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A Randomized Controlled Trial of High-Intensity Exercise and Executive Functioning in Cognitively Normal Older Adults

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ABSTRACT

Background: *There is a paucity of interventional research that systematically assesses the role of exercise intensity and cardiorespiratory fitness, and their relationship with executive function in older adults. To address this limitation, we have examined the effect of a systematically manipulated exercise intervention on executive function.* ***Methods:*** *Ninety-nine cognitively normal participants (age = 69.10 ± 5.2 years; n = 54 female) were randomized into either a high-intensity cycle-based exercise, moderate-intensity cycle-based exercise, or no-intervention control group. All participants underwent neuropsychological testing and fitness assessment at baseline (preintervention), 6-month follow-up (postintervention), and 12-month postintervention. Executive function was measured comprehensively, including measures of each subdomain: Shifting, Updating/ Working Memory, Inhibition, Verbal Generativity, and Nonverbal*

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Reasoning. Cardiorespiratory fitness was measured by analysis of peak aerobic capacity; VO_2peak. ***Results:*** *First, the exercise intervention was found to increase cardiorespiratory fitness (VO_2peak) in the intervention groups, in comparison to the control group ($F = 10.40$, $p \leq 0.01$). However, the authors failed to find mean differences in executive function scores between the high-intensity, moderate intensity, or inactive control group. On the basis of change scores, cardiorespiratory fitness was found to associate positively with the executive function (EF) subdomains of Updating/Working Memory ($\beta = 0.37$, $p = 0.01$, $r = 0.34$) and Verbal Generativity ($\beta = 0.30$, $p = 0.03$, $r = 0.28$) for intervention, but not control participants.* ***Conclusion:*** *At the aggregate level, the authors failed to find evidence that 6-months of high-intensity aerobic exercise improves EF in older adults. However, it remains possible that individual differences in experimentally induced changes in cardiorespiratory fitness may be associated with changes in Updating/ Working Memory and Verbal Generativity.* (Am J Geriatr Psychiatry 2020; ■■:■■−■■)

It has been hypothesized that age-related cognitive decline is associated with reduced structural integrity and decreased functional connectivity in the frontal lobes of the brain.[1] As executive functions (EF) are predominantly frontal lobe processes, they are particularly vulnerable to age-related decline, with cognitive deficits in this domain recognized as one of the first markers of cognitive aging.[2] There have been numerous efforts to outline a comprehensive theoretically-driven model of EF,[3−5] with a general assertion that EF can be seen as both a broad, unitary cognitive domain, as well as separable, but related, subdomains. The nature of these EF subdomains has been the subject of much research, but commonly identified EF abilities include 1) Shifting: The ability to shift between tasks efficiently; 2) Updating/ Working Memory: The ability to manipulate and update information within the working memory; 3) Inhibition: The ability to inhibit and override automatic responses when necessary; 4) Verbal Generativity: The ability to access long-term memory to generate information as required, and 5) Nonverbal Reasoning: The ability to form novel and/ or abstract concepts, monitor errors and adjust behavior accordingly, and general problem solving.[3,4,6] Collectively, EFs mediate the cognitive control of behaviour.[7] Thus, it is unsurprising that executive dysfunction is linked with poor quality of life and decreased ability to live independently.[8] Accordingly, interventions that aim to slow or prevent EF decline have the potential to preserve cognitive function, overall quality of life, and independent living.

There is some evidence to support regular physical activity as a protective factor against cognitive decline in older adults,[1,9] with EF proving more sensitive to cognitive improvements than other aspects of cognition to exercise intervention.[9] However, the literature is ambiguous on the replicability and specificity of these effects. Indeed, two recent meta-analyses reported incongruent findings on the effect of exercise interventions on EF in older adults.[10,11] Young et al.[11] concluded there was not enough evidence to support a benefit from exercise on any of the measured EF subdomains, even when the intervention was shown to lead to improved cardiorespiratory fitness. Conversely, Northey et al.[10] reported significant effects of exercise on EF, supporting earlier meta-analyses.[9] One potential explanation for the lack of consistency across these meta-analyses is methodical differences in the delivery of the exercise intervention in the studies included. Interestingly, in a post hoc analysis, Northey et al.[10] found the beneficial effect was most notable in studies with interventions of at least moderate-intensity (albeit indirectly measured). These findings support observational studies evaluating the role of intensity level in the relationship between physical activity and EF.[12,13] Specifically, Angevaren et al.[13] found higher intensity self-reported physical activity intensity to be positively associated with EF subdomains of Shifting and Inhibition, while Brown et al.[12] found that actigraphy measured intensity was associated with better Updating/Working Memory and Generativity. Conversely, Kovacevic et al.[14] recently reported that, while an aerobic exercise intervention appeared to induce EF benefits in the one subdomain of EF measured (Inhibition), there were no significant differences observed between those participants in the high- versus moderate-intensity exercise modalities. Additionally, congruent with Kovacevic et al's findings, our recent cross-sectional study also failed to find any association between self-reported physical activity intensity and any of the EF subdomains.[15]

In summary, the current state of the literature remains unclear, likely due to methodological differences and limitations in, 1) how physical activity was assessed, e.g., often self-report, without adequate details regarding intensity levels, and 2) how EF was assessed, often measured in a piecemeal fashion without comprehensive assessment of commonly identified EF subdomains. Further, while there have been multiple randomized control trials (RCT) evaluating the role of exercise in improving cognition, none have systemically manipulated the intensity of the of the exercise intervention and evaluated the potential benefits on comprehensively assessed EF over time. The present study aims to address these limitations by using experimental RCT methodology, direct measurement of exercise intensity, and comprehensive measurement of multiple EF subdomains.

Thus, to extend knowledge on the nature of the relationship between exercise and EF in older adults, we have examined the effect of a systematically manipulated exercise intervention (high-intensity versus moderate-intensity versus inactive control) on five EF subdomains (Shifting, Updating/ Working Memory, Inhibition, Generativity, Nonverbal Reasoning) in a group of cognitively normal older adults. We hypothesized that improvements in EF would be greater in the high-intensity and the moderate-intensity aerobic exercise groups, as compared with the control group. Additionally, we hypothesized that improvements in EF would be greater for the high-intensity aerobic exercise group as compared with the moderate-intensity aerobic exercise group.

METHODS

Participants and Design

The current study drew data from the single-blind RCT, the Intense Physical Activity and Cognition (IPAC) study (Australian New Zealand Clinical Trials Registry number: ACTRN12617000643370). Comprehensive details of the IPAC study methodology have been detailed previously.[16] Briefly, 228 community volunteers were screened to exclude those with cognitive impairment (>26 on the Montreal Cognitive Assessment and results of the baseline cognitive assessment;[17]). Additionally, to meet eligibility criteria participants had to be aged between 60 and 80 years, have adequate conversational English, visual and auditory ability to complete cognitive assessment, not have any uncontrolled medical conditions known to influence cognitive function, and did not regularly engage in high intensity physical activity, as evaluated on a case-to-case basis by an Exercise and Sports Science Australia accredited exercise physiologist.

One-hundred and eight participants met eligibility criteria and attended at least one baseline assessment appointment. Based on power calculations, a sample size of 30 per group was required to detect (with 80% power; $\alpha = 0.05$; 2-sided; Cohen's d: 0.25; small effect size) variance between the intervention and control groups. Our recruitment sample (N = 108) allowed for a ~15% attrition rate from baseline to postintervention follow-up.[16] Nine individuals either did not complete all baseline assessments or were excluded after baseline cognitive assessment revealed possible mild cognitive impairment. All other IPAC study participants who completed baseline (N = 99) were randomized, by computer generated block randomization, into a high-intensity exercise, moderate-intensity exercise, or control (no exercise) group. Table 1 summarizes the demographic and clinical characteristics of participants according to their group allocation at the time of randomization.

The study was approved by the Human Research Ethics Committees at Edith Cowan University, Murdoch University, and recognition of approval was granted from the University of Western Australia. All participants provided signed informed consent before enrolment into the study. Procedures of this RCT followed the principles of the Declaration of Helsinki for Human Rights.

Executive Function Assessment

Primary outcome measures for each EF subdomain were included in the neuropsychological battery; previously described in an earlier study.[15] Shifting was assessed using the Trail Making Test (TMT) Part B minus TMT Part A, time in seconds[18]; Updating/ Working Memory was assessed using the CogState 1-

TABLE 1. Demographics and Clinical Characteristics at the Time of Randomization

Characteristic/Measure (Skewness and Kurtosis)	High Intensity (N = 33)	Moderate Intensity (N = 34)	Controls (N = 32)	Statistic (df)	p Value
Age	70.2 (5.3)	68.3 (4.2)	68.7 (6.0)	F = 1.24	0.29
Women (%)	17 (51.5)	18 (54.3)	19 (58.1)	$\chi^2 = 0.46$	0.80
Years of Education	13.5 (2.3)	14.2 (2.4)	14.5 (2.2)	F = 1.68	0.2
APOE ε4 Carriers (%)	9 (27.3)	8 (24.0)	9 (28.1)	$\chi^2 = 0.21$	0.90
VIQ	113.6 (7.1)	116.5 (7.4)	118.9 (6.9)	F = 4.49	0.01*
MoCA	25.7 (2.1)	26.2 (3.0)	26. 6 (2.2)	F = 0.93	0.40
Depression	2.4 (3.0)	1.6 (2.12)	1.7 (1.9)	F = 0.95	0.39
Anxiety	1.4 (1.3)	1.6 (1.79)	1.3 (1.3)	F = 0.30	0.74
Stress	3.7 (2.1)	3.6 (2.9)	3.7 (2.7)	F = 0.03	0.97
PA Duration	22.6 (22.4)	20.5 (14.6)	15.0 (7.9)	F = 1.90	0.15
PA Intensity	3.6 (1.0)	3.8 (0.7)	4.0 (0.8)	F = 1.80	0.17
Weight	73.1 (16.1)	75.7 (15.0)	70.3 (12.0)	F = 1.17	0.32
Height	167.5 (11.5)	170.9 (10.0)	166.4 (7.4)	F = 1.97	0.15
BMI	25.8 (3.7)	26.0 (3.9)	25.3 (3.4)	F = 0.30	0.74
Fitness Outcome Measure					
VO_2 peak (0.6; 0.4)	22.2 (6.3)	24.7 (6.8)	22.8 (5.9)	F = 1.37	0.26
Cognitive Outcome Measures					
Shifting (−0.1; 0.7)	61.3 (40.4)	53.9 (53.5)	47.0 (29.4)	F = 0.94	0.40
Updating/ WM (−1.3; 2.8)	1.32 (0.15)	1.32 (0.24)	1.34 (0.22)	F = 0.19	0.82
Inhibition (−0.5; −0.1)	7.9 (0.68)	7.9 (0.7)	8.1 (0.5)	F = 1.31	0.28
Verbal Generativity (0.1; −0.3)	41.7 (9.1)	46.9 (11.3)	48.8 (10.6)	F = 4.04	0.02*
NVR (0.4; −0.1)	64.7 (25.7)	52.2 (22.3)	56.6 (18.3)	F = 2.68	0.07

Note. Data are expressed as mean (± SD), except where otherwise stated. Skewness and Kurtosis denote post logarithmic transformation for Shifting and Nonverbal Reasoning (NVR) measures. χ^2 is Pearson Chi-squared statistic, degrees of freedom (2); F: ANOVA statistic, degrees of freedom (2, 96). Physical Activity (PA) Duration and Intensity reflect self-report physical activity levels derived from the International Physical Activity Questionnaire. PA duration is hours/week, PA intensity is metabolic equivalents (METs)/ duration. Shifting score is Trail Making Test-Part B minus Part A, time in seconds; Updating/Working Memory score is the CogState 1-back task, accuracy; Inhibition score is the NIH Examiner Flanker task, Flanker composite score; Generativity score is a composite of NIH Examiner phonemic and semantic fluency tasks; Non-verbal reasoning (NVR) score, is the Groton Maze Learning Task, errors. Abbreviations. APOE ε4, apolipoprotein ε4 allele genotype; VIQ, Verbal Intelligence Quotient; MoCA, Montreal Cognitive Assessment; PA, physical activity; BMI, Body Mass Index; VO_2peak, peak volume of oxygen uptake.

* p <0.05; ** p <0.01

back test, accuracy, Inhibition was measured using the NIH Examiner Flanker task score, flanker composite score, Verbal Generativity was assessed using the NIH Examiner fluency task, total phonemic and semantic response score, and Nonverbal Reasoning was assessed using the CogState Groton Maze Learning Task, errors.

Cardiorespiratory fitness

The measure for cardiorespiratory fitness was VO_2peak. Cycle-based assessment required participants to pedal against increasing resistance until volitional fatigue. Heart rate was recorded continuously and expired ventilation was assessed at 15 second mean values, using a Parvo TrueOne (ParvoMedics, USA) metabolic cart, for the measurement of rate of oxygen consumption (VO_2) and carbon dioxide production (VCO_2). VO_2peak was classified as the highest 15 second mean VO_2 value obtained during the last 2 minutes of the test. Additionally, participants must have reached a maximal heart rate greater than 85% of their age predicted maximum (i.e., (220 − age) × 0.85) and a respiratory exchange ratio (VCO_2/VO_2) greater than 1.15.[16]

Covariates

Participants completed questionnaires for assessment of demographic information, medical history, medications, alcohol consumption, smoking status, mood, and physical and leisure activities. An estimate of verbal intelligence quotient (VIQ) was calculated for each participant with the Cambridge Contextualised

Reading test (conducted at baseline only) using the method set out by Beardsall.[19] To determine apolipoprotein (*APOE*) genotype, blood was drawn at baseline and analyzed using standard procedures previously described.[16] Participants were classified into *APOE* groupings based on $\varepsilon 4$ allele carriage; carriers and noncarriers. Supplementary Table 1 provides information related to the timeline of measurement, outcome measures, and interpretation of scores.

Intervention

Intervention procedures have been comprehensively detailed in our protocol paper.[16] Briefly, participants randomized to an intervention group completed 6 months of either a moderate- or high-intensity cycling program consisting of 100 minutes of cycling per week (two sessions at 50-minute per session). Exercise intensity conditions (either moderate- or high-intensity) are set using the 6−20 Borg scale[20] of perceived exertion (6 = no exertion and 20 = maximal exertion; 20). Moderate-intensity exercise participants exercise at a constant intensity (50%−60% aerobic capacity; 13.0 Borg scale), while high-intensity exercise participants begin each session with a 10 minute low-intensity cycling warm-up (30%−40% aerobic capacity; 11.0 Borg scale) followed by 11 intervals of 1 minute of hard exertion (>80% aerobic capacity; 18.0 Borg scale) combined with 2 minutes of active recovery after each interval (30%−40% aerobic capacity; 12.0 Borg scale). All exercise sessions were completed under the supervision of an accredited exercise physiologist. All exercise was completed on a cycle ergometer (WattbikePro; Wattbike, Australia) allowing accurate measurement of intensity (Wattage). Additionally, radiotelemetric heart rate monitors (Garmin HRM1G, Garmin, USA) were used to provide an assessment of physiological intensity.

Participants assigned to the control group were invited to attend an information session on the benefits of diet and exercise with respect to cognition, dementia and brain ageing. Control participants did not receive any other instruction or intervention related to exercise.

Statistical Analyses

TMT and Groton Maze error scores were not normally distributed. Accordingly, scores were logarithmically transformed. Both TMT and Groton Maze had high correlations ($r \geq 0.93$) between the transformed and untransformed variables at all timepoints. For those tests where lower scores denote better performance (TMT, time in seconds; Groton Maze, number of errors), scores were reflected ($1/x$); postlogarithmic transformation. Fitness (VO_2peak) and all other cognitive test data (1-back, Flanker, Fluency) were considered sufficiently normally distributed (skew $< |2.0|$) for the purposes of parametric analyses (see Table 1;[21]). Descriptive statistics were used to summarize group data, ANOVA and χ^2 statistics were used to compare characteristics of participants at randomization.

Primary analyses of the primary cognitive outcome measures (Shifting, Updating/ Working Memory, Inhibition, Verbal Generativity, and Non-verbal Reasoning) were intention to treat,[22] using linear mixed models (randomization × timepoint). Each participant was treated as a random effect. Secondary analyses of the primary outcome measures included only participants in the high- and moderate-intensity intervention groups who attended ≥75% of supervised exercise sessions, and control participants (i.e., as per protocol). Age, gender, and education were entered into both primary and secondary analyses as covariates. Given unbalanced VIQ across groups, comparison analyses were run with and without VIQ as a covariate. Results did not differ in any meaningful way; thus, VIQ was not included in the models.

Post hoc, exploratory analyses examined the association between change in pre- to postintervention cardiorespiratory fitness and change in pre- to postintervention EF (Shifting, Updating/ Working Memory, Inhibition, Generativity, Nonverbal Reasoning). These analyses were conducted separately for control group and intervention group participants for which there were valid baseline and 6-month follow-up data (intervention group participants: $n = 60$; control group participants: $n = 25$). We analyzed intervention and control groups separately in order to assess individual differences in responsiveness to cardiorespiratory fitness training and how that related to EF performance. Change in both EF and VO_2peak was assessed through residual scores estimated from linear regression analysis that predicted postintervention EF/VO_2peak from preintervention EF/ VO_2peak. Outliers ($n = 1$ for VO_2peak in the control group) were identified based on criteria outlined by Hoaglin and Iglewicz[23] and subsequently Winsorized. Age, gender, and education were entered as covariates. Exploratory analyses were performed by way of linear regression models. All statistical analyses were performed using SPSS (version 26; SPSS Inc., Chicago, IL, 2019). Alpha was set at 0.05 and all reported results are two-tailed.

RESULTS

Figure 1 summarizes the flow of the study participants from screening through to 18-month follow-up. By the end of the 6-month intervention period, seven participants were withdrawn from the study. At the 18-month assessment, a further six participants were withdrawn.

An intervention adherence assessment showed participants randomized to the high-intensity exercise group attended exercise sessions as outlined in the protocol[16] at a mean rate of 85.5% (SD = 12.45; range = 50%–100%) and participants randomized to the moderate-intensity exercise group adhered to the exercise sessions at a mean of 86.29% (SD = 9.82; range = 59.62–100). Intervention adherence was not found to be different between the two groups when

FIGURE 1. Flowchart of participants in high-intensity exercise intervention, moderate intensity exercise intervention, and control groups from screening to 18-month follow-up.

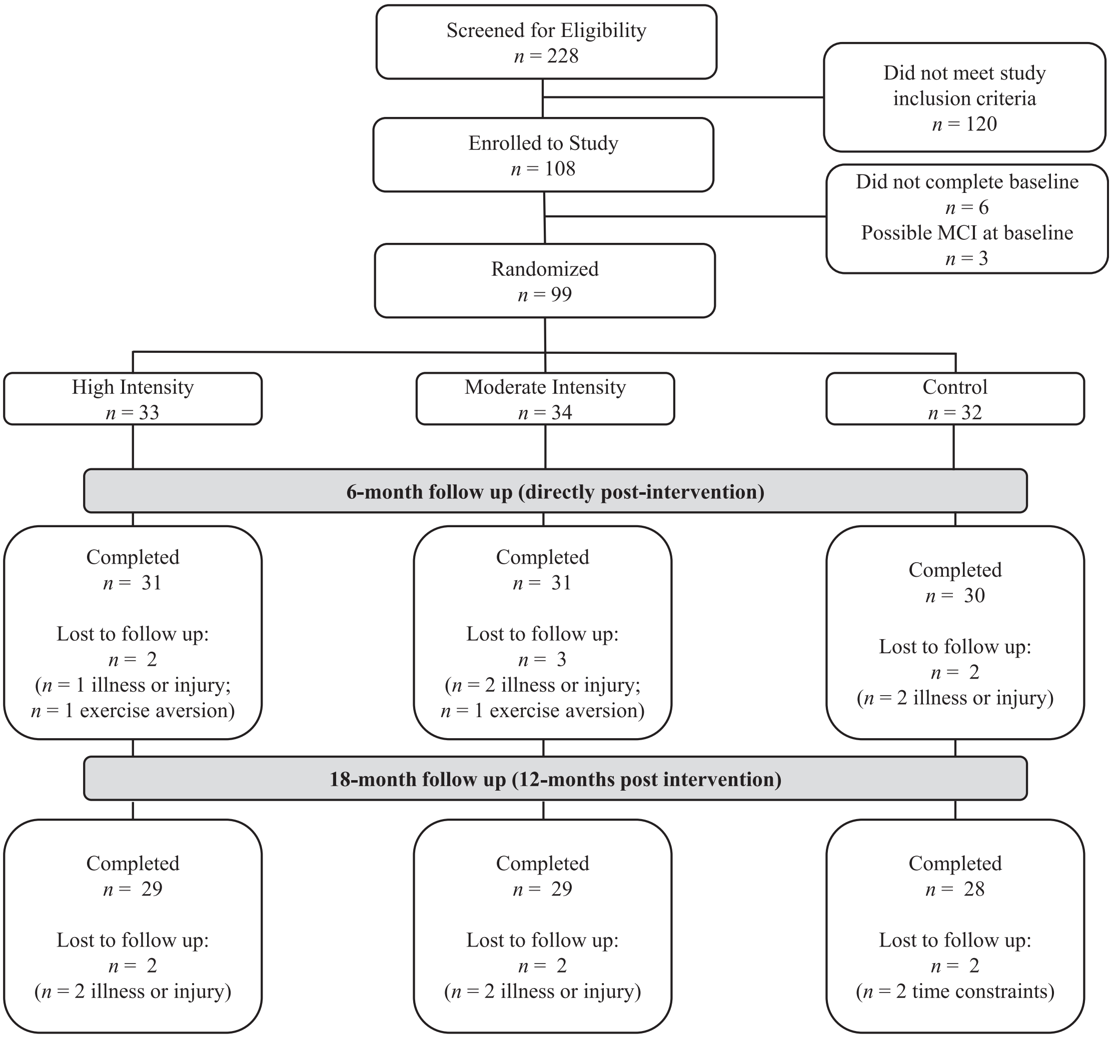


TABLE 2. Observed Raw Mean Difference Compared with Baseline of Cognitive Outcome measures and Cardiorespiratory Fitness over 18 months for High-Intensity Exercise Intervention Participants, Moderate-Intensity Exercise Intervention Participants, and Control Participants

Measure Mean (SD) *Cognitive Variables*	N	High Intensity Mean (SD)	N	Moderate Intensity Mean (SD)	N	Controls Mean (SD)	F (df)	p value
Shifting								
6 Months	33	+1.71 (42.45)	34	−9.71 (33.22)	32	−4.37 (27.97)	0.64	0.99
18-Months	33	+2.34 (32.67)	34	−4.24 (54.01)	32	−2.78 (33.80)	(4, 88.4)	
Updating/ WM								
6 Months	33	+0.02 (0.18)	34	+0.06 (0.24)	32	+0.05 (0.20)	0.84	0.50
18 Months	33	+0.05 (0.15)	34	0.02 (0.17)	32	+0.02 (0.22)	(4, 114.4)	
Inhibition								
6 Months	33	+0.19 (0.66)	34	+0.30 (0.66)	32	+0.15 (0.57)	0.31	0.87
18 Months	33	+0.23 (0.74)	34	+0.36 (0.58)	32	+0.32 (0.48)	(4, 100.3)	
Verbal Generativity								
6 Months	33	+1.55 (7.97)	34	+1.16 (6.44)	32	−0.90 (6.61)	0.62	0.65
18 Months	33	+2.0 (8.68)	34	+1.21 (6.02)	32	−0.57 (6.94)	(4, 93.9)	
NVR								
6 Months	33	−0.76 (32.00)	34	+0.68 (21.70)	32	−2.67 (17.74)	0.10	0.98
18 Months	33	−5.14 (18.17)	34	−7.0 (15.90)	32	−7.89 (16.29)	(4, 102.0)	
Fitness Variables								
Vo$_2$peak								
6 Months	33	+5.40 (3.83)	34	+3.02 (3.17)	32	+0.55 (2.89)	10.23	<0.001**
18 Months	33	+0.78 (3.61)	34	−1.43 (3.12)	32	−0.99 (3.85)	(4, 87.0)	

Note. Raw data are expressed as mean (±SD), except where otherwise stated. F: Linear Mixed Model statistic; df is degrees of freedom (numerator degrees of freedom; denominator degrees of freedom). Shifting score denotes Trail Making Test-Part B minus Part A, time in seconds (higher scores = poorer performance); Updating/ Working Memory (WM) score denotes the CogState 1-back task, accuracy; Inhibition score denotes the NIH Examiner Flanker task, Flanker composite score; Generativity score denotes a composite of NIH Examiner phonemic and semantic fluency tasks; Nonverbal reasoning (NVR) score, denotes the Groton Maze Learning Task, errors (higher scores = poorer performance); VO$_2$peak is peak volume of oxygen uptake. *p <0.05

** p <0.01

analyzed by way of analysis of variance (ANOVA; F (2, 66) = 0.80, p = 0.78).

Change in scores from baseline to 6-month measurement (directly post intervention period), and again at 18-month measurement (12-month postintervention period) are presented in Table 2. There were no group × time effects for any of the EF measures. Cardiorespiratory fitness levels differed across groups; high-intensity and moderate intensity > control from baseline to 6-month follow-up; no group differences from baseline to 18-month follow-up.

Secondary analyses (i.e., per protocol analyses) again revealed no group × time effects for any of the EF measures when analyzed by way of linear mixed effects modelling (Shifting: F (4, 80.0) = 0.14, 80.03, p = 0.97; Updating/Working Memory: F (4, 104.3) = 1.03, p = 0.40; Inhibition: F (4, 92.4) = 0.23, p = 0.92; Verbal Generativity: F (4, 86.9) = 0.73, p = 0.59; Nonverbal Reasoning: F (4, 94.2) = 0.23, p = 0.92). Again, cardiorespiratory fitness differed at a group level (F (4, 77.6) = 10.84, p≤0.001); high-intensity and moderate intensity>control from baseline to 6-month follow-up; no group differences from baseline to 18-month follow-up.

Results from post hoc, exploratory analyses on the association between change in pre- to postintervention cardiorespiratory fitness and EF are presented in Table 3. There were no associations observed for participants in the control group. However, there was a significant association between change in cardiorespiratory fitness and Updating/ Working Memory and Verbal Generativity in intervention group participants; fitness uniquely accounting for 11.6% and 7.8% of the total variance respectively (Fig. 2).

DISCUSSION

In the current study, we examined the effect of a systematically manipulated exercise intervention

TABLE 3. Observed Associations Between Change in Pre- to post 6-Month Exercise Intervention Cardiorespiratory Fitness and Executive Function Subdomains, Assessed Separately for Intervention and Control Group Participants

	Control Participants n = 25			Intervention Participants n = 60		
Measure	β	$R_{s\text{-}p}$	**p value**	β	$R_{s\text{-}p}$	**p value**
Shifting	−0.19	−0.16	0.42	0.60	0.06	0.68
Updating/WM	−0.16	−0.13	0.55	0.37	0.34	0.01**
Inhibition	−0.20	−0.17	0.42	0.25	0.23	0.08
Verbal Generativity	−0.19	−0.16	0.48	0.30	0.28	0.03*
Non-verbal Reasoning	−0.38	−0.31	0.12	0.08	0.07	0.59

Note. Change assessed through residual scores estimated from linear regression analysis that predicted postintervention VO_2peak/ Executive Function from preintervention VO_2peak/ Executive Function. Analyses conducted by way of linear regression modelling. β = Standardized Beta Weight; $r_{s\text{-}p}$ = semipartial correlation. Degrees of freedom for the control group analyses: (4, 20); Degrees of freedom for the intervention groups analyses (4, 55). Model adjusted for age, gender, and education level. Cardiorespiratory fitness measured as VO_2 peak, peak volume of oxygen uptake; Shifting score is Trail Making Test-Part B minus part A, time in seconds; Updating/Working Memory (WM) score is the CogState 1-back task, accuracy; Inhibition score is the NIH Examiner Flanker task, Flanker composite score; Generativity score is a composite of NIH Examiner phonemic and semantic fluency tasks; Nonverbal reasoning score, is the Groton Maze Learning Task, errors.

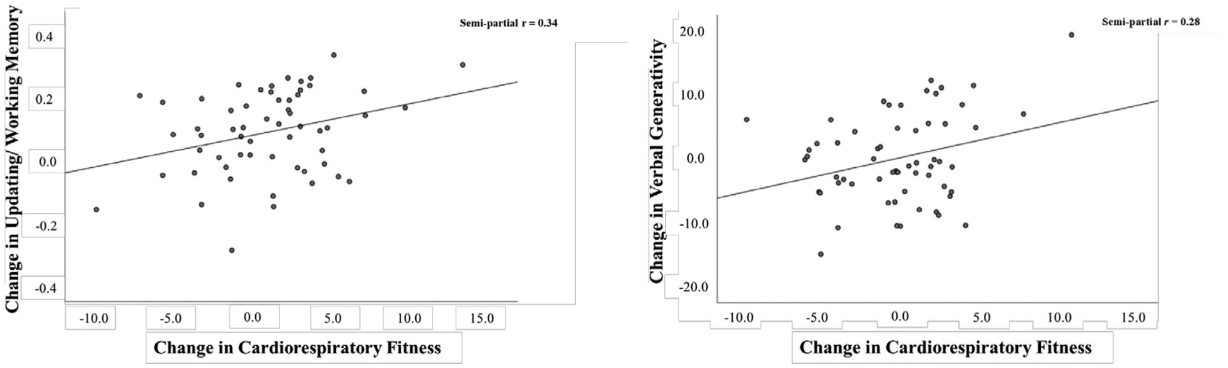
* p <0.05

** p <0.01

(high-intensity versus moderate-intensity versus control) on comprehensively measured EF subdomains (Shifting, Updating/ Working Memory, Inhibition, Verbal Generativity, and Non-Verbal Reasoning) in a group of cognitively normal older adults. Here, we did not observe a statistically significant group effect on EF. However, we did find a significant association between change in cardiorespiratory fitness and both Updating/ Working Memory and Verbal Generativity from pre- to postintervention.

The association between fitness and Verbal Generativity, and suggested theories underlying this association, was reported in our earlier cross-sectional study.[15] The current results also complement the findings from Nocera et al's report of improvements in Generativity and cardiorespiratory fitness, following a cycle-based aerobic intervention[24] and Emery et al. who found a selective effect of exercise-induced cardiorespiratory fitness on Verbal Generativity in older adults with chronic obstructive pulmonary disease.[25] Similarly, the association between fitness and Updating/Working Memory supports earlier findings from Volkers et al.[26] and McAuley et al.,[27] who both reported positive associations between fitness and Updating/Working Memory in older adults.

FIGURE 2. Change in cardiorespiratory fitness was associated with change in Updating/Working Memory and Verbal Generativity from pre- to post 6-month exercise intervention in exercise intervention group participants after controlling for age, gender, and education level.



The hypothetical link between physical activity, cardiorespiratory fitness, and cognitive function holds that changes in fitness precede changes in cognitive function.[28] However, this hypothesis is difficult to evaluate as very few studies report on physical activity, cardiorespiratory fitness, and cognition in a single study, and fewer still report on associations between changes in cardiorespiratory fitness and EF. However, it has been hypothesized that improvements in fitness mediate the protective benefits of physical activity on cognitive function.[29] Increased cardiorespiratory fitness increases both frontal grey matter volume[30] and cerebral blood flow to the cortex which acts to meet metabolic requirements and remove waste from the brain.[31,32] Additionally, in animal studies, increased cardiorespiratory fitness has also been found to induce increased brain-derived neurotrophic factor; a growth factor associated with neurogenesis and neuroprotection.[32]

Unlike the other EF subdomains, Updating/Working Memory and Verbal Generativity rely heavily on nonfrontal structures within, and neural connectivity to, the temporal and parietal lobes.[33−36] Thus, it is highly possible that the selective associations between fitness and these EF subdomains observed in this and previous studies is reflective of fitness induced neuroprotection to the nonfrontal brain regions unique to these particular EFs. Additionally, it is possible that those individuals with lower fitness levels at baseline were able to improve both fitness and cognition to the level required to observe a neurocognitive association for these particular subdomains, but not the others. However, while our findings on the association between postintervention change in fitness, Updating/Working Memory, and Verbal Generativity is promising, these associations will require further replication to confirm the robustness of these associations.

Within the current study, participants in the intervention groups showed improved cardiorespiratory fitness. However, this improved fitness did not induce EF change at a group level in our study, as it has in others.[9] Our results are consistent with Young et al.'s meta- analysis that did not find evidence that exercise improves EF in older adults,[11] but incongruent with primary results in Northey et al's meta-analysis.[10] Thus, factors contributing to the lack of intervention effect in our study are challenging to elucidate, though several factors warrant consideration.

Primarily, similar to Young et al's meta-analysis inclusion criteria,[11] our study examined aerobic exercise only, whereas Northey et al.'s[10] primary analyses included interventions of aerobic exercise, resistance training, multicomponent training, tai chi, and yoga. Physical activity can broadly be divided into two categories: physical and motor activities.[37] Physical activities encompass aerobic and resistance type activities (e.g., running and cycling) while motor activities involve balance, coordination and high neuromuscular versus low metabolic demands (e.g., dancing, martial arts; 37). Importantly, motor activities also require active engagement, attention, perceptual acuity and higher level cognitive processing. In short, motor activities require EF. A number of early and more recent studies that have examined EF, have found minimal or no cognitive benefit from simple aerobic exercise alone (e.g., running or stationary bicycle riding) in older adults.[28,38−40] Thus, it may be that interventions require the synthesis of physical and cognitive activity to induce the neurotrophic factors necessary to increase and/ or protect against most EF decline in older adults.[41]

A further factor to consider in helping to understand our null results is the demographic characteristics of our participant sample. Colcombe and Kramer[9] and Kramer et al.[42] found positive effects of aerobic activity on EF in studies that included participants younger than the present study (inclusion of ≥55 and mean age of 61, respectively versus mean age of 69.1). Whereas, congruent with our sample, mean participant age in studies that found no effect of aerobic activity on EF (e.g., 38, 39, 40) was 66−70 years. Thus, perhaps the benefit of aerobic physical activity on EF decelerates non-linearly as one begins to approach 70 years of age.[7] Additionally, while our intervention was designed based on public health recommendations of 90−100 minutes per week of vigorous exercise for physical health benefits (duration matched between groups to assess the effect of intensity), perhaps a greater weekly duration of high-intensity exercise is required to induce cognitive health.

Furthermore, the participants in the current study were cognitively high functioning and highly educated. Overall mean VIQ in our study participants was 116.33 (7.39), more than one standard deviation above the population mean.[43] Furthermore, overall mean education for our participants was 14.05 years indicating that the majority of our sample completed post schooling studies; whereas education means in recent studies that reported positive effects of aerobic physical activity on EF was (11.75 years; [44]) and 12.3 years,[45] representing education attainment of high-school completion or below. Therefore, it is possible the participants in our study had high levels of cognitive reserve, whereby they had existing neurocognitive protection in the brain regions that mediate EF (frontal lobes), to a degree at which additional exercise effects could not be detected.

Finally, it would be remiss not to briefly acknowledge other factors that might have affected the outcome of our physical activity intervention on EF. Certainly, many studies have found robust associations between cognitive health in older adults and sleep quality,[46] social and environmental enrichment,[47] and adherence to a healthy diet (particularly a mediterranean diet;[48]). Perhaps multiple lifestyle factors have interactive effects on the aging brain and cognition. Thus, future research may wish to consider these additional factors in addition to physical activity intervention.

Limitations

The results reported from the current study should be interpreted within the context of some limitations. Similar to many RCTs, the participants in our study were fairly homogenous in sociodemographic characteristics: most participants were Caucasian, generally of high socioeconomic status, and were generally cognitively high-functioning individuals. Nevertheless, in an effort to counter the effects of studying such a homogenous group, we controlled for VIQ and education level, and used a wide selection of neuropsychological assessments of EF that should have been sensitive to cognitive differences, even in a high-performing cohort. Though, it is acknowledged that even these carefully selected measures may not have been challenging enough to capture subtle cognitive change in this cognitively high functioning cohort (e.g., 24% of our cohort performed at ceiling on the 1-back measure). Finally, we acknowledge that no adjustment was made for multiple analyses conducted in this study in order to maintain the familywise error rate at 0.05. Therefore, there is a chance that significant results reported here may represent a type 1 error. Though, we also acknowledge that many of the analyses within this study were not independent (e.g., the correlations reported in Table 3). Accordingly, an adjustment (e.g., the Bonferroni adjustment), may be considered too conservative in this case. Therefore, we encourage further replication of the results in similar populations.

SUMMARY AND CONCLUSION

In the current study, we examined the effect of a systematically manipulated exercise intervention (high-intensity versus moderate-intensity versus control) on five EF subdomains (Shifting, Updating/ Working Memory, Inhibition, Verbal Generativity, and Nonverbal Reasoning) in a group of cognitively normal older adults. We did not observe a group effect on any of the EF subdomains. However, post hoc investigations showed an association between postintervention change in cardiorespiratory fitness and Verbal Generativity.

There are some encouraging results beginning to emerge in using cognitively-enriched physical activity to protect against decline and/ or improve EF in older adults. Thus, further research in this area of research appears warranted. Further, given that our exercise intervention showed limited results in our already cognitively high-functioning participants, it may be prudent to conduct a similar trials in 'at-risk' populations. Additionally, given the multifaceted nature of the relationship between exercise, brain changes, and EF, sensitive volumetric imaging research may shed some light on the specific brain regions most amenable to exercise associated change that may precede cognitive change. Arguably, future research should include one or more measures of Updating/ Working Memory and Verbal Generativity.

AUTHOR CONTRIBUTIONS

NJF prepared the manuscript and was involved in study design; MW was involved in study design conception, design of the neuropsychological battery and provided critical review of the manuscript; GEG provided critical evaluation of overall statistical analysis plan; SRS was involved in study design and provided revisions of the manuscript; SM was involved in the administrative design and provided revisions of the manuscript; NG was involved in the design of the exercise intervention and fitness testing; HRS designed the neuropsychological battery; SML designed the protocol for genotyping and gene expression analysis; RNM was involved in study design and provided revisions of the manuscript; JP was involved in study design conception and provided revisions of the manuscript; BMB was involved in study design conception and provided critical review of the manuscript.

DISCLOSURE

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SUPPLEMENTARY MATERIALS

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