Effects of Exercise Intensity and Duration at a Predetermined Exercise Volume on Executive Function Among Apolipoprotein E (APOE)-ε4 Carriers

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Author Note

This work was supported by part of a grant from Ministry of Science and Technology in Taiwan (MOST 107-2628-H-003-003-MY3; 110-2410-H-003-142-MY3) and National Taiwan Normal University from the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan to Yu-Kai Chang.

The authors assert that this work complies with the ethical standards approved by the institutional review board of Fu-Jen University in in accord with the 2013 Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. The authors report no potential conflicts of interest.

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Abstract

Emerging evidence indicates that acute exercise improves executive function, but its effects on higher-order executive functioning among people with a risk of Alzheimer’s disease are not well understood. This study addressed the effects of acute exercise on the planning dimension of executive function among late middle-age adults who carried Apolipoprotein (APOE)-ε4. Exercise volume was kept constant, but exercise intensity and duration were manipulated. Eighteen adults in the age range 55–70 years who carried APOE-ε4 were recruited for a laboratory-based study set in a within-subject, counterbalanced design. There was a reading control condition along with three exercise conditions: Acute cycle exercise at a moderate intensity for 30 min (MI-30); higher intensity exercise of a shorter duration (16 min); and lower intensity exercise of a longer duration (40 min). Exercise volume was set with reference to energy expenditure in MI-30. The Tower of London Test was administered at the end of each condition. Acute aerobic exercise improved the cognitive performance in regard to move-related scores and time-related scores, but not violation-related scores, when compared to the control condition in APOE-ε4 carriers. There was no difference in terms of the facilitation effect among the three exercise conditions. The present findings indicate that acute aerobic exercise, regardless of intensity/duration manipulation, facilitates higher-order executive function in late middle-aged APOE-ε4 carriers. Practitioners should, accordingly, consider exercise as a suitable intervention for those at risk of Alzheimer’s disease.

Keywords: aerobic exercise, APOE genotype, executive function, exercise prescription, planning

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APOE-ε4, the ε4 allele of the Apolipoprotein E gene, has emerged as the highest genetic risk factor for late-onset Alzheimer’s disease (Belloy et al., 2019). Notably, its association with the risk of Alzheimer’s disease beyond midlife is sex independent (Neu et al., 2017). APOE-ε4 influences amyloid-β (Aβ) pathology and has been linked with cerebral amyloid angiopathy (Robinson et al., 2021; Xiong et al., 2021) and white matter rarefaction. Specifically, APOE ε4 strengthens the link between white matter rarefaction and neurofibrillary tangles (Nichols et al., 2021). Notable, amyloid plaques and neurofibrillary tangles are neuropathological hallmarks of Alzheimer’s disease (Serrano-Pozo et al., 2011), thereby providing a key mechanism that underlies the APOE-ε4 genotype and Alzheimer’s disease.

APOE ε4 is also associated with reduction in executive function which may be a precursor of the biological changes that are corollaries of Alzheimer’s disease or genetic mechanisms that are distinct from neurodegenerative processes (Reas et al., 2019; Weiss et al., 2021). Executive function refers to a metalevel form of cognition with top-down mental processes that require effortful control to override automatic or instinctive responses in achieving goal-directed behavior (Diamond, 2013). In simpler terms, executive function pertains to the in-the-moment interaction of self-control, working memory, and flexible thinking.

Rather than being a unitary construct, executive function incorporates multiple processes that can be delineated into: (a) three core executive functions (i.e., inhibition, updating/working memory, and shifting/cognitive flexibility); and (b) higher-order executive functions (e.g., planning and problem solving;(Diamond, 2013; Miyake et al., 2000). Executive dysfunction is related to a genetic risk of Alzheimer’s disease (Gustavson et al., 2021) and frontal-subcortical disconnection in dementia patients (Tiel et al., 2019). It can also predict later psychological and behavioral symptoms of dementia in Alzheimer’s disease (Rouch et al., 2020).

The diminution of executive function is environment dependent and several strategies, among which is the inclusion of regular physical exercise, have been proposed to delay decline across the lifespan (Chen et al., 2020; Hoffmann et al., 2021; Taren et al., 2017). *Acute exercise*, or a single bout of exercise, can also have a positive effect on cognitive function regardless of the function assessed immediately following the bout or even a little while later (Chang, Labban, et al., 2012). The benefits of acute exercise on executive function have been detailed in the updated Physical Activity Guidelines for Americans with the grade evidence noted as “strong” (Physical Activity Guidelines Advisory Committee, 2018).

The effects of acute exercise are most pronounced in pre-adolescent children and older adults (Physical Activity Guidelines Advisory Committee, 2018; U.S. Department of Health and Human Services, 2018). From neuro-electric evidence, it appears that acute exercise might facilitate executive function through enhancing attention resource allocation (Chang et al., 2017; Kao, Wang, et al., 2020; Wu et al., 2019) and increasing efficiency in the process of stimulus evaluation and classification to a given task (Kao, Cadenas-Sanchez, et al., 2020; Kao et al., 2017).

There are three gaps that we have identified in the extant literature. First, while the effects of acute exercise on executive function have been observed in adolescents as well as young, middle-aged, and older adults, populations without cognitive impairment have been the primary focus of research (Ishihara et al., 2021; Liu et al., 2020). Whether the benefits of acute exercise extend to populations at risk of Alzheimer’s disease remains unexplored. Additionally, core executive functions, particularly inhibition, have been examined extensively (Ai et al., 2021; Chang, Labban, et al., 2012; Ishihara et al., 2021) but relatively few studies have investigated higher-order executive function (Chang, Ku, et al., 2012; Chang, Tsai, et al., 2011; Hung et al., 2013). This renders the effect of acute exercise on higher-level executive function an area that demands attention from the scientific community.

The third gap in the literature concerns the exact nature of exercise prescription in relation to executive function. Chang et al. (2019) proposed a 3W1H framework (i.e., what, when, who, and how) for customized, acute exercise prescription. Within this framework, the exercise components of intensity (i.e., how hard), duration (i.e., how long), and volume (i.e., total amount of physical work completed) require careful consideration. There is a general consensus that acute exercise at a moderate intensity for 20–30 min facilitates executive function (Chang et al., 2015; Chang, Labban, et al., 2012; Shigeta et al., 2021); however, whether manipulations of intensity and duration with reference to the same volume of exercise lead to similar outcomes remains unknown.

The present study addresses these gaps in the knowledge through determining the effect of acute exercise on the planning aspect of executive function among late middle-aged adults carrying APOE-ε4. Variations of exercise intensity and duration within a designated exercise volume were compared to further understanding of how fundamental facets of exercise prescription can influence executive function. It was hypothesized that acute exercise, regardless of intensity and duration variation, and at a constant volume, would facilitate superior executive function in late middle-aged adults at risk of being afflicted by Alzheimer’s disease.

Method

Participants

Sample size was determined by means of a power analysis on G*Power software (Faul et al., 2009). A one-way, repeated-measures model was used with $f = 0.35$, relating to the effect of acute exercise and executive function (Ludyga et al., 2016), alpha error proportion = 0.05, and power = 0.80. The analysis indicated that a sample size of 13 would be sufficient to detect a significant difference.

Older adults were recruited using flyers, social media, and local referral from physicians in community mental health hubs. Participants’ APOE-ε4 status was determined by means of a whole-blood sample taken by a qualified medical technician during the screening phase. The DNA extraction and genotyping process were conducted in accord with the manufacturer protocol, as adopted at the Union Clinical Laboratory (Taipei, Taiwan). This entailed a polymerase chain-reaction method with modification. Two ApoE single-nucleotide polymorphisms rs429358 (ApoE C112R) and rs7412 (ApoE R158C) were targets for the identification of the three types of ApoE allele. Eighteen participants met the inclusion criteria to enter the experimental phase, which were as follows: (a) Aged 55–70 years; (b) be an APOE-ε4 carrier: ε4/ε4, ε4/ε3, ε4/ε2; 3); (c) cognitively intact in accord with a Mini-Mental State Examination (Pangman et al., 2000; score ≥ 26); (d) no self-reported neurological or psychiatric disorders; (e) able to engage in exercise without medical contraindication, in accord with the Physical Activity Readiness Questionnaire (American College of Sports Medicine, 2022; score ≥ 7); (f) free of cardiovascular diseases; (g) be right-handed; and (h) have normal or corrected-to-normal (color) vision.

All potential participants completed written informed consent forms approved by the institutional review board of ________________ University, in accord with the 2013 Declaration of Helsinki. Descriptive data pertaining to eligible participants’ demographic and physiological characteristics can be found in Table 1.

Exercise Intensity Measure

Heart Rate (HR)

HR was assessed using a strap-on monitor (Polar RS800CX; Polar Electro, Kempele, Finland), which took measurements at the frequency of 1/s. Four HR indices were used: (a) resting HR (this was assessed during the initial visit); (b) pre-exercise HR (i.e., assessed prior to each condition); (c) mean HR during exercise; and (d) HR difference score (difference between mean HR during exercise and pre-exercise HR within each condition).

Rating of Perceived Exertion (RPE) Scale

RPE was assessed by means of the 15-point Borg scale, which has been found to be a valid and reliable measure of perceived exertion during exercise (Borg, 1982). The scale is anchored by 6 (*no exertion at all*) and 20 (maximal exertion), and was administered during the three experimental conditions at 2-min intervals starting at Minute 2.

Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed indirectly through predicting peak oxygen consumption by use of the YMCA Submaximal Cycle Ergometer Test (Golding, 1989). In the associated protocol, the workload begins with 150 kgm/min and the pedal rate is maintained at 50 rpm until the participant reaches voluntary exhaustion. HR and RPE were recorded at Minute 2 and Minute 3 of each stage. In the second stage, the workload was adjusted based on the participant’s current HR rate. Specifically: if HR was > 100 bpm, workload was increased by 300 kgm/min; if it was in the range 90–100 bpm, workload was increased by 450 kgm/min; if it was 80–89 bpm, workload was increased by 600 kgm/min, and if it was 80–89 bpm, workload was increased by 750 kgm/min. Thereafter, workload was increased by 150 kgm/min for each additional stage. On completed of the protocol, VO_{2peak} was calculated along with age-predicted HR_{max} (220 - age).

Exercise Volume Manipulation and Exercise Condition

Three experimental conditions characterized by the same exercise volume but with different exercise intensities/duration were administered, along with a reading control condition. The experimental conditions comprised of moderate-intensity exercise of 30 min duration (MI-30), higher intensity exercise with a shorter duration (HI-SD), and lower intensity exercise with a longer duration (LI-LD). Participants pedaled on the cycle ergometer at a constant frequency of 70 rpm. On initiation, the pedal resistance was set at 30 Watts and increased gradually until the target heart rate zone was reached. The exercise volume of MI-30, which comprised 5-min warm up, 20-min steady-state exercise (50–60% heart rate reserve; HRR), and 5-min cool down, was evaluated using energy expenditure by means of this formula:

$$\text{Energy expenditure (kcal)} = [\text{avg power (watt)} \times \text{duration (s)}]*4.18^{-1}*0.24^{-1}$$

Accordingly, the precise manipulation of exercise intensity and duration was with reference to the energy expenditure associated with a given exercise volume. The energy expenditure associated with MI-30 is roughly equivalent to 16 min of HI-SD and 40 min of LI-LD.

Tower of London Test

Higher-order executive function was assessed by means of the Tower of London Test (Tower of London–Drexel University 2nd ed.; Culbertson & Zillmer, 2005). This neuropsychological instrument is designed to assess executive planning ability in children and adults with the test–retest reliabilities of the categorized scores in the range: r = .42 to .80 (Culbertson & Zillmer, 2005). Construct validity of the test has been determined by use of the performance of children with attention-deficit hyperactivity disorder across a battery of neuropsychological measures sensitive to executive abilities, psychometric intelligence, and memory. The test produce the highest loading on an Executive Planning/Inhibition factor comprised of other executive measures. The Executive Planning/Inhibition measure was separate from factors of Executive Concept Formation/Flexibility, Psychometric Intelligence, and Memory (Culbertson & Zillmer, 1998).

The test equipment is comprised of two wooden boards (30 × 7 × 10 cm) and two sets of beans in blue, red, and green. Each wooden board has three vertical pegs with different heights where the shortest peg (left) can hold one bean, the middle peg can hold two, and the tallest (right) can hold three. One wooden board was administrated by a suitably trained experimenter, and another was controlled by the participant. Ten standard goal configurations were set in the Tower of London Test with gradually increasing levels of difficulty (e.g., requiring a minimum number of 2–7 moves). Participants were instructed to rearrange the beans from a fixed starting configuration to a target configuration, that was presented by the experimenter, using the fewest possible moves (Chang, Ku, et al., 2012; Hung et al., 2013) Figure 1). It took 15–25 min to administer the Tower of London Test.

Seven scores from three categories were taken from the Tower of London Test (Culbertson & Zillmer, 2005): (a) Move-related scores that comprise the total correct score and total moves score; (b) time-related scores that comprise the total initiation time, total execution time, and total problem-solving time; and (c) violation-related scores that comprise the time violation score and rule violation score. The total correct score is the number of problems that are solved in the minimum number of moves. Total move score is the sum of differences between the number of actual bean moves and the minimum number of moves for each configuration. Total initiation time is the duration of the time prior to the first move.

Total execution time is the duration of the time from first move to a complete successful configuration. Total problem-solving time is the sum of the total initiation time plus the total execution time. Total time violation is the time of completing the problem over one minute. Total rule violations are: (a) to place more beans on a peg than the permitted number; and (b) to simultaneously remove more than one bean from a peg.

Experimental Procedure

Participants deemed eligible following the screening phase were requested to visit the laboratory to establish their inclusion status and a period of 5 days ensued prior to the commencement of experimental testing (Figure 2). During the initial visit of the experimental phase, potential participants were instructed to complete an informed consent form, demographic and health history questionnaires, the Physical Activity Readiness Questionnaire, Mini-Mental State Examination, International Physical Activity Questionnaire (Liou et al., 2008), and the Digit Span test of the Wechsler Adult Intelligence Scale (3rd ed.; Wechsler, 1997). Subsequently, eligible participants were instructed to attach the HR monitor to their chest and sit comfortably for 10 min in order to determine their resting HR. Participants then pedaled on the cycle ergometer for the designated exercise protocol, which comprised 5-min warm up, 20-min steady-state exercise (50–60% HR reserve; HRR), and 5-min cool down, to determine the energy expenditure of MI-30. Lastly, the YMCA Submaximal Cycle Ergometer Test was administered to facilitate estimation of the participant’s cardiorespiratory fitness.

The experimental phase of the study comprised of four visits to the laboratory during. During each visit, one of the aforementioned exercise conditions was administered. A within-subjects experimental design was adopted, with partial counterbalancing for the three experimental conditions and the reading control condition. Specifically, there were four predetermined orders (ACBD, BADC, CDAB, and DBCA). The visits took place with at least a 2-day interval. In the control condition, the participant was required to sit in a comfortable chair in the laboratory and read a physical activity-related book for 30 min. Then, the submaximal cycle ergometer test was conducted to evaluate participant’s cardiorespiratory fitness. HR and RPE were measured every 2 min during each condition and the Tower of London Test was administered immediately after the exercise bout/reading task.

Following completion of each condition (~90 min), the participant was given US $25 in compensation. The participant was debriefed (i.e., in regard to the general purpose of the study) at the end of their final visit to the laboratory.

Statistical Analysis

A within-subjects, counterbalanced design was employed with condition as the independent variable (four levels; control, MI-30, HI-SD, and LI-LD). Analyses were conducted using SPSS version 23 (IBM Corp., Armonk, NY, USA).

Regarding the Tower of London Test, three one-way, repeated-measures (RM) multivariate analyses of variance (MANOVAs) using Wilks's λ as the omnibus statistic were computed for each cluster of dependent variables (i.e., move-related scores with total moves and total correct; time-related scores with total initiation time, total execution, and total problem-solving time; and violation-related scores with time violations and rule violations). F tests were subject to Greenhouse–Geisser correction when the assumption of sphericity was violated. Follow-up pairwise comparisons were used to identify where differences lay, with alpha set at .05 prior to Bonferroni correction. Violin plots were generated to illustrate the distribution of the Tower of London Test indices and any differences across the four conditions.

Regarding exercise-related indices, descriptive statistics were computed for both HR and RPE. A one-way RM ANOVA was computed for the HR difference score. Effect sizes are reported as partial eta squared (η_p^2) at both multivariate and univariate levels.

Results

Table 2 provides a summary of descriptive statistics for the Tower of London Test scores and exercise indices across the four conditions.

Move-Related Scores

One-way MANOVA indicated a significant multivariate effect, Wilks's $\lambda = 0.58$, $F(6, 100) = 5.29$, $p < .001$, $\eta_p^2 = .24$, as well as significant univariate effects for total correct score, $F(3, 51) = 7.57$, $p < .001$, $\eta^2 = .31$, and total moves score, $F(3, 51) = 12.46$, $p < .001$, $\eta_p^2 = .42$. Follow-up pairwise comparisons for total correct score indicated that there were fewer correct scores in the control condition when compared to experimental conditions of MI-30, HI-SD, and LI-LD (ps < .05). There were no significant ($p < .05$) differences among the three experimental conditions. An identical pattern of results was observed for the total moves score (Figure 3).

Time-Related Scores

One-way MANOVA indicated a significant multivariate effect, Wilks's $\lambda = 0.55$, $F(9, 119) = 3.72$, $p < .001$, $\eta_p^2 = .18$, as well as significant univariate effects for total initiation time, $F(1.84, 31.21) = 5.15$, $p = .014$, $\eta_p^2 = .23$, total execution time, $F(1.94, 33.01) = 11.26$, $p < .001$, $\eta_p^2 = .40$, and total problem-solving time, $F(3, 51) = 10.35$, $p < .001$, $\eta_p^2 = .38$.

Follow-up pairwise comparisons for total initiation time demonstrated no significant differences among the four conditions. Pairwise comparisons for total execution time and total problem-solving time indicated longer response times in the control condition (*p*s < .05) when compared to the experimental conditions. Again, no differences emerged among the experimental conditions (Figure 3).

Violation-Related Scores

As there were no rule violations, one-way ANOVA was computed for time violation. There was no significant difference for time violation among the four conditions, $F(1.39, 23.62) = 1.00$, $p = .355$, $\eta_p^2 = .06$.

HR Manipulation Check

One-way ANOVA indicated a significant difference for HR difference scores across the four conditions, $F(3, 51) = 114.76$, $p < .001$, $\eta_p^2 = .87$. A significant linear trend among four conditions was also observed, $F(1, 17) = 200.15$, $p <.000$, $\eta_p^2 =.92$. Specifically, the control and higher intensity exercise of a shorter duration conditions elicited the lowest and highest HR, respectively.

Discussion

Acute exercise has been found to facilitate executive function, but its effect on higher-order executive function in adults at risk of Alzheimer’s disease warrants further investigation. The present study sought to address three research gaps in the knowledge through investigating whether acute aerobic exercise with varying intensity and duration at a predetermined exercise volume would improve the Tower of London Test performance in late middle-aged APOE-ε4 carriers. We present evidence indicating that acute aerobic exercise improved the cognitive performance in terms of more-related scores and time-related scores, with no difference in violation-related scores, when the three experimental conditions were compared against a control. There were no differences in any of the Tower of London Test performance scores among the three experimental conditions.

To the best of our knowledge, this is the first study to address the effects of acute exercise on executive function among APOE ε4 carriers. The main finding, that acute exercise has a positive effect on executive function, concurs with the findings of meta-analytic reviews focused on healthy children and adolescents (Ishihara et al., 2021; Liu et al., 2020) as well as healthy young and older adults (Ishihara et al., 2021; Ludyga et al., 2016). Acute exercise has also been shown to improve neurocognitive functions among elderly people in the early stages of dementia and thus presenting with mild cognitive impairment (Tsai et al., 2018). Such improvements have also been demonstrated among individuals with less severe forms of Alzheimer’s disease (Ben Ayed et al., 2021). The present findings indicate that the beneficial effects of acute exercise on executive function extend to APOE ε4 carriers who have yet to receive a diagnosis either for mild cognitive impairment or Alzheimer’s disease. This finding is particularly important given that executive function deficits are associated with a high risk of dementia in later life (Rouch et al., 2020; Shepherd et al., 2021). Allied to this, effective intervention for Alzheimer’s disease comes at the stage prior to mild cognitive impairment (Crous-Bou et al., 2017; Kivipelto et al., 2018).

Rather than examining core executive function, which has been common to many past studies (e.g., Ishihara et al., 2021; Kao, Wang, et al., 2020; Shigeta et al., 2021), the present approach facilitated an exploration of higher-order executive function. The improvement in move-related scores (i.e., total correct scores and total move scores) without violation of time and rules is consistent with the findings of acute aerobic exercise studies that have used the Tower of London Test (Chang, Tsai, et al., 2011; Hung et al., 2013). This test is widely employed in neuropsychological studies and taps planning ability, planning quality, efficiency in problem-solving, and working memory (Hung et al., 2013; Satler et al., 2017).

To optimize Tower of London Test scores, multiple mental processes are implicated; these include recognizing both initial and goal configuration, generating multiple potential approaches, storing representations of intermediate states, and anticipating future events to achieve the specific goal configuration (Chang, Tsai, et al., 2011; Culbertson & Zillmer, 2005). The underlying cognitive components within these processes encompass attention, inhibition, updating, and shifting, thus rendering planning a higher-order executive function (Diamond, 2013). Taken together, our findings suggest that acute aerobic exercise enhances the higher-order executive function of planning quality as well as efficiency in problem solving among adults with a risk of Alzheimer’s disease.

While our results show a significant multivariate effect for the time-related score, univariate analyses showed differences only in total execution time and total problem-solving time; not total initiation time. This finding is somewhat inconsistent with previous studies, which have shown that acute exercise has little-to-no effect on time-related scores (Chang, Chu, et al., 2011; Chang, Tsai, et al., 2011) or superior performance only in total initiation time (Chang, Ku, et al., 2012; Hung et al., 2013). A plausible explanation for this discrepancy might lie in the present choice of exercise mode and time points assessed. Notably, Chang and colleagues examined resistance exercise (Chang, Chu, et al., 2011; Chang, Ku, et al., 2012), and while aerobic exercise was included in their protocols, the influence of initiation time was observed at 30 min and 60 min postexercise (Hung et al., 2013) but not immediately after cessation of exercise (Chang, Tsai, et al., 2011).

The three time-related scores are characterized by specific cognitive processes (Culbertson & Zillmer, 2005; Hung et al., 2013) and while the present findings show limited effects on initiation time, which represents the preparation processes germane to the planning of behavior, the shorter execution time and total problem-solving times suggest that acute aerobic exercise is related to the quality of executive planning and its overall speed, respectively. An alternative explanation is that use of a sample with a risk of Alzheimer's disease or with lower cognitive function, might bear some influence. Recent work has shown that patients with moderate Alzheimer's disease required less time to solve the Tower of Hanoi puzzle following a 20-min bout of aerobic exercise (Ben Ayed et al., 2021).

A novel aspect of the present study was to examine executive function under a constant exercise volume while varying the dimensions of intensity and duration. Twenty to 30 min of acute aerobic exercise at a moderate intensity have been found to facilitate executive function (Chang, Labban, et al., 2012; Shigeta et al., 2021). From the perspective of underlying neurophysiological mechanisms, exercise has been shown to increase levels of salivary cortisol (Wang et al., 2019) and P3 amplitude of event-related potential (Chang et al., 2017; Kao, Wang, et al., 2020; Kao et al., 2017; Wu et al., 2019), in addition to improving performance in executive function tasks. Accordingly, it is likely that exercise engenders an arousal-related neuroendocrine response coupled with neuro-electric activations that could be positively associated with executive function (Basso & Suzuki, 2017).

Notably, executive function performance exhibited no difference across the three exercise conditions employed in the present study (see Figure 2). This suggests that both higher intensity with shorter duration *and* lower intensity with longer duration have similar (positive) effects to the commonly used protocol of 30 min of moderate-intensity exercise (Chang, Labban, et al., 2012; Shigeta et al., 2021). Although the exercise volume in the present protocol remained constant, the mechanism underlying change in executive function performance could differ in accord with intensity and duration. The brain-derived neurotrophic factor (BDNF) might play a salient role in this regard. There is speculation surrounding the role of BDNF induced by acute exercise (Borror, 2017; Dinoff et al., 2017). BDNF is a neurotrophin family of growth factors associated with synaptic plasticity and neuroplasticity at the molecular level and executive function at the behavioral level (Bolat et al., 2022; Kowiański et al., 2018). The defective BDNF biosynthesis is also implicated in

Alzheimer’s disease pathology and associated with APOE-ε4 (Bharani et al., 2020; Sen et al., 2017).

Acute exercise has been shown to induce BDNF and its postexercise release is intensity dependent, with higher-intensity exercise leading to a greater concentration of BDNF (Knaepen et al., 2010). Boyne et al. (2019) showed that high-intensity interval training on a treadmill, but not moderate intensity, continuous treadmill exercise, stimulated greater circulating BDNF and corticospinal excitability. In accord with the related inverted-U hypothesis, exercise at a moderate intensity elicits optimal cognitive function and at high intensity cognitive function is suboptimal. Research has shown that exercise at a hard-to-supramaximal intensity elicits either a negligible (Chang, Labban, et al., 2012) or even a negative effect on cognitive function (Chang, Labban, et al., 2012; McMorris et al., 2015). The implication is that BDNF might not be the underlying mechanism for the effects of exercise at a moderate intensity on cognitive function. Nonetheless, the present findings indicate that the higher exercise intensity/shorter duration condition did not elicit a negative effect on this outcome (see Figure 2).

Along similar lines, BDNF might also be implicated in the effect of exercise at a lower intensity and longer duration observed in the present study. Meta-regression has shown a significant positive linear relationship between exercise duration and BDNF levels. Specifically, exercise in excess of 30 min elicits larger increases in peripheral BDNF relative to bouts of 30 min or less (Dinoff et al., 2017). While BDNF might, generally, be less relevant in exercise of a lower intensity, its relevance to cognitive function increases in long-duration exercise. Taken collectively, the present findings provide novel evidence suggesting that manipulation of exercise intensity and duration is feasible in exercise interventions, once appropriate exercise volume is established. While the BDNF mechanism does not explain the effects of a 30-min bout of exercise at a moderate intensity (Chang et al., 2017), it might well play a salient role in exercise of high intensity/short duration or low intensity/long duration.

Strengths and Limitations

Strengths of the present study include the fact that it addressed a clear gap in the knowledge regarding the effects of acute exercise on executive function in late middle-aged adults at risk of Alzheimer’s disease. A further strength concerns the use of a standardized task (i.e., Tower of London Test) that has been used widely in past related studies and is thus associated with a wealth of data for comparative purposes (Chang, Chu, et al., 2011; Chang, Ku, et al., 2012; Chang, Tsai, et al., 2011; Hung et al., 2013). Moreover, the fact that exercise volume was standardized represents a strength, as intensity and duration components could be isolated.

In terms of limitations, first, while “APOE-ε4 carrier” was an inclusion criterion, only participants with APOE ε4/ε3 were recruited; possibly due to the small percentage of APOE ε4 homozygotes (2–3%) when compared to those with a heterozygous genotype (15–25%; Mahley & Huang, 2012). Further work is needed to explore APOE-ε4 status, because a dose effect of developed Alzheimer’s disease appears as three- to fourfold in heterozygous but ten- to fifteen-fold in homozygotes (Liu et al., 2013), suggesting a differential strength of linkage between APOE and Alzheimer’s disease.

Results indicate that pre-exercise HR in the three exercise conditions is higher than that in the reading control condition. It is possible that the increase in participants’ pre-task HR was due to an expectation effect associated with the imminent exercise bout (Mangine et al., 2019). It should be noted, however, that a significant linear trend for the HR difference score emerged, suggesting that the exercise intensity manipulation was appropriate.

An exploration of exercise volume that was deemed optimal for executive function with manipulation of intensity and duration was our main purpose; nonetheless, this approach limits exploration of the dose–response relationship pertaining to response magnitude as a function of exposure (e.g., varying exercise intensities and duration). Indubitably, further studies are needed to explore the dose–response relationship and these will serve to inform exercise prescription for APOE-ε4 carriers.

Our results should be interpreted with due caution given that the large estimated effect sizes might be associated with a relatively small sample size and the absence of a pretest (Ferguson, 2016). Notably, potential false positives might also emerge as a consequence of separate ANOVA models when sample size derived from a power analysis is determined by use of a single repeated-measures model (Vickerstaff et al., 2019). However, in contrast to previous studies that typically included one index from the Tower of London Test or applied several one-way ANOVAs for each index of Tower of London Test, we applied MANOVAs for three clusters of dependent variables, in which the three clusters are recognized as distinct factors. We contend that our approach serves to strike an appropriate balance between the potential for type-I and type-II errors. Further study with a larger sample size and the addition of a pretest comparison is warranted.

In conclusion, this is the first study to demonstrate that acute aerobic exercise, regardless of manipulation of the intensity and duration components, facilitated the planning aspect of executive function in late middle-aged adults who were APOE-ε4 carriers. The findings illustrate the latitude that exercise practitioners have—in terms of intensity and duration—with the design of interventions to improve higher-order executive function among adults who are predisposed to Alzheimer's disease.

Author Contribution ______, ______, and ______ designed the study protocol. ______, ______, and ______ conducted data collection. ______, ______, and ______ conducted data management, screening, and analysis. ______, ______, and ______ wrote the first draft of the paper. ______, ______, and ______ substantially revised the manuscript.

Availability of Data and Material The data that support the findings of this study are publicly available from Rowan Digital Works: _________________

Funding This research receives a grant from the Ministry of Science and Technology in Taiwan (XXXXX; XXXXX) and _________ University from the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan to _________.

Declarations

Ethical Approval The authors assert this work comply with the ethical standards approved by the institutional review board of _________ University in accordance, in accord with the 2013 Declaration of Helsinki.

Informed Consent Informed consent was obtained from all participants included in the study.

Conflicts of Interest The authors report no potential conflicts of interest.

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Table 1

Descriptive Data Pertaining to Participant Demographics and Physiological Characteristics

	Male (*n* = 7)		Female (*n* = 11)		All (*N* = 18)	
Variables	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age (years)	63.71	4.27	62.27	4.41	62.83	4.29
Education (years)	14.57	2.44	13.00	3.00	13.61	2.83
Height (cm)	170.64	6.85	160.45	5.14	164.42	7.63
Weight (kg)	77.36	11.38	60.80	7.87	67.24	12.29
BMI (kg/m^2)	26.44	2.27	23.65	3.20	24.73	3.13
IPAQ (METs)	1656.33	1611.43	1669.64	1262.45	1664.94	1344.48
Resting HR (bpm)	71.57	10.47	64.18	3.79	67.06	7.80
Peak oxygen uptake (mL·kg^{-1}·min^{-1})	29.13	6.48	25.76	6.65	27.07	6.61
APOE E3/E4 status	7		11		18	
MMSE	29.43	0.79	29.27	0.79	29.33	0.77
Digit Span Forward	11.71	2.21	13.45	1.97	12.78	2.18
Digit Span Backward	9.14	1.68	8.64	2.38	8.83	2.09

Note. BMI = body mass index; IPAQ = International Physical Activity Questionnaire; METs, Metabolic equivalents; Resting HR = Heart rate assessed on the first visiting; MSSE = Mini-Mental State Examination.

Table 2

Tower of London Test Scores and Exercise Manipulation Indices Across Conditions

	Control		LI-LD		MI-30		HI-SD	
Sources	*M*	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
Move-related scores								
Total correct score	5.39	0.47	7.33	0.51	7.67	0.32	7.22	0.38
Total move score (–)	24.67	3.80	10.61	2.35	8.33	1.57	11.94	2.57
Time-related scores								
Total initiation time	62.84	8.70	44.30	6.04	39.83	4.42	41.42	5.62
Total execution time (–)	255.00	22.50	160.43	13.45	114.35	11.87	163.76	15.87
Total problem-solving time (–)	317.87	29.40	204.72	15.16	184.23	14.41	208.50	21.28
Violation-related scores								
Time violation score	0.22	0.13	0.11	0.76	0.06	0.06	0.06	0.06
Rule violation score	–	–	–	–	–	–	–	–
Exercise indices								
Pre-exercise HR (bpm)	68.17	2.08	79.56	2.16	85.67	1.98	90.00	1.99
Mean HR (bpm)	69.53	2.16	102.15	1.70	119.20	1.26	129.76	1.89
HR diff. score (bpm)	1.37	2.82	22.59	7.81	33.53	7.39	39.76	11.16
RPE	-		10.66	0.37	13.43	0.48	14.85	0.40

Note: MI-30 = Moderate intensity with 30 min; HI-SD = Higher intensity with shorter duration (HI-SD); LI-LD = Lower intensity with longer duration; pre-exercise HR = heart rate assessed pre-exercise; Mean HR = mean heart rate during exercise; Diff. Score = Difference score between Mean HR and pre-exercise HR; RPE = rating of perceived exertion; (–) = a lower score represents superior performance.

Figure 1

The Start Position and Examples of Goal Configurations in the Tower of London Test

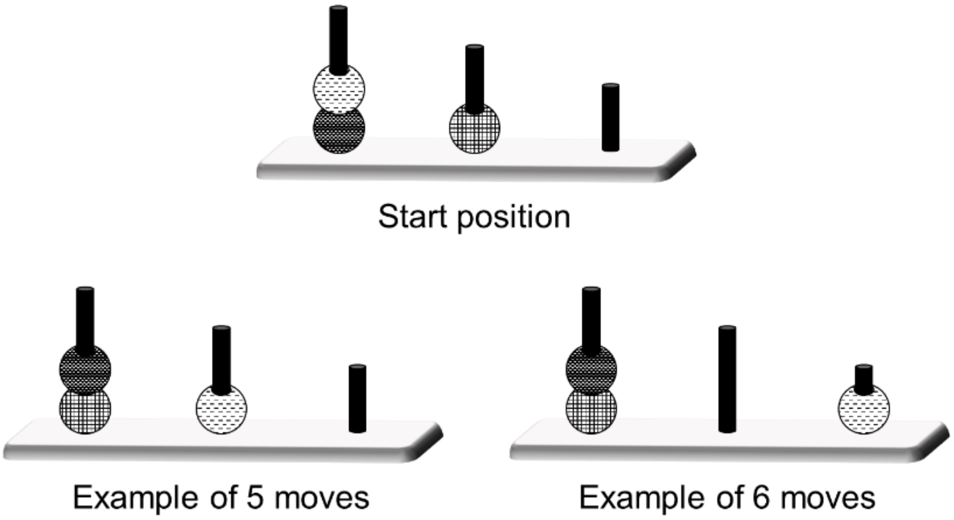
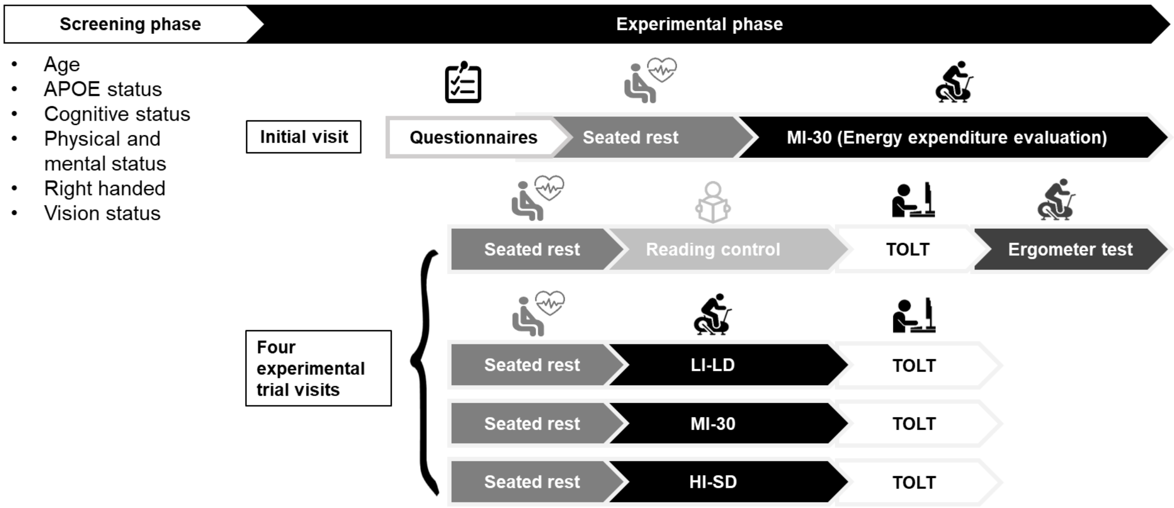


Figure 2

Study Screening and Experimental Phases

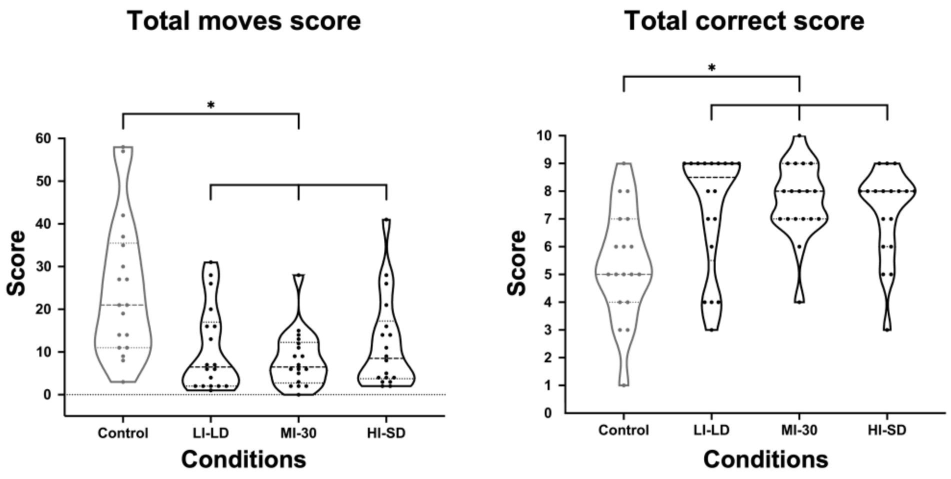


Note. The study procedure with screening and experimental phases that comprise an initial visit followed by four experimental trial visits. The screening phase was used to identify participants' eligibility—particularly APOE genotype status from a whole-blood sample test. The initial visit was used to determine the energy expenditure associated with moderate-intensity exercise (i.e., 50–60% HR reserve for 30 min; MI-30). The four visits with partial counterbalancing formed the experimental phase of the study. HI-SD and LI-LD represent higher intensity exercise with a shorter duration and lower intensity exercise with a longer duration, respectively. TOLT represents administration of the Tower of London Test.

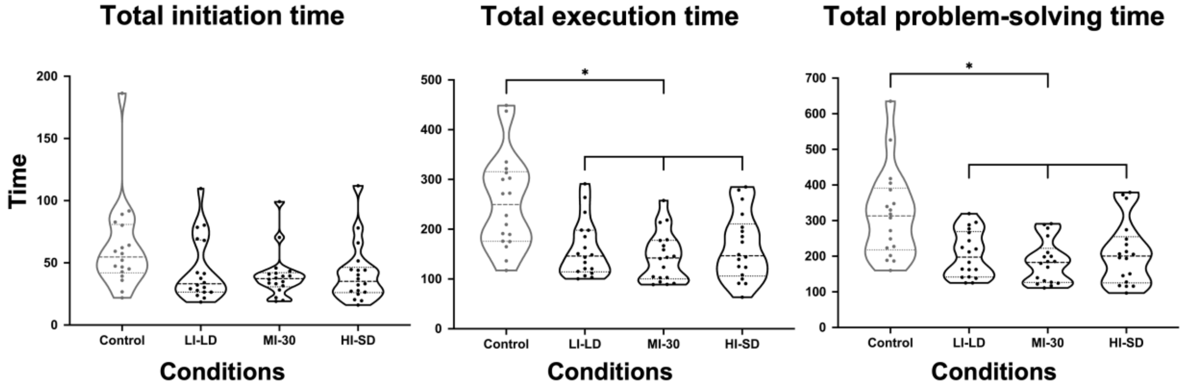
Figure 3

Move- and Time-Related Scores of Tower of London Test Across Four Conditions

a) Move-related scores



b) Time-related scores



Note. a) Violin plot of move-related scores (total correct score and total moves score) across four conditions. Higher total correct scores and lower total moves scores represent superior performance. b) Violin plot of time-related scores (total initiation time, total execution time, and total problem-solving time) across four conditions. Shorter times for total execution time and total problem-solving time represent superior performance. LI-LD = lower intensity with longer duration; MI-30 = moderate intensity with 30 min; HI-SD = higher intensity with shorter duration; * = $p < .05$.