

Featured Article

# Study protocol of the Intense Physical Activity and Cognition study: The effect of high-intensity exercise training on cognitive function in older adults

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## Abstract

**Introduction:** Inconsistent results from previous studies of exercise and cognitive function suggest that rigorously designed randomized controlled trials are urgently needed. Here, we describe the design of the Intense Physical Activity and Cognition (IPAC) study, which will assess the impact of a 6-month high-intensity exercise intervention on cognitive function and biomarkers of dementia risk, compared with a 6-month moderate-intensity exercise intervention and control group (no study-related exercise).

**Methods:** One-hundred and five cognitively healthy men and women aged between 60 and 80 years are randomized into a high-intensity exercise, moderate-intensity exercise, or control group. Individuals randomized to an exercise intervention undertake 6 months of cycle-based exercise twice a week, at 50 minutes per session. All participants undergo comprehensive neuropsychological testing, blood sampling, brain magnetic resonance imaging, fitness testing, and a body composition scan at baseline, 6 months (immediately after intervention), and 18 months (12 months after intervention).

**Discussion:** The IPAC study takes a multidisciplinary approach to investigating the role of exercise in maintaining a healthy brain throughout aging. Rigorous monitoring of exertion and adherence throughout the intervention, combined with repeated measures of fitness, is vital in ensuring an optimum exercise dose is reached. Results from the IPAC study will be used to inform a large-scale multicentre randomized controlled trial, with the ultimate aim of pinpointing the frequency, duration, and intensity of exercise that provides the most benefit to the brain, in terms of enhancing cognitive function and reducing dementia risk in older adults.

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**Keywords:** Exercise; Cognition; Dementia; Study design; Intervention

## 1. Introduction

The relationship between physical activity and cognition has been the subject of consistent study over recent years [1–5]; yet, despite expanding literature on the topic,

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questions still remain regarding the effectiveness of physical activity and exercise as a protective measure against the development of cognitive decline and dementia in older adults. While exercise interventions have demonstrated benefits to cognitive function in older adults [3,6–10], a recent Cochrane review published in 2015 suggested there was insufficient evidence from randomized controlled trials (RCTs) to conclude such a benefit [11]. Since this review, a number of RCTs have published data demonstrating the benefits of exercise using comprehensive batteries of cognitive tasks as outcome measures. Tamura et al. [10] reported that a 2-year exercise intervention was associated with improvements in attention shift, a positive change that was maintained 6 months after intervention. Vidoni et al. [9] evaluated the potential dose response of exercise duration on cognitive function, demonstrating increasing benefits in visuospatial processing across groups exercising 75 min wk<sup>-1</sup>, 150 min wk<sup>-1</sup>, and 225 min wk<sup>-1</sup>. Most recently, a review commissioned by *The Lancet* recommended the prescription of exercise for dementia prevention in older adults [12]. In contrast to the above, a recent large RCT ( $n = 1635$ ) reported no benefits to cognition following a 24-month moderate-intensity (MI) exercise intervention [13]. This study, however, has received methodological criticisms, in particular regarding both the use of relatively short unsupervised exercise sessions and the inability of the investigators to ensure exercise was conducted at a moderate intensity [14]. Importantly, previous observational work indicated that high-intensity (HI) exercise provides greater benefit to cognitive health than low-intensity exercise [15,16]. The aforementioned findings highlight the importance of rigorous methodological procedures in exercise interventions, particularly in regards to ensuring an optimum exercise dose is reached. Thus, RCTs conducting supervised and monitored exercise interventions are vital in examining the true effect of exercise on cognitive health parameters.

The aim of the Intense Physical Activity and Cognition (IPAC) study is to contribute to the growing research base linking exercise to cognition and more specifically provide clarity for researchers, practitioners, and the community in relation to the impact of exercise intensity on cognitive health, and ultimately dementia risk. The IPAC study has been rigorously designed to ensure that criticisms of previous exercise interventions in older adults are considered. More specifically, we propose to undertake repeated aerobic fitness measurements, conduct supervised HI and MI exercise interventions, and monitor participant exertion throughout each exercise session. Our primary objective is to assess whether 6 months of HI exercise is associated with improved cognitive function, compared with an MI exercise intervention or control group. Our secondary objectives are to assess the impact of a 6-month HI exercise intervention on (1) cortical gray matter (GM) volume, region of interest GM volumes (most specifically, hippocampal volume), and default mode network connectivity measured by

magnetic resonance imaging (MRI) and (2) Alzheimer's disease (AD)-related blood-based biomarkers, including proteomics and gene expression, compared with an MI exercise intervention or control group. Our tertiary objectives are to evaluate mediating and moderating variables of the relationship between exercise and cognitive function, that is, evaluating the mediating effect of cardiorespiratory fitness, biomarkers, and brain volume and connectivity and also examining the moderating effect of genotypes associated with increased dementia risk, such as carriage of the apolipoprotein (*APOE*)  $\epsilon 4$  allele or the brain-derived neurotrophic factor (*BDNF*) Val66Met single nucleotide polymorphism.

## 2. Methods

The IPAC study is conducted as a single-centre single-blind RCT and is currently funded by the National Health and Medical Research Council National Institute of Dementia. The human research ethics committees of Edith Cowan University and Murdoch University (Western Australia) have approved this study. The study is registered with the Australian New Zealand Clinical Trials Registry (under identification number ACTRN12617000643370).

### 2.1. Participants and power analysis

The study cohort comprised 105 cognitively healthy men and women (equal ratio) aged 60 to 80 years. Participants are randomized into one of three groups: HI exercise ( $n = 35$ ), MI exercise ( $n = 35$ ), or a control group ( $n = 35$ ; Fig. 1). Participants will be recruited via advertisements in local community and state-wide newspaper publications, presentations to local community organizations, and word-of-mouth. Detailed inclusion and exclusion criteria are listed in Table 1.

Our power analysis is based on our primary outcome variable, cognitive function. Using estimates of change in cognitive composite scores from Vidoni et al. [9], the sample size required to detect differences in cognition (domains assessed in Vidoni et al.: verbal memory, visuospatial processing, and simple attention) between the three groups with at least 80% power and at the 5% level of significance is 28 per group. Assuming a dropout rate of 10% during the 6-month intervention and accounting for possible variance due to covariates in our planned analyses (e.g., age, *APOE*  $\epsilon 4$  allele carriage), 35 subjects will be recruited in each of the 3 groups, giving a total required sample size of 105.

### 2.2. Procedures

In the 4 weeks preceding the start of the exercise intervention (or control period), baseline measurements are obtained in relation to neuropsychological testing, blood sample collection, neuroimaging (MRI), completion of questionnaires, assessments of physical fitness, and a dual-energy X-ray absorptiometry (DXA) scan for the evaluation of

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