ARTICLE CLASS OF EVIDENCE

Effect of aerobic exercise on cognition in younger adults

A randomized clinical trial

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Abstract

Objective
To determine efficacy of aerobic exercise for cognitive function in younger healthy adults.

Methods
In a randomized, parallel-group, observer-masked, community-based clinical trial, 132 cognitively normal individuals aged 20–67 with below median aerobic capacity were randomly assigned to one of two 6-month, 4-times-weekly conditions: aerobic exercise and stretching/toning. Efficacy measures included aerobic capacity; cognitive function in several domains (executive function, episodic memory, processing speed, language, and attention), everyday function, body mass index (BMI), and cortical thickness.

Results
Aerobic capacity increased significantly (β = 2.718; $p = 0.003$), and BMI decreased significantly (β = −0.596; $p = 0.013$) in the aerobic exercise but not in the stretching/toning condition. Executive function improved significantly in the aerobic exercise condition; this effect was moderated by age (β = 0.018 SD/y; $p = 0.028$). At age 40, the executive function measure increased by 0.228 SD (95% confidence interval [CI] 0.007–0.448), and by 0.596 SD (95% CI 0.219–0.973) at age 60. Cortical thickness increased significantly in the aerobic exercise group in a left frontal region and did not interact with age. Controlling for age and baseline performance, individuals with at least one *APOE* ε4 allele showed less improvement in executive function with aerobic exercise (β = 0.5129, 95% CI 0.0381–0.988; $p = 0.0346$).

Conclusions
This randomized clinical trial demonstrates the efficacy of aerobic exercise for cognition in adults age 20–67. The effect of aerobic exercise on executive function was more pronounced as age increased, suggesting that it may mitigate age-related declines. Increased cortical thickness suggests that aerobic exercise contributes to brain health in individuals as young as age 20.

Clinicaltrials.gov identifier
NCT01179958.

Classification of evidence
This study provides Class II evidence that for adults age 20–67 with below median aerobic capacity, aerobic exercise significantly improves executive function but not other measures of cognitive function.

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Glossary

BMI = body mass index; **CI** = confidence interval; **CONSORT** = Consolidated Standards of Reporting Trials; **EF** = executive function; **HR** = heart rate; **ICV** = intracranial volume; **IRB** = institutional review board; **MPRAGE** = magnetization-prepared rapid gradient echo; **OR** = odds ratio; **TIADL** = timed instrumental activities of daily living tasks; **WAIS** = Wechsler Adult Intelligence Scale.

While animal and human studies indicate cognitive benefits from aerobic exercise across the lifespan, controlled exercise studies in humans generally have been restricted to elderly individuals. Several meta-analyses in adults above age 55 have found aerobic effects in the areas of attention, processing speed, executive function (EF), memory, and working memory,[1–3] with some suggesting strongest effects for EF,[3] but there have also been negative conclusions.[4,5] The goal of the present study was to extend the investigation of the effects of aerobic exercise to individuals aged 20–67 in a randomized controlled trial.

Earlier intervention may prevent or delay age-related changes. Alternately, intervention could be more effective as individuals become older, when age-related cognitive decline is more likely to be present. Also, specific cognitive domains that are benefited by aerobic exercise could differ in younger and older individuals. Few studies have examined age moderation of fitness-related improvements in cognition in this lower age range.

We hypothesized that aerobic exercise would have cognitive benefits even in this younger age range, but that age might moderate the nature or degree of the benefit. Aerobic exercise has also been associated with increased gray matter volume or cortical thickness in observational[6–9] and intervention[10–12] studies, particularly in the frontal, temporal, and cingulate cortex, so we included an imaging measure of cortical thickness in order to assess the effect of aerobic exercise on this brain measure. We also considered *APOE* genotype as a possible moderator of exercise effect.

Methods

Study design

This was a randomized, parallel-group, observer-masked clinical trial comparing the effects of 6 months of aerobic exercise to a stretching/toning control condition on cognition and brain structure among cognitively normal individuals from age 20 to 67 years with below median aerobic capacity. The study was originally designed to recruit participants age 25–40 and 50–65 years. We subsequently received institutional review board (IRB) approval to modify the age range to 20–67 years in order maximize recruitment. The full trial protocol is available from the authors. Eligible trial participants were randomly assigned to the 2 conditions with an allocation ratio of 1:1. The randomization schedules were generated by the study statistician and concealed until an eligible participant was ready for enrollment. Due to the nature of the conditions, they were not masked to participants, although participants were not aware of the overall study hypotheses. All study staff who collected outcomes data or analyzed study data were unaware of study group assignments. Participant recruitment and intervention were conducted from May 2011 to April 2016.

Standard protocol approvals, registrations, and patient consents

The study protocol and informed consent form were approved by the IRB of New York State Psychiatric Institute (IRB no. 622). All participants provided written informed consent before enrollment. The trial was overseen by an independent Data and Safety Monitoring Board under the auspices of the National Institute on Aging. The trial was registered on Clinicaltrials.gov (Identifier: NCT01179958).

Study participants

Participants were recruited by posted flyers and social media. They were healthy, cognitively intact, nonsmoking, sedentary habitual nonexercisers who qualified as below average fitness by American Heart Association standards.

A phone screen determined that participants met basic inclusion/exclusion criteria. The Baecke Physical Activity Sports Score[13] excluded regular exercisers, defined as a score of >2 on this 5-point scale, from further participation. The Edinburgh Handedness Questionnaire[14] ensured that the participant was right-handed, a requirement for ancillary imaging studies.

Those who remained attended an in-person visit where they signed an informed consent document and completed the Mattis Dementia Rating Scale[15]; participants with scores below 135 were excluded. They then underwent baseline VO_2 max determination; normal baseline ECG was required. Any ischemic changes, abnormal blood pressure responses, or significant ectopy resulted in exclusion. The baseline aerobic capacity testing was used to establish safe exercise measures and heart rate (HR) targets.

Participants qualifying as below average fitness by American College of Sports Medicine standards (VO_2 max < 41, 39.5, 37.6, 34.8, and 31.6 mL/kg/min for men age 20–29, 30–39, 40–49, 50–59, and 60–69 years, respectively; VO_2 max < 35.2, 33.8, 32.3, 29.4, and 26.6 mL/kg/min for women age 20–29, 30–39, 40–49, 50–59, and 60–69 years, respectively) proceeded to the 2-week run-in period.

Run-in period

Eligible participants went to their choice of 5 YMCA of New York City fitness centers in Manhattan 3 times/week for a 2-week run-in period. They engaged in a fixed schedule of activities that did not include aerobic training. Only those participants who attended at least 5 sessions were permitted to continue in the study.

Conditioning programs

Participants were then randomly assigned to either the aerobic or the stretching/toning condition. For the next 24 weeks, participants came to the Fitness Center for 4 sessions/week according to a schedule they determined. They exercised individually. Fitness Center trainers introduced the exercise programs to the participants. All training sessions in both conditions consisted of 10–15 minutes of warm-up/cool down and 30–40 minutes of workout. Participants were contacted on a weekly basis by coaches to monitor their progress. To exercise at their target HR, participants wore a Polar Electro model s610i HR monitor during each training session. This monitor provides a digital display of HR and records HR throughout the training session. Data from each were downloaded into a computer located in the fitness center. Adherence to the training programs was documented by weekly logs and data from the HR monitors.

Aerobic conditioning

Participants selected from a series of aerobic activities. For weeks 1 and 2, they trained at 55%–65% of maximum HR as established during their qualifying aerobic capacity test. In weeks 3 and 4, they increased their intensity to 65%–75% of maximum HR and in weeks 5–26, they trained at 75% of maximum HR.

Stretching/toning

Under the guidance of their trainers and coaches, participants engaged in a series of stretches and toning exercises designed to promote flexibility and improve core strength. All upper body and lower body major muscle groups were included. Core strengthening exercises included abdominal, back, and pelvic muscles.

Study outcomes

Cognitive function (the primary outcome) and aerobic capacity were assessed 3 times: prior to randomization into exercise/control conditions and after 12 and 24 weeks. Imaging studies were conducted at baseline and 24 weeks.

Aerobic capacity

Maximal oxygen uptake (VO_2 max) was assessed by GXT on an electronic-braked cycle ergometer (Lode Corival, Groningen, the Netherlands), which was connected to a metabolic measurement cart (Ultima CPXTM; MedGraphics, St. Paul, MN). An individualized ramping protocol (10, 15, or 20 W each 2 minutes) was selected according to each participant's perceived exercise capacity to yield a test duration of approximately 10 minutes. Each participant began the test with a 2-minute warm-up against no resistance, and the work rate was then linearly increased at the individualized ramp rate until volitional fatigue. Minute ventilation was measured by a pneumotachometer connected to a mouthpiece. Percentage of expired oxygen (O_2) and carbon dioxide (CO_2) were measured using a paramagnetic O_2 and infrared CO_2 analyzer. Calibrations for airflow and gas concentrations relative to medical grade gases were conducted before each test according to manufacturer specifications. During the exercise test, ECG and respiration gas exchange variables (VO_2, VCO_2, expired ventilation, and respiratory exchange ratio) were continuously monitored and recorded. Blood pressure and perceived exertion (Modified Borg 0–10 scale) were also measured every 2 minutes. Criteria for VO_2 max were a respiratory exchange ratio >1.1, a plateau in the slope of the VO_2–work rate relationship (piece-wise linear regression analysis),[16] and an HR over 90% of the maximum age-predicted HR limit. The highest 15-breath moving median for the test was considered VO_2 max.[17]

Cognitive assessment

Tests were chosen from domains that are sensitive to aerobic exercise manipulations.[2,3] The Wechsler Test of Adult Reading[18] was administered at the initial assessment to estimate IQ. The specific measures used for each outcome were selected prior to initiating analyses. The selection of tests for each outcome domain was validated using factor analysis of the baseline test data, which produced groupings comparable to those included in the listed cognitive outcomes. Standardization of each test was based on mean and SD of baseline values. Mean values of the standardized outcomes of the tests in each domain were used for analysis. CogState tasks[19] had multiple forms across visits; all remaining tasks remained the same.

Executive function

Set switching

Participants performed 2 tasks: letter classification and digit classification.[20,21] In 4 non-switch blocks of 40 trials, only 1 task was presented throughout the block. In 4 switch blocks, the tasks were intermixed. Outcome was difference in mean RT between correct switch and non-switch trials within the switch blocks.

The Groton Maze Learning Test (CogState)

A 10 × 10 grid of tiles was shown on a computer touch screen.[19] A 28-step pathway was hidden among these 100 possible locations. A 28-step pathway through the maze was learned on the basis of trial and error feedback. Outcome was total rule break errors across 5 trials of the task.

Episodic memory

Modified Rey Auditory Verbal Learning Test

Twenty words were presented aurally over 3 trials (list A), followed by one distractor set (list B); free recall of list A and delayed recall of lists A and B at 85 minutes were tested.[22,23] Outcome was number of list A delay words.

Continuous paired associate learning (CogState)

The location of abstract images presented over 5 learning sets was tested.[19] Outcome was number of errors across 5 learning sets.

Processing speed

Digit symbol (Wechsler Adult Intelligence Scale [WAIS]–III digit symbol subtest)

Symbol–digit pairs were presented as a key at the top of a stimulus sheet that contained digits with blank spaces below.[24] The symbol was copied below each digit using the key. Outcome was number of correct symbols copied in 60 seconds.

Groton Maze Chase Test (CogState)

A target appeared on a 10 × 10 computerized grid from one adjacent location to the next. A mouse was used to click on the target at each location.[19] Outcome was number of clicks/s.

Identification task (CogState)

A card was presented on a computer screen with the question, "Is the card red?" A differential button press indicated "yes" or "no."[19] Outcome was mean log10 transformed reaction time for correct responses.

Language

Controlled Oral Word Association Test

Words beginning with the letters F, A, and S were produced within 60 seconds each.[25] Outcome was total valid words produced averaged across the 3 letters.

Animal naming

Animal names were produced within 60 seconds.[26] Outcome was total valid animal names.

Attention

The 2 and 7 test

Target numbers 2 and 7 were intermixed with capital letters in one condition and with other numbers in another condition.[27] Outcome was total number of correct cancellations within 5 minutes.

Working memory

WAIS-III letter–number sequencing

A series of intermixed digits and letters were presented aurally.[28] First letters were recalled in alphabetical order and then numbers in numerical order. Outcome was total number of correct sequence trials.

N-back (CogState)

A series of cards was presented on a computer screen.[19] On each trial, the participant pressed Y if the card was identical to the card just prior for the 1-back task and to the card 2 prior for the 2-back task. Outcome was arcsine transformation of the square root of the proportion of correct responses.

Everyday function and body mass index (BMI)

Timed instrumental activities of daily living tasks (TIADL)

The participant is asked to perform 5 tasks such as find a phone number or make change.[29] Outcome was total errors.

BMI was also assessed at each study visit.

Cortical thickness

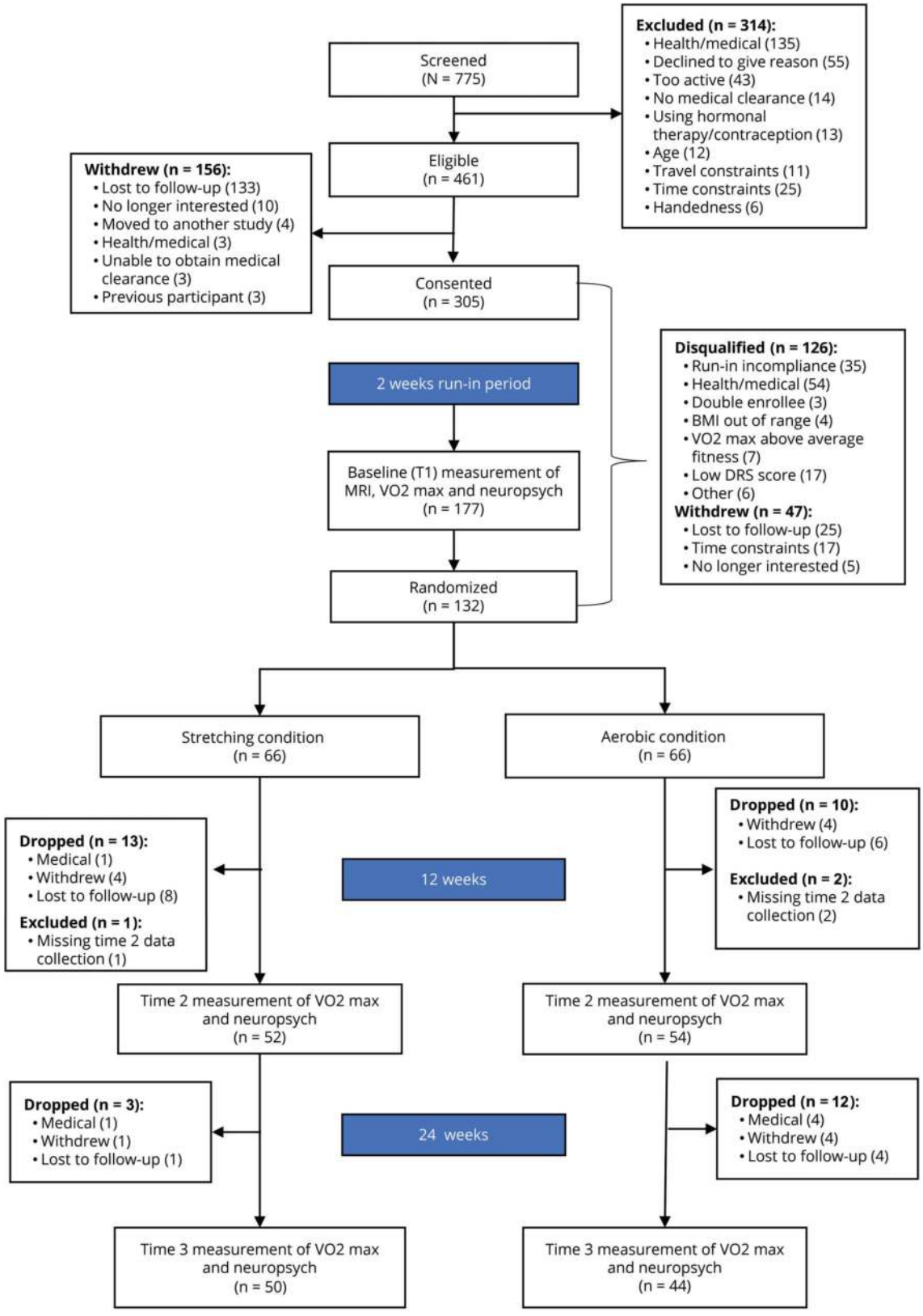
Participants underwent a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scan, acquired on a 3.0T Philips (Best, the Netherlands) Achieva MRI scanner with echo time/repetition time of 3/6.5 ms and flip angle of 8 degrees, in-plane resolution of 256 × 256, field of view of 25.4 × 25.4 cm, and 165~180 slices in axial direction with slice thickness/gap of 1/0 mm. The BrainWash application was used to compute intracranial volume (ICV).[30] The longitudinal T1-weighted MPRAGE images were processed using the FreeSurfer longitudinal pipeline.[31] Scans were visually inspected for any inaccuracy and manually edited per the FreeSurfer guidelines. Symmetrized percent change in thickness from pre- to post-intervention was then calculated at each vertex of the cortical surface. Other imaging modalities were also collected, but are not discussed in this report.

Statistical analysis

The primary analysis was conducted to provide Class II evidence of the effect of aerobic exercise on the cognitive domains. The trial had 80% power at a type I error rate of 5% to detect a medium effect size d = 0.5 with 70% retention rate. All analyses followed the intention-to-treat principle in that all participants who were enrolled and randomly allocated to treatment were included in the analysis and were analyzed in the groups to which they were randomized. Additional analyses addressed the effect of aerobic exercise on VO_2 max, everyday function, cortical thickness, and BMI. All analyses, including those of cortical thickness, were conducted blind to treatment status. Baseline demographic characteristics, VO_2 max, and cognitive variables were compared between the aerobic exercise and stretch and toning groups using Wilcoxon rank test and Fisher exact test for continuous and categorical variables, respectively.

Cognitive outcomes at baseline, 3 months (midpoint assessment), and 6 months (end of intervention period) were compared between groups using mixed effect models, adjusted for baseline age, years of education, and estimated IQ (which could affect cognitive performance). The models included group, time, baseline age, and their 2-way and 3-way interactions (model 1). Baseline age was treated as a continuous variable after centering at age 40. This model tests whether the group differences in the change from baseline to week 12 or the change from baseline to week 24 are moderated by age. The measures at weeks 12 and 24 were simultaneously estimated in the same model for each outcome. The group × time × age interaction would indicate age moderation on the aerobic exercise effect. For TIADL total error, Poisson distribution was used. Residual analyses

Figure 1 Consolidated Standards of Reporting Trials diagram



BMI = body mass index; DRS = Mattis Dementia Rating Scale.

confirmed the assumption of normal error. For the outcomes without significant 3-way interactions, 2-way interaction of group × time was evaluated after dropping 3-way and 2-way interactions with age (model 2). Similarly, *APOE4* moderation was tested. SAS software (version 9.4) was used for all computations. A 2-sided p value of 0.05 or less was interpreted as a statistically significant result. When we found a significant effect of aerobic exercise on a cognitive outcome, we checked whether increments in VO_2 max with exercise mediated the effect. We conducted the mediation analysis using the mediation R-package[32] with 10,000 bootstrapping sampling. For the mediation analysis, we only included the final time point with age, sex, years of education, IQ, baseline VO_2 max, and EF adjusted.

To evaluate change in cortical thickness, we calculated a parametric map that summarized change in thickness over 24 weeks as a function of the study condition, controlling for age, sex, ICV, years of education, and estimated IQ. The extent of cortical thickness was given by the collection of vertices where the change in thickness values was significantly correlated with study condition. We used a 2-sided p value of 0.05, corrected for multiple comparisons using the cluster-wise thresholding method.[33] We also tested a model that included an age × study condition interaction along with covariates. This model tests age moderation of the aerobic exercise effect, which is equivalent to the 3-way interaction in the cognitive analyses.

Data availability

The data from this clinical trial, including anonymized participant-level and study-level data (analyzable data sets) and other information (such as protocols and brain images), will be shared with qualified researchers as necessary for conducting legitimate research through direct request from the study principal investigators (Y.S. at ys11@columbia.edu or R.P.S. at rps7@cumc.columbia.edu).

Results

Figure 1 contains the Consolidated Standards of Reporting Trials (CONSORT) diagram summarizing the process from screening to the end of the study. A total of 132 participants, age 20–67 years, were randomized equally into the stretching and aerobic conditions.

Descriptive statistics for the randomized participants at baseline are summarized in table 1. The 2 groups were equally balanced for age and sex. Median and quartile range for age was also comparable in the 2 groups (aerobic exercise and stretching groups, respectively: median = 39.0, 36.6; quartile range = 22–24). The 2 groups did not differ at baseline in education, estimated IQ, or any of the cognitive outcome measures.

Ninety-four of the 132 participants completed the full 6-month intervention. The attrition rates were 33.33% and 24.24% for aerobic exercise and stretching group, respectively, which was not statistically different (χ^2 = 1.33, p = 0.2487). Analysis of dropouts revealed no difference by group, cognitive outcome measures at baseline, or demographic variables such as age, sex, ethnicity, or years of education. Since age was continuous, we conducted logistic regression to test whether the adherence differed by age group. In the aerobic exercise group, older people tended to adhere better (odds ratio [OR] = 1.054 per year, p = 0.0292), but in the stretching group, there was no age association (OR = 0.997 per year, p = 0.8939).

Tables e-1 and e-2 (doi.org/10.5061/dryad.10n4r3g) list reported medical conditions and medication use in the 2 groups. Medical conditions were rare. The only significant group difference was a higher prevalence of hypertension in

Table 1 Baseline characteristics of the participants

Characteristics	Aerobic condition (n = 66)	Stretching condition (n = 66)
Female	47 (71.21)	46 (69.7)
Age, y	41.56 ± 12.30	39.33 ± 14.46
Education, y	15.79 ± 2.65	16.33 ± 2.19
Estimated IQ	112.39 ± 12.76	111.30 ± 14.76
Ethnicity		
Asian	7 (10.61)	11 (16.67)
Black	20 (30.3)	12 (18.18)
Hispanic	6 (9.09)	14 (21.21)
Other	3 (4.55)	1 (1.52)
White	30 (45.45)	28 (42.42)
Weight, lb	167.85 ± 38.65	163.26 ± 37.09
Height, in	65.65 ± 3.91	65.82 ± 4.09
Body mass index	27.08 ± 5.02	26.33 ± 4.71
VO_2 max, mL/kg/min	27.63 ± 7.46	28.76 ± 6.64
Speed	−0.06 ± 0.80	0.11 ± 0.74
Episodic memory	0.02 ± 0.81	0.06 ± 0.87
Working memory	0.04 ± 0.74	0.02 ± 0.74
Language	0.01 ± 0.86	0.08 ± 0.87
Attention	0.06 ± 0.83	−0.06 ± 0.98
Executive function	−0.07 ± 0.80	0.08 ± 0.60
TIADL total error	0.65 ± 0.87	0.35 ± 0.62
***APOE4*[a]**		
Negative	31 (72.09)	30 (63.83)
Positive	12 (27.91)	17 (37.17)

Abbreviation TIADL = timed instrumental activities of daily living tasks.
Values are n (%) or mean ± SD. Cognitive and functional measures are presented as z scores.
[a] Ninety participants had *APOE4* assessment.

the aerobic (n = 6) than the stretching (n = 0) condition (p = 0.028). There were no group differences for medication.

Outcomes

VO_2 max

Mean VO_2 max values from baseline to 12 and then 24 weeks are summarized in table 2 and illustrated in figure 2. For VO_2 max, there was no 3-way interaction. After dropping age as a moderator, mixed effect models demonstrated that the aerobic exercise group showed increased VO_2 max by the midpoint visit, which remained elevated at the final visit. In contrast, the stretching group showed no increase in VO_2 max (group × time week 12: β = 3.1251 mL/kg/min, 95% confidence interval [CI] 1.4579–4.7923; p = 0.0003; group × time week 24: β = 2.6792 mL/kg/min, 95% CI 0.8910–4.4674; p = 0.0035).

Cognition

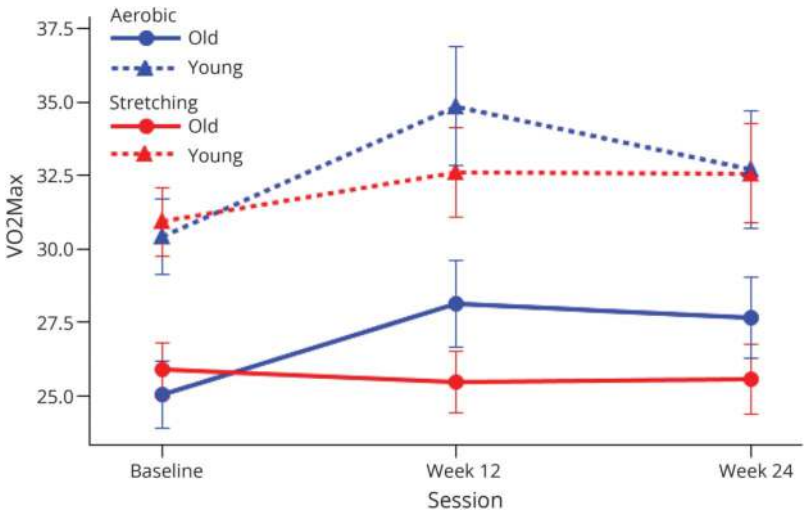
Cognitive outcome scores at each study visit are summarized in table 2. Linear mixed models examined differential change in cognitive outcomes across groups for each of the 6 cognitive domains with age, years of education, and IQ included as covariates. For EF, there was a group effect, with a significant improvement in EF at week 24 in the aerobic exercise group (β = 0.237, 95% CI 0.014–0.461, p = 0.038). However, there was a 3-way interaction effect ($F_{2,188}$ = 8.02, p = 0.0005) such that improvement in EF in the aerobic exercise group was greater as age increased (at week 24: β = 0.0184 per year, 95% CI 0.0020–0.0347; p = 0.028). After aerobic exercise intervention, EF improved 0.0184 SD units per year of age. For example, comparing 30-year-old and 50-year-old participants, aerobic exercise intervention

Table 2 Change from baseline at 12- and 24-week follow-ups for both trial conditions

		Change from baseline				Statistical results							
		Aerobic exercise condition		Stretching condition		Model 1: 3-way interaction (age × group × time)				Model 2: 2-way interaction (group × time)			
	Week	N	Mean ± SE	N	Mean ± SE	β	95% LCI	95% UCI	p Value	β	95% LCI	95% UCI	p Value
VO_2 max, mL/kg/min	12	53	3.63 ± 0.7	47	0.48 ± 0.61	−0.025	−0.149	0.099	0.693	3.139	1.476	4.802	0.000
	24	41	3.32 ± 0.74	42	0.45 ± 0.77	0.000	−0.133	0.133	1.000	2.718	0.931	4.505	0.003
Executive function	12	54	0.33 ± 0.08	52	0.15 ± 0.1	0.031	0.016	0.047	<0.0001	0.166	−0.048	0.379	0.128
	24	44	0.50 ± 0.08	50	0.25 ± 0.11	0.018	0.002	0.035	0.028	0.237	0.014	0.461	0.038
Attention	12	54	−0.34 ± 0.15	51	−0.24 ± 0.12	−0.017	−0.053	0.018	0.330	−0.105	−0.570	0.360	0.657
	24	44	−0.58 ± 0.31	50	−0.37 ± 0.16	−0.011	−0.048	0.026	0.557	−0.233	−0.721	0.254	0.347
Episodic memory	12	54	0.30 ± 0.08	52	0.26 ± 0.09	−0.001	−0.017	0.015	0.886	0.019	−0.193	0.231	0.863
	24	44	0.43 ± 0.09	50	0.48 ± 0.10	−0.014	−0.031	0.002	0.091	−0.037	−0.259	0.185	0.741
Language	12	54	0.09 ± 0.08	52	0.05 ± 0.07	0.006	−0.009	0.020	0.432	0.029	−0.165	0.223	0.771
	24	44	0.13 ± 0.09	50	0.21 ± 0.09	0.002	−0.013	0.018	0.748	−0.062	−0.266	0.141	0.546
Working memory	12	54	0.12 ± 0.11	52	0.33 ± 0.14	−0.004	−0.025	0.018	0.739	−0.214	−0.496	0.068	0.136
	24	44	0.37 ± 0.1	50	0.35 ± 0.10	−0.004	−0.026	0.019	0.754	0.027	−0.267	0.322	0.856
Speed	12	54	0.10 ± 0.06	52	0.05 ± 0.07	−0.005	−0.018	0.008	0.433	0.068	−0.099	0.235	0.425
	24	44	0.14 ± 0.07	50	0.15 ± 0.06	−0.003	−0.016	0.010	0.666	0.007	−0.168	0.181	0.941
TIADL total error	12	—	—	—	—	—	—	—	—	—	—	—	—
	24	44	0.05 ± 0.15	50	0.14 ± 0.11	−0.013	−0.079	0.054	0.711	−0.368	−1.215	0.479	0.390
BMI, kg/m^2	12	52	−0.51 ± 0.18	50	−0.14 ± 0.16	−0.037	−0.070	−0.003	0.032	−0.374	−0.816	0.068	0.096
	24	43	−0.90 ± 0.21	46	−0.27 ± 0.17	−0.021	−0.056	0.014	0.237	−0.596	−1.062	−0.129	0.013

Abbreviations: BMI = body mass index; LCI = lower confidence interval; TIADL = timed instrumental activities of daily living tasks; UCI = upper confidence interval. The group effect is for the change in outcome derived from mixed effect models with the stretching condition used as the reference group and mean-centered age (at 40 years). Statistics of the 3-way interactions (age × group × time) with age treated as a continuous variable for model 1 and the 2-way interaction (group × time) for model 2 among the outcomes without significant 3-way interaction in model 1 are reported. For TIADL only, Poisson distribution was used. All models were adjusted for age, years of education, sex, and IQ.

Figure 2 Change in aerobic capacity



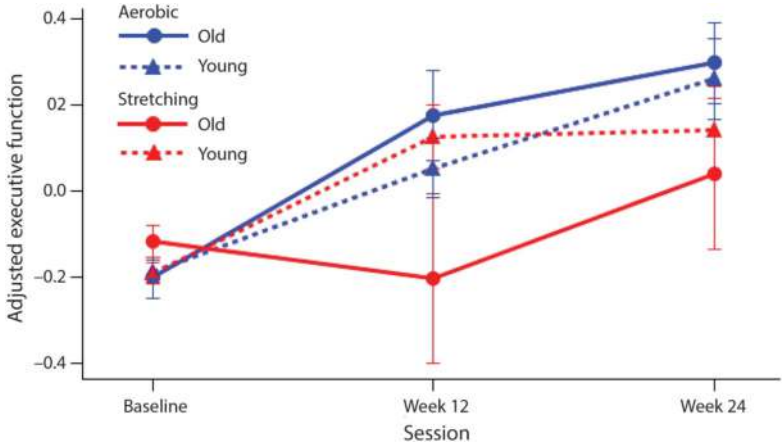
Aerobic capacity (VO_2 max) at each study visit. Data are shown for each study condition by age (split at median, age 38) and condition.

improved EF in older participants by 20*0.0184 = 0.368 SD units more than in younger participants. Overall improvement from baseline to 24 weeks was 0.228 (95% CI 0.007–0.448) SD units at age 40, and 0.596 SD units (95% CI 0.219–0.973) at age 60. Table e-3 (doi.org/10.5061/dryad.10n4r3g) lists the improvements in EF in terms of SD units from age 20 to 65 in 5-year increments. Figure 3 illustrates the change in performance on EF, corrected for the covariates in the model, as a function of age and group. For illustrative purposes, age is dichotomized at the median value. Figure 4 illustrates the group × time × age interaction. At both 12 and 24 weeks, the improvement in EF from baseline increases as a function of age. Age distributions are equivalent in both study groups, and not skewed in either group. Also, the residuals of the mixed effect models were well distributed. Thus, we are satisfied that the interaction is not influenced by the distribution of age. Since VO_2 max declines with age, we checked whether the noted age moderation is in fact moderation by baseline aerobic capacity. When we replaced age with baseline VO_2 max, the 3-way interaction of time × group × baseline VO_2 max was not significant ($p = 0.51$). When we add baseline age as a covariate, it was still not significant ($p = 0.50$).

We also checked whether increments in VO_2 max with aerobic exercise mediated the effect on EF. We found significant mediation (mediation effect 0.082, $p = 0.046$). We also tested whether the mediation of VO_2 max change is moderated by age, but it was not significant ($p = 0.97$).

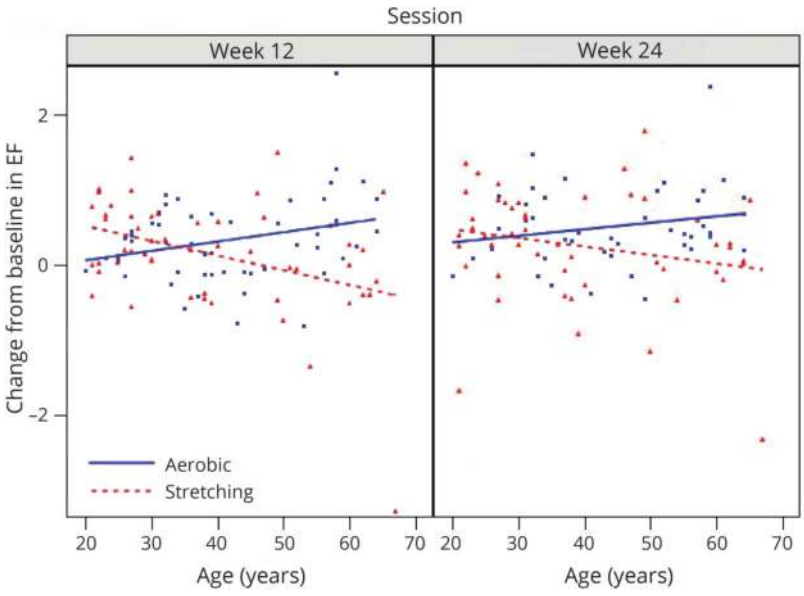
No significant interactions ($ps > 0.18$) for the primary 3-way interaction model or group × time interactions ($ps > 0.21$) for the 2-way interaction model were seen for the other cognitive domains.

Figure 3 Change in executive function



Executive function is presented at each study visit by condition in 2 age groups. Age was dichotomized using median split (38 years old). Executive function scores, measure by a summary Z score, are adjusted for age as a continuous variable, IQ, education and baseline executive function.

Figure 4 Illustration of condition by age interaction for executive function (EF)

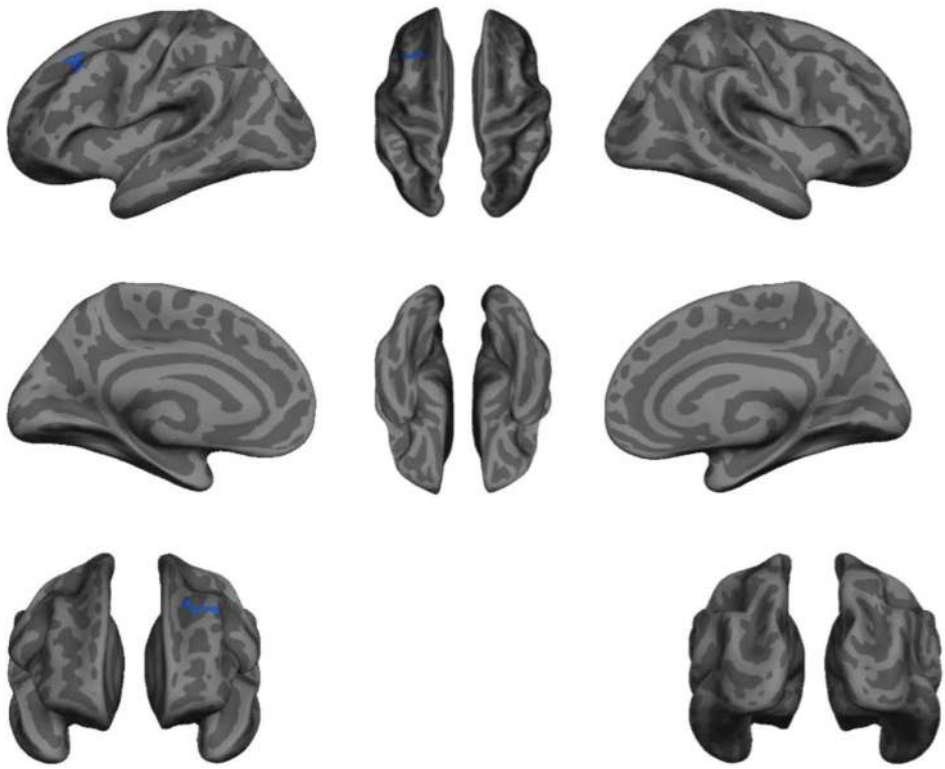


Change in EF (y-axis) is plotted against age (x-axis) at both 12 and 24 weeks. Both individual participants and group trends are plotted for both study groups.

Function and BMI

The TIADL measure is summarized in table 2. There was no effect of exercise intervention. For BMI, there was no significant 3-way interaction, but there was a significant effect of the aerobic exercise intervention on BMI ($F_{2,183}$ = 3.39, p = 0.036) such that the intervention group lost 0.374 units (95% CI −0.816 to 0.068; p = 0.0996) to midpoint, and −0.596 units (95% CI −1.062 to −0.129; p = 0.013) to week 24.

Figure 5 Areas of increased cortical thickness from baseline in the exercise vs stretching/toning condition



Brain imaging

The aerobic exercise condition was associated with significantly increased cortical thickness in left caudal middle frontal cortex Brodmann area (figure 5, Montreal Neurological Institute coordinate −36.9, 23.9, 40.6). There was no exercise × age interaction. We did not find a correlation between change in cortical thickness and change in any cognitive domain.

APOE

For a subset of 90 participants, the *APOE* ε4 genotype information was collected. Only episodic memory differed by *APOE* ε4 status (mean ± SD of negative: −0.07 ± 0.81; positive: 0.07 ± 0.96; Wilcoxon $p = 0.006$) at baseline. Linear mixed models with change score as outcome indicated a significant group × *APOE* ε4 status interaction ($\beta = 0.5129$, 95% CI 0.0381–0.988; $p = 0.0346$), such that improvement on EF in the aerobic exercise group was greater among participants without an *APOE* ε4 allele (figure e-1, doi.org/10.5061/dryad.10n4r3g). The other 5 cognitive domains did not show *APOE* ε4 effects.

Adverse events

There were only 3 adverse events. One was related to bruising from the phlebotomy. Two were related to knee injuries that occurred during the time the participants were enrolled in the study but were not clearly related to the protocol.

Discussion

This randomized clinical trial contributes novel findings on the effects of aerobic exercise on cognition and the brain in several aspects. The key finding was that aerobic exercise increased EF in adults, ranging from age 20 to 67, but that this effect was moderated by age. At age 40, the increase was 0.228 SD units (95% CI 0.007–0.448), increasing to 0.596 SD units (95% CI 0.219–0.973) at age 60. Since baseline performance in this domain was poorer as a function of age, this finding suggests that aerobic exercise is more likely to improve age-related declines in EF rather than increase performance in those without a decline. Aerobic exercise was associated with significantly increased VO_2 max, so we tested whether this increase mediated the improvement in EF. Interestingly, it did, although the mediation was not moderated by age. This suggests that the mechanism for cognitive improvement is associated with increased aerobic capacity.

While reviews of exercise studies in older adults have noted improvements in multiple cognitive domains,[5] several investigators have noted particular improvements in EF in adults over age 65.[34,35] Memory performance is a common concern in the general population, and improvement in this domain was not noted. However, EF is a primary cognitive domain that is affected during aging.

We also demonstrated that aerobic exercise was associated with increased cortical thickness in the left caudal middle frontal area. This effect did not differ by age, and extends[6,10,35] an observation typically noted in older adults to a younger age range. Several observational studies have noted associations between exercise and volume or thickness in frontal areas.[6,8,9] One intervention study in elders found increases in frontal gray matter volume with aerobic exercise,[10] while another found aerobic exercise associated with less reduction over time in cortical thickness in the right fusiform gyrus.[12] An exercise intervention study in younger individuals (not focused on cognition) found thickening in the left hemisphere in large areas of the frontal, temporal, and cingulate cortex.[11] The observed exercise-related increase in cortical thickness did not interact with age. Thus, our findings suggest exercise may improve brain health across ages 20 through 67.

Aerobic exercise was also associated with reduction in BMI in participants of all ages. This has been previously noted in both young[36] and older adults.[37]

Finally, individuals with an *APOE* ε4 allele showed less improvement in EF. We included a planned, a priori investigation of *APOE* as a potential moderator because of conflicting reports about the interaction of exercise and *APOE* genotype. The presence of the *APOE* ε4 allele has been associated with differential serum lipid response to exercise training, and thus could reduce the increase in aerobic capacity produced by exercise training.[38] Also, one study found a significant association between increased physical activity and a low risk of dementia only in *APOE4* noncarriers.[39] In contrast, a recent review suggests that *APOE* ε4 allele is associated with increased benefit from aerobic exercise,[40] and an observational study in older adults found the same.[41] It is possible that *APOE* genotype moderation may differ by age or by outcome measure. Thus, more research on this issue is required.

We are aware of several exercise intervention studies for cognition in younger individuals.[42–45] All of these studies had relatively low enrollment, and none included a randomly assigned control group.

There has been increased interest in public health interventions to improve cognition and function. Participants in this trial scheduled their exercise sessions on their own and exercised by themselves. In addition, they were allowed to choose whatever aerobic exercise modality they preferred, so long as they reached target HRs, enhancing the flexibility of the intervention. This study therefore supports the feasibility of translating this intervention to the general population.

Limitations of this study include its relatively small sample size, which reduces power to see significant effects. It is possible that we would have been able to see effects in other cognitive domains with a larger sample size. It will be important for future studies to assess the sustainability of exercise effects over periods of time beyond the duration of the trial. A large number of participants were lost between consent and randomization for the reasons summarized in the

CONSORT diagram. This experience confirms the challenges of conducting these studies. Although the dropout rate after randomization might also be considered a limitation, it was actually smaller than seen in many exercise studies of this duration. That is because a run-in period helped exclude people who are likely to drop out. We did not correct the analyses of the cognitive outcomes for multiple comparisons. Other limitations include the lack of other outcome measures such as measures of glucose metabolism or insulin resistance, and potential self-selection of the study sample.

This large-scale trial of the effect of aerobic exercise on cognition in the 20- to 67-year age range found that aerobic exercise was associated with improvement in EF and increases in cortical thickness. This study extends the demonstrated benefits of aerobic exercise to individuals as young as 20. These findings have strong public health implications and allow the recommendation of a feasible, flexible intervention for cognitive and brain health for adults of all ages.

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Anna MacKay-Brandt, PhD	Columbia University, New York; Nathan Kline Institute for Psychiatric Research, Orangeburg, NY	Author	Supervised acquisition of data, revised the manuscript for intellectual content
Seonjoo Lee, PhD	Columbia University, New York; New York State Psychiatric Institute, New York	Author	Analyzed and interpreted the data, revised the manuscript for intellectual content
Paula McKinley, PhD	Columbia University, New York	Author	Major role in the acquisition of data
Kathleen McIntyre, LCSW	Columbia University, New York	Author	Major role in the acquisition of data
Qolamreza Razlighi, PhD	Columbia University, New York	Author	Analyzed and interpreted the data; revised the manuscript for intellectual content
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