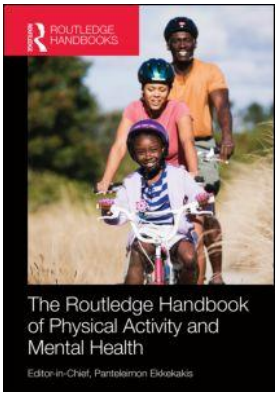

Routledge Handbook of Physical Activity and Mental Health

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PHYSICAL ACTIVITY, COGNITIVE IMPAIRMENT, AND DEMENTIA

Laura E. Middleton, Kristine Yaffe, and Deborah Barnes

Approximately 14% of adults over 70 years old in the United States have dementia (Plassman et al., 2007) and another 22% have milder cognitive impairment (Plassman et al., 2008). It is expected that the number of people who develop dementia worldwide will quadruple over the next 40 years due to the aging of the baby boomer generation and longer life expectancies (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Current medications provide some symptomatic relief but do not cure or change the course of the disease. Therefore, there is tremendous interest in identifying strategies for preventing or delaying the onset of dementia. Physical activity (PA) has emerged as one of the most promising strategies for dementia prevention (Middleton & Yaffe, 2010). In this chapter we will provide a brief overview of cognitive function, cognitive impairment, and dementia and will then summarize the evidence from longitudinal studies and randomized controlled trials (RCTs) regarding the role of physical activity in the prevention of cognitive impairment and dementia.

Cognitive function, cognitive impairment, and dementia

Definitions and diagnosis

Cognitive function refers to mental abilities that enable us to receive, process, and act on information from the environment. Cognitive function is assessed using neuropsychological tests, and key cognitive domains include memory, speed of processing, language, visuospatial function, and executive function (the ability to plan and "execute" tasks). Although cognitive function generally declines with age, rates of decline vary widely, with some individuals experiencing substantial deterioration and others maintaining cognitive abilities until advanced old age (Barnes et al., 2007a).

Mild cognitive impairment (MCI) refers to a decline in one or more aspects of cognitive function that is greater than would be expected for an individual's age and education level but is not severe enough to affect their daily activities. Many different criteria have been developed, but the most commonly used are the Petersen criteria (Petersen et al., 1999). Individuals with MCI have an increased risk of developing dementia within 5 years (Bruscoli & Lovestone, 2004). Specific criteria have been developed to differentiate between MCI subtypes including "amnestic MCI," which primarily involves memory impairment, and "vascular MCI," which is more likely to be associated with executive dysfunction and linked with cerebrovascular disease (Marra, Ferraccioli, Vita, Quaranta, & Gainotti, 2004).

Dementia, in turn, is defined as a decline in memory and at least one other cognitive domain that is severe enough to affect an individual's daily activities such as eating, dressing, bathing, or toileting (American Psychiatric Association, 1994). While there are many types of dementia, Alzheimer's disease (AD) and vascular dementia are the most commonly diagnosed (Alzheimer's Association, 2010). AD is characterized by early symptoms of memory impairment and progressively worse cognitive impairment over the course of the disease. New diagnostic criteria for AD, MCI, and preclinical AD use biomarkers to increase the certainty of diagnosis (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011) (Table 18.1). The symptoms and progression of vascular dementia are more variable across individuals compared to AD and are dictated by the location, severity, and progression of the underlying cerebrovascular disease. However, the neuropathogical features of AD and vascular dementia frequently occur concomitantly. As a result, mixed dementia, a combination of AD and vascular dementia, is likely the most common form of dementia.

Prevalence and prevention

Age is the greatest risk factor for dementia. After 65 years, the prevalence of dementia approximately doubles with every 5 years of age (Ziegler-Graham, Brookmeyer, Johnson, & Arrighi, 2008). Due to demographic changes and more people surviving to ages when dementia is common, the prevalence of dementia worldwide is expected to increase from 27 million in 2006 to 107 million in 2050 (Brookmeyer et al., 2007). Unfortunately, healthcare systems are largely unprepared for the expected rise in dementia prevalence in upcoming years. As a result, increasing attention is being paid to modifiable risk factors, particularly in high-risk populations such as those with more subtle symptoms of cognitive impairment.

Physical inactivity has recently been identified as one of the most important modifiable risk factors for dementia. Because physical inactivity is so common, Barnes and Yaffe (2011) estimated that as many as 13% of dementia cases worldwide and 21% of cases in the United States may be attributable to physical inactivity. A 25% reduction in the prevalence of physical activity could potentially prevent nearly 1 million cases worldwide and 232,000 in the United States. In the

Table 18.1 Overview of new diagnostic criteria proposed by the National Institute on Aging–Alzheimer's Association

Diagnosis	*New proposed diagnostic criteria*
Dementia	Cognitive impairment in at least two domains that reflects a decline from prior levels, is not explained by other factors such as delirium, and interferes with ability to perform usual activities.
Alzheimer's disease	***Probable:*** Dementia with insidious onset, clear evidence of worsening over time, and lack of evidence for other causes (e.g., cerebrovascular disease, Parkinson's disease). Level of certainty increased with causative genetic mutation or biomarker evidence. ***Possible:*** Dementia with atypical course or etiologically mixed presentation.
Mild cognitive impairment	Concern regarding change in cognition, performance lower than expected for age and education in one or more domains, does not interfere with ability to perform usual activities, not caused by other factors. Level of certainty increased with biomarker evidence.
Preclinical Alzheimer's disease	Biomarker evidence of Alzheimer's disease with no or minimal evidence of cognitive change.

following sections, we will summarize the evidence from longitudinal studies and RCTs linking physical activity with a decreased risk of cognitive impairment and dementia.

Longitudinal studies of physical activity, cognitive impairment, and dementia

Longitudinal studies of physical activity and cognitive impairment in late life

In numerous studies in different populations and using various definitions of physical activity, people who are more physically active in late life have been found to have less chance of being diagnosed with dementia over the next 3 to 10 years than people who are sedentary (Rockwood & Middleton, 2007). A recent meta-analysis examined the association between PA and several neurodegenerative diseases including all-cause dementia and AD (Hamer & Chida, 2009). A total of 16 studies (total n = 163,797 participants) were identified; of these, 11 studies (n = 23,168) examined dementia as an outcome and six studies (n = 13,771) examined AD. Most individual studies (Abbott et al., 2004; Ho, Wood, Shame, Chan, & Yu 2001; Larson et al., 2006; Laurin, Verreault, Lindsay, Macpherson, & Rockwood 2001; Podewils et al., 2005; Rovio et al., 2005; Scarmeas et al., 2009; Sumic, Michael, Carlson, Howieson, & Kaye, 2007; Yoshitake et al., 1995), though not all (Fabrigoule et al., 1995; Verghese et al., 2003; Wang, van Belle, Kukull, & Larson, 2002; Wang et al., 2006; Wilson et al., 2002), found a significant protective association between greater PA and reduced risk of dementia (Figure 18.1) or AD (Figure 18.2). The combined results suggested that individuals in the highest PA group had a 28% lower risk of developing dementia (relative risk [RR], 0.72; 95% confidence interval [CI]: 0.60, 0.86) and a 45% lower risk of developing AD (RR, 0.55; 95% CI: 0.36, 0.84) as compared to those in the lowest PA group (Hamer & Chida, 2009).

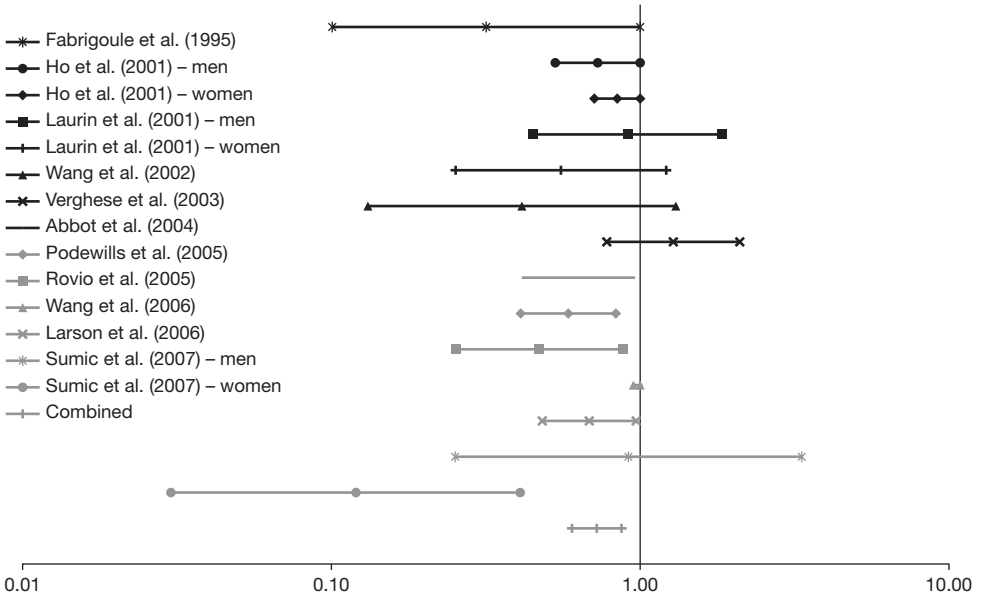

Figure 18.1 Relative risk of dementia comparing most to least physically active (adapted from Hamer & Chida, 2009).

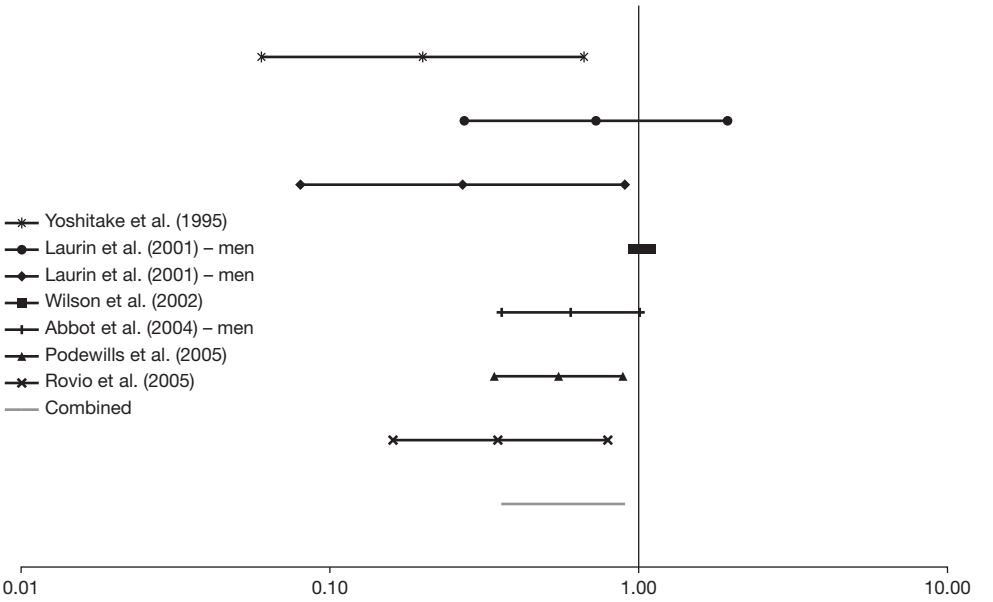

Figure 18.2 Relative risk of Alzheimer's disease comparing most to least physically active (adapted from Hamer & Chida, 2009).

The association between PA and risk of vascular dementia was examined in another recent meta-analysis (Aarsland, Sardahee, Anderssen, & Ballard, 2010). Of the five studies identified (Abbott et al., 2004; Laurin et al., 2001; Podewils et al., 2005; Ravaglia et al., 2008; Yoshitake et al., 1995), only one found a significant association between PA and reduced risk of vascular dementia (Ravaglia et al., 2008). However, the point estimates for vascular dementia were consistently lower in individuals who were physically active, and the combined results from the meta-analysis suggested that people who were more physically active had a 38% lower risk of developing vascular dementia than those who were less physically active (RR, 0.62; 95% CI: 0.42, 0.92). The lack of statistical significance in individual studies was likely due to small sample size because, until recently, vascular dementia has been diagnosed much less often than AD.

Fewer longitudinal studies have examined the association between PA and the risk of developing MCI (Verghese et al., 2006; Middleton, Kirkland, & Rockwood, 2008a; Lee et al., 2011). One study found that PA was more strongly associated with the risk of vascular-type MCI than amnestic-type MCI (Middleton et al., 2008a). However, another study found that cognitive activity, but not PA, was associated with reduced risk of amnestic-type MCI (Verghese et al., 2006). A third study found that PA was associated with reduced risk of all-cause MCI in women but not men (Lee et al., 2011). Additional studies are needed to clarify the association between PA and MCI and to determine whether there are differences in the association based on variables such as MCI type or sex.

Many studies have examined the association between PA and risk of cognitive decline or cognitive impairment based on changes in neuropsychological test performance rather than diagnostic criteria (Etgen et al., 2010; Flicker et al., 2005; Ho et al., 2001; Laurin et al., 2001; Lytle, Vander Bilt, Pandav, Dodge, & Ganguli, 2004; Middleton et al., 2008a; Middleton, Mitnitski, Fallah, Kirkland, & Rockwood, 2008b; Schuit, Feskens, Launer, & Kromhout, 2001; Stewart, Richards, Brayne, & Mann, 2001; Sturman et al., 2005; Weuve et al., 2004; Yaffe,

Barnes, Nevitt, Lui, & Covinsky, 2001). Most of these studies suggest that PA is associated with a reduced likelihood of cognitive decline and cognitive impairment in late life. There also is evidence that PA may not simply lower the risk of experiencing cognitive decline, cognitive impairment, or dementia, but that it may also increase the likelihood of maintaining normal cognitive function in late life. Indeed, one longitudinal study concluded that PA is associated with increased likelihood of stable or improved cognition with aging and not just slower decline (Middleton et al., 2008b).

Evidence for dose response

The presence of a dose-response relationship is often used to support the hypothesis that a relationship in an observational study is causal. Several studies have examined the association between the dose of PA and cognitive outcomes and the results are generally supportive of a dose-response relationship. One analysis from the Nurses' Health Study yielded a significant dose-response relationship between PA and decline in cognitive function 8 to 15 years later (Weuve et al., 2004). PA levels were reported using questionnaires by 18,766 women in 1986 and were used to divide the women into PA quintiles. Cognition was then assessed among the women in 1995–2001 when the women were 70–81 years old and again 2 years later to evaluate their rate of cognitive decline. A significant dose-response relationship was observed such that those who reported the most PA at baseline had the least cognitive decline over the following 2 years. Other studies also confirm a dose response by overall PA level (Laurin et al. 2001), PA intensity (Flicker et al., 2005; van Gelder et al., 2004; Weuve et al., 2004), daily PA duration (Schuit et al., 2001), and blocks walked per week (Yaffe et al., 2001).

Other studies, however, suggest that there may be a threshold effect such that moderate and high levels of PA are associated with similar cognitive benefits. One study followed 1,146 persons at least 65 years old at baseline and recorded self-reported exercise levels and scores on the Mini Mental State Examination (MMSE) (Lytle et al., 2004). Participants were divided into three groups: no exercise, low exercise, and high exercise. The high exercise group was initially defined as those participating in at least 30 minutes of aerobic exercise at least three times per week. Using this criterion, people in the high exercise group had significantly lower odds of cognitive decline (OR = 0.39; 95% CI: 0.19, 0.78). However, when the threshold for high exercise was increased to 5 days per week, the low and high exercise groups had similar risks of cognitive decline, suggesting that threshold for maximum benefits is realized at 3 days per week of activity and that 5 days per week of activity was no more beneficial (Lytle et al., 2004). It is unclear whether there are similar thresholds for intensity or duration of PA with regard to attaining maximum cognitive effects.

Early and mid-life PA, MCI, and dementia

Although longitudinal studies provide consistent evidence that people who are more physically active in late life have lower risk of dementia, cognitive impairment, and dementia, the length of these studies (generally less than 10 years) may be insufficient to rule out the presence of sub-clinical cognitive impairment and neuropathological features of dementia at baseline. Those with subtle cognitive deficits at baseline may also be less likely to be physically active, confounding the findings of these studies. By examining the relationship between PA earlier in life and the subsequent risk of cognitive impairment and dementia, the possibility of pre-clinical cognitive impairment at baseline influencing PA levels is reduced.

Evidence to date suggests that mid-life PA is beneficial to late life cognitive function. One study conducted in Finland examined cognitive function in 1,449 older adults (aged 65 to 79

years) who had previously reported PA levels during mid-life, approximately 21 years earlier (Rovio et al., 2005). Adjusted analyses revealed that people who participated in leisure time PA during mid-life had significantly lower odds of dementia (OR = 0.47, 95% CI: 0.25, 0.90) or AD (OR = 0.35; 95% CI: 0.16, 0.80) as compared with sedentary persons. This odds reduction is at least comparable to the odds reduction reported in studies of PA in late life. Interestingly, another study in this cohort found no association between work-related PA and risk of dementia or AD (Rovio et al., 2007). Although not entirely clear, this lack of relationship may be due to residual confounding factors such as socioeconomic status or level of cognitive stimulation at work. However, more recent studies also report inconsistent results with some (Andel et al., 2008; Middleton, Barnes, Lui & Yaffe, 2010) but not all (Carlson et al., 2008; Yamada et al., 2003) finding a significant association between mid-life PA and reduced rates of cognitive impairment 20 to 40 years later.

A few studies have also examined the relationship between early life (teenage to 30s) PA and late life cognition and found that early life PA is associated with lower rates of cognitive impairment, better information processing speed, and slower memory decline in late life (Dik, Deeg, Visser, & Jonker, 2003; Middleton et al., 2010; Richards, Hardy, & Wadsworth, 2003). Thus, the question arises: is PA more important at one age than another? To answer this question, a recent study examined the rates of late life cognitive impairment in 9,344 women who self-reported PA levels as teenagers, at age 30 years, at age 50 years, and during late life (Middleton et al., 2010). Although PA at any age was associated with reduced likelihood of cognitive impairment, PA during the teenage years was associated with the largest reduction in risk.

Objective measures of PA, MCI, and dementia

A limitation of most observational studies is their reliance on subjective self-reports of PA, which usually focus on moderate or vigorous exercise-related PA but do not adequately capture low-intensity PA, such as chores and movement around the house, which accounts for the majority of activity energy expenditure in people who do not regularly exercise (Donahoo, Levine, & Melanson, 2004). Such activity may be important to health outcomes such as cognitive impairment. In addition, since people with even subtle cognitive deficits may be more likely to misreport PA, there could be systematic misclassification of PA in studies relying on self-reports. Consequently, objective measures of PA are needed to confirm results from studies using self-reports.

Only a few studies have used objective measures of PA to examine the relationship between PA and cognitive function in late life. One early study measured cardiorespiratory fitness, which is primarily determined by PA as well as genetic predisposition, using maximum oxygen consumption ($\dot{V}O_2$ max) in 349 adults aged 55 years or older (Barnes, Yaffe, Satariano, & Tager, 2003). A modified MMSE was administered to each participant at baseline and 6 years later. Analyses revealed a strong dose-response relationship between cardiorespiratory fitness and cognitive decline such that people with better cardiorespiratory fitness at baseline had slower cognitive decline over the 6-year follow-up period.

In a second study, energy expended on activity was measured in 197 older adults using doubly-labeled water methods, arguably the gold-standard of PA measurement (Middleton et al., 2011). Cognitive function was assessed at baseline and 5 to 8 years later. In adjusted analyses, those in the highest tertile of activity at baseline had much lower rates of incident cognitive impairment (OR = 0.19; 95% CI: 0.01, 0.79) at the subsequent measurement, and there was evidence for dose response where increasing levels of activity energy expenditure were associated with decreasing risk of cognitive impairment. The decrease in the odds of cognitive impairment by

tertile of activity energy expenditure was at least as great as those from published studies using self-reported PA. This suggests that total daily PA may be as or even more important than purposeful exercise, which is more readily captured by self-reports.

Strengths and limitations of longitudinal studies

Taken together, longitudinal studies of PA across the life course provide evidence that people who are more physically active have lower risk of dementia, cognitive impairment, and cognitive decline. The findings are reasonably consistent across different study populations, measures of PA, definitions of cognitive decline and dementia, sample sizes, and follow-up times. The evidence is further strengthened by studies suggesting that there is a dose-response relationship, that PA earlier in life is beneficial, and that objective measures of PA yield similar results to those found with subjective measures of PA. However, there are also several limitations. First, few studies examined whether one type of PA is better than another. As a result, the relative merits of different exercise regimens, such as those incorporating different levels of resistance, cardiovascular, and flexibility training, are unclear. One study that examined the rates of cognitive impairment by activity types concluded that ballroom dancing may offer the best protection against incident cognitive impairment (Verghese et al., 2003). Second, most studies assess PA only at study baseline and so our understanding of how PA patterns over time are associated with the development of cognitive impairment is poor. However, two studies provide preliminary data suggesting that rates of cognitive decline are faster in those who decrease their PA levels compared to those who maintain or increase their PA levels (Barnes et al., 2009; Van Gelder et al., 2004). Finally, arguably the most important weakness of observational studies is that people are self-selected to PA levels and not randomly assigned. Consequently, even in analyses that are adjusted for relevant covariates, there may be important residual differences between PA groups that are associated with the risk of cognitive impairment. Thus, it is imperative that RCTs examine the relationship between PA and cognitive function to complement the results from longitudinal, observational studies. The results from RCTs are discussed in the following section as well as in Chapter 17 in this volume.

RCTS of PA, cognitive impairment, and dementia

Most RCTs performed to date have examined the effects of exercise on cognitive change over a period of weeks or months in study populations ranging from healthy elders to individuals with MCI or dementia. Although findings have varied across studies, most have found that exercise—particularly aerobic exercise—results in improvements in some aspects of cognitive function—particularly executive function, motor speed, and attention. However, to date, RCTs have not directly measured whether PA can reduce the risk of or delay the onset of cognitive impairment, AD, or dementia.

Healthy elders

An early meta-analysis identified 18 RCTs of exercise interventions in healthy older adults (Colcombe & Kramer, 2003). Most studies used relatively small samples, with a total of 197 subjects included in the 18 studies. Nonetheless, the meta-analysis found significantly greater improvements in cognitive function over time in the exercise intervention participants (effect size [ES] = 0.48 standard deviations) compared to control participants (ES = 0.16). Improvements were observed for multiple cognitive domains including executive function (ES = 0.68),

controlled processing (ES = 0.46), visuospatial function (ES = 0.43), and speed (ES = 0.27). Effect sizes (the difference between the intervention and control groups in standard deviation units) were slightly larger for combined aerobic and strength training interventions (ES = 0.59) than aerobic-only interventions (ES = 0.41) and for interventions with moderate (31–45 minutes, ES = 0.61) or long (46–60 minutes, ES = 0.47) rather than short (15–30 minutes, ES = 0.18) session durations. In addition, there was evidence that effect sizes were larger for studies with more female participants (ES = 0.60) than for studies with more male (ES = 0.15) participants and for middle-aged (66–70 years, ES = 0.69) and older (71–80 years, ES = 0.55) than younger (55–65, ES = 0.30) participants.

However, a more recent Cochrane systematic review that focused on the effects of aerobic exercise was less conclusive (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008). This review included fewer studies with a total of 11 RCTs with 625 subjects, most of which had non-significant results. When the RCTs were combined, significant effect sizes were observed for cognitive speed (ES = 0.24) and visual attention (ES = 0.26) when aerobic exercise was compared to any control group. Significant effects were observed for motor function (ES = 1.17) and auditory attention (ES = 0.50) only in studies where aerobic exercise was compared to a no-intervention control group. The question of the most appropriate control group remains controversial and options include a stretching and toning group, an educational group, or a no-contact group, each with its own advantages and disadvantages. The most conservative option, a stretching and control group, enables participant blinding but may induce non-trivial cognitive benefits as two studies have shown that resistance training (toning) is associated with positive cognitive changes (Cassilhas et al., 2007; Liu-Ambrose et al., 2010).

A major limitation of the exercise RCTs conducted to date in healthy elders is that they have focused on cognitive change on standardized cognitive tests as their primary outcome. RCTs with cognitively normal older adults that examine whether PA interventions reduce the incidence of MCI and dementia are critically needed (Barnes et al., 2007b). In addition, the lack of standardization in exercise interventions, control group activities, and outcome measures makes comparisons across studies and combination of findings difficult.

Cognitive impairment and dementia

Several recent studies have examined the impact of exercise interventions on cognitive decline in individuals diagnosed with cognitive impairment or dementia. Some studies were conducted in the community and others in residential care. In 2004, a meta-analysis combined the results of RCTs in which the subjects had evidence of cognitive impairment, defined as having a mean MMSE score of less than 26 or a diagnosis of cognitive impairment or dementia (Heyn, Beatriz, & Ottenbacher, 2004). This meta-analysis identified 10 trials including 820 subjects with cognitive impairment and found that those in the exercise groups improved significantly more than controls on measures of cognitive function (ES = 0.57; 95% CI: 0.43, 1.117). Although a more recent Cochrane review with more strict recruitment criteria (only two studies were included) was inconclusive, the results of the 2004 meta-analysis are sufficient to suggest that PA may improve cognitive outcomes even among those already exhibiting symptoms of impairment.

Two recent RCTs provide additional evidence that PA can improve cognitive function in individuals with MCI. In one study, 170 individuals who reported memory problems but did not have dementia were randomized to participate in a 24-week PA intervention or a usual care control group. The exercise group experienced significantly better cognitive outcomes than the control group both over the course of the intervention and after an additional 12-month follow-up (Lautenschlager et al., 2008). Another RCT of 33 individuals with MCI found that aerobic

exercise had sex-specific effects in which the benefits on executive function were larger for women (Baker et al., 2010). Several additional studies that will provide further evidence regarding the cognitive effects of various exercise regimens in elders with MCI or dementia are currently underway, including Fitness for the Aging Brain II (FABS II) (Australia New Zealand Clinical Trials Registry: ACTRN12609000755235); Promotion of the Mind Through Exercise (PROMoTE) (ClinicalTrials.gov Protocol Registration System: NCT01027858); and Preventing Loss of Independence through Exercise (PLIÉ) (ClinicalTrials.gov Protocol Registration System: NCT01371214).

Summary and limitations

Numerous RCTs have examined the effects of exercise interventions on cognitive outcomes in healthy elders with a smaller number testing the effects in elders with MCI or dementia. Most trials have been limited by small sample sizes. In addition, the lack of consistency in intervention, control, and outcome measures makes combining results difficult. As alluded to earlier, the choice of control group is of particular concern and likely affects the magnitude of observed responses. For example, a control intervention that included social engagement would only detect differences based solely on physical movement and would omit effects based on the social aspects of PA. Despite these limitations, studies to date suggest that exercise results in small improvements in cognitive function across all cognitive classifications. Larger, well-controlled RCTs are needed to provide definitive evidence that engaging in PA can lead to a reduced risk of cognitive impairment and dementia and can benefit the cognitive performance of those already experiencing cognitive impairment.

Conclusions and future directions

Robust and consistent results from longitudinal studies provide evidence that PA is associated with reduced risk of cognitive impairment and dementia in late life. Preliminary evidence from RCTs generally provides supportive evidence. However, RCTs that examined the cognitive benefits of PA interventions in people with cognitive impairment are more limited in both sample size and quality. Larger RCTs are needed to investigate the role of PA in relation to cognitive performance and the incidence of dementia. Such trials are underway relative to cognitive performance—for example, the lifestyle interventions and independence for elders (LIFE) study began in 2010 and is randomizing 1,600 healthy older adults to either exercise or control groups for an average of 2.7 years. The PA intervention is comprised of three phases: adoption (8 weeks), transition (12 weeks), and maintenance (to end of trial). Although there will be no clinical cognitive diagnosis, the LIFE study includes cognitive function as a secondary outcome and should provide more definitive data to support or oppose a causal relationship between PA and reduced cognitive decline.

At this time, it is not known whether increased participation in PA will reduce the overall prevalence of cognitive impairment and dementia. No RCTs have followed people long enough to capture the transition from normal cognition to cognitive impairment. However, PA has many other beneficial effects on cardiovascular and metabolic outcomes, and there is no evidence to suggest that it might be harmful. Therefore, while we wait for results from ongoing studies and for future long-term trials, PA can be recommended as a strategy that has many known health benefits, may improve cognitive performance, and may lower risk or delay onset of cognitive impairment and dementia.

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