**The Role of Exercise in Preventing Cognitive Decline: Mechanisms and Therapeutic Potential**

### Abstract

Cognitive decline is a natural process that occurs with aging, and it encompasses reductions in various functions including memory and processign speed. Public health concerns such as dementia are ever-increasing. Exercise is a promising tool for maintaining cognitive function and reducing the risk of dementia. Here, we describe the various pathways through which exercise preserves cognitive function -- in neurological and cardiovascular domains. Future research should examine more standardized procedures of how exactly exercise improves cognitive function, and potentially utilize precision medicine for individualized guidance.

### Introduction of Cognitive Decline

Cognition changes across the lifespan. Subclinical cognitive decline, a normal part of aging, is a phenomenon that includes reductions in executive function, processing speed, and memory [1]. Clinically relevant mild cognitive impairment (MCI) is symptomatic cognitive decline that does not impair independence, contrasted with dementia, where activities of daily living are significantly affected [2]. Annually, ~15% of patients with MCI will transition to dementia [3, 2]. While many forms of dementia exist, Alzheimer’s disease (AD), a type of dementia caused by specific protein abnormalities in the brain, is the most common manifestation [4].

### Exercise Supports Cognition in Older Adults

A protective effect of physical activity on cognition has been documented since at least as early as the 1970s, when two studies found that leisure-time physical activity correlated with cognitive health in aging adults [5, 6]. Subsequent research has aimed to unravel this connection, and to investigate whether exercise can be employed to prevent or slow cognitive decline in older people. In older adults, exercise, muscle strength, and cardiorespiratory fitness are associated with significant protection from cognitive decline. Exercise is thought to benefit overall cognitive performance, risk of dementias including AD, and transition from MCI to dementia [7, 8]. Meta-analyses find that exercise supports cognitive function across populations, including cognitively normal individuals, and those with MCI, AD, or other types of dementia [9, 10, 11, 12]. Meta-analyses also show that exercise reduces risk of developing dementia [13, 14]. One influential meta-analysis encompassing 23,345 individuals found a 40% reduction in AD risk in physically active individuals, though the body of included studies was statistically distinct (being unusually non-heterogeneous) compared to similar analyses [15].

There is little agreement among meta-analyses as to which types of exercise are optimal. For example, some studies find that aerobic exercise is essential for producing cognitive benefit, while others identify resistance training as especially effective [16, 9, 17]. The full extent of exercise’s therapeutic potential in cognitive decline is unknown. The intensity, duration, and type of exercise varies widely between studies, and little work has been done to define optimal exercise programs for protecting cognitive health. Dose-response studies, which attempt to connect outcomes to exercise duration or intensity, have been inconclusive [7, 18]. Exercise that involves cognitive activity, such as dance, may be more beneficial than repetitive exercise of similar duration and intensity [19]. More broadly, there is interest in the potential synergy of exercise training with cognitive training, but to date, it is unclear whether combination training is more effective than exercise alone [20].

Beyond direct effects on cognition itself, exercise reduces risk of negative life experiences. Exercise training reduces falls by 31% [17]. Exercise reduces depressive symptoms in people with dementia [21, 22]. Depression is linked to cognitive decline, and is characterized by brain volume loss that resembles MCI [23]. Better quality of life, in turn, may be associated with better cognitive performance [24, 25, 26].

Overall, the literature shows that exercise is beneficial for supporting cognition and preventing dementia, but large-scale collaborative work is needed to standardize experimental approaches and guidelines for recommended exercise programs.

### Mechanisms Underlying Benefits of Exercise in Cognition

#### Neurological

The plurality of studies connecting exercise and cognitive function at the molecular level focus on a small protein called brain-derived neurotrophic factor (BDNF). BDNF is integral to the current understanding of how exercise benefits cognition. BDNF functions to support the survival, connectivity, and functionality of neurons. It is reduced in the brains of people with dementia [27]. BDNF is produced by neurons and glial (supporting) cells in the brain. Outside of the brain, it is produced in large quantity by skeletal muscle, especially after exercise [28, 29]. Exercise raises blood BDNF levels in older adults [30]. In an interventional exercise study, improvements in cognitive function are associated with increased blood BDNF [31]. In an animal study, blocking the action of BDNF blocked the cognitive benefits of exercise, suggesting that BDNF acts to link exercise and cognition at the molecular level [32].

Dementia is characterized by loss of brain volume, especially in areas linked to memory and executive function. In older adults, aerobic exercise and cardiovascular fitness is associated with slower decline in brain volume and grey matter volume [33]. A 9-year longitudinal study found that individuals with regular physical activity (walking at least 72 blocks per week) had more grey matter and a twofold decreased risk of developing dementia [34].

Dysfunction of the blood-brain barrier has been identified as a cause of cognitive decline in animal models of dementia, but is only beginning to be studied in humans. The blood-brain barrier is a specialized structure that functions to permit only a subset of molecules to pass from the brain microvasculature into the brain tissue itself. When it becomes dysfunctional, infiltration of disallowed molecules can initiate or exacerbate neurotoxic cascades. A recent study found that 14 weeks of exercise training increases the integrity of the blood-brain barrier in older people [35].

#### Cardiovascular

Deficits in brain microvascular circulation have long been recognized as likely contributors to dementia [36]. Individuals with elevated cardiovascular risk profiles are at increased risk of developing MCI and dementia [37]. Even in adults without frank cognitive dysfunction, cardiovascular health correlates positively with cognitive measures including working memory and executive function [38]. In a 72-month longitudinal study, individuals with coronary artery disease had lower baseline cognitive performance and steeper cognitive decline than controls without cardiovascular disease [39]. People with MCI who also have dyslipidemia, hypertension, or diabetes are more likely to develop dementia, and those with a healthier cardiovascular risk profile are more likely to revert to normal cognition [40]. In sum, numerous avenues of evidence point to a connection between poor cardiovascular health and poor cognitive health.

Exercise improves cardiovascular risk factors, such as reducing LDL cholesterol and triglycerides [41]. In older adults undertaking exercise programs, improvements in cardiorespiratory fitness correlate positively with overall cognitive function [42, 43]. Exercise may be most effective at reducing dementia risk in people with low overall cardiorespiratory fitness [7, 44].

In an observational study of older women, fitness, cerebral blood flow, and cognitive function were positively correlated, suggesting that enhanced blood flow may be a mechanism by which exercise supports cognition [45]. An experiment testing the effects of 3 months of exercise found that improvements in cardiorespiratory fitness correlate positively with hippocampus blood flow, hippocampus volume, and cognition [46]. Neurovascular coupling, the process by which brain areas receive more blood flow in response to increased metabolic demand, may be especially important for cognition [47, 48]. Patients with AD have impaired neurovascular coupling [49]. In an animal model, regular exercise protected cognitive function by enhancing neurovascular coupling [50].

#### Metabolic

Insulin resistance is a risk factor for dementia, especially AD. Individuals with diabetes are ~50% more likely to develop dementia than nondiabetic people [51]. Insulin resistance is a feature of AD brains, though glucose uptake is unaffected [52]. In the brain, insulin acts to support neuronal and synaptic health, and inhibits the development of neurotoxic protein aggregates [53]. Acute insulin infusion with normoglycemia improves cognition in older adults, and those with the best systemic insulin sensitivity have the most cognitive benefit [54]. Daily intranasal insulin treatment produces cognitive benefits and enhances brain volume after 2 and 4 months [55]. In a study of patients with MCI or AD, daily intranasal insulin treatment improved cognition, and this was most pronounced in insulin-resistant individuals receiving a high insulin dose [56]. Physical activity is well-known to increase insulin sensitivity in peripheral tissues. Recent evidence also shows that exercise training increases insulin sensitivity in the human brain [57, 58]. However, research that specifically focuses on exercise and insulin sensitivity in the brains of older people is needed.

Exercise results in production of metabolites that may enhance cognitive function by inducing BDNF. Prolonged aerobic exercise results in production of ketones [59]. Increasing circulating ketone levels via supplementation or dietary changes is beneficial to cognition in patients with AD [60]. Ketone supplementation in younger adults without dementia increases cerebral blood flow, enhances cognition, and elevates BDNF in the blood [61]. BDNF likely connects ketones to cognition, since rodent models have shown that ketones induce BDNF expression in neurons [62, 63]. Another metabolite produced in large quantities during exercise is lactate, which has also been shown to induce neuronal BDNF expression in rodent models [64].

#### Inflammatory

Long-term, low-level inflammation is a driver of neuronal death and dysfunction. This effect is mediated by pro-inflammatory cytokines, small proteins that are released into blood or tissue and cause toxic cascades when they reach their receptors on target cells. Pro-inflammatory cytokines are associated with frailty in older adults [65]. Exercise reduces pro-inflammatory cytokines in the blood of older adults [65]. This is also the case for older adults with MCI and dementia, and decreased inflammation tends to correlate with increased BDNF in these studies [66, 67]. In a prospective study of 148 matched pairs, elevated levels of CRP, a marker of inflammation, increased the probability of developing MCI by at least twofold [68].

One important way pro-inflammatory cytokines cause neuronal death is by producing reactive oxygen species (ROS). ROS are unstable molecules that chemically react with essential biomolecules such as proteins, lipids, and DNA, irreversibly damaging them. High levels of ROS are toxic to cells, although some amount of ROS is beneficial for health. Exercise causes a transient, mild induction of ROS, which is one of the beneficial functions of ROS. Antioxidants inhibit ROS and prevent their harmful effects. Exercise increases antioxidant levels and decreases ROS-induced molecular damage in the skeletal muscle [69]. High physical activity levels and good cognition are correlated with total antioxidant capacity in blood in older adults [70].

### Therapeutic Perspective

A recent comparative meta-analysis of 250 AD treatments, including pharmaceutical, dietary, and lifestyle interventions, identified exercise as the most beneficial intervention [71]. Numerous antidepressant medications were also ranked highly, suggesting an interplay between exercise, mood, and cognitive performance [71]. Many of the pathways benefited by exercise have been targeted for pharmaceutical intervention in clinical studies. In fascinating contrast to exercise itself, NSAIDs (affecting inflammation), antihypertensives or statins (affecting cardiovascular health), and metformin (affecting metabolism and insulin signaling) have all proven ineffective in slowing cognitive decline [72, 73].

Conclusion

Through various mechanisms and pathways, exercise is a powerful intervention for preservation of cognitive function and reducing the risk of dementia. Physical activity supports brain health and much research has shown the benefits of exercise, though further studies are needed to investigate individualized approaches to exercise, potentially leveraging precision medicine. Given its broad health benefits and accessibility to the population, exercise should be an integral aspect of dementia prevention, while supporting cognitive health and greater well-being.

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