High-intensity Exercise and Cognitive Function in Cognitively Normal Older Adults: A Randomised Clinical Trial

Belinda Brown (✉ b.brown@murdoch.edu.au)  
Murdoch University  https://orcid.org/0000-0001-7927-2540

Natalie Frost  
University of Western Australia

Stephanie R. Rainey-Smith  
Edith Cowan University

James Doecke  
CSIRO: Commonwealth Scientific and Industrial Research Organisation

Shaun Markovic  
Murdoch University

Nicole Gordon  
Murdoch University

Michael Weinbom  
University of Western Australia

Hamid R. Sohrabi  
Murdoch University

Simon M. Laws  
Edith Cowan University

Ralph N Martins  
Edith Cowan University

Kirk I Erickson  
University of Pittsburgh

Jeremiah J Peiffer  
Murdoch University

Research

Keywords: Exercise, cognition, intensity, genetics, dementia, cardiorespiratory fitness

DOI: https://doi.org/10.21203/rs.3.rs-78125/v1
Abstract

BACKGROUND: Physical inactivity has been consistently linked to increased risk of cognitive decline; however, studies examining the impact of exercise interventions on cognition have produced inconsistent findings. Some observational studies suggest exercise intensity may be important for inducing cognitive improvements; however, this has yet to be thoroughly examined in older adult cohorts. The objective of the current study was to evaluate the effect of systematically manipulated high-intensity and moderate-intensity exercise interventions on cognition. In addition, we investigated individual variability in exercise response by examining effects of relevant genetic factors and changes in cardiorespiratory fitness on cognitive change.

METHODS: This multi-arm randomised clinical trial investigated the effects of 6-months of high-intensity exercise and moderate-intensity exercise, compared with an inactive control, on cognition. Outcome measures were assessed at pre- (baseline), post- (6 months), and 12-months post-intervention. Ninety-nine cognitively normal men and women (aged 60 – 80 years) were enrolled from October 2016 to November 2017. Participants that were allocated to an exercise group (i.e., high-intensity or moderate-intensity) engaged in cycle-based exercise two times per week for 6 months. Cognition was assessed using a comprehensive neuropsychological test battery. Cardiorespiratory fitness was evaluated by a graded exercise test. Apolipoprotein e4 genotype and brain-derived neurotrophic factor Val66Met carriage were identified.

RESULTS: There was a dose-dependent effect of exercise intensity on cardiorespiratory fitness; whereby the high-intensity group experienced greater increases in fitness than the moderate-intensity and control groups. However, there was no direct effect of exercise on cognition. We observed an association between changes in global cognition and executive function and changes in cardiorespiratory fitness from pre- to post-intervention: this relationship was strongest in brain-derived neurotrophic factor non-Met carriers.

CONCLUSIONS We did not observe a direct effect of exercise on cognition. Nevertheless, our data suggests genetics may moderate the relationship between fitness and cognitive change following exercise, and this should be examined further in larger trials.

TRIAL REGISTRATION: This study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000643370). Registered 3rd May 2017 - retrospectively registered. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372780

Introduction

Physical inactivity is considered the greatest modifiable risk factor for dementia (1); however, attempts to provide definitive evidence from randomised-controlled trials (RCTs) of a link between exercise and enhanced cognition have been inconsistent. Indeed, a 2015 Cochrane review (2) of RCTs concluded there is insufficient evidence, in cognitively normal older adults, to suggest an effect of exercise on cognition.
While a more recent meta-analysis (3), assessing a similar cohort, identified positive effects of exercise when session durations were in excess of 45 min and at least of moderate intensity. These conflicting results indicate the need for greater clarity for the use of exercise as a method for preventing cognitive decline, specifically the precise parameters needed for improving brain health.

When compared with the total volume of physical activity, observational work has reported a stronger association between objectively measured intensity of physical activity and cognitive function (4, 5). Furthermore, acute bouts of high-intensity exercise improve memory and executive function to a greater extent than moderate-intensity continuous exercise bouts (6, 7). Although previous work in the area is promising, the importance of exercise intensity in enhancing cognitive health requires rigorous examination in RCTs. A recent 12-week intervention in older adults demonstrated greater improvements in memory after undertaking high-intensity compared with moderate-intensity exercise, or a stretching control (8). The use of high-intensity exercise is safe in older populations (9) and provides a time-effective method to increase physical health, yet, until more consistent and rigorous evidence is available, the widespread use of high-intensity exercise to enhance cognitive health will continue to be questioned.

Variability across studies might also be explained by factors moderating exercise-induced changes in cognition. Genetic factors, such as the apolipoprotein E (APOE) ε4 allele and the brain-derived neurotrophic factor (BDNF) Val66Met single nucleotide polymorphism, may modulate the relationship between exercise and brain health (10–12). The literature in these fields is predominantly sourced from observational studies, which have contributed to largely inconsistent findings. In addition, variability in cognitive response may be due to variability in cardiorespiratory fitness change following exercise (13, 14). Evidence from RCTs is needed to gain a greater understanding of these potential mediating and moderating effects on cognition.

The current proof-of-concept RCT was designed to provide a head-to-head comparison of work-matched moderate-intensity and high-intensity exercise on cognition in cognitively normal older adults. We hypothesised that both intervention groups would receive benefits to cognition, but the high-intensity group would receive additional benefit beyond the moderate-intensity group in a dose-dependent fashion. Based on the hypothesis that increases in cardiorespiratory fitness are an important factor in the relationship between exercise and cognition, we investigated whether change in fitness is associated with improved cognition. Finally, we investigated whether targeted genetic factors (APOE ε4 carriage and BDNF Val66Met) moderate the effect of exercise on cognition, and the relationship between altered fitness and cognitive changes. Based on previous literature, we hypothesised that APOE ε4 carriers and BDNF Val66Met carriers would receive the greatest benefit from exercise, in terms of cognitive improvements (12, 15).

Methods

Trial design
The Intense Physical Activity and Cognition (IPAC) study was a single-site parallel randomised controlled trial conducted between October 2016 and September 2019 at Murdoch University and the Australian Alzheimer’s Research Foundation, Western Australia. An open access protocol paper for the IPAC study has been published previously (16). Participants were randomised to either six-months of supervised high-intensity exercise, supervised moderate-intensity exercise, or an inactive control group.

The IPAC study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000643370). The human research ethics committees at Murdoch University and Edith Cowan University approved the conduct of this study, and all participants provided written informed consent.

**Participants and Randomisation**

Participants were recruited between October 2016 and November 2017 from a number of sources, including media advertisement, flyers, and word-of-mouth. A full list of inclusion and exclusion criteria and calculations of sample size have been described previously (17). A block randomisation protocol (conducted by a researcher who was not collection outcome data) was used to randomly assign participants to one of the following three groups: high-intensity exercise, moderate-intensity exercise, or a control group.

**Interventions**

Participants that were allocated to an exercise group (i.e., high-intensity or moderate-intensity) engaged in exercise two times per week (under the supervision of an Accredited Exercise Physiologist) for 6 months. Each exercise session lasted 50 minutes and was conducted on a cycle ergometer (Wattbike Pro; Wattbike, Australia). Target intensity was set using the 6 to 20 Borg Scale of Perceived Exertion (18). Further details of the exercise interventions can be found within the supplementary material.

Adherence to the intervention was measured via session attendance. In addition, exercise intensity was calculated for each participant in the moderate- and high-intensity groups: the percentage of peak aerobic power (measured via a graded exercise test) was calculated for each session (not including the warm-up, cool-down, and for the high-intensity group, the recovery between intervals). The percentage of peak aerobic power in the initial three months were calculated using baseline peak aerobic power output, while months four to six were calculated using peak aerobic power output from the mid-intervention fitness test.

Participants randomised to the control group were provided with an information session regarding the benefits of exercise for overall physical health and known benefits to the brain. Participants in the control group did not receive any exercise instructions.

**Procedures and outcome measures**

Full methodological detail regarding outcome measures can be found in the supplementary material.
Cognitive assessment

A comprehensive battery of neuropsychological tests was administered to all participants at baseline, 6-months, and 18-months. Composite scores for global cognitive function, attention, episodic memory and executive function were calculated.

Physical assessment

At baseline, 3-, 6-, and 18-months, all participants underwent a cycling-based graded exercise test to quantify peak aerobic capacity ($V_{O2}$peak) and peak power. All participants also underwent a dual-energy X-ray absorptiometry (DXA) scan, using a Hologic Discovery Bone Densitometer (Hologic, USA), in order to quantify volume of fat, muscle and bone tissue in the body.

Genotyping

TaqMan genotyping assays were performed (19) to determine $APOE$ genotype (rs7412, assay ID: C____904973_10; rs429358, assay ID: C___3084793_20) and $BDNF$ Val66Met single nucleotide polymorphism (rs6265, assay ID: C__11592758_10). Dichotomous variables indicating $APOE$ ε4 carriers or non-carriers and $BDNF$ Val66Met carriers or non-carriers were created.

Statistical methods

Analyses were conducted in R statistical computing packages version 3.6.2 (20) and Statistical Package for the Social Sciences Version 24 (IBM). Data were inspected to determine parametric testing was appropriate for all physiological and cognitive variables.

Descriptive statistics

Descriptive statistics were calculated to compare baseline information across study groups. Analyses of variance (for continuous variables) and chi-square analyses (for categorical variables) were conducted to identify differences.

Intervention group analysis

All participants that completed a baseline assessment were included in the intention-to-treat (ITT) analyses, regardless of adherence to session attendance, or study withdrawal. To examine the effect of study group on cognition over time, a series of linear mixed models (LMMs) were conducted. Repeated cognitive composite scores were entered as dependent variables, and age, gender, education, time (years), group, and time*group were entered as fixed factors, and participant identification number as a random factor, into the model. Post-hoc group comparisons were conducted for any significant time*group interactions (high-intensity as reference group). LMMs were conducted for baseline and 6-month data only, and then again for baseline, 6- and 18-month data. We report raw mean change scores from baseline and 95% confidence intervals, and unstandardized beta coefficients (B) and their standard error.
A positive B represents a positive slope for the moderate/high-intensity groups, compared with the control group.

The per-protocol analyses were run in the same manner as the LMMs described above, yet this was only conducted for participants that attended at least 75% of exercise sessions.

We ran LMMs (for ITT data only) to investigate the moderating effects of $BDNF$ Val66Met and $APOE\,\varepsilon4$ carriage on cognitive performance over the intervention. Each LMM had an additional interaction of either $BDNF^{*}time^{*}group$ or $APOE^{*}time^{*}group$ entered into separate models.

**Individual variability analysis**

The relationships between change in cognition and change in cardiorespiratory fitness (VO$_{2\text{peak}}$) from pre- to post-intervention within the high-intensity group only, and for all study participants, were examined. Residualised change scores were generated by entering post-intervention score as the dependent variable and pre-intervention score as the independent variable. Linear models were run with the residualised cognitive change as the dependent variable and residualised fitness change as the independent variable (age, gender, and education as covariates) (21). For all study participants, the linear models were re-run with the inclusion of either $BDNF^{*}\text{fitness change}$ or $APOE^{*}\text{fitness change}$. The cohort was then stratified by $BDNF$ Val66Met carriage or $APOE\,\varepsilon4$ carriage and the linear models re-run.

**Results**

One hundred and eight participants were enrolled, with ninety-nine completing all baseline assessments and subsequent randomisation to a study group (Fig. 1; descriptive data, Table 1). Seven participants withdrew during the six-month intervention.
Table 1
Descriptive baseline characteristics of study cohort

|                            | High-intensity (n = 33) | Moderate-intensity (n = 34) | Control (n = 32) | Test statistic |
|---------------------------|-------------------------|-----------------------------|-----------------|---------------|
| **Age, years**            | 70.2 ± 5.3              | 68.4 ± 4.2                  | 68.7 ± 5.9      | F = 1.22      |
| **Gender, % Female (n)**  | 51.5 (17)               | 52.9 (18)                   | 59.4 (19)       | χ² = 0.79     |
| **APOE ε4 allele carriers, % (n)** | 27.3 (9) | 23.5 (8)                  | 28.1 (9)        | χ² = 0.90     |
| **BDNF Val66Met carriers, % (n)** | 33.3 (11) | 32.4 (11)                 | 50 (16)         | χ² = 2.70     |
| **Years of education**    | 13.5 ± 2.2              | 14.2 ± 2.5                  | 14.5 ± 2.1      | F = 1.65      |
| **Global cognition, MoCA score** | 26.0 ± 2.1            | 26.4 ± 2.8                  | 26.7 ± 2.0      | F = 0.64      |
| **Baseline VO₂peak (ml/kg/min)** | 22.2 ± 6.3             | 24.7 ± 6.9                  | 22.8 ± 6.1      | F = 1.36      |
| **Baseline peak power (W)** | 128.9 ± 49.4            | 145.0 ± 51.1                | 126.4 ± 37.1    | F = 1.57      |
| **Alcohol, Units per week** | 5.7 ± 5.9               | 5.1 ± 5.5                   | 6.4 ± 6.1       | F = 0.44      |
| **Time from baseline to 6-mo assessment (wks)** | 33.0 ± 3.7             | 34.7 ± 4.7                  | 34.1 ± 2.3      | F = 1.60      |
| **Time from baseline to 18-mo assessment (wks)** | 85.3 ± 3.6             | 88.3 ± 5.6                  | 87.1 ± 3.9      | F = 3.38*     |
| **Physical activity (Met.min/wk⁻¹)** | 4379 ± 3708             | 4372 ± 2488                 | 3533 ± 1981     | F = 0.94      |
| **DASS Depression score** | 2.3 ± 3.0               | 1.61 ± 2.1                  | 1.7 ± 1.9       | F = 0.95      |
| **Daily kilojoule intake** | 6709 ± 2459             | 7430 ± 3286                 | 6059 ± 1896     | F = 2.01      |
| **BMI (kg/m²)**           | 25.8 ± 3.7              | 26.0 ± 3.9                  | 25.3 ± 3.4      | F = 0.30      |
| **Waist-hip ratio**       | 0.87 ± 0.08             | 0.88 ± 0.07                 | 0.88 ± 0.08     | F = 0.08      |

*P < 0.05, post-hoc Tukey’s significant difference between high-intensity group and moderate-intensity group. Test statistics determined by one-way analysis of variance for continuous variables and chi-square for categorical variables. Abbreviations: APOE, Apolipoprotein E; BDNF Val66Met, brain-derived neurotrophic factor Valine66Methionine single nucleotide polymorphism; BMI, body mass index; DASS, Depression, Anxiety and Stress Scales; Met.min/wk⁻¹, metabolic minutes per week (subjective habitual physical activity measurement); MoCA, Montreal Cognitive Assessment; VO₂peak, peak aerobic capacity (fitness measurement); W, wattage. aDaily kilojoule intake quantified from the Cancer Council of Victoria Food Frequency Questionnaire.
Individuals excluded from the per-protocol analyses ($n = 13$; based on low adherence or withdrawal from study) reported higher education (15.3 ± 2.1 y), compared with those included (13.9 ± 2.3 y; $t = 2.17$, $p < 0.05$; eTable 1).

**Adherence to prescribed intervention**

There was no difference in exercise session attendance between the high-intensity (85.5 ± 12.4%) and moderate-intensity (86.3 ± 9.8%) groups.

The high-intensity group maintained 120.6 ± 25.1% of peak aerobic power during the high-intensity intervals, while the moderate-intensity group cycled continuously at 70.1 ± 16.3% of peak aerobic power.

There were no serious adverse events recorded.

**Group comparisons**

In both the intention-to-treat and per-protocol analyses, a time*group effect was observed for cardiorespiratory fitness, peak aerobic power, and body fat from pre- to post-intervention (Table 2). The high-intensity group experienced greater improvements in cardiorespiratory fitness (+24.3%) compared with the moderate-intensity group (+12.4%; $B = 3.92$, $p < 0.01$), and control group (+2.4%; $B = 7.36$, $p < 0.001$). The high-intensity group also experienced greater improvements in peak aerobic power (+29%; $B = 55.62$, $p < 0.001$) and decreases in percentage body fat (-3.5%; $B = -1.59$, $p < 0.05$), compared with the control group (peak power change, +1.3%; percentage body fat change, 0.0%).
Table 2  
Effects of the exercise interventions on physiological measures and cognitive composite scores

|                          | Raw mean change from baseline (95% CI) | Time*Group (ITT) | Time*Group (PP) |
|--------------------------|----------------------------------------|------------------|-----------------|
|                          |                                        | Unstandardized B (standard error) | Unstandardized B (standard error) |
|                          |                                        | Time to 6 months | All timepoints   | Baseline to 6 months | All timepoints |
| High-intensity           |                                        |                  |                 |
| (n = 33)                 |                                        |                  |                 |
| Moderate-intensity       |                                        |                  |                 |
| (n = 34)                 |                                        |                  |                 |
| Control (n = 32)         |                                        |                  |                 |
| Baseline to 6 months    |                                        |                  |                 |
| **VO\textsubscript{2}peak** (ml/kg/min) |                                        |                  |                 |
| 6                        | 5.40 (4.00, 6.81)                      | 3.67 (0.72)**    | 0.35 (0.38)     |
| 18                       | 0.78 (-0.62, 2.18)                     | -1.43 (-2.78, -0.08) | -0.99 (-2.85, 0.86) |
| **Peak power (Watts)**   |                                        | 27.33 (4.24)**   | 3.18 (2.51)     |
| 6                        | 37.2 (29.4, 45.1)                      | 1.60 (-3.12, 6.33) |                  |
| 18                       | 7.2 (-0.6, 15.1)                       | 0.14 (-6.56, 6.85) | -9.59 (-16.7, -2.43) |
| **% Body fat**           |                                        | -0.80 (0.37)*    | -0.09 (0.23)    |
| 6                        | -1.04 (-1.83, -0.25)                   | -0.48 (-1.05, 0.10) | 0.00 (-0.64, 0.63) |
| 18                       | 1.73 (0.39, 3.07)                      | 2.64 (1.85, 3.44) | 1.97 (0.70, 3.24) |
| **Global Cognitive composite** |                                        | -0.04 (0.07)    | -0.02 (0.03)    |
| 6                        | 0.11 (-0.03, 0.24)                     | 0.19 (0.09, 0.28) | 0.13 (-0.02, 0.27) |

Intention-to-treat analyses, n = 99; Per-protocol analyses, n = 86. *p < 0.05, **p < 0.001. Baseline to 6 months is pre- to immediately post-intervention. ‘All timepoints’ includes the full study period of baseline, 6 months, and an 18-month follow-up (i.e. 12 months post-intervention). Abbreviations: CI, confidence intervals; ITT, Intention-to-treat analyses; PP, Per-protocol analyses; VO\textsubscript{2}peak, peak aerobic capacity (fitness measurement). All models include age, gender, and years of education as covariates.
| Raw mean change from baseline (95% CI) | Time*Group (ITT) | Time*Group (PP) |
|---------------------------------------|------------------|------------------|
|                                       | Unstandardized B (standard error) | Unstandardized B (standard error) |
| 18 0.18 (0.05, 0.30)                  | 0.00 (0.09)      | 0.04 (0.09)      |
|                                        | 0.21 (0.07, 0.34) | 0.02 (0.04)      |
|                                       | 0.23 (0.08, 0.38) | 0.02 (0.04)      |
| **Executive Function composite**      |                  |                  |
| 6 0.17 (-0.00, 0.34)                  | 0.13 (-0.03, 0.30) |                  |
| 0.31 (0.14, 0.49)                     |                  |                  |
| 18 0.30 (0.12, 0.47)                  | 0.18 (0.00, 0.35) |                  |
| 0.31 (0.06, 0.56)                     |                  |                  |
|                                       | 0.02 (0.11)      | -0.04 (0.04)     |
| **Episodic Memory composite**         |                  |                  |
| 6 0.19 (-0.04, 0.43)                  | 0.13 (-0.07, 0.34) |                  |
| 0.15 (-0.00, 0.30)                    |                  |                  |
| 0.32 (0.12, 0.53)                     |                  |                  |
| 18 0.20 (-0.04, 0.43)                 |                  |                  |
| 0.25 (0.07, 0.44)                     |                  |                  |
|                                       | 0.01 (0.15)      | 0.09 (0.16)      |
| **Attention composite**               |                  |                  |
| 6 -0.17 (-0.50, 0.15)                 | -0.22 (-0.48, 0.04) |                  |
| 0.11 (-0.12, 0.35)                    |                  |                  |
| -0.02 (-0.26, 0.23)                   |                  |                  |
| 18 -0.09 (-0.30, 0.13)                | -0.10 (-0.33, 0.13) |                  |
| -0.02 (-0.26, 0.23)                   |                  |                  |

Intention-to-treat analyses, \( n = 99 \); Per-protocol analyses, \( n = 86 \). *\( p < 0.05 \), **\( p < 0.001 \). Baseline to 6 months is pre- to immediately post-intervention. ‘All timepoints’ includes the full study period of baseline, 6 months, and an 18-month follow-up (i.e. 12 months post-intervention). Abbreviations: CI, confidence intervals; ITT, Intention-to-treat analyses; PP, Per-protocol analyses; \( \text{VO}_2\text{peak} \), peak aerobic capacity (fitness measurement). All models include age, gender, and years of education as covariates.

There were no significant time*group effects on any of the cognitive composite scores. Main effects for time were significant for the executive function composite variable \( (p < 0.05) \), likely indicating a small practice effect experienced on the tasks assessing this cognitive domain. Similarly, there were no significant effects of the genotype*time*group interactions on the cognitive composite scores.

**Individual variability analysis**

Within the high-intensity group only, changes in cardiorespiratory fitness were associated with changes in global cognitive function \( (F = 4.91, p < 0.05, \eta^2_p = 0.18) \) and executive function \( (F = 13.89, p < 0.001, \eta^2_p = \)
Increases in cardiorespiratory fitness were associated with improvements in global cognition ($F = 4.37, p < 0.05, \eta_{p}^2 = 0.06$) and executive function ($F = 4.83, p < 0.05, \eta_{p}^2 = 0.06$) from pre- to post-intervention in the whole sample.

### Table 3
Changes in cardiorespiratory fitness (residuals) and cognitive function (residuals) from pre- to immediately post-intervention

| Independent Variable ($F$ statistic) | High-intensity group | Whole cohort |
|--------------------------------------|----------------------|--------------|
|                                      | Fitness change $^{a}$ | Fitness change $^{a} \times BDNF$ Val/66Met | Fitness change $^{a} \times APOE$ $\varepsilon$4 carriage |
| **Global Cognition change**          | 4.91*                | 4.37*        | 5.13*        | 2.50 |
| **Executive Function change**        | 13.89**              | 4.83*        | 4.54*        | 0.33 |
| **Episodic Memory change**           | 0.68                 | 0.84         | 4.96*        | 2.57 |
| **Attention change**                 | 0.94                 | 2.23         | 0.01         | 0.13 |

$^{a}$Residualised change scores created from a linear model where the baseline score was entered as an independent variable and post score (6 months) as the dependent variable. *$p < 0.05$, **$p < 0.001$.

Covariates: age, gender, years of education. Abbreviations: $APOE$, Apolipoprotein E; $BDNF$ Val66Met, brain-derived neurotrophic factor Valine66Methionine single nucleotide polymorphism.

The $BDNF$*fitness change interaction term was significant for global cognition ($F = 5.13, p < 0.05, \eta_{p}^2 = 0.07$), executive function ($F = 4.54, p < 0.05, \eta_{p}^2 = 0.06$), and episodic memory ($F = 4.96, p < 0.05, \eta_{p}^2 = 0.07$). Post-hoc analyses of these interactions revealed non-Met carriers (i.e. $BDNF$ Val/Val homozygotes) received benefit in terms of a relationship between change in cardiorespiratory fitness and global cognitive function ($F = 7.52, p < 0.01, \eta_{p}^2 = 0.16$) and executive function ($F = 8.83, p < 0.01, \eta_{p}^2 = 0.18$; Figs. 2A-C); i.e., greater improvements in cardiorespiratory fitness were associated with greater improvements in cognitive performance post-intervention among non-Met carriers.

We did not observe an effect of $APOE$*fitness change on any of the cognitive change scores (Table 3). However, following stratification by $APOE$ $\varepsilon$4 carriage, only $\varepsilon$4 carriers demonstrated an association between increases in cardiorespiratory fitness and improvements in global cognition ($F = 4.92, p < 0.05, \eta_{p}^2 = 0.23$; eFigure 2).

**Discussion**
The current study compared the impact of six months of supervised high- and moderate-intensity exercise on cognition in a group of cognitively normal older adults. Our intervention successfully delivered high-intensity exercise and resulted in greater increases in cardiorespiratory fitness, compared with the moderate-intensity group. We did not observe any beneficial effects to cognition when comparing group performance from pre- to post-intervention. However, changes in cardiorespiratory fitness from pre- to post-intervention were associated with changes in global cognition and executive function in the high-intensity group, and the entire cohort. Furthermore, we observed moderating effects of the \textit{BDNF} Val66Met polymorphism, whereby the relationship between change in cognition and change in fitness was only evident in Val/Val homozygotes (i.e., non-Met carriers).

When examining the group-level data, we found no effect of either the high- or moderate-intensity exercise interventions on cognitive performance. These findings are inconsistent with a recent RCT which demonstrated improvements on a single high-interference memory task, following a 12-week high-intensity exercise intervention, compared to moderate-intensity exercise (8). As the cohort within the current study and that investigated by Kovacevic et al. were similar for age, cognitive status, and health, a methodological difference between studies may instead account for the disparate findings. It is possible that more frequent exercise, at least thrice-weekly (delivered by Kovacevic and colleagues), is required to induce cognitive benefit, even with a shorter intervention period (12 weeks). Indeed, the induction of neurotrophic factors (e.g., BDNF) may be required on a more ‘frequent’ basis to contribute to detectable neural benefits (22). It would not be surprising that duration and frequency, in addition to intensity, play an important role in exercise-induced cognitive response. Thus, future studies are required to further elucidate the optimal exercise parameters for benefiting cognition.

Within the entire cohort, and high-intensity group alone, increases in cardiorespiratory fitness were associated with improvements in global cognitive performance and executive function, with moderate to high effect sizes observed. These data support prior work that has reported relationships between exercise-induced improvements in cardiorespiratory fitness and cognitive changes (13, 21, 23, 24). The high-intensity exercise intervention in the current study increased cardiorespiratory fitness levels greater than prior similar RCTs in older adults (typically 10–15% increases) (8, 13, 25). It therefore remains puzzling as to why the observed associations between changes in cardiorespiratory fitness and cognition did not yield group-level differences in cognitive outcomes. While it is possible that individuals with the poorest baseline cognition and fitness levels were more likely to experience fitness-associated cognitive improvement irrespective of exercise intervention, our statistical analysis at least partially corrected for this potential bias. It is also important to consider whether the cognitive assessments used within this generally high-functioning sample were sensitive enough to detect differences between groups.

The associations between changes in cardiorespiratory fitness and global cognition, executive function, and episodic memory were strongest in \textit{BDNF} Val/Val homozygotes. Increases in BDNF levels is one of the most well-supported mechanistic theories underlying the relationship between exercise and brain health (26). BDNF is synthesized in cells as a precursor molecule (pro-BDNF), which undergoes proteolytic cleavage to yield the mature form. Carriage of the \textit{BDNF} Met allele can negatively alter the
processing of pro-BDNF to mature BDNF in neurons: based on our data, it is possible that exercise may not be potent enough to counteract this detrimental phenotype. Consistent with our findings, a recent systematic review on this topic revealed Val/Val homozygotes are more likely to gain benefit from exercise in terms of better memory performance, compared with Met carriers (27). Moreover, we also observed a relationship between fitness and global cognition in APOE ε4 carriers, but not non-carriers; however, the interaction term APOE*fitness change was not significant (indicating that a moderating effect does not exist). It is likely that combinations of genetic factors influence the relationship between cardiorespiratory fitness and cognition. Previous studies have detected cumulative effects of APOE ε4 carriage and BDNF Val66Met carriage on cognitive decline (28); however, our study was not sufficiently powered to examine the APOE*BDNF interaction. Consequently, appropriately powered exercise interventions coupled with hypothesis-driven genetic investigation may reveal more on the ability of exercise to either provide added benefit to those with optimal genetic factors, or alternatively counteract detrimental genotypes.

Strengths and limitations

The lack of an active control group within the current study contributed to differences in exposure (e.g., social interactions) between our exercise groups and inactive control groups. Nevertheless, as we did not detect group differences across cognitive outcomes, this is unlikely to have affected the results reported here. Our cohort was a generally homogenous sample of highly educated, Caucasian older adults living in the community, and our results may not be applicable to the wider population. Strengths of the study include the three-group design that aimed to detect intensity differences, and our ability to objectively examine intensity levels throughout the intervention. Indeed, our use of rate of perceived exertion to monitor within-subject intensity proved to be an effective method in our older adult cohort, allowing individuals to maintain appropriate intensity targets without the need for frequent testing or the use of monitoring equipment (e.g., heart rate monitors).

Conclusions

We found that in a cohort of cognitively normal older adults, six-months of supervised high-intensity and moderate-intensity exercise did not directly contribute to improvements in cognition, compared to an inactive control group. Our data did, however, suggest improvements in cardiorespiratory fitness are important for inducing cognitive change, and that genetics may play a role in this response. Overall, our data does not provide evidence that high-intensity exercise can contribute to cognitive change in all individuals. Future work in this field should be appropriately designed and powered to examine numerous factors that could contribute to individual variability in response to intervention; ultimately leading to individualised prescription of exercise to induce cognitive change and ultimately reduce dementia risk.

Declarations
Ethics approval and consent to participate

The IPAC study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000643370). The human research ethics committees at Murdoch University and Edith Cowan University approved the conduct of this study, and all participants provided written informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to additional secondary analyses currently being conducted, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The IPAC study is supported by a National Health and Medical Research Council Dementia Research Development Fellowship awarded to Belinda M Brown (grant number: GNT1097105).

Authors contributions

BB designed the study, collected data, analysed the data and drafted the manuscript; NF collected cognitive data and provided a critical analysis of the manuscript; SRS was involved in study design and critical review of the manuscript; JD assisted with the analytic design, provided biostatistical oversight and a critical review of the manuscript; SM collected cognitive data and provided a critical review of the manuscript; NG delivered the exercise intervention, collected physical test data and provided a review of the manuscript; MW designed the cognitive test battery and provided critical review of the manuscript; HRS designed the cognitive battery, assisted with cognitive test interpretation and provided a critical review of the manuscript; RNM was involved in study design and critical review of the manuscript; KIE was involved in analytical design and provided a critical review of the manuscript; JP was involved in study design, provided
oversight of exercise delivery, interpretation of study findings and provided a critical review of the manuscript.

Acknowledgements

All authors would like to thank the IPAC study participants for their generous participation and contribution of time.

References

1. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 2014;13(8):788-94.
2. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev. 2015(4):CD005381.
3. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. Br J Sports Med. 2018;52(3):154-60.
4. Brown BM, Peiffer JJ, Sohrabi HR, Mondal A, Gupta VB, Rainey-Smith SR, et al. Intense physical activity is associated with cognitive performance in the elderly. Transl Psychiatry. 2012;2:e191.
5. Angevaren M, Vanhees L, Wendel-Vos W, Verhaar HJ, Aufdemkampe G, Aleman A, et al. Intensity, but not duration, of physical activities is related to cognitive function. Eur J Cardiovasc Prev Rehabil. 2007;14(6):825-30.
6. Tsukamoto H, Suga T, Takenaka S, Tanaka D, Takeuchi T, Hamaoka T, et al. Greater impact of acute high-intensity interval exercise on post-exercise executive function compared to moderate-intensity continuous exercise. Physiology & behavior. 2016;155:224-30.
7. Alves CR, Tessaro VH, Teixeira LA, Murakava K, Roschel H, Gualano B, et al. Influence of acute high-intensity aerobic interval exercise bout on selective attention and short-term memory tasks. Perceptual and motor skills. 2014;118(1):63-72.
8. Kovacevic A, Fenesi B, Paolucci E, Heisz JJ. The effects of aerobic exercise intensity on memory in older adults. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2019:1-10.
9. Keating CJ, Parraga Montilla JA, Latorre Roman PA, Moreno Del Castillo R. Comparison of High-Intensity Interval Training to Moderate-Intensity Continuous Training in Older Adults: A Systematic Review. Journal of aging and physical activity. 2020:1-10.
10. Brown BM, Bourgeat P, Peiffer JJ, Burnham S, Laws SM, Rainey-Smith SR, et al. Influence of BDNF Val66Met on the relationship between physical activity and brain volume. Neurology. 2014;83(15):1345-52.
11. Brown BM, Castalanelli N, Rainey-Smith SR, Doecke J, Weinborn M, Sohrabi HR, et al. Influence of BDNF Val66Met on the relationship between cardiorespiratory fitness and memory in cognitively
normal older adults. Behav Brain Res. 2019;362:103-8.

12. Brown BM, Peiffer JJ, Taddei K, Lui JK, Laws SM, Gupta VB, et al. Physical activity and amyloid-beta plasma and brain levels: results from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing. Mol Psychiatry. 2013;18(8):875-81.

13. Vidoni ED, Johnson DK, Morris JK, Van Sciver A, Greer CS, Billinger SA, et al. Dose-Response of Aerobic Exercise on Cognition: A Community-Based, Pilot Randomized Controlled Trial. PLoS One. 2015;10(7):e0131647.

14. Komulainen P, Lakka TA, Kivipelto M, Hassinen M, Helkala EL, Haapala I, et al. Metabolic syndrome and cognitive function: a population-based follow-up study in elderly women. Dement Geriatr Cogn Disord. 2007;23(1):29-34.

15. Brown BM, Bourgeat P, Peiffer JJ, Burnham S, Laws SM, Rainey-Smith SR, et al. Influence of BDNF Val66Met on the relationship between physical activity and brain volume. Neurology. 2014;83(15):1345-52.

16. Brown BM, Rainey-Smith SR, Castalanelli N, Gordon N, Markovic S, Sohrabi HR, et al. Study protocol of the Intense Physical Activity and Cognition study: The effect of high-intensity exercise training on cognitive function in older adults. Alzheimer's & dementia (New York, N Y). 2017;3(4):562-70.

17. Brown BM, Rainey-Smith SR, Castalanelli N, Gordon N, Markovic S, Sohrabi HR, et al. Study protocol of the Intense Physical Activity and Cognition study: The effect of high-intensity exercise training on cognitive function in older adults. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2017;3(4):562-70.

18. Borg G. Borg's perceived exertion and pain scales: Human kinetics; 1998.

19. Porter T, Villemagne VL, Savage G, Milicic L, Lim YY, Maruff P, et al. Cognitive gene risk profile for the prediction of cognitive decline in presymptomatic Alzheimer's disease. Personalized Medicine in Psychiatry. 2018;7:14-20.

20. R Foundation for Statistical Computing. R Development Core Team, R: A language and environment for statistical computing. Vienna, Austria2019.

21. Voss MW, Heo S, Prakash RS, Erickson KI, Alves H, Chaddock L, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. Hum Brain Mapp. 2013;34(11):2972-85.

22. Marston KJ, Newton MJ, Brown BM, Rainey-Smith SR, Bird S, Martins RN, et al. Intense resistance exercise increases peripheral brain-derived neurotrophic factor. Journal of science and medicine in sport. 2017;20(10):899-903.

23. Reiter K, Nielson KA, Smith TJ, Weiss LR, Alfini AJ, Smith JC. Improved Cardiorespiratory Fitness Is Associated with Increased Cortical Thickness in Mild Cognitive Impairment. J Int Neuropsychol Soc. 2015;21(10):757-67.

24. Komulainen P, Kivipelto M, Lakka T, Savonen K, Hassinen M, Kiviniemi V, et al. Exercise, fitness and cognition—A randomised controlled trial in older individuals: The DR's EXTRA study. European Geriatric Medicine. 2010;1(5):266-72.
25. Fenesi B, Fang H, Kovacevic A, Oremus M, Raina P, Heisz JJ. Physical Exercise Moderates the Relationship of Apolipoprotein E (APOE) Genotype and Dementia Risk: A Population-Based Study. J Alzheimers Dis. 2017;56(1):297-303.

26. Liu PZ, Nusslock R. Exercise-Mediated Neurogenesis in the Hippocampus via BDNF. Frontiers in neuroscience. 2018;12:52.

27. Liu T, Li H, Colton JP, Ge S, Li C. The BDNF Val66Met Polymorphism, Regular Exercise, and Cognition: A Systematic Review. Western journal of nursing research. 2020:193945920907308.

28. Lim YY, Villemagne VL, Laws SM, Pietrzak RH, Snyder PJ, Ames D, et al. APOE and BDNF polymorphisms moderate amyloid beta-related cognitive decline in preclinical Alzheimer's disease. Mol Psychiatry. 2015;20(11):1322-8.

Figures
The number of cases may vary according to outcome measure due to missing data

**Figure 1**

CONSORT diagram for Intense Physical Activity and Cognition study
Figure 2

Linear relationships between change in cardiorespiratory fitness (residuals) and change in (A) Global cognition (residuals); (B) Episodic Memory (residuals); (C) Executive Function (residuals); from pre- to immediately post-intervention (6 months) in BDNF Val66Met carriers and non-Met carriers Abbreviations: BDNF Val66Met, brain-derived neurotrophic factor Valine66Methionine single nucleotide polymorphism; VO2peak, peak aerobic capacity (fitness measurement).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
