Exercise and Alzheimer's Disease Biomarkers in Cognitively Normal Older Adults

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Objective: In addition to the increasingly recognized role of physical exercise in maintaining cognition, exercise may influence Alzheimer's disease (AD) pathology, as transgenic mouse studies show lowered levels of AD pathology in exercise groups. The objective of this study was to elucidate the association between exercise and AD pathology in humans using Pittsburgh compound-B (PIB), amyloid-β ($A\beta$)$_{42}$, tau, and phosphorylated tau (ptau)$_{181}$ biomarkers.

Methods: Sixty-nine older adults (17 males, 52 females) aged 55 to 88 years, were recruited and confirmed to be cognitively normal. A questionnaire on physical exercise levels over the past decade was administered to all. Cerebrospinal fluid samples were collected from 56 participants, and amyloid imaging with PIB was performed on 54 participants.

Results: Participants were classified based on biomarker levels. Those with elevated PIB ($p = 0.030$), tau ($p = 0.040$), and ptau$_{181}$ ($p = 0.044$) had significantly lower exercise, with a nonsignificant trend for lower $A\beta_{42}$ ($p = 0.135$) to be associated with less exercise. Results were similar for PIB after controlling for covariates; tau ($p = 0.115$) and ptau$_{181}$ ($p = 0.123$) differences were reduced to nonsignificant trends. Additional analyses also demonstrated that active individuals who met the exercise guidelines set by the American Heart Association had significantly lower PIB binding and higher $A\beta_{42}$ levels with and without controlling for covariates (PIB: $p = 0.006$ and $p = 0.001$; $A\beta_{42}$: $p = 0.042$ and $p = 0.046$). Last, the associations between exercise engagement and PIB levels were more prominent in *APOE* epsilon 4 noncarriers.

Interpretation: Collectively, these results are supportive of an association between exercise engagement and AD biomarkers in cognitively normal older adults.

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With the disproportionate growth of the elderly population, Alzheimer's disease (AD)—the most common form of dementia among older adults—is poised to become a public health crisis. Although research on novel therapeutic strategies is gathering momentum with several new drugs entering clinical trials, it is still unclear what will be successful.[1] Coupled with the lack of current treatments that can halt this disease, there is great impetus toward efforts concerning early detection and prevention of AD. Lifestyle practices that could potentially deter or slow disease progression are especially important, considering that neurodegeneration in AD can begin a decade or more before the appearance of clinical symptoms.[2,3] Physical exercise may be an effective tool in this regard, with its increasingly recognized role in preserving not only cardiovascular but also brain and cognitive health in older adults.[4] Recommended by the Alzheimer's Association[5] to clinicians as a way to maintain cognitive functioning in AD and enhance a patient's quality of life (eg, by lowering depression), studies now suggest that exercise may also reduce risk of cognitive decline and dementia.[6,7]

There has been recent attention to how exercise affects AD pathology as quantified by imaging and neurochemical measures. The accumulation of amyloid plaques and neurofibrillary tangles involved in the neurodegenerative process of AD are correlated with several useful biomarkers. First, fibrillar amyloid-β deposition can be detected through positron emission tomography (PET) studies with Pittsburgh compound-B (PIB) as radiotracers to image the amyloid-β ($A\beta$) aggregates, with plaque formation indicated by higher uptake of PIB.[8] In addition, amyloid deposition can be assayed using lumbar puncture to measure the cerebrospinal fluid (CSF) level of $A\beta_{42}$ (a primary constituent of plaques), with reductions in CSF levels of $A\beta_{42}$ indicative of plaque formation. Third, neurofibrillary tangles are composed of hyperphosphorylated tau proteins (ptau), and an increased CSF level of $ptau_{181}$ is observed in AD.[9] Last, AD axonal death and neuronal degeneration are reflected in atrophy of brain regions such as the hippocampus and increased CSF levels of normally intracellular tau protein.[10,11] These biomarkers—PIB, $A\beta_{42}$, tau, $ptau_{181}$, and magnetic resonance imaging (MRI) brain volumetry—chart AD pathology and may serve as early diagnostic indicators.[12,13]

Using these biomarkers, researchers have investigated the effects of physical exercise on structural brain integrity and AD pathology. Structural imaging studies indicate beneficial effects of exercise and aerobic fitness on brain structure in healthy older adults[14,15] and individuals with AD.[16,17] Investigations of the effects of environmental enrichment, including wheel running, in transgenic AD mouse models have demonstrated improvements in cognitive performance but varying results in terms of amyloid deposition, with reports of reduced,[18–20] stable,[21] and increased[22] levels. Examination of exercise specifically in transgenic AD mice has also produced discrepant results, with lower levels of amyloid deposition and lower tau observed in some investigations,[23–25] but no effect of exercise on amyloid reported by others.[26,27] Divergent results in these studies may be attributable to use of different genetic mouse models, whether exercise onset is before or at the time of symptom onset, and/or type and duration of exercise.[28] The association between exercise and human AD pathology, however, as measured by PET-PIB and CSF neurochemical biomarkers such as $A\beta_{42}$, tau, and $ptau_{181}$, remains unexplored. The primary goal of the current study was to examine associations between exercise engagement and biomarker levels in older adults without clinical symptoms of AD.

Patients and Methods

Participants

Older adults, aged 55 to 88 years, were recruited from the Washington University Alzheimer's Disease Research Center and screened for neurologic illnesses or injury (eg, cerebrovascular disease, Parkinson disease). Based on the Washington University Clinical Dementia Rating (CDR), a validated and reliable interview-based measurement sensitive in detecting the earliest stages of dementia,[29,30] all participants were classified as nondemented (CDR = 0). An exercise engagement questionnaire (see below for details) was administered to all 69 participants, CSF samples were collected from 56 participants, and amyloid imaging with PIB was performed on 54 participants. Power was 0.80 to detect an effect size (Cohen's *d*) of 0.77 in the CSF sample and 0.79 in the PIB sample.

Individuals were CDR = 0 at all clinical assessments. Clinical assessment was within ±6.0 months (standard deviation [SD], 4.5) of the PET scan and ±4.0 months (SD, 2.2) of the CSF assessment. Exercise assessment was within ±2.8 years (SD, 2.1) of the PET scan and ±1.7 years (SD, 0.7) of CSF assessment. The interval between clinical and exercise assessments was ±5.8 months (SD, 5.4) for the PIB sample and ±6.2 months (SD, 4.9) for the CSF sample. Exercise assessment was subsequent to the PET scan for 45/54 participants and subsequent to CSF assessment for 54/56 participants. All participants consented to participation in accordance with guidelines of the Washington University Human Research Protection Office. Exercise and structural MRI data on a subset of these individuals (n = 52) was reported previously.[14]

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.[31] The measure was significantly correlated with cardiorespiratory fitness measured via treadmill test in a sample of 5063 individuals aged 18 to 80 years. Stable correlations were observed between retrospective self-report of activity for a particular year and aerobic fitness for that year across the 10 1-year assessment periods, suggesting that participants across the examined age range were capable of relatively accurate self-report over this extended time span.

PROCEDURE. The questionnaire was administered by telephone, and participants reported number of months/year, number of workouts/wk, 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 for each participant was derived by estimating metabolic equivalent (MET) values using the compendium of physical activities,[32] as described previously.[31] The index of exercise engagement was average MET hours/wk over the past 10 years. As a reference, an individual who followed the physical exercise recommendation of the American Heart Association (AHA) for older adults (30 minutes of moderate exercise 5 days/wk) would score 7.5 MET-hours/wk.[31,33]

Cerebrospinal Fluid Collection, Processing, and Biomarker Measurement

CSF (20–30ml) free from any blood contamination was collected by lumbar puncture in polypropylene tubes at 8:00 am after overnight fasting, as described previously.[8] 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 total tau, ptau$_{181}$, and Aβ_{42} were completed using commercial enzyme-linked immunosorbent assay (Innotest; Innogenetics, Ghent, Belgium). For all biomarker measures, samples were continuously kept on ice with only a single thaw after initial freezing before assays.

PET-PIB Imaging

In vivo amyloid imaging via PET with PIB ([N-methyl-(^{11}C)]2-[4$'$-methylaminophenyl]-6-hydroxybenzothiazole)[34] was performed as described previously.[12] Approximately 12mCi of [11C]PIB was administered intravenously simultaneous with initiation of a 60-minute dynamic PET scan in 3-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 magnetization prepared rapid acquisition gradient echo). 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.[12]

APOE Genotyping

TaqMan assays (Applied Biosystems Inc. [ABI], Foster City, CA) 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 6 possible *APOE* genotypes were included on the genotyping plate. Individuals were then classified as ε4+ (44, 34, 24) or ε4− (33, 23, 22) depending on whether or not at least 1 ε4 allele was present.

Diagnostic Biomarker Thresholds

Although use of CSF biomarker thresholds in determining risk of AD is prevalent, standard diagnostic cutoff values are lacking, as noted previously.[35] This study used a PIB cutoff of 0.20 MCBP, because regional brain atrophy in cognitively normal individuals with PIB levels at or above this level has been demonstrated.[13] Individuals with MCBP $\geq$ 0.20 were considered PIB+ ("at risk" phenotype); those below this cutoff were considered PIB− ("normal" phenotype). For CSF Aβ_{42}, 500pg/ml was chosen, as this level is indicative of brain amyloid as assessed by PET-PIB,[8,36] and is associated with whole brain and hippocampal atrophy in cognitively normal individuals.[37] For

CSF tau and ptau$_{181}$, there was less precedent in existing literature for predetermined cutoffs, as a wide range of values are reported to distinguish AD from controls with no clear guidelines.[9,35] Therefore, we plotted the data, and as apparent in the Figure, C–D, there was a behavior that seemed to be best expressed with tau and ptau$_{181}$ thresholds of 425pg/ml and 72pg/ml, respectively, which are within the range of diagnostic values reported previously.[35,36] Individuals with low CSF Aβ_{42} (<500pg/ml, "at risk") were considered Aβ_{42}+; those with high Aβ_{42} ($\geq$500pg/ml, "normal") were considered Aβ_{42}−. Similarly, those with CSF tau and ptau$_{181}$ values above the cutoffs were classified as tau+ and ptau$_{181}$+ ("at risk"), respectively; those below the cutoffs were classified tau− and ptau$_{181}$− ("normal").
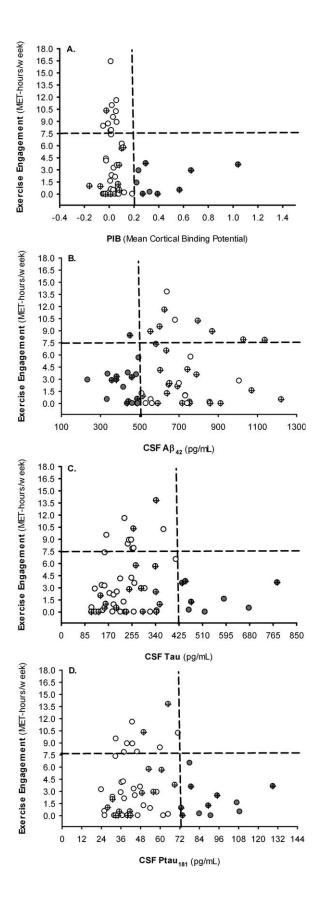
Statistical Analyses

All analyses were conducted using SPSS/PASW 17.0 (SPSS Inc., Chicago, IL). All statistical significance tests were 2-tailed, with α = 0.05. We first tested for group differences in demographic variables, *APOE* status, and medical conditions using Student *t* tests for continuous variables and chi-square or Fisher exact test for dichotomous variables (Tables 1 and 2). With 2 exceptions (see Table 1 and Results section), there were no significant differences between biomarker groups or between exercise groups.

Primary questions regarding associations between exercise and biomarkers were examined with Student *t* test for groups with equal variance; unequal variance *t* tests were used when the assumption of equal variances was unmet. Although age, gender, and education were not significantly associated with dependent variables (with 2 exceptions noted above), analyses were also conducted controlling for these potentially confounding factors. In these analyses, residuals of the dependent variable after adjustment for age, gender, and education were submitted to *t* tests. Values $\geq$3 SD from the mean were considered outliers. Unless otherwise specified in the Results section, results were unchanged when outliers were removed.

Results

Individuals with At-Risk Biomarker Levels Evidence Less Exercise Engagement

Examination of graphs plotting exercise engagement against biomarker levels (see Fig) suggests that individuals with elevated PIB, CSF tau, or ptau$_{181}$, or decreased CSF Aβ_{42} (at-risk phenotypes), consistently exercised less. Based on categorization of individuals into PIB+ and PIB− groups, there was significantly greater exercise in the PIB− group (*t*[34.4] = 2.393, *p* = 0.022; covariates controlled: *t*[22.0] = 2.314, *p* = 0.030). For Aβ_{42}, there was a nonsignificant trend for greater exercise in the Aβ_{42}− group (*t*[52.1] = −1.518, *p* = 0.135; covariates controlled: *t*[50.8] = 1.310, *p* = 0.196). Individuals in the negative tau and ptau$_{181}$ groups evidenced significantly greater exercise engagement (*t*[22.8] = 2.175, *p* =

0.040 and $t[29.9] = 2.104$, $p = 0.044$, respectively). However, these effects were reduced to nonsignificant trends with covariates controlled (tau: $t[24.2] = 1.598$, $p = 0.115$; ptau$_{181}$: $t[21.7] = 1.641$, $p = 0.123$).

AHA Exercise Engagement Levels Are Associated with Reduced Amyloid Deposition

We also assessed whether biomarker levels differed between individuals who did or did not satisfy AHA guidelines of 7.5 MET-hours/wk of exercise (Table 2). Individuals who met or exceeded the recommended exercise had significantly lower MCBP ($t[48.7] = 2.854$, $p = 0.006$) than those not meeting recommendations. The difference was not significant after controlling for age, gender, education, and significant biomarker group differences in *APOE* status ($t[52] = 1.106$, $p = 0.274$). However, when an outlier value was removed, there was a significant difference in MCBP between exercise groups (covariates controlled: $t[46.5] = 3.477$, $p = 0.001$), and *APOE* status no longer differed between groups. There was a nonsignificant trend for exercisers to have higher Aβ_{42} levels ($t[54] = -1.739$, $p = 0.088$; covariates controlled: $t[54] = 1.680$, $p = 0.099$). When an outlier value was removed, however, there was a significant difference in Aβ_{42} levels between exercise groups ($t[53] = -2.082$, $p = 0.042$; covariates controlled; $t[53] = 2.040$, $p = 0.046$). There were no significant differences in tau ($t[39.0] = 0.662$, $p = 0.512$; covariates controlled: $t[37.3] = 0.140$, $p = 0.890$) or ptau$_{181}$ ($t[27.5] = 0.948$, $p = 0.351$; covariates controlled: $t[28.7] = 0.332$, $p = 0.743$) levels between exercise groups.

Exercise Effects by APOE Genotype

There were significant differences in Aβ_{42} levels depending on *APOE* genotype, with $\varepsilon4+$ individuals having lower Aβ_{42} levels ($\varepsilon4+$: 564pg/ml; $\varepsilon4-$: 679pg/ml; t[54] = 2.024, $p = 0.048$). There was also a nonsignificant trend for $\varepsilon4+$ individuals to have higher MCBP ($\varepsilon4+$: 0.214, $\varepsilon4$: 0.048; $t[15.8] = -2.070$, $p = 0.055$). There were, however, no significant differences in tau or ptau$_{181}$ levels depending on *APOE* genotype (tau, $\varepsilon4+$: 303pg/ml, $\varepsilon4-$: 264pg/ml, $t[54] = -1.021$, $p = 0.312$; and ptau$_{181}$, $\varepsilon4+$: 58pg/ml, $\varepsilon4-$: 50pg/ml, t (54) = -1.337, $p = 0.187$).

FIGURE: Associations between exercise engagement and biomarker levels. (A) Mean cortical binding potential; (B) cerebrospinal fluid (CSF) amyloid-β (Aβ)$_{42}$; (C) CSF tau; (D) CSF hyperphosphorylated tau protein (ptau)$_{181}$. Quadrants are formed by crossing biomarker thresholds with AHA recommended level of exercise; note the L-shaped distributions in which individuals with positive biomarker status (*gray-filled circles*) are all sedentary, with 1 exception in panel B. Crossed circles represent $\varepsilon4+$ individuals. MET = metabolic equivalent value; PIB = Pittsburgh compound-B.

TABLE 1: Participant Characteristics for Biomarker Groups

Characteristic	MCBP		$A\beta_{42}$		Tau		Ptau$_{181}$	
	At Risk	Normal	At Risk	Normal	At Risk	Normal	At Risk	Normal
No.	9	45	18	38	8	48	11	45
Mean age, yr (SD)	73 (8)	70 (10)	71 (8)	65 (8)[a]	70 (10)	66 (8)	68 (9)	67 (8)
Gender (F/M)	5/4	35/10	12/6	31/7	7/1	36/12	10/1	33/12
Mean education, yr (SD)	16 (6)	16 (3)	17 (4)	15 (3)	16 (4)	16 (3)	16 (4)	16 (3)
BMI (normal/overweight/obese)	3/6/0	17/19/9	3/10/5	17/12/9	4/3/1	16/19/13	5/3/3	15/19/11
Diabetes (−/+)	9/0	43/2	17/1	36/2	8/0	45/3	11/0	42/3
Hypertension (−/+)	7/2	24/21	8/10	23/15	4/4	27/21	6/5	25/20
Heart problems (−/+)	7/2	35/10	13/5	29/9	4/4	38/10	6/5	36/9
Depression (−/+)	9/0	43/2	18/0	36/2	8/0	46/2	10/1	44/1
APOE ε4 (−/+)	3/6	35/10[a]	9/9	26/12	4/4	31/17	5/6	30/15
AHA exercise group (−/+)	9/0	34/11	17/1	29/9	8/0	38/10	11/0	35/10
Mean exercise score (SD)	1.7 (1.6)	3.7 (4.3)[a]	2.4 (2.3)	3.7 (4.0)	1.8 (1.6)	3.5 (3.8)[a,b]	1.9 (2.0)	3.6 (3.8)[a,b]

AHA exercise group represents whether individuals met the AHA's recommended exercise levels (see text for details), with + indicating those who met recommendations.
[a] $p < 0.05$.
[b] Nonsignificant trend only after controlling for age, gender, and education.
MCBP = mean cortical binding potential; $A\beta$ = amyloid-β; Ptau = hyperphosphorylated tau protein; SD = standard deviation; F = female; M = male; BMI = body mass index; AHA = American Heart Association.

Therefore, we examined the relationship between exercise and amyloid deposition separately for ε4+ and ε4− groups (see Tables 1 and 2 for sample sizes).

For the ε4− group, there was a nonsignificant trend for PIB− individuals to report greater exercise ($t[7.417] = 2.231$, $p = 0.059$; covariates controlled: $t[34.91] = 1.993$, $p = 0.054$). There was a nonsignificant trend for MCBP levels to be lower in exercisers ($t[35.9] = 1.707$, $p = 0.096$; covariates controlled: $t[35.1] = 1.600$, $p = 0.119$). For the ε4+ group, there were no significant biomarker group differences in exercise ($t[14] = 0.714$, $p = 0.487$; covariates controlled: $t[13] = 0.887$, $p = 0.391$). Notably, only 1 ε4+ individual exercised at or above the recommended level, although mean exercise scores did not differ between ε4+ and ε4− groups ($t[42.2] = 1.236$, $p = 0.223$) in the PIB sample.

In terms of $A\beta_{42}$, for ε4− individuals, there were no significant differences in exercise between $A\beta_{42}$ groups ($t[20.3] = -1.310$, $p = 0.205$; covariates controlled: $t[20.3] = 1.023$, $p = 0.319$), nor were there significant differences in $A\beta_{42}$ levels between exercise groups ($t[33] = -1.184$, $p = 0.245$; covariates controlled: t[33] $= 0.944$, $p = 0.352$). When an outlier was removed, there was a nonsignificant trend for higher $A\beta_{42}$ levels in the exercise group ($t[32] = -1.584$; $p = 0.123$; covari-

ates controlled: $t[32] = 1.319$, $p = 0.197$). For the ε4+ group, there was no significant difference between $A\beta_{42}$ groups ($t[19] = -0.484$, $p = 0.634$; covariates controlled: t[19] $= 0.238$, $p = 0.814$). There were only 2 ε4+ individuals who met AHA recommendations, although exercise did not differ between ε4+ and ε4− groups ($t[54] = 0.632$, $p = 0.530$).

Discussion

Emerging evidence from human structural imaging and AD transgenic mouse studies suggests physical exercise may have beneficial effects on AD-related pathology and/or cognition.[16,17,23–27] The purpose of the current investigation was to extend this knowledge base to include human findings regarding exercise engagement and biomarkers, including amyloid deposition measured with PET-PIB and CSF levels of $A\beta_{42}$, tau, and ptau$_{181}$. We observed novel associations between exercise engagement and biomarker levels in cognitively normal older adults.

Visual inspection of graphs plotting exercise engagement against biomarker levels suggests strong associations, with individuals dispersed in an L-shaped distribution (see Fig). Most notable is that at one end of the distribution, individuals with greater physical exercise have lower MCBP, CSF tau, and ptau$_{181}$, or higher CSF

TABLE 2: Participant Characteristics for Exercise Groups

Characteristic	PIB Sample		CSF Sample	
	Exerciser	Non-exerciser	Exerciser	Non-exerciser
No.	11	43	10	46
Mean age, yr (SD)	68 (10)	71 (10)	64 (7)	67 (9)
Gender (F/M)	6/5	34/9	6/4	37/9
Mean education, yr (SD)	17 (2)	16 (4)	16 (3)	16 (4)
BMI (normal/overweight/obese)	4/6/1	16/19/8	4/5/1	16/17/13
Diabetes (−/+)	11/0	41/2	10/0	43/3
Hypertension (−/+)	7/4	24/19	8/2	23/23
Heart problems (−/+)	10/1	32/11	9/1	33/13
Depression (−/+)	11/0	41/2	10/0	44/2
APOE $\varepsilon 4$ (−/+)	10/1	28/15	8/2	27/19
Mean MCBP (SD)	0.02 (0.03)	0.10 (0.16)[a,b]	—	—
Mean $A\beta_{42}$ (SD), pg/mL	—	—	739 (217)	600 (185)[a,c]
Mean tau (SD), pg/mL	—	—	263 (58)	282 (152)
Ptau$_{181}$ (SD), pg/mL	—	—	49 (13)	54 (25)

Exercise groups are based on the American Heart Association's recommended exercise levels (see text for details).
[a]Data with one outlier removed (see text for details).
[b]$p < 0.01$; [c]$p < 0.05$.
PIB = Pittsburgh compound-B; CSF = cerebrospinal fluid; SD = standard deviation; F = female; M = male; BMI = body mass index; MCBP = mean cortical binding potential; $A\beta$ = amyloid-β; Ptau = hyperphosphorylated tau protein.

$A\beta_{42}$, whereas individuals with at-risk levels of biomarkers at the other end of the distribution are all relatively sedentary. This observation was somewhat confirmed by comparing exercise scores of those with at-risk biomarker levels against those with normal levels. Participants with elevated MCBP, tau, or ptau$_{181}$ exercised significantly less, and there was a nonsignificant trend for lower exercise in those with decreased $A\beta_{42}$. However, associations for tau and ptau$_{181}$ were reduced to nonsignificant trends with age, gender, and education controlled, suggesting that these variables accounted for a portion of the variance despite the lack of significant group differences in these variables. Past research indicates that cognitively normal individuals who are PIB+ exhibit regional brain atrophy and longitudinal cognitive decline compared to PIB− individuals.[13] In addition, reduced CSF $A\beta_{42}$ in cognitively normal individuals has been associated with whole brain and hippocampal atrophy in cognitively normal individuals[37] and elevated MCBP.[8,36] Collectively, results are suggestive of differing levels of exercise across biomarker status, such that individuals potentially at greater risk for AD engaged in less exercise.

Comparing biomarker levels of those who did or did not meet AHA exercise guidelines provided further insights into associations between exercise and AD pathology. Active individuals exhibited significantly lower MCBP and higher CSF $A\beta_{42}$ levels. However, no differences in tau and ptau$_{181}$ levels were found between exercise groups. This may be attributable to alterations in tau and ptau$_{181}$ potentially occurring subsequent to amyloid plaque formation later in the course of AD disease progression,[37–39] thereby resulting in less evident exercise effects on these biomarkers in a cognitively normal population. Past research is suggestive that beneficial effects of exercise on tau levels in a transgenic mouse model may be observed at the time at which tau is typically expressed.[24] Current findings for MCBP and $A\beta_{42}$ do converge to suggest that greater exercise engagement is associated with healthier amyloid profiles.

Previous investigations have observed elevated levels of amyloid and tau as measured by PET-PIB and PET–fluorine-18 2-dialkylamino-6-acylmalononitrile substituted naphthalenes (PET-FDDND) in cognitively normal adults with an *APOEε4* allele.[40,41] In this study, ε4+ individuals displayed elevated MCBP and lowered $A\beta_{42}$,

but no differences in tau or ptau$_{181}$. In separate analyses of associations between amyloid and exercise for e4+ and e4− groups, results for $\varepsilon 4-$, but not for $\varepsilon 4+$, individuals essentially mirrored findings in the full sample for MCBP. Considering that past literature indicates greater exercise-related benefits for cognition for $\varepsilon 4+$ individuals,[6,42–44] a larger exercise effect on biomarkers in this group might be expected. It is notable that in the current study, although mean exercise scores did not significantly differ between $\varepsilon 4+$ and $\varepsilon 4-$ individuals, there were fewer $\varepsilon 4+$ individuals exercising at AHA recommended levels (see Table 2). Therefore, there is some indication that presence of this risk factor for AD (and altered biomarker levels) may lead to reduced exercise levels. Beneficial effects of exercise on cognition in $\varepsilon 4+$ individuals observed previously may relate to mechanisms other than direct effects on neuropathology, such as increased brain-derived neurotrophic factor and synaptogenesis.[45] Current analyses are limited by differential sample sizes between the $\varepsilon 4+$ and $\varepsilon 4-$ groups. It would be of particular interest to determine whether gene × environment interactions exist such that exercise actually moderates associations between $\varepsilon 4+$ status and greater amyloid deposition in larger samples.

Although current results suggest a relatively robust relationship between exercise engagement and examined AD biomarkers, particularly in terms of amyloid levels, the direction of causality between exercise and human AD pathology remains uncertain, considering our cross-sectional design. Furthermore, the current self-report measure of exercise engagement is significantly but not perfectly related to cardiorespiratory fitness, and may also be limited by the ability of older adults to accurately recall and report their exercise over a 10-year span. In addition, although our exercise measure captured engagement at the PET-PIB or CSF assessment for most participants, it is possible that exercise behavior changes occurred for individuals whose PET-PIB or CSF assessment followed measurement of exercise engagement. The study is also limited by the lack of well-established, research-guided thresholds for determining at-risk levels of biomarkers, particularly for tau and ptau$_{181}$, and also by the relatively small sample size. To further elucidate whether physical exercise directly deters AD pathology, an interventional study in cognitively normal and AD individuals is needed. Future investigations might also include cognitive and brain atrophy outcome measures while comparing combinations of exercise, social, and cognitive interventions.[46] The novel findings of this study, in conjunction with positive results in transgenic AD mouse models, suggest a further rationale for clinicians to prescribe exercise regimens as not only symptomatic relief for AD patients, but as potentially preventive care as well.

Acknowledgments

Potential Conflicts of Interest

Nothing to report.

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