Is there a role for physical activity in preventing cognitive decline in people with mild cognitive impairment?

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Abstract

Mild cognitive impairment (MCI) is a common clinical syndrome that identifies people at high risk of developing dementia. Although treatments for MCI are currently unavailable, preliminary evidence has identified potential neuro-protective effects of physical activity, which may lead to improved outcomes. However, there is uncertainty regarding the effectiveness, feasibility and acceptability of this treatment strategy. These uncertainties require further investigation before physical activity interventions can be recommended for routine care.

Keywords: dementia, prevention, exercise therapy, cognition, ageing

Introduction

Mild cognitive impairment (MCI) is defined as cognitive decline greater than expected for an individual’s age and level of education, which does not interfere notably with functional activities [1]. MCI identifies people at high risk of developing dementia. In people aged 70 years and older, the reported prevalence of MCI ranges from 14 to 18% and the progression rate to dementia is 5–15% per year [2]; considerably greater than the 1–6% per year for people without MCI [1]. However, MCI is a complex clinical syndrome and recent evidence has suggested that not everybody with MCI develops dementia and some people may even improve over time [2].

In people with MCI, neuro-pathological changes characteristic of dementia have been identified. Alzheimer’s disease changes appear to be most common, but infarcts and mixed changes are also frequently observed [3]. As cumulative neuronal loss is considered critical in the pathological process of the dementias [4], it has been proposed that interventions targeted at preserving neuronal function in MCI may prevent or postpone cognitive decline into dementia [1]. Successful interventions may therefore also help to reduce the economic burden of dementia which, in the UK, currently exceeds that for stroke, heart disease and cancer combined [5]. Physical activity (PA) is one such possible intervention and this article reviews the evidence for PA in preventing cognitive decline in people with MCI. PA refers to any bodily movement produced by skeletal muscle that requires energy expenditure [6]. Exercise training is a sub-set of PA that is planned, structured and repetitive and has the objective of improving or maintaining physical fitness [6]. Exercise training is one method to increase PA levels.

Potential mechanisms of neuro-protection through physical activity

Several biologically plausible mechanisms through which PA may exert neuro-protective effects have been identified in cognitively normal human and animal models (Figure 1). Exercise training has been shown to up-regulate and increase the activity of several neurotrophic and vascular growth factors, including insulin-like growth factor-1, brain-derived neurotrophic factor and vascular endothelial growth factor [7]. These changes are thought to increase neurogenesis, angiogenesis, synaptic plasticity and dendritic spine density in the hippocampus [7].
Increased PA may have an additional positive influence on cognition through improving vascular risk factors [8] and cerebral blood flow [9], with associated reductions in small vessel ischaemic disease [10, 11]. Obesity, high blood pressure, hypercholesterolaemia, hyperhomocysteinaemia and insulin resistance are all risk factors for vascular disease that are potentially modifiable through PA [11]. Furthermore, improved insulin resistance may directly increase synaptic plasticity and energy metabolism [12]. Exercise training has also been shown to enhance the expression of genes that regulate the production of free-radical scavenging enzymes, which may reduce free radical damage to neurons and neurodegenerative diseases [13, 14]. Exercise training may also increase production of mitochondria in neurons [15] and thus enhance energy metabolism in the brain, ensuring energy supply to neurons.

Anatomical evidence from cross-sectional studies

There is currently no literature which examines differences in brain structure and function between physically active and inactive people with MCI. However, a study involving cognitively normal older people has reported greater grey and white matter volume (measured by magnetic resonance imaging) in people with higher aerobic capacity compared with those with lower aerobic capacity [16]. Additionally, aerobic fitness has also been associated with better integrity of the ascending and descending white matter tracts of the prefrontal cortex, independent of age and gender [17]. Although there are other potential confounding variables, this anatomical evidence supports the hypothesis that increased PA may be neuro-protective. The extent to which this applies to people with MCI requires further investigation.

Cognitive evidence from observational studies

The association between PA levels, risk of MCI and subsequent progression to dementia has yet to be reliably established. Two observational studies have investigated relationships between the level of PA and risk of MCI. A population-based case–control study found that moderate PA was associated with reduced risk of MCI both in mid-life (odds ratio, OR, 0.61, 95% confidence interval, CI, 0.43–0.88, \( P = 0.008 \)) and late-life (OR: 0.68, 95% CI: 0.49–0.93, \( P = 0.02 \)) [18]. A prospective cohort study,
however, reported a suggestive but non-significant association between PA and reduced risk of MCI [19].

Evidence from general populations suggests a protective effect of PA on cognition. A meta-analysis of 16 prospective studies calculated the pooled relative risk of dementia as 0.72 (95% CI: 0.60–0.86, P < 0.001) for the most physically active group compared with the least active group [20]. A further meta-analysis of 15 prospective studies investigated the association between PA and risk of cognitive decline in cognitively normal older adults [21]. In people with high levels of PA, the hazard ratio for cognitive decline over 1–12 years follow-up was 0.62 (95% CI: 0.54–0.70, P < 0.001), and even moderate levels of PA showed significant protection against cognitive decline (hazard ratio 0.65; 95% CI: 0.57–0.75, P < 0.001). These associations between PA, vascular disease risk factors, neuronal growth factors, brain structure/function and cognitive function make it a possible candidate for manipulation in order prevent or postpone cognitive decline. Whether increasing levels of PA after the onset of MCI can be effective in preventing or slowing cognitive decline is unknown and has begun to be investigated in randomised controlled trials (RCTs).

**Evidence from randomised controlled trials**

Three recently published RCTs have investigated the effect of high intensity and moderate intensity PA upon cognition in older adults with MCI. One RCT in the USA investigated the efficacy of a 6 month, high-intensity aerobic exercise intervention to improve cognitive function and associated biomarkers in 29 participants with MCI [22]. Participants in the exercise group trained at a target heart rate of 75–85% heart rate reserve for 45–60 min a day on 4 days of the week. Following aerobic training the exercise group improved in aspects of executive function (F(5,19) = 3.05; P = 0.04). Greater effects were reported in women than men and these effects were associated with reduced insulin resistance and the cortisol level.

The two other RCTs assessed moderate intensity exercise training/PA interventions. One study in the Netherlands randomised 152 community-dwelling older people with MCI to a 12 month moderate intensity group-based walking exercise intervention twice a week, or a low intensity activity programme as control [23]. Intention-to-treat analysis found no significant effect of walking upon cognition. However, a per protocol analysis revealed that memory improved in men attending at least 75% of the walking programme sessions (auditory verbal learning test difference of 1.5 words, 95% CI: 0.1–3.0; in walking group compared with the control group, P = 0.04). In women, although attendance to walking sessions was frequently very low, increased session attendance was related to improved attention (performance in the Stroop colour word test improved by 0.3 s, P = 0.04). These exploratory analyses are consistent with a treatment effect upon some domains of cognitive function in people with MCI who adhere to training. One further RCT of a moderate intensity intervention was conducted in Australia [24]. One hundred and seventy participants with either a memory complaint or objectively measured MCI were randomised to a 24-week PA (usually walking) plus education, or usual care plus an education intervention. At 6 months follow-up those in the PA group had a small improvement in the Alzheimer’s Disease Assessment Scale—Cognitive subscale (ADAS-Cog) score (absolute difference of −1.3 points, 95% CI: −2.38 to −0.22, relative to control). At 18-month follow-up the benefit were sustained, albeit attenuated; those in the intervention improved −0.73 points on ADAS-Cog (95% CI −1.27 to 0.03) compared with changes in the control group of −0.04 points (95% CI: −0.46 to 0.88). Although the findings from these three trials are encouraging and suggest a potential benefit of PA for cognition in MCI, the trials have several important limitations. The first had a small samples size, a selective population and limited generalisability [22]; the second, poor intervention adherence [23] and the third included both people with subjective memory complaint and people with objective MCI, without a sensitivity analysis exploring the effect of the intervention on these different groups [24].

**Challenges of developing physical activity interventions for people with MCI**

The design and delivery of an appropriate PA programme for people with MCI is challenging. First, older people report a reluctance to start exercise, report fear of injury or pain, have chronic illness, and report no social support to exercise [25]. Second, people with MCI may have cognitive obstacles to overcome such as slow acquisition of skill and difficulty in remembering routines. One US intervention, Resources and Activities for Lifelong Independence (RALLI) has attempted to address these issues through an exercise intervention that incorporates a structured exercise regimen, behaviour change strategies and health promotion information [26]. Following a successful pilot study, the RALLI intervention is currently being tested in an RCT.

**Conclusion**

There is preliminary evidence to support the role of PA to prevent neuronal loss, preserve neuronal function and prevent or postpone cognitive decline. Recent basic science research has identified biologically plausible mechanisms of neuronal protection through exercise, and observational research has provided evidence for an association between high levels of PA and enhanced cognition. Although there is evidence from a small number of RCTs, there remains uncertainty about the extent to which PA can stimulate the potential biological mechanisms of neuro-protection in people with MCI and prevent further cognitive decline and dementia and further large-scale trials are needed. Given the challenges of engaging older people with cognitive
improvement in PA, the identification of practical solutions to initiate PA behaviour change in people with MCI are of particular importance when designing future interventions.

Key points

- MCI identifies people at increased risk of dementia.
- In older people, higher levels of PA are associated with lower risk of cognitive decline and dementia.
- RCTs of PA interventions for people with MCI have reported early promising results.
- Further large-scale randomised controlled trials are needed.
- Future research should consider behaviour change strategies to improve intervention adherence.

Conflicts of interest

There are no financial, personal, or professional interests that could be construed to have influenced the paper.

References


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