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Fitness and exercise effects on brain age: A randomized clinical trial

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Abstract

Background: Midlife lifestyle factors, including physical activity, are associated with late-life brain health, yet the role of aerobic exercise on structural brain health in early and mid-adulthood remains poorly understood. This study aimed to examine the effect of aerobic exercise on structural brain age and to explore potential mediators.

Methods: In a single-blind, 12-month randomized clinical trial, 130 healthy participants aged 26−58 years were randomized into a moderate-to-vigorous intensity aerobic exercise group or a usual-care control group. The exercise group attended two supervised 60-min sessions per week in a laboratory setting plus engaged in home-based exercise to achieve 150 min of exercise per week. Brain-predicted age difference (brain-PAD) and cardiorespiratory fitness (CRF) were assessed at baseline and 12 months. Both intention-to-treat (ITT) and completers analyses (including participants who completed post-intervention assessments) were performed.

Results: The 130 participants (67.7% female) had an age of 41.28 ± 9.93 years (mean ± SD). At baseline, higher CRF (peak oxygen uptake, VO_{2peak}) was associated with smaller brain-PAD ($\beta = -0.309$, $p = 0.012$). After the intervention, the exercise group showed a decrease in brain-PAD (estimated mean difference (EMD) = −0.60; 95% confidence interval (95%CI): −1.15 to −0.04; $p = 0.034$) compared to the control group (EMD = 0.35; 95%CI: −0.21 to 0.92; $p = 0.217$); time × group interaction (between-group difference (BGD) = −0.95; 95%CI: −1.72 to −0.17; $p = 0.019$). VO_{2peak} improved in the exercise group (EMD = 1.60; 95%CI: 0.29−2.90; $p = 0.017$) compared to the control group (EMD = −0.78; 95%CI: −2.17 to 0.60; $p = 0.265$); time × group interaction (BGD = 2.38; 95%CI: 0.52−4.25; $p = 0.015$). Body composition, blood pressure, and brain-derived neurotrophic factor levels were unaffected. None of the proposed pathways statistically mediated the effect of exercise on brain-PAD. The results from completers were similar.

Conclusion: Engaging in 12 months of moderate-to-vigorous exercise reduced brain-PAD in early-to-midlife adults. The pathways by which these effects occur remain unknown.

Keywords: Aerobic exercise; Aging; Brain; Cardiorespiratory fitness

1. Introduction

Early adulthood through midlife is a dynamic period in which risk factors for age-related brain atrophy, deterioration, and dementia can be modified by lifestyle behaviors and vascular risk factors.[1−4] For example, midlife hypertension and obesity confer risks for late-life dementia, while greater

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amounts of physical activity (PA) protect against cognitive decline and Alzheimer's disease (AD) pathology in late adulthood.[5,6] Observational studies suggest a cumulative and protracted neural impact of cardiometabolic health and lifestyle that begins decades before clinical manifestation of age-related cognitive impairment.[3] Despite the importance of midlife risk factors, most physical exercise interventions designed to improve cardiorespiratory fitness (CRF) and examine emergent brain health outcomes have been limited to late adulthood.[7−10] Moreover, such studies have largely focused on the morphology and function of specific rather than global brain health or brain aging indicators, such as the volume of the hippocampus and prefrontal cortex. In these regards, there remains a need to clarify whether exercise in early and mid-adulthood could modify the trajectory of biomarkers that reliably reflect aging-related brain health.

To elaborate, recent studies have proposed brain-predicted age difference (brain-PAD) as a marker that is sensitive to various attributes of brain health. Based on brain structure, determined using structural magnetic resonance imaging (MRI), an estimate of an individual's brain age can be calculated using machine learning algorithms. Brain-PAD quantifies the gap between chronological age and predicted brain age, interpreted as a surrogate biomarker indicating how much "older" or "younger" a given brain appears relative to the person's chronological age. The machine learning approaches used to estimate brain age are more sensitive than traditional neuroimaging techniques for detecting small differences in brain morphology, which is particularly useful when studying an age range in which individual variation in brain structure is more subtle than in later life.[11] While cross-sectional evaluations of brain age cannot be used to infer rates of aging *per se*,[12] greater brain-PAD values predict future poorer cognitive performance,[13,14] earlier mortality,[15] and accelerated neurocognitive decline and dementia, including progression from mild cognitive impairment to AD[16,17] and other dementias.[12,18] Therefore, brain-PAD may be capturing several important attributes of brain health that are predictive of long-term clinical endpoints.

Calculations of brain age and brain-PAD have excellent test-retest reliability with a high intraclass correlation coefficient (ICC) over short between-scan intervals and track chronological age progression over intervals exceeding 1 year. This provides an important methodological prerequisite for examining changes in brain aging in longitudinal clinical trials.[19] Importantly, recent intervention studies demonstrated that brain-PAD is not merely a static biomarker but can be modified: an 18-month combined diet and exercise intervention in adults with obesity yielded an 8.9-month attenuation of brain age,[20] and a decrease in brain age was reported in a bariatric surgery intervention study.[21] These emerging findings further support the possibility that brain-PAD may be a sensitive biomarker that can be changed by intervention.

In addition, the biological and physiological factors that mediate the effects of exercise on brain health remain poorly understood.[22,23] Several studies suggest that exercise-induced increases in CRF might be a prerequisite and mediator for improvements in brain health. In fact, higher CRF is associated with elevated cognitive performance and reduced risk for dementia,[24,25] and interventions that modify CRF are effective at offsetting age-related declines in brain morphology.[26,27] In addition, exercise-induced decreases in cardiometabolic risk factors, such as blood pressure, have also been identified as candidate pathways because sustained elevations in blood pressure have negative consequences for brain health and risk for dementia.[28] Moreover, other studies have suggested that exercise-induced changes in body mass and composition could alter various signaling and inflammatory pathways that impact the brain, thereby leading to improved brain health and function.[29,30] Finally, exercise-induced changes in neurotrophic factors such as brain-derived neurotrophic factor (BDNF) have been speculated to drive changes in brain morphology.[26] Yet, despite this speculation about the mediators of exercise on brain health, there is limited evidence in support of these pathways in humans. One reason for this lack of clarity is that few of these possible mediators have been examined in the context of a randomized clinical trial of exercise that examines brain outcomes, especially in early to midlife adults.

In this study, our objectives were to evaluate (a) the cross-sectional association between CRF and brain-PAD and (b) the effects of a 12-month aerobic exercise intervention on brain-PAD. We hypothesized that higher CRF would be associated with a "younger" brain age (reduced brain-PAD) and that a 12-month aerobic exercise intervention would reduce brain-PAD in those randomly assigned to engage in moderate-to-vigorous aerobic exercise, which has consistently demonstrated strong feasibility, adherence, and scalability in midlife populations. We also explored several possible mediators of the exercise intervention on brain age, including intervention-induced changes in CRF, body mass and composition, blood pressure, and BDNF.

2. Methods

The trial protocol and statistical analysis plan are provided in Supplementary Material 1. Methodological details are in the Supplementary Methods in Supplementary Material 2.

2.1. Study design and participants

Adults aged 26−58 years were recruited for participation in this single-center, parallel-arm randomized controlled trial (RCT) (Exercise, Brain, and Cardiovascular Health—eBACH) (ClinicalTrials.gov: NCT03841669). The study protocol and informed consent were approved by the University of Pittsburgh Institutional Review Board (IRB ID: 19020218). Participants provided written informed consent *prior to* data collection. The Consolidated Standards of Reporting Trials (CONSORT) reporting guideline was followed.[31] Participants were eligible if they reported no history or presence of neurological disorders or current use of prescribed blood pressure medication, fewer than 100 min per week of structured physical activity, and peak oxygen uptake (VO_{2peak}) not exceeding the 75th percentile based on American College of Sports

Medicine criteria. More details are available regarding participant eligibility and study design in the published protocol.[32]

2.2. Randomization and blinding

Participants were randomly assigned to either a moderate-to-vigorous intensity aerobic exercise condition or to a health information control condition for 12 months. Randomization was conducted using stratified block randomization on a web-based system through the research electronic data capture (REDCap) randomization module by the study biostatistician (CK) to ensure unbiased allocation of participants to the 2 intervention groups by age and sex. All investigators and staff involved in data collection were blinded to group assignment. Only staff involved in the implementation of the exercise intervention, scheduling of sessions, and study coordination were unblinded to group assignment.

2.3. Exercise intervention and control

Participants were randomly assigned to either a moderate-to-vigorous intensity aerobic exercise condition or to a health information control condition for a 12-month intervention period. Moderate-to-vigorous intensity exercise has been associated with lower rates of musculoskeletal injury compared to vigorous intensity only and high-intensity interval training protocols, especially in previously inactive or sedentary populations,[33,34] and it demonstrated comparable improvements in CRF when adherence was considered.[35–37] Participants engaged in individual supervised exercise 2 times a week (up to 60 min per session) in a laboratory setting at the University of Pittsburgh, along with home-based exercise, to achieve the prescribed 150 min of exercise per week. Participants were encouraged to walk, jog, or run on a treadmill as well as to record the use of other types of aerobic exercise equipment such as bikes, elliptical machines, stair climbers, and rowers. Levels of exercise intensity were prescribed based on resting heart rate and the maximal responses during the initial graded exercise test (GXT). For Weeks 1–6, the prescribed intensity was 50%–60% of the maximum heart rate reserve (HRR) and a rating of perceived exertion (RPE) of 11–12. For the remainder of the intervention, participants increased their intensity to 60%–75% of HRR and an RPE of 13–14. Participants were allowed to go into the vigorous range (75%–85% of HRR) as long as it was considered safe by the monitoring exercise physiologist and trainer. Participants wore a heart rate monitor (Polar A370 or Unite Watch; Polar USA, Lake Success, NY, USA) during all supervised sessions to ensure that exercise was occurring within the target heart rate zone. Exercise attendance, intensity, frequency, and safety were monitored by certified exercise instructors. Compliance with home-based exercise was monitored by exercise diaries and heart rate monitors. Participants were instructed to record all unsupervised exercise sessions and average heart rate during the exercise as indicated on the heart rate monitors. All exercise sessions consisted of 5–10 min of warm-up and cool-down periods.

During pandemic-related shutdowns in 2020, exercise trainers and other staff remained in frequent contact with participants and asked all participants to continue to record all exercise behaviors at home. Heart rate monitors were used to record exercise intensity during home exercise sessions under the guidance of exercise physiologists. As soon as university facilities reopened, we encouraged all participants to return to supervised exercise as long as it was safe and feasible for them, given family and illness constraints. As a result, 89.1% of participants chose to return to the supervised exercise.

Participants assigned to the health information control group were asked not to change their behavior or exercise patterns and were encouraged to perform activities as they normally would. They were provided information about the health benefits of engaging in PA and were contacted approximately every 6 weeks for continued contact with the investigative team.

2.4. Outcome measurements

2.4.1. Brain-PAD

The MRI acquisition and preprocessing steps are detailed in Supplementary Material 2. Brain age estimation was performed on T1-weighted images using brainageR (v2.1), an open-access software for generating brain-predicted age (github.com/james-cole/brainageR).[38] BrainageR was pre-trained to predict brain age from normalized brain volumetric maps of 3377 healthy adults (aged 18–92 years) from 7 publicly available datasets using a Gaussian Process Regression model.[39] The pre-trained brainageR model was applied to the preprocessed T1-weighted images in the current study to estimate a brain-predicted age score for each participant at each time point. Brain-PAD was calculated as the deviation of predicted brain age from chronological age. In particular, a floor function was applied to the decimal-year age (calculated from the date of birth to the date of the MRI session) to assign each participant an integer chronological age.

2.4.2. CRF

CRF was measured with a GXT using a modified Balke Protocol[40] at both baseline and 12-month assessment. VO_{2peak} (mL/kg/min) was the highest VO_2 value obtained during the maximal test and represents the measure of CRF used here.

2.4.3. Biological measures

Body mass index (BMI, kg/m^2) was calculated by dividing weight (kg) and height (m^2) recorded before the GXT. Body composition, including waist circumference (WC), height, weight, and percentage of body fat, were measured at both baseline and follow-up. Additionally, resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were computed from seated resting blood pressures obtained with an Omron IntelliSense© BP Monitor (model HEM-907XL; Omron Healthcare, Hoffman Estates, IL, USA). Mean arterial pressure (MAP) was further calculated from SBP and DBP. Finally, plasma levels of BDNF were measured from fasting blood samples. More information about the blood assays is provided in Supplementary Material 2.

2.5. Power and sample size

We were powered to detect effect sizes between 0.5 and 0.6 (Cohen's *d*) for changes in brain volume and cardiovascular disease biomarkers resulting from the exercise intervention. Sixty participants per group was deemed a sufficient number for testing our hypotheses with an α error of 5% at 80% power after accounting for an estimated 20% attrition rate.

2.6. Statistical analysis

Multiple linear regression was used to investigate the association between CRF and brain-PAD at baseline, adjusting for chronological age, sex, years of education, and BMI. By including chronological age as a covariate, we ensured that any residual linear association between chronological age and brain-PAD was removed, while retaining the interpretation of brain-PAD as "years older or younger than peers". Previous studies have shown that brain age is affected by noise and motion artifacts,[41] so the image quality rating (IQR) generated from the computational anatomy toolbox (CAT12) was also included as a covariate. Statistical inferences were conducted at the significance level of 0.05 ($p < 0.05$).

We assessed the effect of the exercise intervention on brain-PAD, CRF, and other biological measures using linear mixed modeling (LMM). The LMM models included the fixed effect for treatment (12-month aerobic exercise, control), time (baseline, Month 12), and their interaction. We also included a random intercept for individual participants to account for the within-individual correlation among repeated measures at baseline and 12 months. For brain-PAD, we adjusted for baseline chronological age, sex, years of education, BMI, and IQR. For CRF, we controlled for age, sex, years of education, and BMI. The LMM considers all available data, which conforms to the intention-to-treat (ITT) analytical framework. A secondary analysis of the completers sample (i.e., participants who completed the 12-month assessments) was conducted.

Finally, we conducted mediation analyses within a path analysis framework to test for possible mediators of the intervention effect on brain-PAD. The path analysis framework allows for the simultaneous examination of changes in mediating variables from baseline to post-intervention in the exercise intervention group compared to the control. The group variable was dummy-coded (1 = exercise, 0 = control) and used as the independent variable. Baseline measures of the mediator and outcome were included in the models to control for autoregressive effects. Covariance between the baseline mediator and outcome was also estimated. A schematic path diagram was provided to demonstrate the mediation model (Supplementary Fig. 1). The path coefficients were estimated via the maximum likelihood method, and indirect effects were computed using the product-of-coefficients approach, with standard errors (SE) and 95% confidence intervals (95%CIs) estimated using the nonparametric bootstrapping method (based on 5000 bootstrapped samples). Unstandardized B, standardized β, SE, *p*, and 95%CI of the indirect effect (Path $a \times b$) were reported. Hypothesized mediators, including CRF, body composition, blood pressure, and BDNF were assessed separately in different models.

All analyses were performed using R software (Version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria). Key packages and their versions include *lme4* 1.1-34 for LMM and *lavaan* 0.6-19 for structural equation modeling (SEM). Data were analyzed from November 2023 to June 2024.

3. Results

The participant flow diagram is presented in Fig. 1. Participants were recruited from May 2019 to October 2022 and followed up with through February 2024. In total, 811 participants were assessed for eligibility, 130 were randomized equally into the aerobic exercise and control conditions, and 81 (62.3%) completed post-intervention assessments.

The number of missing data points from the original randomized sample were as follows: exercise group: $n = 23$; control group: $n = 26$. A χ^2 of the completion ratio between groups was not significant ($p = 0.68$), suggesting the proportion of missing data did not differ by group assignment. Moreover, of the 130 randomized participants, 129 successfully completed baseline MRI scans, and 81 successfully completed MRI scans at both baseline and 12-month follow-up. A comparison of the subsample who did not successfully complete the follow-up MRI to the sample who completed both baseline and follow-up MRI scans revealed no differences in age, percentage of females, or BMI (all $p > 0.05$). However, missingness of the follow-up MRI scans was significantly associated with education levels. Participants who completed 12-month MRI scans had higher education than those with missing MRI scans at 12 months ($t = 2.476$, $p = 0.015$). Based on these associations, our primary regression models were adjusted for the effect of education, assuming missing data were missing at random (MAR), including covariate-dependent missing completely at random (MCAR) as a special case of MAR.

3.1. Participants

Demographic characteristics are described in Table 1. Baseline demographic characteristics were balanced between randomized groups; however, a significant difference in baseline VO_{2peak} between control and exercise intervention groups was observed. The control group had a slightly higher VO_{2peak} than the exercise group ($B = 2.435$, $p = 0.005$) after adjusting for sex, age, years of education, and BMI.

Adherence for the exercise intervention group ($n = 40$), evaluated by the ratio of total prescribed minutes exercised, was 93%, with an average of 138.9 min of exercise per week accounting for supervised and home-based sessions. Attendance to the supervised exercise sessions was 73%. The average exercise intensity was 124% of the 60% HRR, with an average RPE of 12.91.

3.2. Cross-sectional relationship between CRF and brain-PAD

When examining the entire sample, brain-PAD was 0.97 ± 5.93 years at baseline and 0.55 ± 6.03 years at the

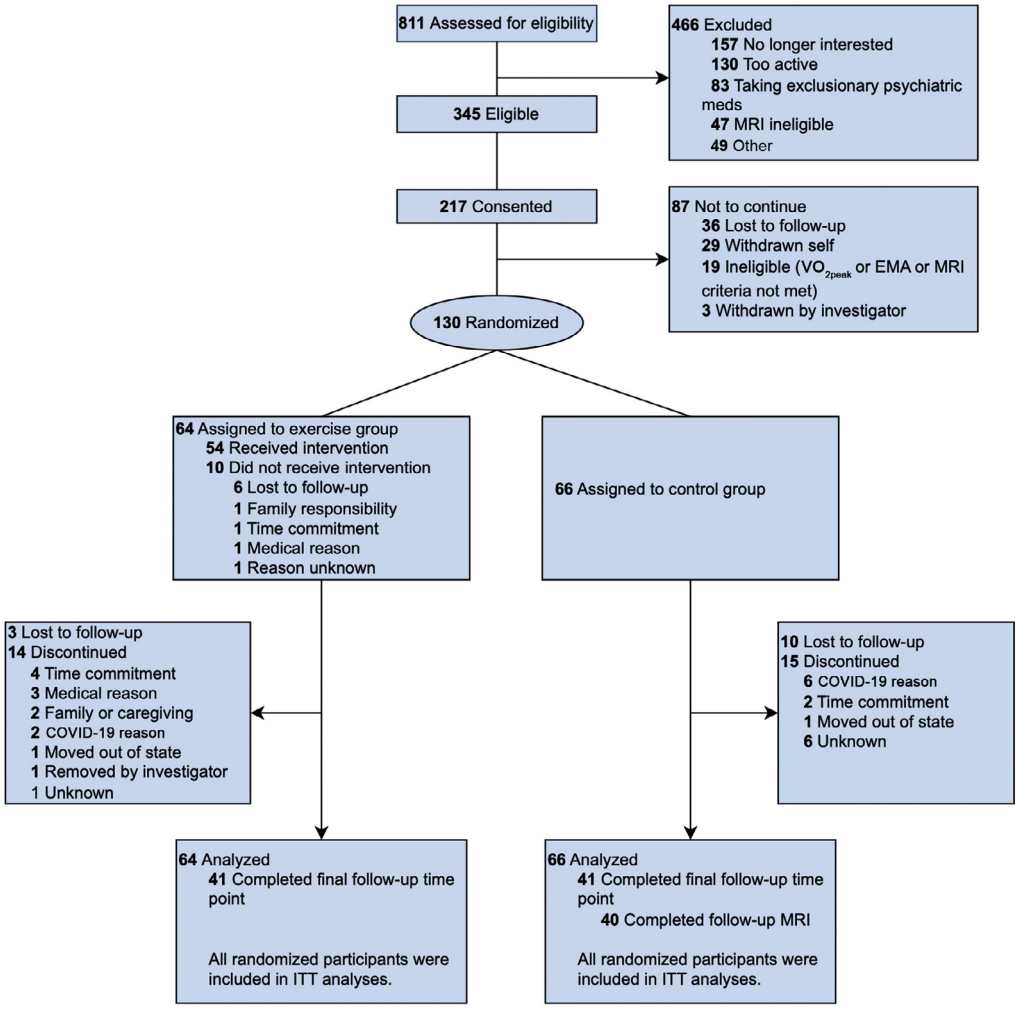

Fig. 1. CONSORT flowchart of sample inclusion. Four participants who withdrew from the exercise intervention returned for follow-up assessments. CONSORT = Consolidated Standards of Reporting Trials. COVID-19 = coronavirus disease 2019; EMA = ecological monitoring assessment; ITT = intention-to-treat; MRI = magnetic resonance imaging; VO_{2peak} = peak oxygen uptake.

12-month follow-up. We evaluated brain-PAD for age bias, as the predicted brain age may be underestimated for older individuals and overestimated for younger individuals.[42,43] Consistent with this, we found a significant correlation between brain-PAD and chronological age (baseline: r (127) = −0.294, $p < 0.001$; 12-month: r (79) = −0.333, $p = 0.002$). A graphical illustration of brain-PAD and the age bias[42,43] is presented in Supplementary Fig. 2.

At baseline, higher CRF was associated with lower brain-PAD ($\beta = -0.309$, $p = 0.012$; Fig. 2), controlling for covariates. For every 1SD increase in VO_{2peak} (about 7 mL/kg/min), brain-PAD decreased by about 1.83 years. There was no significant main effect of sex, years of education, or BMI on brain-PAD (all $p > 0.05$; Supplementary Table 1).

3.3. Effect of the exercise intervention on brain-PAD

Consistent with our predictions, the exercise intervention group showed decreased brain-PAD at the 12-month follow-up compared to baseline (−0.60 years, 95%CI: −1.15 to −0.04, $p = 0.034$). The control group did not show a significant change in brain-PAD from baseline to 12 months (0.35 years, 95%CI: −0.21 to 0.92, $p = 0.217$) (Table 2 and Supplementary Table 2).

We found a significant time × group interaction such that the exercise intervention group showed a significant decrease in brain-PAD from baseline to 12 months compared to the control group, with a marginal mean difference of −0.95 (95%CI: −1.72 to −0.17, $p = 0.019$) adjusting for covariates (Table 2 and Fig. 3A). The intervention effect on brain-PAD remained after further controlling for baseline differences in VO_{2peak}. Analyses on completers yielded similar results (Supplementary Fig. 3A and Supplementary Table 3).

3.4. Effect of the exercise intervention on CRF

The aerobic exercise group showed significant improvement in VO_{2peak} at 12 months compared to baseline (1.60 mL/kg/min, 95%CI: 0.29−2.90, $p = 0.017$), whereas the control group had a slightly decreased VO_{2peak} from

Table 1
Baseline characteristics by study arm.

Variable	150 min AEx	Control	Total group	p[a]
Number (*n*)	64	66	130	
Age (year)	41.55 ± 10.48	41.03 ± 9.43	41.28 ± 9.93	0.856
Sex				0.904
Female	43 (67.2)	45 (68.2)	88 (67.7)	
Male	21 (32.8)	21 (31.8)	42 (32.3)	
Race				0.350
African American/Black	11 (17.2)	5 (7.6)	16 (12.3)	
Caucasian/White	42 (65.6)	49 (74.2)	91 (70.0)	
Asian	5 (7.8)	9 (13.6)	14 (10.8)	
All others	6 (9.4)	3 (4.6)	9 (6.9)	
Ethnicity				0.270
Hispanic or Latinx	5 (7.8)	2 (3.0)	7 (5.4)	
Not Hispanic or Latinx	59 (92.2)	64 (97.0)	123 (94.6)	
Education (year)	17.16 ± 3.11	17.30 ± 2.82	17.23 ± 2.95	0.341
BMI (kg/m^2)	30.24 ± 6.66	28.66 ± 6.44	29.44 ± 6.57	0.143
VO_{2peak} (mL/kg/min)	26.85 ± 6.60	30.23 ± 6.93	28.57 ± 6.95	**0.011**
Waist circumference[b] **(cm)**	100.23 ± 15.84	98.69 ± 17.00	99.44 ± 16.39	0.631
Body fat[b] **(%)**	34.17 ± 9.43	32.57 ± 10.73	33.35 ± 10.10	0.358
SBP[c] **(mmHg)**	122.93 ± 16.27	116.61 ± 10.64	119.69 ± 13.98	**0.020**
DBP[c] **(mmHg)**	79.27 ± 10.26	77.80 ± 8.80	78.51 ± 9.52	0.430
MAP[c] **(mmHg)**	97.38 ± 12.10	94.06 ± 8.96	95.67 ± 10.69	0.110
Brain-predicted age (year)	42.22 ± 9.46	42.22 ± 10.54	42.22 ± 9.99	0.912
Brain-PAD (year)	0.73 ± 5.28	1.19 ± 6.53	0.97 ± 5.93	0.577

Notes: As part of eligibility screening, participants reporting ≥ 100 min/week of structured physical activity (via staff interview) or with VO_{2peak} > 75th percentile (ACSM criteria) were excluded. Data are shown as mean ± SD or *n* (%). Bold values indicate statistically significant difference in baseline charateristics between the exercise group and control group.

[a] Baseline differences between groups were determined using the 2-samples Wilcoxon rank sum test for continuous variables and X^2 test for categorical variables. Statistically significant values at $p < 0.05$ are shown in bold.

[b] Fourteen participants did not have waist circumference and body fat data (7 in 150 min AEx group and 7 in control group).

[c] Fifteen participants did not have SBP, DBP, and MAP data (8 in 150 min AEx group and 7 in control group).

Abbreviations: ACSM = American College of Sports Medicine; AEx = aerobic exercise; BMI = body mass index; brain-PAD = brain-predicted age difference; DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; VO_{2peak} = peak oxygen uptake.

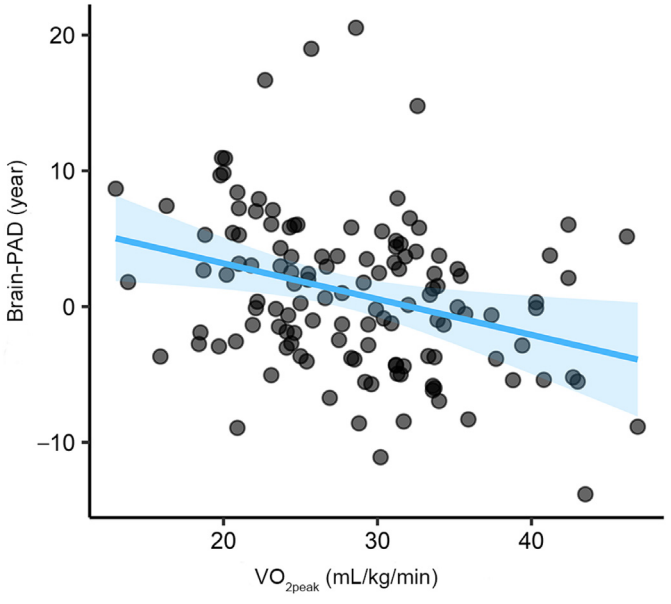

Fig. 2. The cross-sectional relationship between CRF and brain-PAD in the entire sample at baseline. The shaded area reflects a 95% confidence interval. Brain-PAD = brain-predicted age difference; CRF = cardiorespiratory fitness; VO_{2peak} = peak oxygen uptake.

baseline to 12-months (−0.78 mL/kg/min, 95%CI: −2.17 to 0.60, $p = 0.265$) (Table 2).

A significant time × group interaction was found for VO_{2peak} such that there was an increase from baseline to 12 months in the exercise intervention group compared to controls, with a marginal mean difference of 2.38 (95%CI: 0.52−4.25, $p = 0.015$) adjusting for covariates (Table 2). Changes in VO_{2peak} by group assignment are shown in Fig. 3B. Analyzes on completers also yielded similar results (Supplementary Fig. 3B and Supplementary Table 3).

3.5. Mediation of CRF and other biological measures

We explored possible physiological and biological mediators that may explain how the exercise intervention led to a decrease in brain-PAD. We found no significant mediation of exercise-induced changes in VO_{2peak} on the intervention effect on brain-PAD (indirect effect: $B = -0.100$, SE = 0.088, 95%CI: −0.31 to 0.02, $p = 0.256$; Fig. 4).

The exercise intervention did not modify body composition or blood pressure, as demonstrated by non-significant time × group interactions (all $p > 0.05$; Table 2). There was a marginally significant time × group interaction for BDNF such

Table 2
Estimated marginal means for brain-PAD, CRF, and biological measurements comparing the intervention and control arms.

Variable	Mean ± SE (95% CI)[a]		Difference between arms[b]	
	150 min AEx	Control	Mean ± SE (95% CI)	*p*
Brain-PAD (year)	−0.60 ± 0.28 (−1.15 to −0.04)	0.35 ± 0.29 (−0.21 to 0.92)	−0.95 ± 0.40 (−1.72 to −0.17)	**0.019**
CRF				
VO_{2peak} (mL/kg/min)	1.60 ± 0.66 (0.29−2.90)	−0.78 ± 0.70 (−2.17 to 0.60)	2.38 ± 0.96 (0.52−4.25)	**0.015**
Body composition				
BMI (kg/m^2)	0.30 ± 0.20 (−0.09 to 0.69)	0.48 ± 0.20 (0.08−0.89)	−0.19 ± 0.28 (−0.74 to 0.37)	0.515
Body fat (%)	0.14 ± 0.41 (−0.68 to 0.96)	0.54 ± 0.43 (−0.31 to 1.39)	−0.40 ± 0.59 (−1.56 to 0.76)	0.497
WC (cm)	0.47 ± 0.92 (−1.37 to 2.31)	2.37 ± 0.96 (0.46−4.29)	−1.91 ± 1.33 (−4.51 to 0.70)	0.156
Blood pressure (mmHg)				
SBP	−2.02 ± 1.71 (−5.43 to 1.38)	1.24 ± 1.76 (−2.26 to 4.75)	−3.27 ± 2.45 (−8.01 to 1.58)	0.186
DBP	−0.82 ± 1.40 (−3.61 to 1.96)	−0.70 ± 1.44 (−3.57 to 2.16)	−0.12 ± 2.00 (−3.99 to 3.87)	0.952
MAP	−1.44 ± 1.43 (−4.29 to 1.41)	−0.01 ± 1.47 (−2.94 to 2.92)	−1.43 ± 2.05 (−5.39 to 2.64)	0.487
Blood biomarker				
log BDNF (pg/mL)	0.35 ± 0.14 (0.07−0.62)	−0.04 ± 0.14 (−0.32 to 0.24)	0.39 ± 0.20 (0.01−0.78)	0.053

Note: Bold values indicate statistically significant time x group interaction.
[a] Differences were calculated as values at 12 months minus baseline.
[b] Differences between arms were calculated as 150 min AEx group minus control group.
Abbreviations: 95% CI = 95% confidence interval; AEx = aerobic exercise; BDNF = brain-derived neurotrophic factor; BMI = body mass index; brain-PAD = brain-predicted age difference; CRF = cardiorespiratory fitness; DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; SE = standard error; VO_{2peak} = peak oxygen uptake; WC = waist circumference.

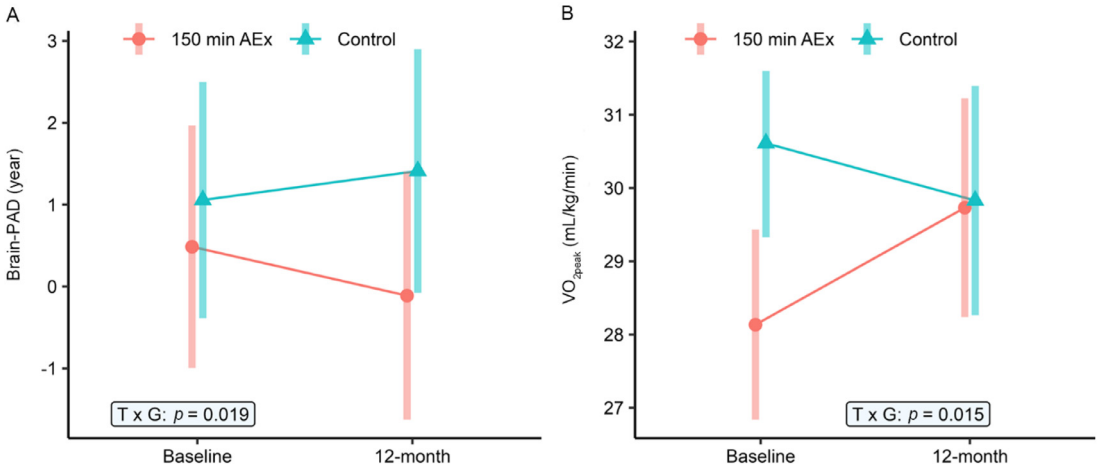

Fig. 3. Intervention effect with changes in marginal mean values of (A) brain-PAD and (B) VO_{2peak} from baseline to 12 months by ITT allocation. Error bars indicate 95% confidence intervals. T × G stands for the time × group interaction. AEx = aerobic exercise; Brain-PAD = brain-predicted age difference; ITT = intention to treat; VO_{2peak} = peak oxygen uptake.

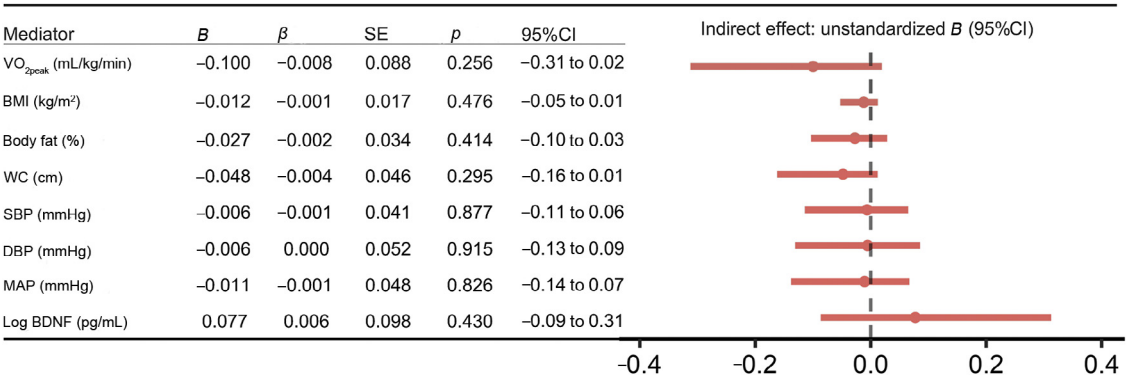

Fig. 4. Statistical results of longitudinal indirect effects of potential mediators. *B* indicates unstandardized regression coefficient, and *β* indicates standardized regression coefficient. The forest plot reflects unstandardized coefficients *B* of the indirect effect and 95%CI. 95%CI = 95% confidence interval; BDNF = brain-derived neurotrophic factor; BMI = body mass index; DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; VO_{2peak} = peak oxygen uptake; WC = waist circumference.

that the exercise group demonstrated greater increases in plasma BDNF levels compared to the controls (95%CI: 0.01−0.78 $p = 0.053$; Table 2). Additionally, we did not find that the intervention effect on brain-PAD was mediated by body composition, blood pressure, or BDNF (indirect effect: all $p > 0.2$; Fig. 4). After further adjusting for age and sex in the models, the indirect effects remained non-significant (data not shown). This suggests that none of these possible biological pathways mediated the effect of the intervention on brain age.

3.6. Adverse events

A total of 7 adverse events were reported (Supplementary Table 4), with no causal relationships to the exercise intervention. In the aerobic exercise group, one participant had a serious adverse event related to tumor removal, 5 reported musculoskeletal issues, and 1 had a cardiovascular-related event.

4. Discussion

We predicted that higher CRF would be associated with lower brain age and that participation in a 12-month exercise intervention would decrease brain age. We also explored potential biological mediators of the exercise intervention. Consistent with our predictions, higher CRF was associated with younger brain age, and participation in the 12-month exercise intervention significantly reduced brain age. These findings indicate that a structured 12-month aerobic exercise program could promote a "younger" appearing brain based on MRI features of brain structure.

Multiple studies report associations between aerobic exercise, CRF, brain volume, and cognitive function in late adulthood.[8,44,45] However, few studies have examined the relationship between exercise, CRF, and brain age, particularly in early to midlife. Given that midlife is recognized as an inflection point for age-related changes in brain health and cognition,[3] our results suggest that moderate-to-vigorous intensity exercise at current public health recommendations for 12 months could alter the trajectory of age-related changes in brain morphology. In short, our results emphasize the significant impact of exercise in decelerating brain aging.

We found that every standard deviation increase in VO_{2peak} (about 7 mL/kg/min) was associated with approximately 1.83 years decrease in brain-PAD. These results suggest that elevated fitness levels may make the brain less vulnerable to midlife aging, even after adjusting for other confounders. This is consistent with the literature in which self-reported physical activity was associated with younger brain-predicted age[46,47] and evidence linking CRF with gray matter volume and white matter integrity.[48−50] However, caution is warranted when interpreting cross-sectional data, as a positive brain-PAD is more strongly associated with early life influences as compared to behaviors during middle and older adulthood. In contrast, results from an intervention eliminate some of these challenges to interpretation.

Our analyses demonstrated that the 12-month exercise intervention decelerated brain aging. After 12 months, the brain-PAD of participants in the exercise group decreased by an average of 0.6 years. Note that in recent studies of brain age, every additional year of brain-PAD incurred a 3% relative increased risk of a future dementia diagnosis.[39] To our knowledge, the current study provides novel evidence that brain age can be reversed by engaging in moderate-to-vigorous aerobic exercise over a 12-month period. Other studies have focused on the effect of aerobic exercise on regional brain volumes or thickness (e.g., hippocampal volume,[51] frontal gray matter volume, and cortical thickness[52,53]), but few have examined a brain age variable that compares the volumetric information to that of a normative sample. In contrast to our results, a recent study reported no significant changes in brain age after a 6-month exercise intervention in a cohort of cognitively normal older adults aged 65−84 years.[54] Such inconsistency could be related to exercise intensity, duration, and individual characteristics of participants. There also might be greater benefits of a longer exercise intervention in midlife *prior to* more accelerated brain aging in later life. However, these explanations remain speculative, as there is no study that investigated dose-response relationships between training duration and changes in brain structure in younger or midlife adults.[22]

To explore possible biological mediators of the intervention effect on brain-PAD, we considered the effect of mediation through CRF, body composition, blood pressure, and BDNF levels. First, we examined whether changes in CRF could be mediating the effect of the intervention on brain-PAD and found limited evidence for this. Although we found a significant time × group interaction on CRF, with an average increase of 1.60 mL/kg/min in the exercise group and a slight decrease in the control group, changes in CRF did not statistically mediate the intervention effect on brain-PAD. It is worth noting that prior studies demonstrating a positive relationship between fitness and brain structure typically focus on the morphology of specific brain regions, such as the hippocampus or frontal lobe, rather than considering the entire brain or more specific aging indicators, such as brain age. The few studies that do assess the whole brain show mixed findings with small effect sizes.[55,56] Given the large number of brain regions/features contributing to the brain-PAD score, it is possible that changes in CRF may influence specific brain regions but do not sufficiently impact the global brain age scores. An alternative explanation is that the exercise-induced changes in CRF as measured by VO_{2peak} reflect the lifestyle-modifiable component of CRF, whereas familial factors (shared environment and genetic factors) contribute significantly to CRF variance when measured cross-sectionally.[57,58] It is possible that the magnitude of the intervention-driven improvements in CRF is insufficient for mediating measurable changes in brain-PAD over 12 months, but that does not rule out the importance of long-term growth and maintenance of CRF. An additional consideration is that the mediating role of CRF may be more pronounced in individuals with elevated cardiovascular risk. Our sample of generally healthy, middle-aged adults showed little variability in cardiovascular disease (CVD) profile, which may mask any mediation that only emerges in those with subclinical or overt vascular pathology. Future studies should therefore consider targeting or stratifying

participants by cardiovascular risk factors (e.g., hypertension, dyslipidemia, prediabetes) to determine whether CRF mediates the exercise effect on brain-PAD in higher-risk subgroups.

We did not find that the 12-month exercise intervention significantly changed body composition, blood pressure, or BDNF levels, nor did the changes in these measures mediate the intervention effect on brain-PAD. However, this might be attributable to the modest sample size in each group and our relatively healthy sample at baseline. The results of the current study warrant future research with larger sample sizes to further explore the mechanisms by which exercise benefits early-to-midlife brain age. Although statistical power limits inferences about the null effects regarding the tested mediators, it is possible that other pathways, such as anti-inflammatory signaling (e.g., reduced interleukin-6 (IL-6)/tumor necrosis factor-α (TNF-α)), mitochondrial biogenesis, enhanced neurovascular function, and metabolic pathways, could explain the reduction in brain-PAD induced by the intervention.[59−63] Future research with larger samples and repeated longitudinal assessments is warranted to test these alternative pathways, as well as those examined here.

It is also worth noting that since brain-PAD is a global metric derived from structural MRI features across the whole brain, it does not identify which specific anatomical structures drive the observed changes. Prior work demonstrates that certain regions, particularly prefrontal and parietal cortical thickness and hippocampal volume, contribute to brain age prediction or relate to brain-PAD.[64,65] Notably, these same regions have been shown to respond to aerobic training, with exercise-induced preservation or increases in volume and thickness.[26,66] Therefore, future studies may pair the global brain age metrics with regions of interest (ROI)-level or voxel-wise analyses to pinpoint the anatomical substrates underlying the exercise-induced reductions in brain-PAD, which may help elucidate potential mechanisms.

This study has several strengths. First, we focused on early to midlife, which is a period of the lifespan that has received relatively little attention in the context of exercise and brain health.[22,67] Therefore, we provide novel evidence that aerobic exercise influences structural markers of brain health during a critical period of the lifespan when cognitive and brain health may start to decline. Second, the brain age measure allowed us to assess the comparative estimated biological age of the brain against chronological age. This provided a snapshot of the participants' current aging trajectories and enhanced the utility of our findings for informing future clinical trials. Third, VO_{2peak} provided an objective, gold-standard index of CRF and, therefore, eliminated errors from proxy or self-reported measures. Finally, the longitudinal randomized controlled trial helped to elucidate the causal relationship between CRF, exercise, and brain health outcomes.

Limitations of this study include its relatively small sample size, which reduced statistical power to detect effects. With a larger sample size, we would have been better powered to examine the mediating role of CRF and other biological measures and to explore the possible moderating influence of chronological age, sex at birth, socioeconomic status, and body composition on intervention effects. Next, the study was influenced by the COVID-19 pandemic. Many participants were hampered during the pandemic by illness, family and child-rearing limitations, or professional challenges that heightened the attrition rate. However, despite the challenges of conducting an exercise intervention in the context of stay-at-home advisories, our adherence rate remained impressively high. Our results indicate that data were likely missing at random and equivalently across groups. Finally, we did not consider other lifestyle risk factors, including alcohol consumption, smoking, *etc*., which have been reported to influence brain age.[68,69]

5. Conclusion

A 12-month moderate-to-vigorous intensity aerobic exercise intervention improved early-to-midlife brain health by modifying brain age. Moreover, we found an association between elevated CRF levels and younger brain age. Our findings complement the scarce literature examining the effects of exercise on brain health in early to midlife and confirm the neuroprotective role of aerobic exercise against accelerated brain aging. Notably, the observed decrease in brain-PAD after the exercise intervention suggests that maintaining exercise may provide resilience against age-related brain changes, potentially lowering the long-term risk of dementia. Additional research is necessary to understand the mechanisms of exercise on brain age, which may improve biological targets for altering brain aging.

Authors' contributions

KIE, PJG, and LW participated in the design of the study, and contributed to data analysis and interpretation of the results; CMH, MEC, GG, RLL, MD, MRS, and ALM contributed to data acquisition, analysis, and interpretation of data; CK and JR participated in statistical analysis; TWK and MFM participated in the design of the study and provided material support. All authors contributed to the manuscript writing. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Declaration of competing interest

KIE consults for MedRhythms, Inc. and Neo Auvra, Inc. These organizations had no involvement in the study design and writing of the manuscript or the decision to submit it for publication. The other authors declare that they have no competing interests. Given his role as editorial board member, KIE had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor.

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Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2025.101079.

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