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The influence of a 16-week exercise program, APOE status, and age on executive function task performance: A randomized trial

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ABSTRACT

Previous research has shown beneficial cognitive changes following exercise training in older adults. However, the work on the potential moderating effects of Apoliprotein E (APOE) ε4 carrier status has been mixed, and the role of exercise intensity remains largely unexplored. The present study sought to examine the influence of APOE ε4 status and exercise intensity on measures of cognitive performance in a group of older adults. Cross-sectional comparisons between a group of younger inactive adults ($n = 44$, age = 28.86 ± 0.473 SD, 60.5% female) and a group of older inactive adults ($n = 142$, age = 67.8 ± 5.4, 62.7% female) were made on baseline measurements of APOE ε4 status, VO_2peak, and cognitive performance in the domain of executive functioning. The older adults also participated in a randomized controlled exercise trial, exercising three times per week for 16-weeks in either a low-intensity continuous training (LICT) group or a moderate-intensity continuous training plus interval training (MICT+IT) group at the Center for Health and Neuroscience, Genes, and Environment (CUChange) Exercise Laboratory. Follow-up measurements of VO_2peak and cognitive performance were collected on the older adults after the exercise intervention. Cross-sectional comparisons between the older and younger adults demonstrated significant impairments among older adults in Stroop effect on error and time, Category Switch mixing effects, and Keep Track task. This impairment was not moderated by APOE ε4 carrier status. Improvements from pre- to post-exercise intervention were observed in both exercise groups in Stroop effect on error ([$F(1, 256) = 9.381$, $p < 0.01$, $\eta^2 = 0.031$]) and Category Switch switching effect reaction time ([$F(1, 274) = 4.442$, $p < 0.05$, $\eta^2 = 0.020$]), with no difference between exercise groups. The moderating effects of APOE ε4 carrier status were mixed. Exercise did not improve the Stroop effect on error among ε4 carriers assigned to MICT+IT when improvements were seen in all other groups. Further research is needed to examine the mechanisms of action by which exercise impacts cognitive task performance, and possible moderators such as genetic variability and exercise intensity.

Due to advances in medical science people are living longer than ever before (He et al., 2016). Yet as more people live to older ages, the burden of age-related disease and disability increases, compromising individual quality of life (Courtney-Long et al., 2015; Dobriansky et al., 2007; He et al., 2016; Rowe et al., 2016). Even in the absence of disease, numerous studies have demonstrated that older adults demonstrate a decline in cognitive ability compared to younger adults (Fjell et al., 2017; Grady, 2012; Hayes et al., 2016; Salthouse, 2019), and quality of life may be affected by difficulties adjusting to age-related impairments in cognition, especially those pertaining to the broad domain of executive function (Braver and Barch, 2002; Grady, 2012; Hasher and Zacks, 1988; Hedden and Gabrieli, 2004; Salthouse, 2019).

How executive function (EF) is defined has been a subject of debate (Baggetta and Alexander, 2016; Banich, 2009; Chun et al., 2011; Mccabe et al., 2010). Broadly, EF is agreed to be "a set of general-purpose control mechanisms often linked to the prefrontal cortex of the brain that regulate the dynamics of human cognition and action" (Friedman et al., 2006; Miyake and Friedman, 2012; Miyake et al., 2000), as this definition was shown in a recent review to be the most often adopted framework among researchers in this area (Baggetta and Alexander,

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2016). Mechanisms associated with EF are highly interrelated but also structurally distinguishable (Friedman et al., 2006; Miyake et al., 2000), and most frequently conceptualized as overlapping domains of inhibition, shifting, and updating (Baggetta and Alexander, 2016; Friedman et al., 2006; Miyake et al., 2000). Individual differences in task switching and inhibition appear to predict social strain (Tun et al., 2013), and age-related decrements in inhibition can have negative ramifications for social functioning (Hutter et al., 2012; Pushkar et al., 2000; von Hippel et al., 2008; Von Hippel and Dunlop, 2005). A deeper understanding of the neurobiological mechanisms of EF and how to preserve or improve EF through the life course would greatly enhance efforts to improve quality of life.

Numerous meta-analyses and reviews detail the benefits of exercise among older adults for cognition (Barnes and Yaffe, 2011; Colcombe and Kramer, 2003; Erickson et al., 2011; Hernández et al., 2015; Heyn et al., 2004; Kramer et al., 2004; Kramer and Erickson, 2007; Paillard et al., 2015; Smith et al., 2010). The effects of fitness training on cognitive function may be strongest for EF as compared to other cognitive domains (Bunce and Murden, 2006; Kramer and Willis, 2002; Yu et al., 2013) and are greater in the mid-old to old-old (> 66) with longer program durations and longer exercise bout durations (Colcombe and Kramer, 2003; Buchman et al., 2012; Ludyga et al., 2016; Moreau and Chou, 2019). However, previous work has not fully explored how exercise intensity may moderate improvements in EF following an exercise program. For instance, while some studies do include a single aerobic exercise condition, that condition was in comparison to a non-aerobic condition such as resistance, strength training, or stretching (Brinke et al., 2015; Colcombe et al., 2006; Erickson et al., 2011; Mekari et al., 2020; Sanders et al., 2020; Tse et al., 2015), or a sedentary condition (Lautenschlager et al., 2008; Muscari et al., 2009).

Another potential moderator may be the ε4 allele of the APOE gene, carried by roughly 13.7% of the population (Liu et al., 2013) and well documented as a risk factor for cognitive decline (Farlow et al., 2004; Harris and Deary, 2011; Reas et al., 2019; Schuff et al., 2008; Verghese et al., 2011). Research on the effects of exercise on cognition for ε4 allele carriers has produced mixed results. Some work suggests diminishing returns from exercise on cognitive performance for ε4 carriers as compared to non-carriers (Brown et al., 2013; Fenesi et al., 2017; Ku et al., 2017; Obisesan et al., 2012; Podewils et al., 2005). Pre-clinical (Chaudhari et al., 2016) and positron emission tomography (PET) imaging studies (Bugg et al., 2012) suggest ε4 carriers may benefit overall from higher levels of physical activity (Woodard et al., 2012), while other research suggests that better performance on tests of aerobic fitness is associated with better memory performance among older adults who were also ε4 carriers (Etnier et al., 2007; Tsai et al., 2019, 2021). Exploring the moderating role of APOE ε4 allele status in the context of a study that directly targets cardiorespiratory fitness via high intensity exercise may thus be particularly informative.

The data described here come from a large study that explores age differences in structural and functional brain imaging, and cognitive performance related to EF, as well as the impacts for each of those domains of increasing physical activity among older adults. In the broader study, older adults were compared to younger adults who were relatively closely matched on current physical activity levels. Then, older adults only participated in a 16-week supervised exercise program comparing the effects of low intensity continuous training (LICT) and moderate intensity continuous training plus high intensity interval training (MICT+IT). The current analysis utilizes measures of cognitive performance in the EF domains of updating, shifting, and inhibition. It was hypothesized that older adults would demonstrate poorer cognitive performance and cardiovascular health than younger adults before older adults initiated 16 weeks of fitness training, older adults in both exercise conditions would improve on measures of cognitive performance after participation the 16-week intervention, that there might be stronger effects from MICT+IT versus LICT, and that there would be an interaction between ε4 allele carrier status and exercise condition among older adults.

1. Materials & method

1.1. Study sample and recruitment

Recruitment and data collection took place in the Denver-Boulder, Colorado area between April 2014 and November 2018. Multiple recruitment strategies were used including Craigslist, ResearchMatch, targeted mailings, electronic advertisements placed in campus bulletins, flyers posted on the University of Colorado Boulder campus and at community centers and recreation centers, and advertisements on social media websites. Participants were eligible for inclusion if they were younger adults aged 25–35 or older adults aged 60 or over, if they reported less than 60 min per week of moderate intensity physical activity in the last six months as reported at screening, they were physically capable of safely engaging in moderate intensity exercise as assessed by the study physician, able to successfully complete a maximal oxygen uptake (VO_2max) test without evidence of cardiac or other abnormalities, and able to make fewer than three errors on the Pfeiffer Mental Status test (Pfeiffer, 1975). The weekly fitness threshold for inclusion was selected because the goal was to work with a population that wasn't already highly active, 60 min/week is well below the recommendation of the American College of Sports Medicine (*Physical Activity Guidelines for Americans*, 2008), and to ensure safety for older adults given that both experimental conditions were aerobic.

Participants were excluded if they reported heavy smoking (> 20 pack years), uncontrolled diabetes (hemoglobin A1C > 7%) or diabetes treated by insulin or sulfonylureas, uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg), magnetic resonance imaging (MRI) contraindications or body size exceeding the capacity of the MRI (given that aspects of the larger study involved structural and functional MRI measures), current use of antipsychotic medications, or diagnosis of bipolar disorder, schizophrenia, dementia, or Alzheimer's disease. Study procedures were reviewed and approved by the University of Colorado Boulder Institutional Review Board.

1.2. Changes to eligibility

Some eligibility criteria were amended after the commencement of the study to broaden our ability to recruit participants. These included changing eligible age for the older group from 65 and older to 60 and older, inclusion of individuals with controlled diabetes who were not taking insulin or sulfonylureas, and inclusion of individuals with depression or anxiety. Additionally, for both older and younger groups, the maximum limit of 60 min of exercise per week was increased to 80 min per week. Finally, overall enrollment was increased to account for participant loss due to attrition and excessive magnetic resonance imaging (MRI) scan motion. All changes to eligibility were reviewed and approved by the University of Colorado Boulder Institutional Review Board.

1.3. Study design

The data presented here were collected as part of a larger randomized controlled trial with multiple aims called Fitness, Older Adults, and Resting State Connectivity Enhancement (FORCE). Funding for this study was provided by R01AG43452 (NIA). Clinical- trials.gov identifier: NCT0206861. The overall aim of FORCE was to examine the relationship between changes in physical activity and changes in brain network connectivity and cognitive, social, emotional, and financial functioning among older adults. MRI data, as well as measures of social, emotional, and financial functioning were collected but are not included in the present analysis. Older adults participated in a randomized controlled exercise trial with two conditions, MICT+IT or LICT. A group

of younger adults was also enrolled in the study for a baseline session but did not participate in either exercise condition. Older and younger adult participants completed a blood draw for SNP analysis, a demographics questionnaire, and a cognitive performance assessment at baseline, and older adult participants completed a follow-up cognitive performance assessment after the conclusion of their 16-week exercise participation.

1.4. Randomization and masking

A random assignment table for each gender was created using a random number generator. Upon completion of consent and assent and following assessment by a study physician, a research assistant block-randomized older adult participants by gender to either the MICT+IT or LICT intervention. It was not possible for participants to be fully blind to condition given the nature of a behavioral trial. They were however blind to the nature of the other intervention condition as well as the study hypotheses.

1.5. Study procedures

1.5.1. Training protocol

Older adults in both exercise conditions were asked to attend exercise sessions three times per week for 16 weeks at the Center for Health and Neuroscience, Genes, and Environment (CUChange) Exercise Laboratory on the University of Colorado Boulder campus. Exercise sessions lasted approximately 30 min and were supervised by trained research assistants. Participants were fitted with a heart rate monitor (Polar T31, Kempele, Finland) and predominantly exercised on the treadmill, however participants with orthopedic limitations or balance concerns were allowed to exercise on an elliptical or cycle ergometer. Exercise prescription was based off of percentages of the maximum heart rate (HRmax) achieved during two exercise tests prior to the exercise intervention. The MICT+IT program was progressive in design, increasing intensity and increasing the frequency of interval training over the course of the program to make it safe for and tolerable to older adults. This group performed approximately 2 min of warm-up at a low intensity at the beginning of each exercise session. During the first three weeks of this program, participants exercised for 30 min at 60% of HRmax (e.g., a "moderate level of exertion). During weeks 4-6, participants began interval training during one session per week. Interval training included 15 minutes of exercise at 75-80% HRmax, followed by 3 X 3 minute intervals at 85-95% HRmax. Each interval was separated by two minutes of active recovery. Non-interval sessions included 30 minutes at 75-80% HRmax. During weeks 7-9, participants completed interval training two times per week. In weeks 10-16, interval training was completed three times per week. Participants were allowed to cool down for approximately five minutes, or until heart rate returned to near resting values. The LICT group exercised for 30 minutes at 50% of HRmax (e.g., a "low" level of exertion) for all 16 weeks Fig. 1).

1.6. Measures

1.6.1. Demographics

Participants in both groups (older and younger adults) completed a demographics questionnaire on a laptop computer. Demographics data were collected and managed using Research Electronic Data Capture (REDCap) (Harris et al., 2009) and included sex, age, race, ethnicity, marital status, highest level of education, and employment status.

1.6.2. Cardiopulmonary fitness

Cardiopulmonary fitness was assessed as peak oxygen uptake (VO_2peak) at baseline for younger and older adults and at follow-up for older adults using an incremental graded exercise test with breath-by-breath gas collection (MGC Diagnostics Ultima, Saint Paul, MN) on a motorized treadmill (Full Vision Inc. Trackmaster, Newton, KS) at the Clinical Translational Research Center (CTRC) on the University of Colorado Boulder campus. In contrast to VO_2max, (Cade et al., 2018), VO_2peak is the highest value of oxygen uptake that one reaches on a specific high intensity exercise test, and was calculated as the highest 30 s average during the test. VO_2peak was selected as an objective measure of fitness given that it's not uncommon for untrained research participants to tire before reaching the VO_2 plateau requirements to measure VO_2 max. According to the Balke protocol (American College of Sports Medicine, 2013), treadmill speed remained constant and grade was increased by 2% every 2 min until exhaustion. Treadmill speed was chosen to elicit approximately 70% of age predicted maximum heart rate and a rating of perceived exertion (RPE) of 13 (Borg; 6–20 scale) (Borg, 1970), and heart rate was continuously monitored using a 12-lead electrocardiogram (EKG). Two participants completed the VO_2peak assessment on a cycle ergometer (Lode Excalibur; Lode Groningen, The Netherlands) due to an orthopedic limitation or balance concern on the treadmill. One of these participants performed the exercise intervention on a cycle ergometer and the other performed it on a treadmill. All other participants completed exercise testing on a treadmill. The cycle

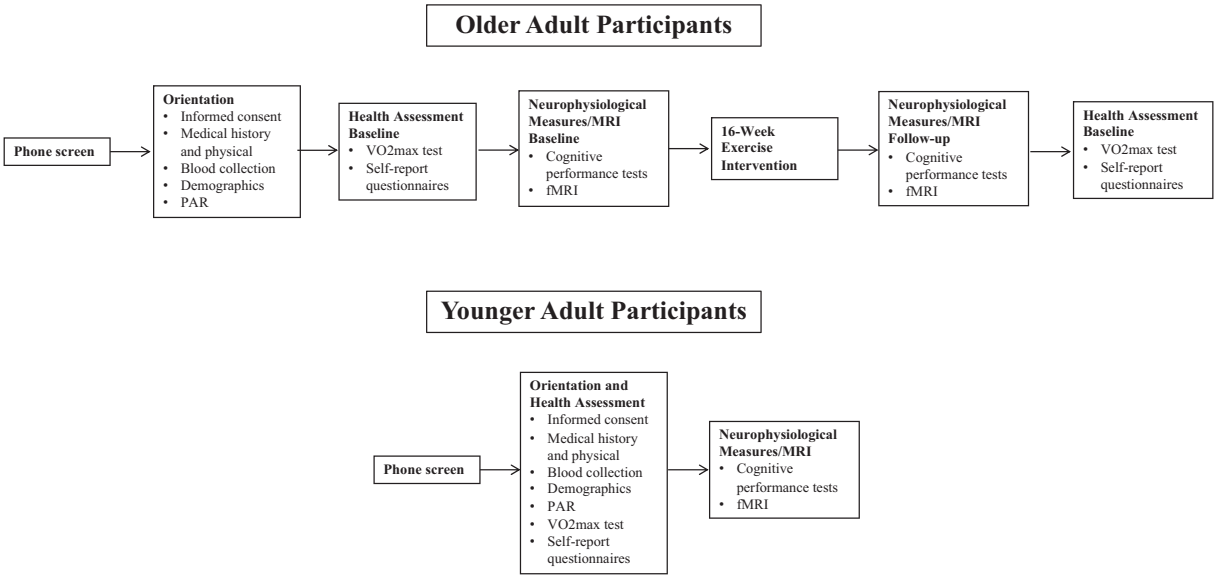

Fig. 1. Research flowchart for older and younger study participants.

ergometer tests began at a resistance of 0 W and increased by 20–25 W every 2 min until exhaustion.

1.6.3. Cognitive performance

Cognitive performance was measured at baseline for younger and older adults and at follow-up for older adults using three EF tasks (Friedman et al., 2006; Miyake and Friedman, 2012; Miyake et al., 2000) that measured inhibition (Stroop task), shifting (Category Switch task), and updating (Keep Track task). The cognitive tests were administered by trained research assistants using *E*-Prime software (Psychology Software Tools, Sharpsburg, PA) running on a laptop computer with stimuli displayed on a monitor. A response device was used for the Stroop and Category Switch tasks. Verbal responses were recorded for the Keep Track task.

The Stroop task (Golden and Freshwater, 1978) asked participants to identify the ink color of the word presented and ignore the meaning of the word. The ink colors used in this task were red, yellow, green, and blue. The task included congruent trials in which the meaning of the word matched the ink color of the word, as well as incongruent trials in which the meaning of the word corresponded to a color different than the ink color presented. Participants completed two blocks of eight practice trials that included only neutral trials, where X's were presented rather than a word. Participants then completed four blocks of 48 trials, where two of the blocks were comprised of 25% incongruent trials, and two blocks contained 75% incongruent trials. The blocks alternated between 25% and 75%. Participants were block randomized by exercise condition to receive the 25% or 75% block first. The ordering of the blocks was the same for participants at baseline and follow-up. Trials were pseudorandomized within each block.

In the Category Switch task (Gibson, 1941; Jersild, 1927) participants were asked to categorize words regarding their animacy (living or non-living) or size (smaller or larger than a soccer ball). A cue appeared above the word to signify the dimension to apply (N/L or S/L) using a button box. Participants completed two blocks of 34 trials each assessing a single dimension preceded by 12 practice trials. Participants then completed two blocks of 68 trials that included a mixture of both dimensions, preceded by 24 practice trials. The two dimensions were queried equally across each mixed block, with 33 trials involving a switch between dimensions. As a manipulation of difficulty, mixed blocks further varied by cue-stimulus onset latency (1250 ms and a shorter, more difficult 750 ms latency). Participants were block randomized by exercise condition to receive a set of trials in one of two possible orders at baseline and received another set of trials in the same order at follow-up.

In the Keep Track task (Yntema, 1963; Yntema and Mueser, 1962), a series of words belonging to one of six categories (relatives, distances, metals, animals, colors, and countries) was presented one at a time. After two practice trials, participants completed nine trials in which they were asked to keep track of and report the last word presented from two to four categories. Three trials included two categories, three trials included three categories, and three trials included four categories. Each word was presented for 2 sec, with the applicable categories at bottom of the screen. Participants were block randomized by exercise condition to receive one of two sets of trials in one of two possible orders at baseline. Participants received the other set of trials in the same order at follow-up.

1.7. APOE allele status

1.7.1. DNA extraction

Blood samples for DNA extraction were collected from participants following a four hour fast and prior to the start of the exercise intervention. The blood was stored in EDTA tubes at 4 °C until extraction. The Gentra Puregene kit (QIAGEN, Hilden, Germany) for whole blood was used following the manufacturer's instructions optimized for 10 mL of blood with several exceptions: the RNase A optional step was not taken, DNA was vortexed in DNA hydration solution until no longer visible, and DNA was immediately stored at +4 °C for at least 24 h prior to quantification rather than the 65 °C and room temperature incubation steps. DNA concentrations were assessed for genotyping using the Quant-iT Qubit 1.0 fluorometer (ThermoFisher Scientific, Waltham, Massachusetts) and protocol following all manufacturer instructions. Samples were then stored at -80 °C until analysis.

1.7.2. SNP analysis

From the whole blood DNA extracted, genotyping analyses were conducted on the SNPS rs7412 and rs429358 in order to assess APOE ε4 carrier status. rs7412 genotype was identified in 98% of participants, rs429358 in 93.9% of participants, and APOE ε 4 carrier status assayed with 92.7% success. Participants with one or more undetermined alleles were excluded from analyses involving APOE genotype, while ambiguously genotyped participants were combined with unambiguous ε4 carriers for analysis. Both assayed SNPs were in Hardy-Weinberg equilibrium ($p > 0.16$). TaqMan SNP Genotyping Assays and TaqMan Genotyping Master Mix (ThermoFisher Scientific, Waltham, Massachusetts) were used to prepare 384-well plates with samples in duplicate. The genotyping PCR reaction was conducted on the QuantStudio 6 Flex Real-Time PCR system (ThermoFisher Scientific, Waltham, Massachusetts) on VIC/FAM genotyping settings for a 5ul reaction and 42 cycles. Data were analyzed using QuantStudio Real-Time PCR Software (ThermoFisher Scientific, Waltham, Massachusetts).

2. Analysis

Analyses were conducted using R and R Studio (RStudio: Integrated development for R, *2015*) and SPSS statistical software (IBM SPSS Statistics (25.*0), 2017*). Stroop effects on reaction time were calculated as the difference in mean response time (RT) between incongruent trials and congruent trials divided by the mean response time of congruent trials, yielding a proportion effect to control for baseline differences in reaction time. Stroop effects on error rate were calculated as the difference in mean error rate between incongruent and congruent trials. These calculations were performed across, and by, the two different levels of block difficulty. Trials with reaction times 200 ms or lower were regarded as spurious responses (e.g. accidental button pressing) and removed from analyses. Participants that were unable to generate any accurate responses across all blocks of a specific difficulty at a given time point were removed from analyses examining Stroop effects.

For Category Switch, switch effects were calculated as the difference in mean response time for switch trials and repeat trials within mixed blocks divided by the mean response time of repeat trials within the mixed blocks to yield a proportion switch RT effect. The mixing effect was calculated as the mean difference in response time between repeat trials in switch blocks and repeat trials in repeat blocks. These calculations were performed across, and by, the two different levels of block difficulty (25% incongruent trials and 75% incongruent trials). Trials with reaction times 200 ms or lower were regarded as spurious responses (e.g. accidental button pressing) and removed from all analyses.

The Keep Track was scored by taking the total number of correct responses across all trials.

To examine differences in cognitive function between the older and younger adults pre-intervention independent samples *t*-tests were conducted, assuming equal variance when deemed appropriate by an F test. Two-way ANOVAs were conducted to examine whether APOE ε4 carrier status moderated any age differences on cognitive function pre-intervention. Mixed design ANCOVAs were constructed to examine differential effects of the MICT+IT vs LICT exercise conditions on changes in each cognitive task, where time (pre-intervention versus post-intervention) was a within subjects independent variable and exercise condition (MICT+IT vs LICT) was a between subjects independent variable. Mixed design ANCOVAs were also constructed to examine whether APOE ε4 carrier status moderated any of the effects of the

interventions on changes in performance on the cognitive tasks. These analyses mirrored those for the prior analyses described above except that the main effect of APOE ε4 carrier status and all possible interactions with time and intervention condition were added to the model. Age and SES were again included as covariates.

3. Results

3.1. Demographics

Enrolled participants included 273 older adults and 44 younger adults living in the Denver-Boulder area. Of those, 62 older adults were excluded after being found to not meet eligibility criteria or choosing to discontinue participation. A total of 211 older adults were randomized to either LICT or MICT+IT (133 Female; 78 Male). 50 older adults were lost to attrition following randomization. A further 19 older adults and one younger adult were excluded due to incomplete genotyping. Final participant flow is described in Fig. 2, whereas participant characteristics by age group and exercise condition are described in Table 1.

3.2. Age differences in and exercise effects on cardiopulmonary fitness

Four older adult participants were excluded from this analysis because they had incomplete VO_2 data ($n = 138$). At baseline, as expected, VO_2 peak was greater in younger adults than older adults [$t(55.057) = 8.036$, $p < 0.001$, Cohen's $d = 1.58$]. For older adults who completed the exercise intervention, there was a significant main effect of time [$F(1,136) = 11.116$, $p < 0.01$, $\eta^2 = 0.076$] such that VO_2 peak increased from pre- to post-exercise (Fig. 3). Finally, there was a significant time X condition interaction [$F(1, 136) = 19.192$, $p < 0.001$, $\eta^2 = 0.124$] such that MICT + IT exercisers had a larger increase in VO_2 peak (1.324 ± 1.991 mL/kg/min) than LICT exercisers (−0.18 ± 2.00 mL/kg/min) (Fig. 2).

Table 1
Participant descriptives.

	Older adults			Younger adults
	MICT + IT	LICT	All	
	78	64	142	44
% APOE ε4 carrier (n homozygous/n heterozygous)	25.6^ (1/19)	12.5 (2/6)	19.7 (3/25)	29.5 (1/12)
% > college education	85.9	82.8	84.5	69.0*
Age	67.49 ± 0.585	68.12 ± 0.722	67.77 ± 0.456	28.86 ± 0.473 ***
% Female	64.1	60.9	62.7	60.5
PAR Days[a]	0.99 ± 1.24	1.72 ± 2.03	1.33 ± 1.69	1.8 ± 1.95
% Income >60,000$/yr	63.0	52.3	58.0	9.1***
% Hispanic/Latino	5.1	4.7	4.9	14.0
% White	93.6	92.2	93.0	67.4***
% Am. Indian/Alaska Native	0	1.6	0.7	0
%Asian	3.8	3.1	3.5	11.6*
%Black or African American	0	0	0	2.3
% More than one race	1.3	1.6	1.4	18.6***

[a] PAR Days is an item from the interviewer-led Physical Activity Recall assessing how many of the previous 7 days the participant engaged in activity that was moderate intensity or greater for at least 30 min.

^ $p < 0.05$ MICT vs. Older LICT.

* $p < 0.05$ vs all Older.

*** $p < 0.001$ vs all Older, survives Sidak correction $ $p < 0.05$ vs LICT.

3.3. Age differences on cognitive tasks

3.3.1. Differences in cognitive function between the older and younger adults pre-intervention

Stroop effects on error rate and RT across block difficulty and in 25%

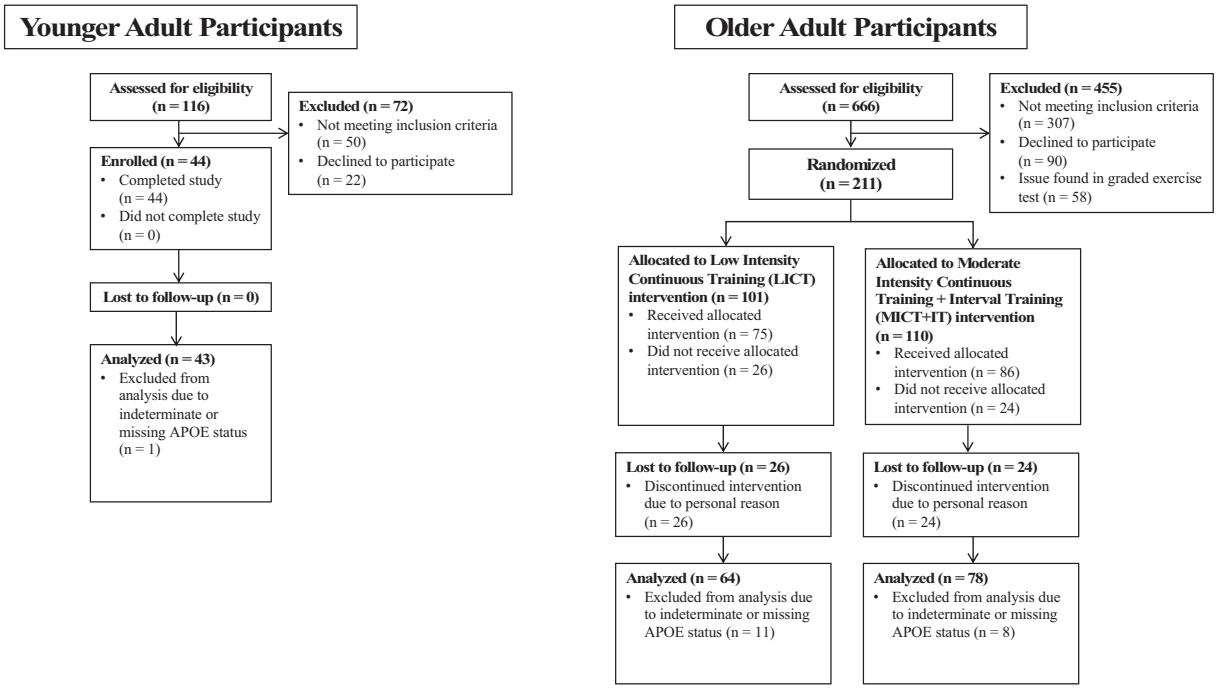

Fig. 2. CONSORT diagram for older and younger study participants.

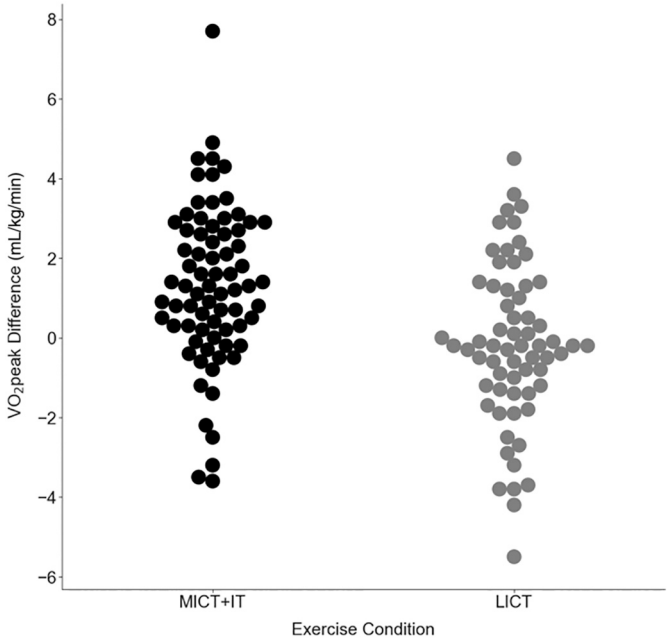

Fig. 3. Change in VO_2peak By Exercise Condition.

and 75% incongruent blocks were larger in older adults than younger adults pre-intervention. There were no differences between older and younger adults in the Category Switch switch effect RT across block difficulty or in 750 ms or 1250 ms blocks pre-intervention. The mixing effect RT was larger in older adults across block difficulty and in both 750 ms and 1250 ms blocks pre-intervention. Younger adults significantly outscored older adults in the Keep Track task. Notably, age differences emerged regardless of task difficulty across domains. Thus, for parsimony, subsequent analyses of the influence of the exercise intervention on task performance, and moderation of those analyses by APOE ε 4 status on the Stroop and Category Switch tasks were conducted only for the overall effects collapsed across difficulty. The Keep Track task also showed significant age differences and was retained as is for subsequent analyses. Results are summarized in Table 2.

3.3.2. *Moderation of age differences in cognitive task performance by APOE ε4 carrier status*

While all age group differences reported above and in Table 2 were replicated with APOE ε 4 carrier status in the model, there were no main effects of APOE ε4 status and it did not moderate any of the age differences on cognitive task performance at baseline. Results are summarized in Table 3.

3.4. *Effects of exercise condition on cognitive task performance*

As age was correlated with performance on each task ($0.085 < r < 0.285$), it was included as a covariate in all analyses. Based on literature suggesting that socioeconomic status (SES) is associated with executive function in the context of aging (Steptoe and Zaninotto, 2020), SES was also included as a covariate. However, given the restricted range for SES in this sample, income equal to or greater than $60,000 per year was coded as 1 and income less than $60,000 was coded as 0. Given the high correlation between SES and education, and because controlling for education did not appreciably change the direction or significance of any effects, the simpler models controlling for only age and income are reported for parsimony. Pre- and post-intervention means by condition and significance tests appear in Table 4.

There were no significant main effects of time or exercise condition, nor was there a condition X time interaction for the Stroop Effect on RT. Significant main effects of time showed that the Stroop effect on error decreased (i.e., improved) from pre- to post-intervention, but there was no condition X time interaction. Significant main effects of time showed that the Category Switch switching effect RT decreased (i.e., improved) from pre- to post-intervention, but no condition X time interaction was found. No effects of time or condition were found for Category Switch mixing effect RT.

A trending main effect of condition was found [$F(1, 264) = 2.982$, $p = 0.085$, $\eta^2 = 0.011$] for the Keep Track task that was modified by a significant time X condition interaction. Keep Track scores trended toward increasing (i.e., improving) from pre- to post-intervention in MICT+IT exercisers [$t(261) = 2.427$, $p = 0.072$, Tukey HSD] but were unchanged in LICT exercisers [$p = 0.9743$, Tukey HSD].

Table 2
Cognitive performance at baseline for older adults compared to younger adults.

	Mean ± St. dev. (Younger)	Mean ± St. dev. (Older)	Cohen's d	t	p
Stroop RT (ms)	0.103 ± 0.072	0.142 ± 0.0769	0.524	2.879	p < 0.01
Stroop RT 25%	0.141 ± 0.089	0.178 ± 0.106	0.378	1.995	p < 0.05
Stroop RT 75%	0.091 ± 0.070	0.126 ± 0.076	0.479	2.668	p < 0.01
Stroop error (%)	0.022 ± 0.036	0.090 ± 0.111	0.824	6.121	p < 0.001[a]
Stroop error 25%	0.040 ± 0.064	0.148 ± 0.161	0.882	6.306	p < 0.001[a]
Stroop error 75%	0.011 ± 0.044	0.070 ± 0.114	0.683	4.894	p < 0.001[a]
Category switch RT (ms)	0.161 ± 0.155	0.126 ± 0.140	0.237	1.372	p = 0.172
Category switch RT 750 ms	0.145 ± 0.165	0.190 ± 0.168	0.271	1.274	p = 0.127
Category switch RT 1250 ms	0.110 ± 0.159	0.125 ± 0.181	0.088	0.852	p = 0.395
Category switch mixing RT	194.218 ± 151.235	334.502 ± 202.135	0.786	5.397	p < 0.001[a]
Category switch mixing RT 750 ms	225.784 ± 185.567	398.280 ± 260.991	0.762	4.821	p < 0.001[a]
Category switch mixing RT 1250 ms	163.568 ± 148.952	310.213 ± 219.351	0.782	5.016	p < 0.001[a]
Keep track (n)	22.61 ± 3.64	20.60 ± 2.29	0.661	4.302	p < 0.05

[a] Survives Sidak correction.

3.5. *Moderation of exercise effects on cognitive task performance by APOE ε4 carrier status*

There were no significant main effects of condition, time, or APOE ε4 carrier status, nor were any significant interactions noted for the Stroop Effect on RT. As with the prior analysis of the Stroop effect on error, there were significant main effects of time [$F(1, 256) = 9.381$, $p < 0.01$, $\eta^2 = 0.031$] showing that participants in both conditions improved after exercise. Additionally, a time X condition X APOE status interaction was found [$F(1, 256) = 4.2455$, $p < 0.05$, $\eta^2 = 0.014$], such that APOE ε4 carriers assigned to the MICT+IT exercise condition performed worse in terms of the Stroop effect on error after the exercise intervention, whereas all other participants improved (Fig. 4).

Again, significant main effects of time [$F(1, 274) = 4.442$, $p < 0.05$, $\eta^2 = 0.020$] were found for Category Switch such that the switching effect RT decreased from pre- to post-intervention. A trending main effect of APOE ε4 carrier status was found [$F(1, 274) = 2.763$, $p = 0.098$, $\eta^2 = 0.007$] such that switching effect RT was shorter (i.e., better) in ε4 carriers than non-ε4 carriers. Trending main effects of time [$F(1, 274) = 2.806$, $p = 0.095$, $\eta^2 = 0.010$] were again noted for Category Switch mixing RT, and there was also a trending main effect of APOE status [F

Table 3
APOE ε4 moderation of age effects on cognitive task performance.

	Younger (Mean ± St.dev)		Older (Mean ± St.dev)		Age		APOE		APOE x age	
	ε4	Non-ε4	ε4	Non-ε4	p	η^2	p	η^2	p	η^2
Stroop RT	0.123 ± 0.100	0.096 ± 0.061	0.141 ± 0.070	0.142 ± 0.079	0.005	0.047	0.644	0.001	0.38	0.004
Stroop RT 25%	0.179 ± 0.089	0.129 ± 0.086	0.163 ± 0.106	0.181 ± 0.106	0.047	0.022	0.948	0.024	0.108	0.015
Stroop RT 75%	0.119 ± 0.068	0.081 ± 0.069	0.137 ± 0.072	0.124 ± 0.077	0.008	0.042	0.156	0.011	0.426	0.004
Stroop error	0.025 ± 0.036	0.022 ± 0.037	0.089 ± 0.100	0.091 ± 0.113	0.0001[a]	0.008	0.97	0.000	0.9	0.000
Stroop error 25%	0.015 ± 0.033	0.048 ± 0.071	0.141 ± 0.155	0.149 ± 0.163	0.00004[a]	0.093	0.568	0.002	0.678	0.001
Stroop error 75%	0.038 ± 0.054	0.005 ± 0.039	0.075 ± 0.118	0.068 ± 0.113	0.0015	0.059	0.555	0.002	0.715	0.001
Category switch RT	0.100 ± 0.100	0.182 ± 0.166	0.105 ± 0.142	0.131 ± 0.140	0.17	0.012	0.102	0.014	0.317	0.005
Category switch RT 750 ms	0.113 ± 0.147	0.216 ± 0.170	0.137 ± 0.137	0.148 ± 0.172	0.126	0.014	0.236	0.008	0.173	0.010
Category switch RT 1250 ms	0.086 ± 0.096	0.151 ± 0.200	0.075 ± 0.183	0.119 ± 0.152	0.394	0.005	0.0907	0.016	0.753	0.000
Category switch mixing RT	225.456 ± 168.102	183.478 ± 146.311	400.149 ± 315.685	343.200 ± 179.857	0.000008[a]	0.107	0.146	0.010	0.855	0.000
Category switch mixing RT 750 ms	268.932 ± 190.525	210.952 ± 184.543	468.616 ± 378.260	381.004 ± 221.991	0.00008[a]	0.086	0.0731	0.016	0.7672	0.000
Category switch mixing RT 1250 ms	183.402 ± 171.961	156.750 ± 142.593	333.260 ± 305.777	304.552 ± 193.734	0.000066[a]	0.086	0.45	0.003	0.981	0.000
Keep track	23.818 ± 1.888	22.219 ± 2.338	20.815 ± 3.803	20.351 ± 3.612	0.0003[a]	0.068	0.211	0.008	0.413	0.003

[a] survives Sidak correction.

Table 4
Cognitive performance from baseline to follow-up by condition.

Task	Means by condition		Effect of time		Time x condition	
	MICT+IT	LICT	F	η^2	F	η^2
Stroop effect on RT						
Pre-intervention	0.129 ± 0.065	0.152 ± 0.085	0.020	0.000	1.374	0.005
Post-intervention	0.138 ± 0.070	0.141 ± 0.072				
Stroop effect on error						
Pre-intervention	0.102 ± 0.114	0.081 ± 0.107	8.789**	0.032	0.036	0.000
Post-intervention	0.066 ± 0.087	0.050 ± 0.066				
Cat.switch switching effect RT						
Pre-intervention	0.142 ± 0.148	0.113 ± 0.133	5.632*	0.021	1.340	0.005
Post-intervention	0.089 ± 0.104	0.095 ± 0.121				
Cat. switch mixing effect RT						
Pre-intervention	351.909 ± 194.112	356.496 ± 229.185	2.722	0.010	0.032	0.000
Post-intervention	316.743 ± 207.516	312.798 ± 173.492				
Keep track						
Pre-intervention	19.59 ± 4.26	21.18 ± 2.84	2.367	0.006	4.268*	0.014
Post-Intervention	21.00 ± 3.23	20.93 ± 3.26				

* $p < 0.05$.

** $p < 0.001$, survives Sidak correction.

(1, 274) = 3.149, $p = 0.077$, $\eta^2 = 0.019$]. In contrast to the switching effect RT, the mixing effect RT was longer (i.e., worse) in ε4 carriers than non-carriers. Finally, the condition X time interaction from the prior Keep Track analysis decreased to a trend level once APOE status was included in the model [F(1, 260) = 2.907, $p = 0.089$, $\eta^2 = 0.014$], though the direction of the interaction was in the same pattern. No effects involving APOE status were found.

Finally, we felt it was warranted to conduct a sensitivity analysis to see whether cardiopulmonary fitness itself was related to task performance. We first looked at correlations between VO_2peak and cognitive task performance in the younger sample and found no evidence of significant relationships between VO_2peak and performance on any of the tasks. In contrast, for older adults, VO_2peak was negatively associated with Stroop errors overall ($r = -0.241$, $p < 0.01$) and for both levels of difficulty ($r_{25\%} = -0.193$, $p < 0.05$, $r_{75\%} = -0.205$, $p < 0.05$). There was no association between VO_2peak and performance on either of the other tasks nor on Stroop RT.

To explore whether *increases* in cardiovascular fitness were associated with *improvements* in cognitive performance, we then looked correlations between change in VO_2peak and change in cognitive task performance among older adults. Here there was only one significant relationship, such that increases in VO_2peak were significantly associated with a decrease in Stroop errors, but only in the 75% incongruent blocks of that task ($r = -0.227$, $p < 0.01$). In sum, while there is some evidence that cardiovascular fitness is positive associated with the ability to correctly inhibit a prepotent response among older adults as measured in the Stroop task, that association did not extend to measures of the shifting or updating aspects of EF.

4. Discussion

In this study of aerobic fitness and cognitive performance, it was hypothesized that older adults would demonstrate poorer cognitive performance and cardiovascular health than younger adults before older adults initiated 16 weeks of fitness training, older adults in both exercise conditions would improve on measures of cognitive performance after participation the 16-week intervention, that there might be stronger effects on one condition versus the other, and that there would be an interaction between ε4 allele carrier status and exercise condition among older adults. Despite being relatively closely matched in terms of current physical activity levels, older adults generally had worse cardiovascular fitness and cognitive performance than younger adults at baseline, consistent with previous literature demonstrating the effect of aging on cognition (Fjell et al., 2017; Grady, 2012; Salthouse, 2019). One exception to this was Category Switch switch effects, where no age differences were found. APOE ε4 allele carrier status did not moderate any of the age group differences on the cognitive tasks.

Following the 16-week intervention, older adults in both conditions significantly improved in cardiovascular fitness, though MICT + IT exercisers had a larger increase in VO_2peak than LICT exercisers. Those in the MICT+IT condition improved more than those in the LICT condition, and there were few group differences. These results are consistent with previous work supporting that exercise overall is likely beneficial for

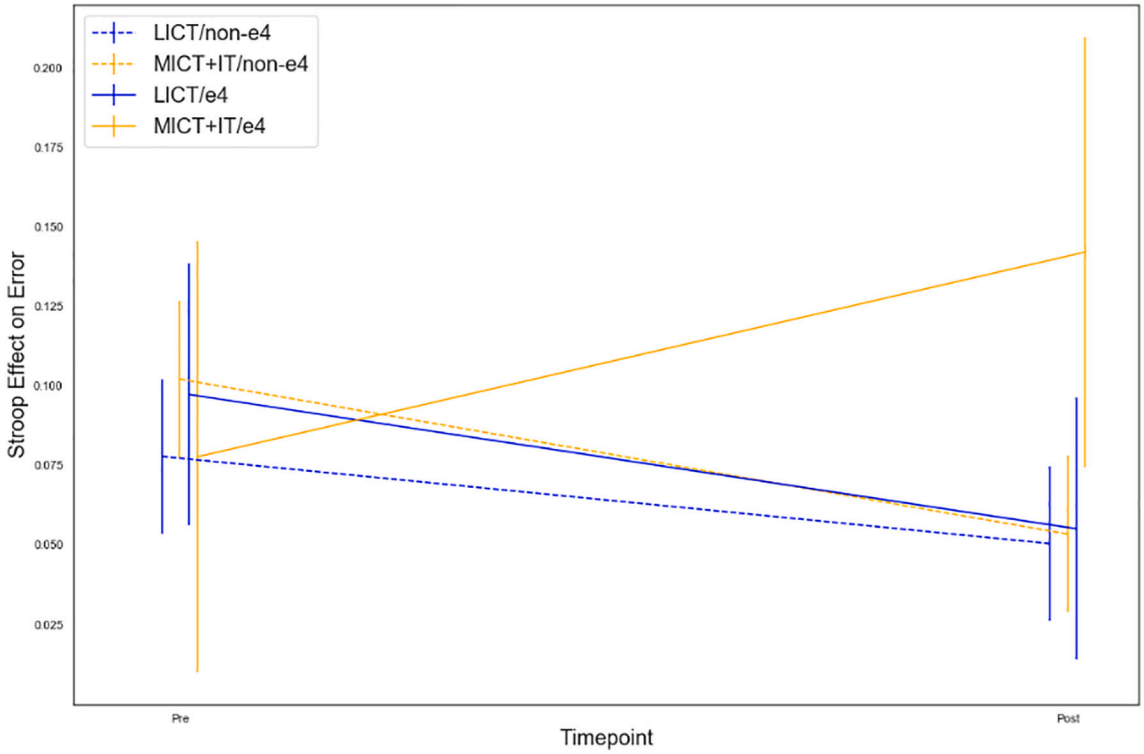

Fig. 4. Stroop effect on error from baseline to follow-up by condition and APOE status.

cognitive performance (Badenhop et al., 1983; Berryman et al., 2014; Fu et al., 2013), but they do not shed light on any particular mechanistic hypothesis. Authors of another dose-response trial of the effects of aerobic exercise on cognition have suggested that an individualized response to fitness as quantified by outcomes such as VO_2peak may be "a better predictor of cognitive gains than exercise dose" (Vidoni et al., 2015). Given this suggestion and the fact that our study yielded few significant results according to group, we chose to make a final analysis of the relationship between VO_2peak and cognitive task performance. However, few significant results were obtained from these analyses as well. Given that our analysis of the effect of VO_2peak on cognitive performance was only significant for the Stroop task with 75% incongruent blocks, it may be that the mechanism of the effects of physical activity on cognitive task performance may be either tangentially related or even unrelated to cardiovascular fitness. Our findings are consistent with a recently published trial that showed similar trending improvements in executive functioning in older adults following twelve weeks of moderate intensity versus twelve weeks of high intensity interval training (Kovacevic et al., 2020), suggesting a diminished role of intensity in improving executive functioning.

Finally, it was hypothesized that older adults in the MICT+IT intervention who were also APOE ε4 allele carriers would demonstrate more improved cognitive performance than other participants at follow-up. However, exercise did *not* improve the Stroop effect on error for these individuals, and their Stroop effect on error even increased after the exercise intervention. This result is interesting both because it demonstrates a differential negative effect for inhibition only, and for APOE ε4 allele carriers only. Pre-clinical and human studies have both supported (Chaudhari et al., 2016; Head et al., 2012; Soto et al., 2015) and refuted (Brown et al., 2013; Obisesan et al., 2012; Podewils et al., 2005) a relationship between APOE, exercise, and cognition, in that some studies suggest more benefits from exercise, some suggest less benefit, and some do not support a benefit at all . In the case of this study where Stroop effect on error increased after the exercise intervention for APOE ε4 carriers, we speculate that perhaps neuronal injury in the prefrontal brain region may already be present as a result of possible amyloid-beta (Aβ)- or tau protein accumulation, which is associated with the increased risk of being an ε4 allele carrier. In other words, since neurofibrillary tangles (NFTs) and Aβ plaques are known to accumulate years before symptoms of cognitive decline emerge (Dubois et al., 2016; Jack et al., 2013) and ε4 allele carriers are at a higher risk for this type of neuropathology (Ohm et al., 1995), it is possible that these injuries may further limit benefits from exercise to the prefrontal cortex, a brain region central to response inhibition (Blasi et al., 2006). It should be noted though, that this is a hypothesis which is not currently explored by the literature, and further investigation into this possible mechanism would be of benefit to the field. Overall, while the benefit of exercise to cognition is supported by these results, it is unclear if there are benefits to executive function unique to a particular intensity level of physical activity.

More broadly, the moderating effects of APOE status on exercise in the Stroop task versus the null results demonstrated for the Category Switch and Keep Track tasks provides further support for the heterogeneous nature of executive function (Miyake and Friedman, 2012). Normal aging may exert heterogeneous effects on executive function, and recent meta-analytic findings suggest that Stroop performance seems to be especially impaired in older adults (Maldonado et al., 2020). Indeed, in the current study, age differences at baseline were strongest on the Stroop task, and Stroop error rate showed the largest overall change in performance following the exercise interventions. Notably, our results diverge from those of Sanders et al. (2020), who demonstrated that the APOE ε4 allele did not significantly moderate the effect of low vs. high intensity exercise on cognitive performance in participants with dementia, including on the Stroop task (Sanders et al., 2020). However, in contrast to Sanders et al., our older participants were all cognitively "normal" (i.e. lacked a clinical status of dementia), and completed a longer (16 weeks as compared to 12 weeks) and more intense exercise intervention. Another possible reason for finding an association with the Stroop task is that this task has been demonstrated to engage a variety of cognitive control mechanisms, each of which relies on portions of prefrontal cortex (Banich, 2019), a brain region known to be differentially affected in aging. While it is unclear as to why

the Stroop task, *in particular*, showed a condition x time x APOE ε4 carrier status interaction in the current study, we emphasize that our findings should be replicated and interpreted with caution given low sample sizes in the APOE ε4 allele group.

This study presents some notable limitations that should be considered. The participants in this study comprised a healthy sample who were not necessarily at increased risk for Alzheimer's Disease nor were they actively experiencing cognitive decline. The study also lacked a no-exercise control group matched for study participation and contact with researchers with which to compare the cognitive effects of low- and moderate-intensity aerobic training. Despite our attempts to match the older and younger groups, the younger group was slightly more physically active and was significantly more diverse than the older group. Further, study recruitment occurred in the Denver-Boulder area, which has been noted as a particularly "healthy" region of the U.S. (Riffkin, 2014). As a result, the inclusion criteria were more generous than previous work, in that participants could have already been exercising before they started the study (i.e., someone could have already been exercising for 50 min a week when they began the intervention). This may impact both the size and direction of effects of exercise on cognition and may also impact generalizability to other geographical regions.

Several strengths also underly the results of this study. Whereas previous work has primarily focused on a brain volume, but not cognitive measures of executive function (Varma et al., 2015), or a *single aerobic exercise group* versus resistance training or stretching groups (Brinke et al., 2015) the present study's inclusion of *both exercise groups* (low-intensity and moderate-intensity with higher intensity interval training) allows for greater specificity in understanding the benefits of exercise. Further, the inclusion of APOE ε4 carrier status, especially given the use of a non-clinical sample without increased risk for cognitive impairment, is also a strength given that research on cognitive impairment is increasingly focused on improving and maintaining cognitive performance among asymptomatic/prodromal individuals.

5. Conclusions

The results of this study support previous work suggesting exercise is broadly beneficial to cognitive performance, but it does not support any particular hypotheses of the mechanisms of action of exercise effects on cognition. APOE ε4 allele carrier status did not moderate any of the age group differences on the cognitive tasks, and while there were significant effects of time showing that participants in both conditions had improved Stroop effect on error, exercise did *not* improve the Stroop effect on error for APOE ε4 allele carriers. In fact, Stroop effect on error increased after the exercise intervention for APOE ε4 allele carriers in the MICT-IT condition, demonstrating a differential negative effect for inhibition only, and for APOE ε4 allele carriers only. Further work is needed to examine the relationship between exercise intensity, cognition, and the moderating role of APOE ε4 carrier status, potentially leveraging (VO_2peak) as an individual-level predictor of cognitive performance.

CRediT authorship contribution statement

RMW: Conceptualization, Data Curation, Software, Writing – original draft, review, & editing

BAM: Investigation, Formal Analysis, Visualization, Data Curation, Validation, Visualization, Writing – original draft, review & editing

GRG: Investigation, Data curation, Validation, Visualization, Resources, Visualization, Software, Software, Writing – original draft, review & editing

RW: Formal Analysis, Writing – original draft, review & editing

JAH: Methodology, Resources, Supervision, Writing – original draft, review & editing

MTB: Methodology, Resources, Supervision, Writing – original draft, review & editing

ADB: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, review, & editing

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References

American College of Sports Medicine, 2013. ACSM's Guidelines for Exercise Testing and Prescription, 9th ed. Lippincott Williams & Wilkins, Philadelphia, PA.

Badenhop, D.T., Cleary, P.A., Schaal, S.F., Fox, E.L., Bartels, R.L., 1983. Physiological adjustments to higher- or lower-intensity exercise in elders. Med. Sci. Sports Exerc. 15 (6), 496–502 https://doi.org/10.1249/00005768-198315060-00010.

Baggetta, P., Alexander, P.A., 2016. Conceptualization and operationalization of executive function. Mind Brain Educ. 10 (1), 10–33. https://doi.org/10.1111/mbe.12100.

Banich, M.T., 2009. Executive function: the search for an integrated account. Curr. Dir. Psychol. Sci. 18 (2), 89–94. https://doi.org/10.1111/j.1467-8721.2009.01615.x.

Banich, M.T., 2019. The Stroop effect occurs at multiple points along a cascade of control: evidence from cognitive neuroscience approaches. Front. Psychol. 10.

Barnes, D.E., Yaffe, K., 2011. The projected impact of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 10 (9), 819–828. https://doi.org/10.1016/S1474-4422(11)70072-2.

Berryman, N., Bherer, L., Nadeau, S., Lauzière, S., Lehr, L., Bobeuf, F., Lussier, M., Kergoat, M.J., Tuong, T., Vu, M., Bosquet, L., Berryman, N., Bosquet, L., Bherer, L., Lehr, L., Bobeuf, F., Lussier, M., Kergoat, M.J., Vu, T.T.M., Lauzière, S., 2014. Multiple roads lead to Rome: combined high-intensity aerobic and strength training vs. gross motor activities leads to equivalent improvement in executive functions in a cohort of healthy older adults. Age 36 (9710). https://doi.org/10.1007/s11357-014-9710-8.

Blasi, G., Goldberg, T.E., Weickert, T., Das, S., Kohn, P., Zoltick, B., Bertolino, A., Callicott, J.H., Weinberger, D.R., Mattay, V.S., 2006. Brain regions underlying response inhibition and interference monitoring and suppression. Eur. J. Neurosci. 23 (6), 1658–1664. https://doi.org/10.1111/j.1460-9568.2006.04680.x.

Borg, G.A.V., 1970. Perceived exertion as an indicator of somatic stress. Scand. J. Rehabil. Med. 2, 92–98.

Braver, T.S., Barch, D.M., 2002. A theory of cognitive control, aging cognition, and neuromodulation. Neurosci. Biobehav. Rev. 26 (7), 809–817. https://doi.org/10.1016/S0149-7634(02)00067-2.

Brinke, L.F. Ten, Bolandzadeh, N., Nagamatsu, L.S., Hsu, C.L., Davis, J.C., Miran-Khan, K., Liu-Ambrose, T., 2015. Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial. Br. J. Sports Med. 49 (4), 248–254. https://doi.org/10.1136/BJSPORTS-2013-093184.

Brown, B.M., Peiffer, J.J., Taddei, K., Lui, J.K., Laws, S.M., Gupta, V.B., Taddei, T., Ward, V.K., Rodrigues, M.A., Burnham, S., Rainey-Smith, S.R., Villemagne, V.L., Bush, A., Ellis, K.A., Masters, C.L., Ames, D., Macaulay, S.L., Szoeke, C., Rowe, C.C., Martins, R.N., 2013. Physical activity and amyloid-β plasma and brain levels: results from the Australian imaging, biomarkers and lifestyle study of ageing. Mol. Psychiatry 18 (8), 875–881. https://doi.org/10.1038/mp.2012.107.

Buchman, A.S., Boyle, P.A., Yu, L., Shah, R.C., Wilson, R.S., Bennett, D.A., 2012. Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology 78 (17), 1323–1329. https://doi.org/10.1212/WNL.0b013e3182535d35.

Bugg, J.M., Bugg, J.M., Goate, A.M., Fagan, A.M., Mintun, M.A., Benzinger, T., Holtzman, D.M., Morris, J.C., 2012. Exercise engagement as a moderator of the effects of <emph type="ital">APOE</emph> genotype on amyloid deposition. Arch. Neurol. 69 (5), 636. https://doi.org/10.1001/archneurol.2011.845.

Bunce, D., Murden, F., 2006. Age, aerobic fitness, executive function, and episodic memory. Eur. J. Cogn. Psychol. 18 (2), 221–233. https://doi.org/10.1080/09541440540000185.

Cade, W.T., Bohnert, K.L., Reeds, D.N., Peterson, L.R., Bittel, A.J., Bashir, A., Byrne, B.J., Taylor, C.L., 2018. Peak oxygen uptake (VO2peak) across childhood, adolescence and young adulthood in Barth syndrome: data from cross-sectional and longitudinal studies. PLoS One 13 (5), 1–12. https://doi.org/10.1371/journal.pone.0197776.

Chaudhari, K., Wong, J.M., Vann, P.H., Sumien, N., 2016. Exercise, but not antioxidants, reversed ApoE4-associated motor impairments in adult GFAP-ApoE mice. Behav. Brain Res. 305, 37–45. https://doi.org/10.1016/J.BBR.2016.02.014.

Chun, M.M., Golomb, J.D., Turk-Browne, N.B., 2011. A taxonomy of external and internal attention. Annu. Rev. Psychol. 62 (1), 73–101. https://doi.org/10.1146/annurev.psych.093008.100427.

Colcombe, S., Kramer, A.F., 2003. Fitness effects on the cognitive function of older adults. Psychol. Sci. 14, 125. https://doi.org/10.1111/1467-9280.t01-1-01430.

Colcombe, S.J., Erickson, K.I., Scalf, P.E., Kim, J.S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D.X., Hu, L., Kramer, A.F., 2006. Aerobic exercise training increases brain volume in aging humans. J. Gerontol. Ser. A Biol. Med. Sci. 61 (11), 1166–1170. https://doi.org/10.1093/gerona/61.11.1166.

Courtney-Long, E.A., Carroll, D.D., Zhang, Q.C., Stevens, A.C., Griffin-Blake, S., Armour, B.S., Campbell, V.A., 2015. Prevalence of disability and disability type among adults–United States, 2013. MMWR Morb. Mortal. Wkly Rep. 64 (29), 777–783. https://doi.org/10.15585/mmwr.mm6429a2.

Dobriansky, P.J., Suzman, R.M., Hodes, R.J., 2007. Why Population Aging Matters - A Global Perspective. US Department of State, pp. 1–32 doi:0 7 - 6 1 3 4.

Dubois, B., Hampel, H., Feldman, H.H., Scheltens, P., Aisen, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Blennow, K., Broich, K., Cavedo, E., Crutch, S., Dartigues, J.F., Duyckaerts, C., Epelbaum, S., Frisoni, G.B., Gauthier, S., Genthon, R., Jack, C.R., 2016. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimer's and Dementia 12 (3). https://doi.org/10.1016/j.jalz.2016.02.002.

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E., Kramer, A.F., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. U. S. A. 108 (7), 3017–3022. https://doi.org/10.1073/pnas.1015950108.

Etnier, J.L., Caselli, R.J., Reiman, E.M., Alexander, G.E., Sibley, B.A., Tessier, D., Mclemore, E.C., 2007. Cognitive performance in older women relative to ApoE-ε4 genotype and aerobic fitness. Med. Sci. Sports Exerc. 39 (1), 199–207. https://doi.org/10.1249/01.mss.0000239399.85955.5e.

Farlow, M.R., He, Y., Tekin, S., Xu, J., Lane, R., Charles, H.C., 2004. Impact of APOE in mild cognitive impairment. Neurology 63 (10), 1898–1901. https://doi.org/10.1212/01.WNL.0000144279.21502.B7.

Fenesi, B., Fang, H., Kovacevic, A., Oremus, M., Raina, P., Heisz, J.J., 2017. Physical exercise moderates the relationship of Apolipoprotein E (APOE) genotype and dementia risk: a population-based study. J. Alzheimers Dis. 56 (1), 297–303. https://doi.org/10.3233/JAD-160424.

Fjell, A.M., Sneve, M.H., Grydeland, H., Storsve, A.B., Walhovd, K.B., 2017. The disconnected brain and executive function decline in aging. Cereb. Cortex 27 (3), 2303–2317. https://doi.org/10.1093/cercor/bhw082.

Friedman, N.P., Miyake, A., Corley, R.P., Young, S.E., DeFries, J.C., Hewitt, J.K., 2006. Not all executive functions are related to intelligence. Psychol. Sci. 17 (2), 172–179. https://doi.org/10.1111/j.1467-9280.2006.01681.x.

Fu, T.C., Wang, C.H., Lin, P.S., Hsu, C.C., Cherng, W.J., Huang, S.C., Liu, M.H., Chiang, C. L., Wang, J.S., 2013. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. Int. J. Cardiol. 167 (1), 41–50. https://doi.org/10.1016/j.ijcard.2011.11.086.

Gibson, J.J., 1941. A critical review of the concept of set in contemporary experimental psychology. Psychol. Bull. 38 (9), 781–817. https://doi.org/10.1037/h0055307.

Golden, C.J., Freshwater, S.M., 1978. Stroop Color and Word Test.

Grady, C., 2012. The cognitive neuroscience of ageing. Nat. Rev. Neurosci. 13 (7), 491–505. Nature Publishing Group. https://doi.org/10.1038/nrn3256.

Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. 42 (2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010.

Harris, S.E., Deary, I.J., 2011. The genetics of cognitive ability and cognitive ageing in healthy older people. Trends Cogn. Sci. 15 (9), 388–394. https://doi.org/10.1016/j.tics.2011.07.004.

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: a review and a new view. In Psychology of Learning and Motivation - Advances in Research and Theory (Vol. 22, Issue C, pp. 193–225). doi:https://doi.org/10.1016/S0079-7421(08)60041-9.

Hayes, S.M., Forman, D.E., Verfaellie, M., 2016. Cardiorespiratory fitness is associated with cognitive performance in older but not younger adults. J. Gerontol. B Psychol. Sci. Soc. Sci. 71 (3), 474–482. https://doi.org/10.1093/geronb/gbu167.

He, W., Goodkind, D., & Kowal, P. (2016). An aging world: 2015. In International Population Reports (Issue March P95/16-1).

Head, D., Bugg, J.M., Goate, A.M., Fagan, A.M., Mintun, M.A., Benzinger, T., Holtzman, D.M., Morris, J.C., 2012. Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. Arch. Neurol. 69 (5), 636–643. https://doi.org/10.1001/archneurol.2011.845.

Hedden, T., Gabrieli, J.D.E., 2004. Insights into the ageing mind: a view from cognitive neuroscience. Nat. Rev. Neurosci. 5 (2), 87–96. https://doi.org/10.1038/nrn1323.

Hernández, S.S.S., Sandreschi, P.F., Silva, F.C., Arancibia, B.A.V., Silva, R., Gutierres, P.J. B., Andrade, A., 2015. What are the benefits of exercise for Alzheimer ' s disease ? A systematic review of the past 10 years. J. Aging Phys. Act. 23, 659–668.

Heyn, P., Abreu, B.C., Ottenbacher, K.J., 2004. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis11No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon th. Arch. Phys. Med. Rehabil. 85 (10), 1694–1704. https://doi.org/10.1016/j.apmr.2004.03.019.

Hutter, R.R.C., Wood, C., Dodd, G.F., 2012. Resolving conflicting social categories: the role of age-related executive ability. Br. J. Psychol. 103 (1), 28–43. https://doi.org/10.1111/j.2044-8295.2011.02037.x.

IBM SPSS Statistics (25.0), 2017. IBM Corp.

Jack, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12 (2), 207–216. https://doi.org/10.1016/S1474-4422(12)70291-0.

Jersild, A.T., 1927. Mental set and shift. In: Archives of Psychology.

Kovacevic, A., Fenesi, B., Paolucci, E., Heisz, J.J., 2020. The effects of aerobic exercise intensity on memory in older adults. Appl. Physiol. Nutr. Metab. 45 (6), 591–600. https://doi.org/10.1139/apnm-2019-0495.

Kramer, A.F., Bherer, L., Colcombe, S.J., Dong, W., Greenough, W.T., 2004. Environmental influences on cognitive and brain plasticity during aging. J. Gerontol. Ser. A Biol. Med. Sci. 59 (9), M940–M957. https://doi.org/10.1093/gerona/59.9.M940.

Kramer, Arthur F., Erickson, K.I., 2007. Effects of physical activity on cognition, well-being, and brain: human interventions. Alzheimers Dement. 3 (2 Suppl), S45–S51. https://doi.org/10.1016/j.jalz.2007.01.008.

Kramer, Arthur F., Willis, S.L., 2002. Enhancing the cognitive vitality of older adults. Curr. Dir. Psychol. Sci. 11 (5), 173–177. https://doi.org/10.1111/1467-8721.00194.

Ku, P.-W., Steptoe, A., Chen, L.-J., 2017. Prospective associations of exercise and depressive symptoms in older adults: the role of apolipoprotein E4. Qual. Life Res. 26 (7), 1799–1808. https://doi.org/10.1007/s11136-017-1537-1.

Lautenschlager, N.T., Cox, K.L., Flicker, L., Foster, J.K., Van Bockxmeer, F.M., Xiao, J., Greenop, K.R., Almeida, O.P., 2008. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 300 (9), 1027–1037. https://doi.org/10.1001/jama.300.9.1027.

Liu, C.-C., Liu, C.-C., Kanekiyo, T., Xu, H., Bu, G., 2013. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat. Rev. Neurol. 9 (2), 106–118. https://doi.org/10.1038/nrneurol.2012.263.

Ludyga, S., Gerber, M., Brand, S., Holsboer-Trachsler, E., Pühse, U., 2016. Acute effects of moderate aerobic exercise on specific aspects of executive function in different age and fitness groups: a meta-analysis. Psychophysiology 53 (11), 1611–1626. https://doi.org/10.1111/psyp.12736.

Maldonado, T., Orr, J.M., Goen, J.R.M., Bernard, J.A., 2020. Age differences in the subcomponents of executive functioning. J. Gerontol. Psychol. Sci. 75 (6), e31–e55.

Mccabe, D. P., Roediger, H. L., McDaniel, M. A., Balota, D. A., & Hambrick, D. Z. (2010). The relationship between working memory capacity and executive function. Neuropsychology, 24(2), 222–243. doi:10.1037/a0017619.

Mekari, S., Neyedli, H.F., Fraser, S., O'Brien, M.W., Martins, R., Evans, K., Earle, M., Aucoin, R., Chiekwe, J., Hollohan, Q., Kimmerly, D.S., Dupuy, O., 2020. High-intensity interval training improves cognitive flexibility in older adults. Brain Sci. 10 (11), 796. https://doi.org/10.3390/brainsci10110796.

Miyake, A., Friedman, N.P., 2012. The nature and organization of individual differences in executive functions: four general conclusions. Curr. Dir. Psychol. Sci. 21 (1), 8–14. https://doi.org/10.1177/0963721411429458.

Miyake, Akira, Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cogn. Psychol. 41 (1), 49–100. https://doi.org/10.1006/cogp.1999.0734.

Moreau, D., Chou, E., 2019. The acute effect of high-intensity exercise on executive function: a meta-analysis. Perspect. Psychol. Sci. 14 (5), 734–764. https://doi.org/10.1177/1745691619850568.

Muscari, A., Giannoni, C., Pierpaoli, L., Berzigotti, A., Maietta, P., Foschi, E., Ravaioli, C., Poggiopollini, G., Bianchi, G., Magalotti, D., Tentoni, C., Zoli, M., 2009. Chronic endurance exercise training prevents aging-related cognitive decline in healthy older adults: a randomized controlled trial. Int. J. Geriatr. Psychiatry 25 (10), 1055–1064. https://doi.org/10.1002/gps.2462.

Obisesan, T.O., Umar, N., Paluvoi, N., Gillum, R.F., 2012. Association of leisure-time physical activity with cognition by apolipoprotein-E genotype in persons aged 60 years and over: the National Health and Nutrition Examination Survey (NHANES-III). Clin. Interv. Aging 7, 35–43. https://doi.org/10.2147/CIA.S26794.

Ohm, T.G., Kirca, M., Bohl, J., Scharnagl, H., Groß, W., März, W., 1995. Apolipoprotein E polymorphism influences not only cerebral senile plaque load but also Alzheimer-type neurofibrillary tangle formation. Neuroscience 66 (3), 583–587. https://doi.org/10.1016/0306-4522(94)00596-W.

Paillard, T., Rolland, Y., de Souto Barreto, P., 2015. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: a narrative review. J. Clin. Neurol. (Seoul, Korea) 11 (3), 212–219. https://doi.org/10.3988/jcn.2015.11.3.212.

Pfeiffer, E., 1975. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients†. J. Am. Geriatr. Soc. 23 (10), 433–441. https://doi.org/10.1111/j.1532-5415.1975.tb00927.x.

Physical Activity Guidelines for Americans, 53(4), 2008. The Oklahoma Nurse, p. 25. https://doi.org/10.1249/fit.0000000000000472.

Podewils, L.J., Guallar, E., Kuller, L.H., Fried, L.P., Lopez, O.L., Carlson, M., Lyketsos, C. G., 2005. Physical activity, APOE genotype, and dementia risk: findings from the cardiovascular health cognition study. Am. J. Epidemiol. 161 (7), 639–651. https://doi.org/10.1093/aje/kwi092.

Pushkar, D., Basevitz, P., Arbuckle, T., Nohara-LeClair, M., Lapidus, S., Peled, M., 2000. Social behavior and off-target verbosity in elderly people. Psychol. Aging 15 (2), 361–374. https://doi.org/10.1037//0882-7974.15.2.361.

Reas, E.T., Laughlin, G.A., Bergstrom, J., Kritz-Silverstein, D., Barrett-Connor, E., McEvoy, L.K., 2019. Effects of APOE on cognitive aging in community-dwelling older adults. Neuropsychology 33 (3), 406–416. https://doi.org/10.1037/neu0000501.

Riffkin, R., 2014. Boulder, Colo., residents still least likely to be obese. Available at: https://news.gallup.com/poll/168230/boulder-colo-residents-least-likely-obese.aspx?ref=image. (Accessed 5 September 2019).

Rowe, J.W., Fulmer, T., Fried, L., 2016. Preparing for better health and health care for an aging population. JAMA 316 (16), 1643–1644. American Medical Association. https://doi.org/10.1001/jama.2016.12335.

RStudio: Integrated development for R, 2015. RStudio Team. RStudio, Inc. http://www.rstudio.com/.

Salthouse, T.A., 2019. Trajectories of normal cognitive aging. Psychol. Aging 34 (1), 17–24. https://doi.org/10.1037/pag0000288.

Sanders, L.M.J., Hortobágyi, T., Karssemeijer, E.G.A., Van Der Zee, E.A., Scherder, E.J.A., Van Heuvelen, M.J.G., 2020. Effects of low- and high-intensity physical exercise on physical and cognitive function in older persons with dementia: a randomized controlled trial. Alzheimers Res. Ther. 12 (1), 1–15. https://doi.org/10.1186/s13195-020-00597-3.

Schuff, N., Woerner, N., Boreta, L., Kornfield, T., Shaw, L.M., Trojanowski, J.Q., Thompson, P.M., Jack, C.R., Weiner, M.W., 2008. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. Brain 132 (4), 1067–1077. https://doi.org/10.1093/brain/awp007.

Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., Browndyke, J.N., Sherwood, A., 2010. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom. Med. 72 (3), 239–252. https://doi.org/10.1097/PSY.0b013e3181d14633.

Soto, I., Graham, L.C., Richter, H.J., Simeone, S.N., Radell, J.E., Grabowska, W., Funkhouser, W.K., Howell, M.C., Howell, G.R., 2015. APOE stabilization by exercise prevents aging neurovascular dysfunction and complement induction. PLoS Biol. 13 (10), e1002279 https://doi.org/10.1371/journal.pbio.1002279.

Steptoe, A., Zaninotto, P., 2020. Lower socioeconomic status and the acceleration of aging: an outcome-wide analysis. Proc. Natl. Acad. Sci. U. S. A. 117 (26), 14911–14917. https://doi.org/10.1073/pnas.1915741117.

Tsai, C.-L., Erickson, K.I., Sun, H.-S., Kuo, Y.-M., Pai, M.-C., 2021. A cross-sectional examination of a family history of Alzheimer's disease and ApoE epsilon 4 on physical fitness, molecular biomarkers, and neurocognitive performance. Physiol. Behav. 230, 113268 https://doi.org/10.1016/j.physbeh.2020.113268.

Tsai, Sun, Kuo, Pai, 2019. The role of physical fitness in cognitive-related biomarkers in persons at genetic risk of familial Alzheimer's disease. J. Clin. Med. 8 (10), 1639. https://doi.org/10.3390/jcm8101639.

Tse, A.C.Y., Wong, T.W.L., Lee, P.H., 2015. Effect of low-intensity exercise on physical and cognitive health in older adults: a systematic review. Sports Med. 1, 37.

Tun, P.A., Miller-Martinez, D., Lachman, M.E., Seeman, T., 2013. Social strain and executive function across the lifespan: the dark (and light) sides of social engagement. Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn. 20 (3), 320–338. https://doi.org/10.1080/13825585.2012.707173.

Varma, V.R., Chuang, Y.-F., Harris, G.C., et al., 2015. Low-intensity daily walking activity is associated with hippocampal volume in older adults. In: Hippocampus, 25 (5). John Wiley & Sons, Ltd, pp. 605–615. https://doi.org/10.1002/hipo.22397.

Verghese, P.B., Castellano, J.M., Holtzman, D.M., 2011. Apolipoprotein E in Alzheimer's disease and other neurological disorders. Lancet Neurol. 10 (3), 241–252. https://doi.org/10.1016/S1474-4422(10)70325-2.

Vidoni, E.D., Johnson, D.K., Morris, J.K., Van Sciver, A., Greer, C.S., Billinger, S.A., Donnelly, J.E., Burns, J.M., 2015. Dose-response of aerobic exercise on cognition: a community-based, pilot randomized controlled trial. PLoS One 10 (7). https://doi.org/10.1371/journal.pone.0131647.

Von Hippel, W., Dunlop, S.M., 2005. Aging, inhibition, and social inappropriateness. Psychol. Aging 20 (3), 519–523. https://doi.org/10.1037/0882-7974.20.3.519.

von Hippel, W., Henry, J.D., Matovic, D., 2008. Aging and social satisfaction: offsetting positive and negative effects. Psychol. Aging 23 (2), 435–439. https://doi.org/10.1037/0882-7974.23.2.435.

Woodard, J.L., Sugarman, M.A., Nielson, K.A., Smith, J.C., Seidenberg, M., Durgerian, S., Butts, A., Hantke, N., Lancaster, M., Matthews, M.A., Rao, S.M., 2012. Lifestyle and genetic contributions to cognitive decline and hippocampal structure and function in healthy aging. Curr. Alzheimer Res. 9 (4), 436–446. https://doi.org/10.2174/156720512800492477.

Yntema, D.B., 1963. Keeping track of several things at once. Hum. Factors 5 (1), 7–17. https://doi.org/10.1177/001872086300500102.

Yntema, D.B., Mueser, G.E., 1962. Keeping track of variables that have few or many states. J. Exp. Psychol. 63 (4), 391–395. https://doi.org/10.1037/h0045706.

Yu, F., Nelson, N.W., Savik, K., Wyman, J.F., Dysken, M., Bronas, U.G., 2013. Affecting cognition and quality of life via aerobic exercise in Alzheimer's disease. West. J. Nurs. Res. 35 (1), 24–38. https://doi.org/10.1177/0193945911420174.