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Physical Activity for Brain Health in Older Adults

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TITLE: Physical Activity for Brain Health in Older Adults

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ABSTRACT

Physical activity is a promising strategy for dementia prevention and disease modification. Here, we provide a narrative review the current evidence from epidemiological and intervention studies on the role of physical activity and exercise in promoting cognitive health in older adults both without and with cognitive impairment. We highlight some of the potential underlying mechanisms and discuss biological sex as a potential moderating factor. We conclude with limitations and future directions for this rapidly expanding line of research.

Keywords: Physical Activity, Exercise, Brain Health, Cognitive Health, Aging, Older Adults

INTRODUCTION

Aging is characterized by multifaceted changes in cognitive function, brain structure, and brain function, including declines in cognitive performance related to memory, speed, reasoning, and executive functions, and atrophy in various brain regions, especially the prefrontal cortex and medial temporal lobes (Salthouse, 2011a). However, the deleterious effects of aging do not impact every individual equally, as there is a significant proportion of the population who maintain cognitive function, even in the face of significant brain pathology (Tucker & Stern, 2011). Thus, successful cognitive aging is possible and cognitive impairment may be delayed or averted.

Worldwide, over 47 million people suffer from dementia and this number is expected to reach 74.7 million by the year 2030 and 131.5 million by 2050 (Prince et al., 2015); the estimated total worldwide economic burden will be 2 trillion dollars by 2030 (Prince et al., 2015). Thus, the societal value of identifying and developing effective prevention and intervention strategies is of utmost importance (Brookmeyer et al., 2007).

As effective pharmacological treatments of mild cognitive impairment (MCI) and dementia remain elusive (Raschetti et al., 2007), there is much interest in lifestyle approaches for preventing or treating dementia (Phillips, 2017). Notably, a 10-25% reduction in modifiable risk factors such as smoking, mid-life obesity, hypertension, type 2 diabetes, depression, and physical inactivity has been estimated to prevent as many as 3 million prevalent cases of dementia worldwide (Barnes & Yaffe, 2011). Physical activity, in particular, has been investigated as a primary behavioural prevention strategy to mitigate cognitive decline. Notably, physical activity significantly reduces key cardiometabolic risk factors, such as hypertension and type 2 diabetes (Barnes & Yaffe, 2011; Baumgart et al., 2015), for both Alzheimer's Disease (AD) and vascular cognitive impairment (VCI) – the two most common types of dementia worldwide.

Despite its overall therapeutic potential, substantial variation exists in exercise efficacy on cognitive health at the individual level (Barha, Davis, et al., 2017; S. Colcombe & Kramer, 2003; Gates et al., 2013; Ohman et al., 2014). Thus, it is important to identify key moderators (ie, who) – factors that either attenuate or amplify the effects of exercise – to allow greater precision in recommendations, as well as benefits, for individuals with similar characteristics (ie, subgroups) (Barha, Galea, et al., 2017). Notably, biological sex appears to be a key endogenous moderator of exercise efficacy, especially for the effects of aerobic exercise on cognitive function (Barha, Davis, et al., 2017; Barha, Falck, et al., 2017; S. Colcombe & Kramer, 2003). Given the greater prevalence of AD and faster rate of progression from MCI to AD in women compared with men (Podcasy & Epperson, 2016), there is a need to assess potential sex differences in exercise efficacy.

Here, we review the current evidence from epidemiological and intervention studies on the role of physical activity and exercise in promoting cognitive health in older adults both without and with cognitive impairment. We highlight some of the potential underlying mechanisms and discuss biological sex as a potential moderating factor. We conclude with limitations and future directions for this rapidly expanding line of research.

Definitions

We provide an overview of the terms that will be used throughout this review. The term 'physical activity' refers to any bodily movement produced by skeletal muscles that requires energy expenditure (Caspersen, 1985). Physical activity in daily life can be categorized into occupational, sports, conditioning, household, or other activities (Caspersen, 1985). Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective for the improvement or maintenance of physical fitness (Caspersen, 1985). Broadly, there are two main types of exercise: 1) aerobic exercise training (e.g., brisk walking), aimed at improving cardiovascular health, and 2) resistance training (e.g., lifting weights), aimed at improving muscle mass and strength. Each type of exercise training has its own distinct physiology and benefits (Wanderley et al., 2013).

We will discuss two primary study designs used to investigate the association between physical activity and cognition in older adults – prospective cohort or epidemiological studies, and randomized controlled trials. Epidemiological studies are observational in nature and examine whether engagement in physical activity is associated with changes in cognitive function or risk for dementia. Although prospective cohort studies typically include larger samples of individuals than randomized controlled trials (discussed below), causality cannot be established and the potential for unmeasured confounding variables is often present.

Randomized controlled trials are studies in which participants are randomly allocated to one of several experimental groups. Well-designed trials allow for the measurement of causal effects. One of the experimental groups is the standard of comparison or control. To reduce both known (e.g., socialization) and unknown confounding effects, it is has been advocated that randomized controlled trials of targeted exercise training and cognitive health use an active control arm that consists of equivalent in-person contact as the exercise training. Further, an active control arm consisting of light stretching or low-intensity exercise training is needed in studies that focus on ascertaining the impact of exercise intensity on cognitive function, such as whether exercise needs to be of at least a moderate intensity to induce cognitive benefits (Krogh-Madsen et al., 2011). However, special consideration needs to be paid to the nature of the low-intensity exercise, as certain low-intensity exercises (e.g., yoga) may produce beneficial cognitive effects (Gothe & McAuley, 2015).

CRITICAL REVIEW

Prospective Cohort Studies

Epidemiological studies have largely focused on assessing the association between the amount of physical activity and cognitive health. Historically, physical activity in epidemiological studies has been recorded by self-report questionnaires that typically ask participants to recall their level of physical activity over the last seven days.

Majority of epidemiological data indicate that physical activity predicts subsequent changes in cognitive performance and incidence of dementia among older adults independent of other behaviors and pre-existing factors. A meta-analysis of 16 prospective studies on the incidence of neurodegenerative disease found that more physical activity at baseline predicted a 28% lower risk of developing dementia (resulting from all causes) and a 45% lower risk of developing AD, after adjusting for confounding variables (Hamer & Chida, 2009). A second meta-analysis of 15 prospective studies among individuals without dementia found that high levels of physical activity were associated with a 38% lower risk of cognitive decline, while low to moderate levels of physical activity were associated with a 35% reduced risk (Sofi et al., 2011). A study not included in these previous meta-analyses found that moderate-to-high levels of physical activity might be especially protective against future cognitive decline among those older adults who do not show evidence for cognitive impairment at the initial assessment (Willey et al., 2016).

Epidemiological studies have also investigated the neural correlates underlying the link between physical activity and maintenance of cognitive performance with increasing age. Erickson and colleagues (Erickson, Raji, et al., 2011) used structural magnetic resonance imaging (MRI) to provide insight into the underlying brain regions positively impacted by regular physical activity. In 299 community-dwelling older adults (mean age 78 years) with normal cognitive function from the Cardiovascular Health Study, baseline physical activity was quantified as the number of blocks walked in one week and structural MRIs were acquired 9 years later. Clinical adjudication for cognitive impairment occurred 13 years after baseline. The researchers observed that greater physical activity at baseline was associated with greater gray matter volumes of frontal, occipital, entorhinal, and hippocampal regions 9 years later, and in turn, greater gray matter volume was associated with a two-fold reduction in the risk for cognitive impairment at year 13.

Extending the work of Erickson and colleagues (Erickson, Raji, et al., 2011), Best and colleagues (Best et al., 2017) examined the effects of *maintaining* physical activity over an extended period of time on subsequent changes in older adults' cognition and brain structure. Participants were 141 initially well-functioning community-dwelling older adults (aged 70-79 years at baseline; 60% female; 42% black) enrolled in the Health, Aging, and Body Composition Study and followed over a 13-year period. Physical activity (self-reported time spent walking) was assessed annually from years 1 to 10. Magnetic resonance imaging with diffusion tensor was performed at years 10 and 13. Independent of initial time spent walking, demographics, and APOE e4 status, better maintenance of time spent walking over the decade predicted less reduction in hippocampal volume, smaller increases in global gray matter mean diffusivity and white matter axial diffusivity, and maintenance of general cognitive performance. Physical activity at baseline and at year 10, as well as changes in physical activity over a five-year period, was less predictive of future changes in brain structure and cognition. Thus, how physical activity levels change over longer periods of time may be an important contributor to cognitive and neural protection.

Results from studies with objective measures of physical activity provide additional support for the positive association between physical activity and cognitive function. For example, Buchman and colleagues (Buchman et al., 2012) reported that greater total daily physical activity as assessed by 10 days of continuously monitored actigraphy (physical activity detected from sensors worn on the body) was associated with a two-fold reduced risk of AD over a four-year period in 716 older adults, even after controlling for self-reported physical activity.

Objective measures of physical activity also allow the examination of the association between sedentary behaviour and cognitive function. Sedentary behaviour is defined as any behaviour that incurs ≤1.5 METs and includes behaviours such as sitting, television watching and lying down (Pate et al., 2008). Emerging evidence suggests sedentary behaviour is associated with impaired cognitive function. Falck and colleagues (Falck et al., 2016) conducted a systematic review ascertaining the relationship between sedentary behaviour and cognitive function in adults. This systemic review included studies if they were: 1) observational studies (ie, cohort, case-control or cross-sectional); 2) peer reviewed and 3) published in the English language between 1 January 1990 and 6 February 2016. Falck and colleagues (Falck et al., 2016) found that sedentary behaviour is associated with lower cognitive performance, although the attributable risk of sedentary time to all-cause dementia incidence is unclear. This is, in part, due to a paucity of prospective cohort studies investigating this relationship using objectively measured sedentary behaviour.

A recently published prospective study by Ku and colleagues (Ku et al., 2017) examined the relationship between objectively assessed sedentary behaviour and future cognitive abilities in a cohort of older adults. This study included 285 community-dwelling older adults and was conducted over 22.12 ± 1.46 months. Cognitive ability was ascertained using a Chinese version of the Ascertain Dementia 8-item Questionnaire and sedentary behaviour was captured by 7 days accelerometer data. High levels of sedentary behaviour were associated with an increased risk of worse cognitive ability at follow up (adjusted rate ratio (ARR) 1.09 (95% CI: 1.00 to 1.19)), with the strongest relationship evident in those engaging in over 11 h of sedentary behaviour (ARR 2.27 (95%CI: 1.24 to 4.16)). The relationship remained evident after adjusting for depressive symptoms and physical activity.

In regards to providing specific physical activity recommendations to promote cognitive health in older adults, a major limitation of prospective cohort studies is that they typically do not distinguish between different types of physical activity. A study by Lee and colleagues (Lee et al., 2015) addressed this gap by examining the amount and type of physical exercise that might reduce the future risk of dementia in community-living older people. This six-year observational study included a total of 15,589 community-living individuals aged 65 years and older with no history of stroke, clinical dementia, or Parkinson disease when they completed the baseline health assessment. Self-reported habitual physical exercise patterns in the past one month, including the frequency, duration, and type of exercise, at baseline and three years later were analyzed. The study outcome was incident dementia over six years. Compared with those who developed dementia, those who remained dementia-free performed more aerobic and mind-body exercises (i.e., Tai Chi or yoga). However, stretching and toning exercises did not reduce the risk of dementia. A key limitation of this study is the exclusion of resistance training in the questionnaire.

In general, a key limitation of prospective cohort studies is that causality cannot be established and the potential for unmeasured confounding variables is often present. Notably, the positive associations observed in prospective cohort studies may be due to *reverse causality* (Ahlskog et al., 2011). In other words, those with very early, preclinical degenerative disease may be less inclined to be physically active. Conversely, it is possible that those individuals who engage in more physical activity have a more robust genetic profile against cognitive impairment and dementia. Notably, the Whitehall II Cohort Study (Ahlskog et al., 2011), with 10,308 participants aged 35-55 years at study inception, showed no association between physical activity and subsequent 15 year cognitive decline. Thus, we need to refer to data garnered from randomized controlled trials to better understand the causal relationship between exercise and cognitive health.

Randomized Controlled Trials of Aerobic Exercise Training

Within the context of randomized controlled trials, much of the research has focused on aerobic exercise training. Seminal work was conducted by Kramer and colleagues (S. J. Colcombe et al., 2003; S. J. Colcombe et al., 2006; Kramer et al., 1999). In a sample of 124 cognitively healthy, but low-fit older adults that were randomized to six-months of either an aerobic exercise intervention (i.e., brisk walking) or to a stretching-and-toning control condition, Kramer and colleagues (Kramer et al., 1999) demonstrated that the aerobic exercise group, compared with control group, significantly improved executive function. Executive function is an umbrella term for the cognitive processes that underlie goal-directed behavior and allow one to inhibit automatic or otherwise prepotent behaviour; executive function has been shown to be particularly vulnerable to age-related decline (West, 1996). Thus, the results of this randomized controlled trial suggest that even cognitive processes that are highly susceptible to age-related changes appear to be amendable to aerobic exercise interventions. In a follow-up study, Colcombe and colleagues (S. J. Colcombe et al., 2006) found that six-months of aerobic exercise increased brain volume, including gray and white matter, in temporal and prefrontal regions of the brains. Importantly, these regions are known to be susceptible to age-related brain atrophy (Persson et al., 2014).

In a subsequent 12-month randomized controlled trial with 120 older adults and published in 2011, Erickson, Kramer, and colleagues (Erickson, Voss, et al., 2011) demonstrated that three times per week of aerobic exercise training increased hippocampal volume, which is a brain region critical to learning and memory. Specifically, aerobic exercise training increased hippocampal volume by 2%. These findings represent the first experimental evidence directly linking changes in exercise to changes in both hippocampal volume and cognitive performance in older adults in the context of a randomized controlled trial. Moreover, the authors found that increased hippocampal volume correlated with improvements in spatial memory performance and with increases in serum levels of brain derived neurotrophic factor (BDNF), a neurotrophic factor implicated in hippocampal neurogenesis, over the six-month intervention period within the aerobic exercise group. For an overview of the proposed mechanisms by which aerobic exercise promote brain health, please refer to the work of Cotman (Cotman & Berchtold, 2002; Cotman et al., 2007).

Prior to their conducting randomized controlled trials of aerobic exercise, Colcombe and Kramer (S. Colcombe & Kramer, 2003) published a highly influential meta-analysis of 18 randomized controlled trials that included aerobic exercise as an intervention. They concluded that targeted aerobic exercise training has robust but selective benefits for cognition, with the largest aerobic exercise-induced benefits occurring for executive function. Notably, Colcombe and Kramer (S. Colcombe & Kramer, 2003) also found that aerobic-based training programs combined with resistance training had a greater positive effect on cognition than aerobic training alone, suggesting a role for non-aerobic exercise in promoting cognitive health.

In 2015, a meta-analysis of aerobic exercise in healthy older adults by Young and colleague (Young et al., 2015) examined 12 studies of aerobic exercise interventions ranging from 8 to 26 weeks and found no evidence that aerobic exercise promotes cognition in this population relative to active or passive control conditions. One potential explanation for the discrepancy between these two meta-analyses is that Young and colleagues used more restrictive inclusion criteria than did Colcombe and Kramer, by excluding studies without fitness outcomes, studies that included multi-component interventions, and studies that included participants with depressive symptoms or signs of cognitive impairment. A 2018 systematic review of 16 randomized controlled trials of physical activity interventions with inactive controls also concluded there is insufficient evidence to suggest that short-term, single-component physical activity interventions promote cognitive function and prevent cognitive decline or dementia in older adults (Brasure et al., 2018). However, it is important to consider that majority of the trials included in this systematic review were not powered to detect new cases of MCI or dementia.

Randomized Controlled Trials of Resistance Training

As reported in the 2003 meta-analysis by Colcombe and Kramer (S. Colcombe & Kramer, 2003), resistance training may have an important role in maintaining cognition in older adults. Resistance training has a broad range of systemic benefits in older adults (Borst, 2004; Layne & Nelson, 1999; Skelton et al., 1995; D. Taaffe et al., 1999; Trappe et al., 2002) but compared with aerobic training, it has received far less attention in the area of exercise and cognitive neuroscience. Like aerobic exercise, resistance training reduces cardiometabolic risk factors (Cornelissen & Fagard, 2005; Hovanec et al., 2012; Strasser et al., 2010; D. R. Taaffe et al., 2007; Williams et al., 2007) associated with cognitive impairment and dementia, and promotes neurotrophic factors that are beneficial for the brain (Cassilhas et al., 2012; Cassilhas et al., 2007). Specifically, in humans, resistance training is associated with increased blood levels of insulin growth factor-1 (IGF-1), while aerobic exercise training is associated with increased levels of BDNF (Cassilhas et al., 2016; Cassilhas et al., 2007; Erickson, Voss, et al., 2011). Thus, aerobic and resistance exercise might produce positive effects on cognition through distinct physiological pathways.

Recent findings from randomized controlled trials in older adults indicate that resistance training does indeed have benefits for cognitive and brain health (Best et al., 2015; Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Nagamatsu et al., 2012). A seminal randomized controlled trial supporting the notion that resistance training is beneficial for cognitive function was conducted by Cassilhas and colleagues (Cassilhas et al., 2007). They demonstrated that resistance training three times per week for 24 weeks significantly improved several measures of cognitive function among 62 community-dwelling senior men aged 65 to 75 years, including measures of memory, processing speed, and executive function. Notably, comparable benefits were observed for both high- and moderate-intensity groups, defined as 80% and 50% of single-repetition maximum lift (i.e., 1 RM), respectively.

Extending the work of Cassilhas and colleagues (Cassilhas et al., 2007), Liu-Ambrose and colleagues (Liu-Ambrose et al., 2010) found that both once- and twice-weekly moderate intensity resistance training significantly improved the executive processes of selective attention and conflict resolution in senior women. Specifically, community-dwelling senior women participated in a 12-month randomized controlled trial that required them to engage in resistance training either one or two days per week. The intensity of the training stimulus was at a work range of six to eight repetitions to fatigue with a 60-second rest between each set; two sets in total. Compared with a balance and tone control group, those in the resistance training groups performed significantly better on the Stroop Color-Word Test at trial completion. Changes in functional activation in cortex were also examined in a subset of participants in each of the three groups (Liu-Ambrose et al., 2012). Interestingly, only the twice-weekly resistance training group showed increased neural activation in two key regions of cortex integral for response inhibition – the anterior portion of the left middle temporal gyrus and the left anterior insula extending into lateral occipital frontal cortex. Thus, while resistance training once per week may improve executive functions at a behavioural level, twice-weekly training may be required for functional plasticity at the neural level. Moreover, Best and colleagues (Best et al., 2015) showed participants of both once- and twice-weekly resistance retained benefits for executive functions one year after training cessation. Additionally, participants of twice-weekly resistance training had better performance, reduced cortical white matter atrophy (d=.45), and increased peak muscle power compared with those in the balance and tone control group. These findings suggest resistance training may have a long-term impact on cognition and white matter volume in older women.

There is also emerging evidence that resistance training may impact pre-existing pathology in the brain. In a secondary analysis of the 12-month randomized controlled trial of progressive resistance training mentioned above (Liu-Ambrose et al., 2010), Bolandzadeh, Liu-Ambrose, and colleagues (Bolandzadeh et al., 2015) provided preliminary evidence that compared with balance and tone training (i.e., control), twice-weekly moderate intensity resistance training significantly reduced the progression of white matter lesions in the brain. Moreover, reduced white matter lesion progression over 12 months was significantly associated with maintenance of gait speed. However, the magnitude of correlation between white matter lesion progression and gait speed was similar to that of white matter lesion progression and executive functions ($r = -0.31$ for gait speed versus r = 0.30 for executive functions). These results provide novel insight as to how resistance training may promote both mobility and cognitive outcomes in older adults.

Randomized Controlled Trials in At-Risk Older Adults

There is now much interest in assessing the effect of exercise in individuals at risk for dementia, such as those with MCI. Longitudinal studies report that older adults with MCI develop AD at a rate of 10-30% annually (Petersen et al., 1999), compared to 1-2% of seniors without MCI (Petersen et al., 1999). MCI is characterized by cognitive decline that is greater than expected for an individual's age and education level, but does not significantly interfere with everyday function (Petersen et al., 2001). Thus, MCI represents a critical window of opportunity for intervening and altering the trajectory of both cognitive decline and loss of functional independence in older adults.

Lautenschlager and colleagues (Lautenschlager et al., 2008) conducted one of the first high quality randomized controlled trials of physical activity in those with MCI. In 170 adults aged 50 years or older who reported memory problems but did not meet criteria for dementia, they demonstrated that a 24-week home-based program of physical activity significantly improved cognitive function as measured by the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). The physical activity intervention focused on encouraging participants to partake at least 150 minutes of moderate intensity physical activity per week. Participants in the intervention group improved 0.26 points (95% CI: -0.89 to 0.54) and those in the usual care group deteriorated 1.04 points (95% CI: 0.32 to 1.82) on the ADAS-Cog at the end of the intervention.

In the largest randomized controlled trial of exercise with cognitive outcomes to date, Sink and colleagues (Sink et al., 2015) examined the effects of a 24-month home- and center-based exercise program versus health education program among 1635 older adults at risk of mobility disability based on objective mobility performance. Exercise consisted of aerobic, resistance, and balance training components that were progressed to a moderate intensity over the course of the intervention. In the primary analyses of the entire sample, there were no significant effects of exercise training on cognitive performance; however, in secondary analyses, there was tentative evidence that exercise might be beneficial among the oldest participants (80+ years), those with the greatest mobility impairment, and those with some evidence for cognitive impairment (3MSE < 90). Thus, a moderate-intensity training program might be most efficacious among those with some degree of impairment and among the oldest participants.

Alternatively, perhaps higher-intensity exercise training would impart more durable effects to cognition. Baker and colleagues (Baker et al., 2010) examined the efficacy of high-intensity aerobic exercise training on cognitive function in older adults with MCI. They randomized 33 older adults with MCI to either an aerobic exercise training group or to a stretching control group for four days per week for 6 months. The aerobic exercise group trained under the supervision of a fitness trainer at 75% to 85% of heart rate reserve for 45 to 60 minutes per day, four days per week for six months. The stretching control group carried out supervised stretching activities according to the same schedule but maintained their heart rate at or below 50% of their heart rate reserve. Interestingly, compared with the stretching control group, they found that the aerobic exercise significantly improved cognitive function in women, but not in men. It is noteworthy that this sex-specific effect was also reported in the meta-analysis conducted by Colcombe and Kramer (S. Colcombe & Kramer, 2003). However, it should also be noted that the sample size was small, especially with regard to the sex-stratified analyses.

Aerobic exercise may augment cognitive function in those with MCI by improving neural efficiency. Among 70 older adults with mild VCI, Liu-Ambrose and colleagues (Liu-Ambrose et al., 2016) showed that six months of aerobic exercise training significantly improved ADAS-Cog performance compared with the usual care plus education group (-1.71 point difference , 95% CI: -3.15 to -0.26). Examination of secondary measures showed between-group differences at intervention completion favoring the aerobic exercise group in 6-minute walk distance (30.35 meter difference, 95% CI: 5.82 to 54.86) and in diastolic blood pressure (-6.89 mm Hg difference, 95% CI: -12.52 to -1.26). Among a subset of individuals who underwent functional MRI, Hsu and colleagues (Hsu et al., 2017) showed that compared with usual care plus education, aerobic training significantly reduced activation in the left lateral occipital cortex and right superior temporal gyrus. Reduced activity in these brain regions was significantly associated with improved (i.e., faster) flanker task performance at trial completion. The results of the partial correlation analysis support the notion of neural efficiency, which is defined as the level of activity a neural network requires in order to complete the task at hand (Barulli & Stern, 2013).

Extending Erickson and colleagues (Erickson et al., 2009) work among healthy older adults, which showed a positive impact of aerobic training on hippocampal volume, ten Brinke and colleagues (ten Brinke et al., 2015) demonstrated that compared with balance and tone exercises, thrice-weekly aerobic exercise significantly increased left, right and total hippocampal volumes ($p \leq 0.03$) in older adults with MCI.

Further supporting the role of aerobic exercise within the context of at-risk populations, a 2016 meta-analysis of aerobic exercise among individuals with MCI found positive effects on cognitive performance (Zheng et al., 2016). The meta-analysis covered 11 randomized controlled trials and showed that aerobic exercise training significantly improved global cognitive ability as measured by Mini-Mental State Examination or Montreal Cognitive Assessment. Additionally, aerobic exercise training had a small but positive effect on the specific cognitive domain of memory.

As with aerobic exercise, there is interest in whether resistance training might be an effective tool to mitigate cognitive decline among individuals with MCI. In 86 older women with MCI, Nagamatsu and colleagues (Nagamatsu et al., 2012) demonstrated that six months of twice-weekly moderate intensity resistance training significantly improved the executive cognitive processes of selective attention and conflict resolution compared with balance and tone training (i.e., control). They also found improvements in associative memory – or the ability to remember items that were previously presented simultaneously. In conjunction, regional patterns of functional plasticity were found in the resistance training group. Specifically, three key regions in cortex showed greater functional activation during the associative memory task after six months of training – the right lingual gyrus, the right occipital-fusiform gyrus, and the right frontal pole. Notably, the improvements observed in executive performance were after only six months of resistance training in those with MCI, compared with twelve months in otherwise cognitively healthy older adults (Liu-Ambrose et al., 2010). Thus it appears that the benefits of moderate intense resistance training can be observed earlier in those with a larger opportunity for change or improvement (i.e., older adults with MCI).

The SMART (Study of Mental and Resistance Training) trial also demonstrated the positive impact of resistance training on ADAS-Cog performance and white matter lesions (Suo et al., 2016). This trial included 100 older adults with MCI who were randomized to two supervised interventions: active or sham physical training (high intensity progressive resistance training vs seated calisthenics) plus active or sham cognitive training (computerized, multidomain cognitive training vs watching videos/quizzes), 2-3 days/week for 6 months with 18-month follow-up. The investigators found that progressive resistance training but not computerized cognitive training significantly improved global cognition as well as expanded gray matter in the posterior cingulate, and these changes were related to each other (r = 0.25). Progressive resistance training also significantly reduced progression of white matter lesions in the SMART trial.

More studies are also now examining the effects of exercise among older adults with dementia. In a 12-month randomized controlled trial of 210 older adults with AD (Ohman et al., 2016), researchers randomized participants to home-based exercise, group-based exercise, or usual care for 12 months. Participants in either of the exercise programs were encouraged to engage in two 1-hour sessions of exercise per week; each session included aerobic, resistance, balance, and dual-task training components. Although the data did not support a significant effect in the most rigorous analyses, the authors provide some suggestion that home-based exercise improved executive function performance as compared to the usual care group; the group-based exercise program produced intermediate effects and did not differ compared to either the usual care or home-based exercise participants.

Recently, Lamb and colleagues (Lamb et al., 2018) conducted a large randomized controlled trial of 494 people with dementia examining the effect of 4 months of supervised moderate- to high-intensity aerobic and strength training plus unsupervised home-based exercise program on ADAS-Cog performance at 6- and 12-months. Compared with the usual care control group, the exercise group showed slight declines in ADAS-Cog performance at 12-months. Interestingly, 61% of the participants in this trial were men and compliance with the supervised exercise classes was greater in men than women. Although this exercise program did not improve cognitive function in older adults with dementia in the long term, it is not known whether improvements would have been observed immediately after the completion of the 4-month supervised program. Together with the previous studies on MCI, it is possible that a modest degree of cognitive decline might be ameliorated by exercise, yet more severe cognitive decline might be less so. Nevertheless, it is noteworthy that in the 2018 practice guideline update summary for MCI (Petersen et al., 2018), the American Academy of Neurology states that while no high-quality evidence exists for pharmacological treatments of MCI, exercise is likely to provide benefit.

Moderating Effect of Biological Sex on Exercise Efficacy

Colcombe and Kramer (S. Colcombe & Kramer, 2003) first suggested that women show greater cognitive benefits from aerobic exercise in their 2003 meta-analysis. Also, greater amount of low-intensity walking objectively measured was associated with statistically larger hippocampal volume among older women, but not among older men (Varma et al., 2015). In a 2017, Barha and colleagues (Barha, Davis, et al., 2017) published a systematic review and meta-analysis to specifically examine whether or not the efficacy of exercise training on cognitive function differed between men and women. Barha and colleagues (Barha, Davis, et al., 2017) found that aerobic training, resistance training, and multimodal training (i.e., both aerobic and resistance training) were beneficial for executive functions – particularly in randomized controlled trials with a higher percentage (i.e., over 71%) of women. This suggests that women may benefit more from targeted exercise training than men. A similar female-advantage was found for rodent studies that utilized forced aerobic exercise but not voluntary aerobic exercise for hippocampus-dependent learning and memory (Barha, Falck, et al., 2017).

Extending the earlier findings of Baker and colleagues (Baker et al., 2010), in a six-month randomized controlled trial of thrice-weekly aerobic exercise in older adults with mild VCI, Barha and colleagues (Barha, Hsiung, et al., 2017) demonstrated that aerobic exercise significantly improved the executive function of set-shifting in women but not men, an effect that was retained six months after trial completion. In addition, aerobic exercise significantly increased BDNF levels in women but decreased levels in men. Conversely, aerobic exercise training led to significant gains in functional fitness capacity in men only. These results suggest that sex differences exist in aerobic exercise efficacy on brain health as well as in the biological mechanisms subserving aerobic exercise. Whether sex-differences in resistance training efficacy is not known to date. Hence, more research is needed to better understand how factors, such as biological sex, moderate the benefit of targeted exercise training on cognitive health (Barha, Galea, et al., 2017).

Barha and colleagues (Barha, Galea, et al., 2017) suggest the apparent sex difference in the exercise-induced cognitive response may be related to several factors, including differential regulation of BDNF. Further, females typically demonstrate lower fitness levels and smaller lung size, airway diameter, and maximal expiratory flow rates compared with males (Sheel et al., 2004) and thus it may be that the female-advantage seen in executive functioning after aerobic exercise could be in part due to potential greater gains in fitness in females. Interestingly, in the study by Barha and colleagues (Barha, Hsiung, et al., 2017), female participants showed greater cognitive gains but did not show significant increases in fitness capacity whereas males did. The sex difference in exercise efficacy may also be related in part to possible sex differences in specific cognitive domains including working memory and episodic memory (Andreano & Cahill, 2009). Moreover, biological sex may also interact with different genes identified as potential risk factors for dementia and AD to explain variability seen in exercise efficacy (Duzel et al., 2016; Prakash et al., 2015). For example, the ε4 allele of the apolipoprotein ε (*APOE*) gene confers increased risk for accelerated cognitive decline and late onset AD (Corder et al., 1993). Carriers of the *APOE* ε4 allele are at increased risk to develop AD, as well as to develop AD at an earlier age (Corder et al., 1993; Meyer et al., 1998). Importantly, the deleterious effects of the *APOE* ε4 allele are more pronounced in women than in men in terms of risk for AD, AD-related pathology, and cognitive decline (Mielke et al., 2014). Given the greater effect of this allele in women, it is possible that discrepancies in results between studies of exercise may be related to biological sex of participants.

FUTURE DIRECTIONS

The current evidence suggests that physical activity – including aerobic and resistance exercise training – may improve aspects of cognition and counteract age-related changes in brain regions implicated in executive function and memory in otherwise cognitively-healthy older adults, as well as older adults with MCI. Changes to blood-based neurotrophic factors (e.g., IGF-1, BDNF) implicated in cognitive and brain health have also been observed and have been shown to correlate with improvements in cognitive health (Leckie et al., 2014).

However, it appears that many of the published randomized controlled trials are underpowered, which undermines the reliability of their results, whether positive or negative. The recent meta-analysis of aerobic exercise in MCI mentioned previously (Zheng et al., 2016) estimated an effect on memory (whether immediate or delayed recall) of approximated 0.25 standard deviation units; assuming this effect size approximates the true effect, future trials testing the effects of aerobic exercise on memory performance in participants identified as having MCI should aim to recruit a minimum of 506 participants to participate in a two-arm randomized controlled trial to achieve 80% power with an error rate of 0.05. As an alternative to recruiting larger samples, it is perhaps possible that a larger effect could be achieved with longer train duration (i.e., > 6 months), higher intensity training, greater frequency of training, combined training (e.g., aerobic plus resistance), or more female participants.

Moreover, previous studies have included multiple cognitive outcome measures that are often inconsistent across studies. This is problematic for at least two reasons. First, it necessitates that the researcher correct for multiple comparison in order to control the error rate but at the expense of statistical power. In the absence of multiple testing correction, the reliability of positive results is cast into doubt. One solution is to use a latent variable approach to create latent (unobserved) variables that represent the shared variance across a set of cognitive tasks. As an example, five distinct executive function tasks might be reduced to a single latent executive function variable. In addition to reducing the number of outcomes, this approach reduces task-specific variation and other forms of measurement error (Salthouse, 2011b). Such an approach can benefit statistical power in two ways: first by eliminating the need for multiple testing corrections and second by potentially increasing the effect size through improved sensitivity of the outcome measure. Second, the lack of equivalent measures across studies makes it difficult to determine whether there is consistency across studies. Thus, a standardized set of cognitive measures (or a single measure derived from latent variable modeling) should be created and utilized across studies. In the same spirit, standardized exercise protocols should be created and shared by researchers.

To maximize the beneficial effects of exercise for brain health and dementia prevention, it is critical to identify key moderators and the underlying mechanisms of different types of exercise training. We propose that to increase the utility and efficacy of "**exercise as medicine**", the priority of future studies should be to determine what type of exercise elicits the greatest benefits for cognition and brain function and for whom using sufficiently powered randomized controlled trials. Large samples are especially important in genetic analyses in which the distribution of the variant allele may be low, prohibiting the ability to examine interactions with biological sex.

CONCLUSIONS

Current research suggests that physical activity might play a role in mitigating age-related cognitive decline. Although there are still inconsistencies in the literature and research questions that still need to be answered, it is important to highlight that there are several appealing features of physical activity to promote healthy aging. Foremost, physical activity has various positive physical health effects, including reduced vascular risk factors (e.g., hypertension, high blood sugar levels) and better maintenance of muscle mass with age, with minimal side effects. Thus, older adults should be encouraged to be as active as possible even if the effects on cognition are modest. Moreover, there are likely few other intervention strategies that could be feasibly implemented at the population level that produce the myriad positive effects that physical activity does. Thus, it is strongly recommended that we keep the aging population active for as long as possible.

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