brain Res. 2008; 192:42–60. [PubMed: 18468702]
23. Low LF, Yap MH, Brodaty H. Will testing for apolipoprotein E assist in tailoring dementia risk reduction? A review. Neurosci Biobehav Rev. 2010; 34:408–437. [PubMed: 19720080]
24. Deeny SP, Poeppel D, Zimmerman JB, et al. Exercise, APOE, and working memory: MEG and behavioral evidence for benefit of exercise in epsilon4 carriers. Biol Psychol. 2008; 78:179–187. [PubMed: 18395955]
25. Etnier JL, Caselli RJ, Reiman EM, Alexander GE, Sibley BA, Tessier D, McLemore EC. Cognitive performance in older women relative to ApoE-epsilon4 genotype and aerobic fitness. Med Sci Sports Exerc. 2007; 39:199–207. [PubMed: 17218903]
26. Kivipelto M, Rovio S, Ngandu T, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med. 2008; 12:2762–2771. [PubMed: 18318693]
27. Niti M, Yap KB, Kua EH, Tan CH, Ng TP. Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon 4 genotype in Chinese older adults. Int Psychogeriatr. 2008; 20:237–251. [PubMed: 18190728]

28. Rovio S, Kåreholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 2005; 4:705–4711. [PubMed: 16239176]
29. Schuit AJ, Feskens EJ, Launer LJ, Kromhout D. Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. Med Sci Sports Exerc. 2001; 33:772–777. [PubMed: 11323547]
30. Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002; 156:445–453. [PubMed: 12196314]
31. Sabia S, Kivimaki M, Kumari M, Shipley MJ, Singh-Manoux A. Effect of Apolipoprotein E epsilon4 on the association between health behaviors and cognitive function in late midlife. Mol Neurodegener. 2010; 5:23–29. [PubMed: 20515477]
32. Taaffe DR, Irie F, Masaki KH, et al. Physical activity, physical function, and incident dementia in elderly men: the Honolulu-Asia Aging Study. J Gerontol A Biol Sci Med Sci. 2008; 63:529–535. [PubMed: 18511759]
33. Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. Am J Epidemiol. 2005; 161:639–651. [PubMed: 15781953]
34. Xiong C, Roe C, Buckles V, et al. Family history of Alzheimer’s disease independently influences biomarker abnormalities in the Adult Children Study. Arch Neurol. in press.
35. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]
36. Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology. 2006; 67:467–473. [PubMed: 16894109]
37. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. Neurobiol Aging.
38. Bowles HR, FitzGerald SJ, Morrow JR Jr, Jackson AW, Blair SN. Construct validity of self-reported historical physical activity. Am J Epidemiol. 2004; 160:279–286. [PubMed: 15258001]
39. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol. 2006; 59:512–519. [PubMed: 16372280]
40. Mintun MA, Larossa GN, Sheline YI, et al. [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. Neurology. 2006; 67:446–452. [PubMed: 16894106]
41. Morris JC, Roe CM, Grant EA, et al. Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. Arch Neurol. 2009; 66:1469–1475. [PubMed: 20008650]
42. Sheline YI, Raichle ME, Snyder AZ, et al. Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. Biol Psychiatry. 2010; 67:584–587. [PubMed: 19833321]
43. Nichol K, Deeny SP, Seif J, Camaclang K, Cotman CW. Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. Alzheimers Dement. 2009; 5:287–294. [PubMed: 19560099]
44. Huang Y. Mechanisms linking apolipoprotein E isoforms with cardiovascular and neurological diseases. Curr Opin Lipidol. 2010; 21:337–345. [PubMed: 20531185]
45. Mahley RW, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet. 2000; 1:507–537. [PubMed: 11701639]
46. Nation DA, Hong S, Jak AJ, Delano-Wood L, Mills PJ, Bondi MW. Stress, exercise, and Alzheimer’s disease: A neurovascular pathway. Med Hypotheses. 2011; 76:847–854. [PubMed: 21398043]
47. Radak Z, Hart N, Sarga L, et al. Exercise plays a preventive role against Alzheimer’s disease. J Alzheimers Dis. 2010; 20:777–783. [PubMed: 20182027]
48. Um HS, Kang EB, Leem YH, et al. Exercise training acts as a therapeutic strategy for reduction of the pathogenic phenotypes for Alzheimer’s disease in an NSE/APPsw-transgenic model. Int J Mol Med. 2008; 22:529–539. [PubMed: 18813861]
49. Tolboom N, van der Flier WM, Yaqub M, et al. Relationship of cerebrospinal fluid markers to 11C-PiB and 18F-FDDNP binding. J Nucl Med. 2009; 50:1464–1470. [PubMed: 19690025]

50. Cairns NJ, Ikonomovic MD, Benzinger T, et al. Absence of Pittsburgh Compond B detection of cerebral amyloid beta in a patient with clinical, cognitive, and cerebrospinal fluid markers of Alzheimer disease: a case report. Arch Neurol. 2009; 66:1557–1562. [PubMed: 20008664]

51. Fagan AM, Head D, Shah AR, et al. Decreased cerebrospinal fluid Abeta(42) correltes with brain atrophy in cognitively normal elderly. Ann Neurol. 2009; 65:176–183. [PubMed: 19260027]

52. Ikonomovic MD, Klunk WE, Abrahamson EE, et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain. 2008; 131:1630–1645. [PubMed: 18339640]

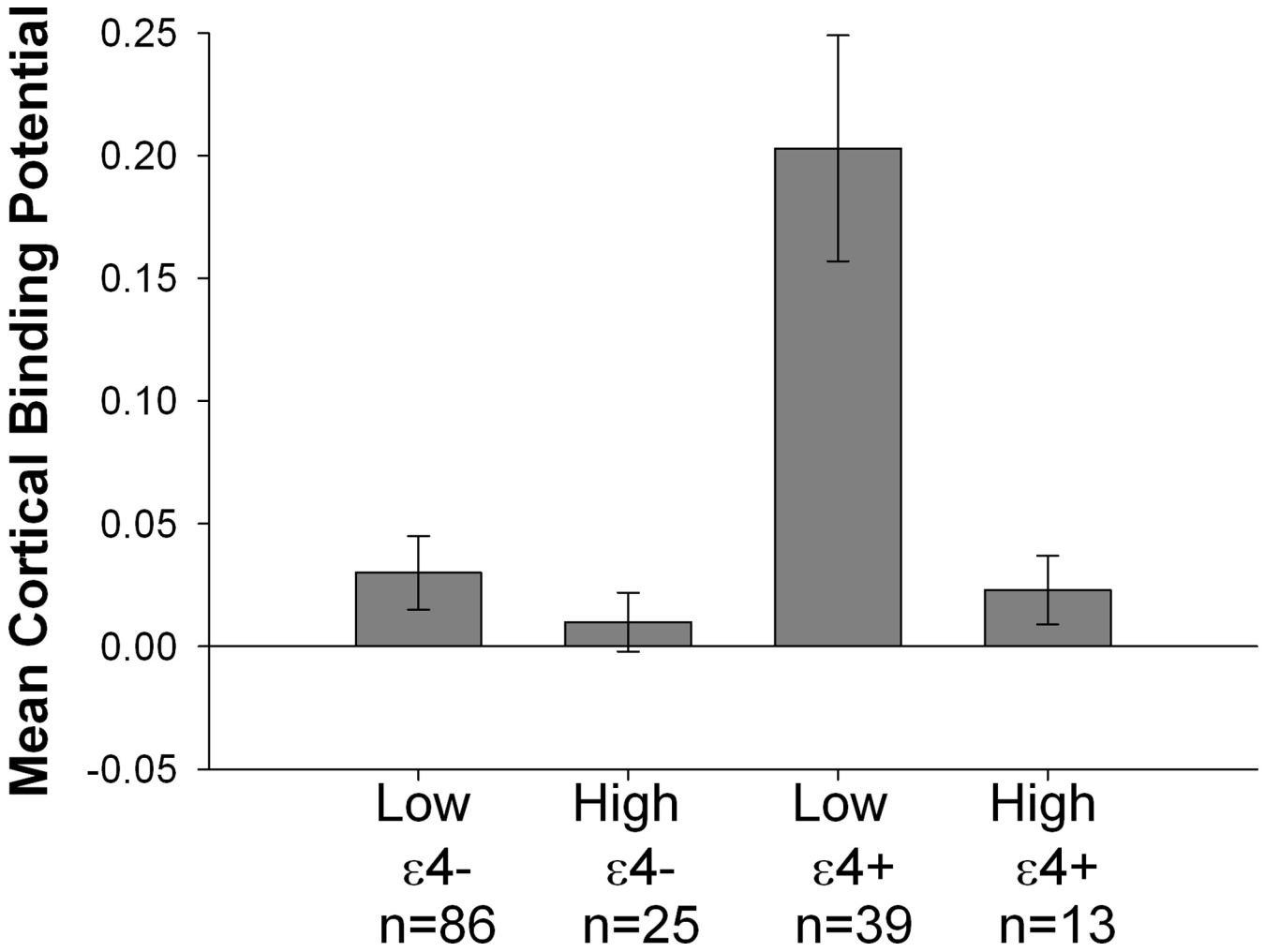

Figure 1.
Association between *APOE* status and exercise engagement for MCBP. There was a significant *APOE* status × exercise engagement interaction such that a more sedentary lifestyle was significantly associated with higher PIB for ε4 carriers but not for ε4 non-carriers. See text for details.

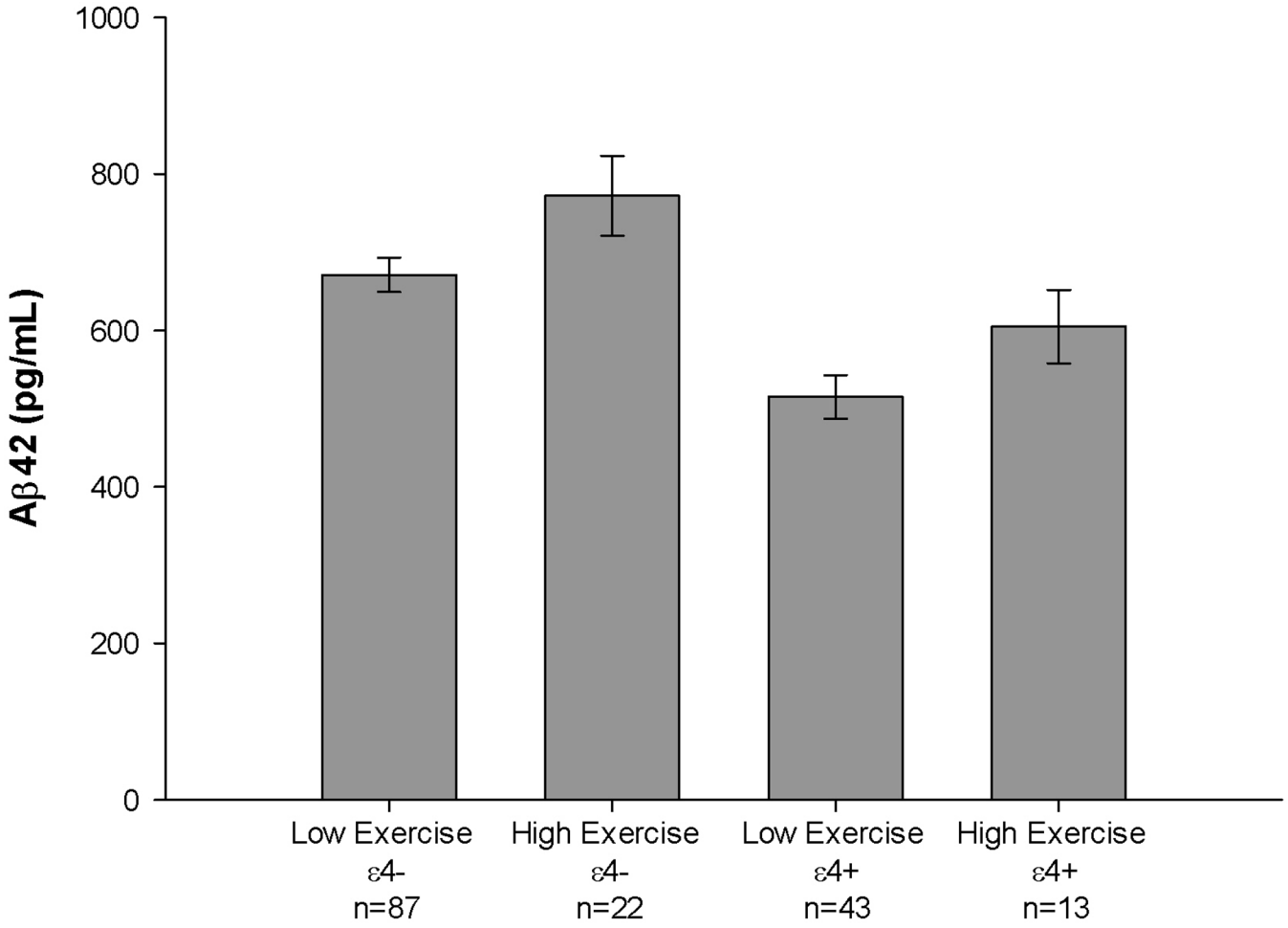

Figure 2.

Association between *APOE* status and exercise engagement for CSF $A\beta_{42}$. *APOE* ε4 carriers evidenced lower CSF $A\beta_{42}$. Sedentary individuals evidenced lower CSF $A\beta_{42}$. The *APOE* status × exercise engagement interaction was not significant. See text for details.

Table 1

Participant characteristics for *APOE* groups.

	PET Sample		CSF Sample	
	APOE ε4+	***APOE ε4−***	***APOE ε4+***	***APOE 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 $A\beta_{42}$ (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	
	Exercisers	***Non-exercisers***	***Exercisers***	***Non-exercisers***
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 ε4 (−/+)	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 $A\beta_{42}$ (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
Main Effects Step:	.167	16.707 (2, 156)			<.001
AHA Exercise Group			−.079 (−.124; −.034)	−.188	<.001
APOE status			.141 (.071; .211)	.371	<.001
Interaction Step:	.029	6.021 (1, 155)			.002
AHA Exercise Group × *APOE* status			−.154 (−.257; −.050)	−.236	.002

Table 4

Regression results for CSF $A\beta_{42}$ cohort

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