Healthy Brain Aging: Role of Exercise and Physical Activity

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KEYWORDS

• Exercise • Cognition • Dementia • Physical activity
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During the last 2 decades, it has been shown that the risk of numerous chronic diseases, such as congestive heart disease[1] or colon[2] and breast[3] cancer, can be reduced by increasing physical activity. The benefits that exercise can provide to brain functioning have been less thoroughly studied. However, the occurrence of dementia can be attributed to an accumulation of risk and protective factors during the lifespan,[4] and physical activity may contribute to the maintenance of a healthy aging brain. Recently, arguments from epidemiologic and basic research have emphasized that inactivity, a modifiable lifestyle factor, may affect age-related cognitive decline and the development of Alzheimer disease (AD).

Clinical and basic research in this area has intensified. Evidence suggests that potential preventive strategies such as a physically active lifestyle may help to delay the onset of cognitive decline and slow down disease progression. Such a nonpharmacologic therapeutic approach may be an appealing low-cost, low-risk alternative treatment of this major public health priority. In 2007, there were more than 5 million people in the United States with AD and there is still no pharmacologic treatment. Even a modest decrease in the incidence of the disease would have a significant effect on social and economic cost. It has been reported that a 5-year delay in the onset of dementia would result in a 50% decrease in the number of dementia cases.[5] In the absence of curative treatment, physical exercise seems a reasonable basis for prevention trials.[6] Only a few large randomized controlled trials (RCTs)[7,8] have been

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conducted to show the benefit of physical activity on brain health. They support the benefit of physical activity on cognitive decline but none have shown that physical activity can prevent dementia. Trials involving physical activity in the prevention of cognitive decline and dementia have specific design challenges. Subjects who agree to engage in physical activity programs are likely to differ in many other lifestyle domains.[6] It is difficult to maintain compliance with a physical activity program for a long period, and it is difficult to assess the program. Like other nonpharmacologic trials, clinical research on physical activity is characterized by the impossibility of maintaining double-blind conditions, and the difficulty of defining an adequate control group. Despite these difficulties, the results of a well-designed RCT are needed.

In addition to many other reasons for engaging in physical activity, preserving brain health could be a strong and convincing argument for promoting activity in the population and could have a major effect on medical practice and public health education.

At present, there are no specific recommendations for physical programs to prevent cognitive decline, mainly because of the lack of RCTs. However, the strategy to prevent AD may target multiple aspects of lifestyle habits, including specific physical activity programs.

PHYSICAL ACTIVITY AND THE PREVENTION OF DEMENTIA, AD, OR COGNITIVE DECLINE

Clinical Research

All clinical evidence related to the prevention of dementia or AD by physical activity is derived from case-control studies and cross-sectional and longitudinal epidemiologic studies. There is currently no evidence, based on RCTs, to state that physical activity is effective in preventing or delaying the onset of dementia or AD. In a recent review,[9] 24 longitudinal epidemiologic studies were reported evaluating the possible effect of physical activity on cognitive decline, dementia, or AD. Most of them found an association between physical activity and cognitive decline or dementia, suggesting a protective effect of physical activity. Recently, 2 RCTs reported an improvement of cognitive function in an elderly population.[7,8]

Most of the current clinical evidence for the benefits of physical activity on the prevention of AD relies on epidemiologic studies.[9] Most of these studies investigated the relationship between physical activity and the risk of dementia or AD in particular. Others examined the relationship between physical activity and risk of cognitive decline. Despite similar outcomes, these longitudinal epidemiologic studies differ in many respects. However, the prospective cohort studies that have assessed the protective role of regular physical activity highlighted a significant and independent preventive effect of physical activity on cognitive decline or dementia. Most of the longitudinal epidemiologic studies that evaluated the association between physical activity and dementia or cognitive decline are reported in **Tables 1** and **2**. All these results were controlled for potential confounders underlying dementia and diminished physical activity. Five of the 16 longitudinal epidemiologic studies failed to find a statistically significant association between physical activity and dementia, and 2 of the 16 failed for cognitive decline (see **Table 2**).

Definitive conclusions based on these observational results must be discussed carefully as these epidemiologic studies are exposed to many sources of bias. In most of the studies the reliability of the physical activity assessment is questionable. The assessment of physical activity relies on 1 single question, a composite score based on physical activity during leisure and at work, and estimated average energy expenditure. Few research protocols have used validated standardized physical activity scales. The collection of self-reported activities also introduces a reporting bias. The type, frequency, and duration of activity are usually not quantified. Physical activity is assessed at study baseline but this assessment may not correspond to a mean stable and long-term regular activity and even less to activity over the subject's lifetime. The time elapsing between physical activity assessment and the onset of dementia or cognitive decline is variable. The mean follow-up between physical activity assessment and cognitive assessment varies from 2.5 to 21 years. An important limitation of these epidemiologic studies is that initial cognitive decline is associated with functional decline.[33–35] Inactivity may be a manifestation of the early phase of dementia rather than a risk factor. Most epidemiologic studies have tried to reduce this potential effect of behavior changes on physical activity in the early phase of AD by excluding subjects with low cognitive function at baseline or those who converted to AD in the early phases of follow-up. However, behavior disturbances such as depression, not assessed at baseline, usually precede AD and result in low physical activity.[36] The mean follow-up is short (3–7 years) compared with the decade or more before pathologic changes begin to be symptomatic and enable the diagnosis of dementia to be confirmed. Only 1 study investigated the long-term association between midlife physical activity and the risk of dementia or AD.[23] Another limitation in interpreting these epidemiologic studies is that despite adjustment for several potential confounders, sedentary participants differ from exercisers in many ways. Numerous other potential confounders may influence the relationship between exercise and risk of dementia. Physical activity involves cognitive functions (in addition to energy expenditure and mobility) that may enhance cognitive performances. Physical, social, and cognitive activities usually overlap. It is thus difficult to ascertain the specific and individual effect of each component on brain functioning.

Case-control studies also suggest that physical activities may have a direct influence on the neuropathology of AD. Most of these studies found that elderly participants who performed better on cognitive testing self-reported higher levels of physical activities in their past.[37,38] Physically fit aged individuals performed better in cognitive tests exploring reasoning, working memory, vocabulary, and reaction time than their sedentary counterparts. For example, in 1990, Broe and colleagues[39] reported that a low level of physical activity in the recent and the distant past was associated with AD. Others have reported that patients with AD were less active during their adulthood than subjects without dementia.[40–45] These case-control studies are even more prone to methodological bias.

The beneficial effects of physical exercise on the cognitive performances of nondemented participants have also been reported in several RCTs,[46–50] although others found no cognitive improvement in physically active groups.[41,51–53] Most of these RCTs were based on small samples of young-old participants, and were short-term trials, none of which were designed to assess incidence of AD or dementia as the main outcome. These RCTs concluded that compared with controls, individuals assigned to a physical exercise program improved[48,51–56] or maintained[57] their cognitive function. In a young-old population, Molloy and colleagues[58] also suggested that the acute effects of an exercise program on neuropsychological function were not long-lasting.

Other small RCTs, in elderly people living in the community or in nursing-home residents, have failed to show any improvement of cognitive function.[47,55,57,59–64] One explanation may be that most exercise programs last a few months, whereas physical activity may protect cognitive function in the long-term.

Colcombe and Kramer[65] in 2003 performed a meta-analysis of 18 interventional studies published between 1966 and 2001 and reported a significant but selective

Table 1
Observational studies of physical activity and risk of AD or dementia

Author and Study Name	Longitudinal Nondemented Population-Based Study	Summary of Major Findings (Adjusted for Confounders)
Li et al[10]	1090 individuals aged 60 years or more	Individuals with limited physical activity had a higher risk for developing dementia
Stern et al[11]	593 individuals aged 60 years or more	Individuals with low lifetime occupational attainment had a higher risk for developing dementia (RR 2.25, 95% CI 1.32–3.84)
Yoshitake et al[12] Hisayama Study	828 individuals aged 65 years or more	Physical activity was a significant preventive factor for AD
Fabrigoule et al[13] Paquid Study	2040 individuals aged 65 years or more	Physically active individuals had a lower risk of dementia (RR 0.33, 95% CI 0.10–1.04)
Broe et al[14] Sydney Older Persons Study	327 individuals aged 75 years or more	No statistically significant association between physical activity and dementia
Laurin et al[15] Canadian Study of Health and Aging	6434 individuals aged 65 years or more	High levels of physical activity were associated with reduced risks of cognitive impairment (OR 0.58, 95% CI 0.41–0.83), AD (OR 0.50, 95% CI 0.28–0.90), and dementia of any type (OR 0.63, 95% CI 0.40–0.98)
Scarmeas et al[16] Health Care Financing Administration Study	1772 individuals aged 65 years or more	Subjects with high leisure activities (RR 0.62, 95% CI 0.46–0.83) Walking for pleasure or going on an excursion (RR 0.73, 95% CI 0.55–0.98)
Ho et al[17]	2030 individuals aged 70 years or more	Sedentary behavior was associated with an increased risk of cognitive impairment
Lindsay et al[15] Canadian Study of Health and Aging	6434 individuals aged 65 years or more	Regular physical activity was associated with a reduced risk of AD (OR 0.69, 95% CI 0.5–0.96)

Wang et al[18] Kungsholmen Project	776 individuals aged 75 years or more	Daily physical activity was associated with no significant reduction in risk of dementia (RR 0.41, 95% CI 0.13–1.31)
Yamada et al[19] Radiation Effect Research Foundation Adult Health Study	1774 individuals	No statistically significant association between physical activity and dementia
Verghese et al[20] Bronx Aging Study	469 individuals aged 75 years or more	Leisure cognitive activities were associated with a reduced risk of dementia but physical activity was not Dancing was the only physical activity associated with a lower risk of dementia (HR 0.24, 95% CI 0.06–0.99)
Abbott et al[21] Honolulu-Asia Aging Study	2257 men aged 71–93 years	Men who walked less than 0.25 miles/d experienced a 1.8-fold excess risk of dementia compared with those who walked more than 2 miles/d (HR 1.77, 95% CI 1.04–3.01)
Podewils et al[22] Cardiovascular Health Cognitive Study	3375 individuals aged 65 years or more	Individuals in the highest quartile of physical energy expenditure had lower risk of dementia (RR 0.85, 95% CI 0.61–1.19) compared with those in the lowest quartile; individuals engaging in more than 4 activities had lower risk of dementia (RR 0.51, 95% CI 0.33–0.79) compared with those engaging in 0–1 activity
Rovio et al[23] Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE)	1449 individuals aged 65–79 years	Leisure-time physical activity, at least twice a week, was associated with a reduced risk of dementia and AD (OR 0.48, 95% CI 0.25–0.91 and 0.38, 95% CI 0.17–0.85, respectively)
Larson et al[24] Adult Change in Thought	1740 individuals aged 65 years or more	Active (more than 3 times/wk) compared with fewer than 3 times/wk (HR 0.68, 95% CI 0.48–0.96 for dementia and 0.69, 95% CI 0.45–1.05 for AD)

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Table 2
Observational studies of physical activity and risk of cognitive decline

Author and Study Name	Longitudinal Nondemented Population-Based Study	Summary of Major Findings (Adjusted for Confounders)
Albert et al[25] MacArthur Study	1192 individuals aged 70–79 years	Strenuous physical activity but not moderate physical activity was associated with a reduced risk of cognitive decline
Broe et al[14] Sydney Older Persons Study	327 individuals aged 75 years or more	No statistically significant association between physical activity and cognitive decline
Schuit et al[26]	347 individuals aged 65 years or more	Low physical activity group had a 2-fold risk of cognitive decline (OR 2.0, 95% CI 0.9–4.8)
Yaffe et al[27] Study of Osteoporotic Fractures	5925 individuals aged 65 years or more	Highest quartile compared with the lowest quartile of blocks walked (OR 0.66, 95% CI 0.54–0.82)
Pignatti et al[28] Brescia Study	364 individuals aged 70–85 years	Inactivity was associated with a higher risk of cognitive decline (RR 3.7, 95% CI 1.2–11.1)
Dik et al[29]	1241 individuals aged 62–85 years	Active men at low or moderate level displayed faster processing speed
Barnes et al[30] Sonoma study	349 individuals aged 55 years or more	Cognitive decline is associated with baseline peak oxygen consumption (VO_2) Lowest VO_2 tertile = −0.5 (−0.8 to 0.3)/middle VO_2 tertile = −0.2 (−0.5 to 0.0)/highest VO_2 tertile = 0.0 (−0.3 to 0.2) $P = .002$ for trend over tertiles
Lytle et al[31] Monongahela Valley Independent Elders Survey (MoVIES)	1146 individuals aged 65 years or more	High exercise (OR 0.39, 95% CI 0.19–0.78) Threshold = 5 times/wk
Weuve et al[32] Nurses' Health Study	18,766 women aged 70–81 years	Women in the highest quintile of activity had lower cognitive decline (OR 0.80, 95% CI 0.67–0.95) Walking at least 1.5 hours/wk at a pace of 21–30 min/mile was associated with a significantly higher cognitive score

effect of fitness training on cognitive function, with the main benefits occurring in executive-control processes. In 2006, the same investigators[66] reported a significant increase in brain volume in volunteers aged 60 to 79 years who participated in a 6-month aerobic program. Their findings provide convincing support for the hypothesis that physical activity prevents age-related cognitive decline.

In 2008, Lautenschlager and colleagues[8] published the first trial to show that a physical activity program (about 20 min/d) modestly improved the cognitive function of 170 older adults with subjective and objective mild cognitive impairment. An average improvement of 1.3 points on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) relative to the usual care control group after 6 months and 0.69 points at 18 months was reported. These results compare favorably with the benefit reported with the use of donepezil.[67] Recently, Williamson and colleagues[7] reported the results from the cognitive substudy of the Lifestyle Interventions and Independence for Elders pilot (LIFE-P) study. In this RCT pilot study, 102 older adults at risk for mobility disability participated in a physical activity intervention for 1 year. The investigators reported a significant correlation between physical and cognitive performance.

In a recent Cochrane review Angevaren and colleagues[68] assessed the effectiveness of physical activity on cognitive function in people older than 55 years without cognitive impairment. Eight of 11 RCTs that compared aerobic physical activity programs with any other intervention or no intervention reported an improvement in cognitive capacity that coincided with the increased cardiorespiratory fitness of the intervention group. The largest effects on cognitive function were found on motor function and auditory attention. The investigators reported an effect size of 1.17 for the motor function and 0.50 for auditory attention, which were the cognitive domains with the largest effects. For cognitive speed and visual attention, a moderate effect was observed, with an effect size of 0.26 for both domains.

Larger studies are still required to increase knowledge regarding the relationship between exercise and cognitive function in humans. However, most RCTs of physical activity in older adults suggest a selective improvement in executive control processes.[53,68] Aerobic exercise intervention enhances executive function, although other cognitive functions seem to be insensitive to physical exercise (aerobic exercise affected cognitive and neural plasticity in a cross-sectional study).[51]

The specificity that aerobic exercise has on executive function suggests some specificity for aerobic exercise on brain function that requires further research.[68] Research on neuroimaging suggests that prefrontal and parietal circuits in the brain, the regions of the brain that are most involved in executive control, retain more plasticity. For example, in a cross-sectional study, Colcombe and colleagues[69] reported that fitter older subjects had a greater volume of gray matter in the prefrontal, parietal, and temporal regions and a greater volume of white matter in the genu of the corpus callosum than their less fit counterparts, after controlling for potential confounders.

Epidemiologic studies have also reported that low physical performance[70–72] is associated with higher rates of cognitive decline and dementia. Low physical activity is 1 of the main factors for poor physical performance. A poor score on tests such as walking speed,[70–72] or poor results on the timed chair-stand test, standing balance, or grip-strength tests,[72] are associated with higher rates of cognitive decline and dementia. In cross-sectional studies, cardiovascular fitness was associated with attention and executive function[73,74] or visuospatial function.[75] In the Sydney Older Person Study, participants with cognitive impairment and slow gait were most likely to progress to dementia during a 6-year period.[76] The REAL FR study reported that an abnormal 1-leg balance predicts higher rate of cognitive decline.[77] On the other hand, during the 7-year follow-up of the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE), participants with poor cognition had a steeper decline in physical performance than those with good cognition.[78] These results reinforced the growing evidence of the links between physical performance and cognition.

Basic Research

Numerous studies on rodents suggested that exercise improves acquisition and retention in memory-dependent tasks such as the radial arm maze,[79] the Morris water maze,[80,81] passive avoidance,[82] and object recognition.[83] There is no clear explanation for this relation between physical activity and brain function. However, numerous hypotheses have been put forward and growing evidence from animal research suggests that physical activity may directly modulate the formation of β-amyloid protein through several biologic mechanisms. A review published in 2007 by Cotman and colleagues[84] examined the multiple underlying mechanisms promoted by physical activity to ensure brain health. One hypothesis is an improvement in cerebral vascular functioning and brain perfusion. Animal[85] and human[86] studies have shown that physical activity can stimulate brain perfusion and angiogenesis within a few weeks of aerobic training. Physical activity is associated with increased blood perfusion of brain regions that modulate attention. The common pathway of the other mechanisms involved may be a preventive effect of physical activity on the inflammatory pathway and its deleterious consequences on growth factor signaling.[84] These effects may be mediated by activation of insulinlike growth factor 1, vascular endothelial growth factor, brain-derived neurotrophic factor, and endorphins. The neurotrophin brain-derived neurotrophic factor is considered to be the most important factor upregulated by physical activity. It has an important role in cell genesis and growth. The synaptogenesis, neurogenesis, and attenuation of neural responses to stress stimulated by physical activity explain brain plasticity.[87,88] These mechanisms may also enhance brain cytoarchitecture and electrophysiologic properties, suggesting that the brain retains the capacity to regenerate new connections and new neurons. An external stimulus such as physical activity may influence the age-related neurologic process or the neuropathological AD processes. Participation in physical activity may thus lower the risk of cognitive decline and dementia by improving cognitive reserve.[13,15,16,18,50,89,90]

Higher cognitive reserve may help the subject engage in regular physical activity to cope with the first cognitive symptoms of AD. This effect may delay the onset of the clinical manifestations of the disease, which may become apparent only later. The recent basic research has yielded convincing arguments that physical activity acts as a stimulus of neurogenesis, enhances the brain cytoarchitecture and electrophysiologic properties, and may influence neuropathologic processes such as the formation of β-amyloid protein during AD.

With a view to preventing cognitive decline, dementia, and AD, it remains unclear how much physical activity, what type, and at what time of lifespan, is optimally effective in preventing cognitive decline and dementia. Although conclusive evidence is lacking to answer these questions, epidemiologic and animal studies suggest the conditions (intensity, type, frequency, and duration) under which physical activity may reduce the risk of dementia. It also remains to be determined whether voluntary and forced exercise result in the same improvement.

SUMMARY

Regular physical activity is a key component of successful aging. Increasing evidence suggests that an active life has a protective effect on brain functioning in the elderly population. Epidemiologic studies, short-term RCTs in nondemented participants, and biologic research suggest that physical activity improves cognitive functioning in older subjects. However, no RCT has yet shown that regular physical activity prevents dementia. Additional interventional studies are needed to examine this relationship. Moreover, type, duration, and intensity of physical exercise, and its precise impact on the different aspects of cognitive function, need to be determined in RCTs. Future research should focus on developing specific exercise programs to postpone or reduce the risk of dementia, or slow down disease progression. In the coming decade, large ongoing RCTs may provide some of the answers to these questions. Preventive approaches to dementia could then be the basis of recommendations to the community. The main challenge, however, is how to change lifestyle habits and promote physical activity in the older population in the long-term. In primary care, prevention of many diseases already relies on a healthy diet and lifestyle, control of cardiovascular risk factors, ongoing learning experiences, and regular physical activity. Prevention of cognitive decline and dementia could be a decisive argument to convince patients and modify public health policy.

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