

Mini review

What do we know from clinical trials on exercise and Alzheimer's disease?

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Abstract

Alzheimer's disease (AD) is the most common form of dementia in elderly with major symptoms of a general term for memory loss and other intellectual abilities impairment which are serious enough to interfere with daily life. While there is no treatment can prevent and revise the cognitive function impairment in AD, physical activity becomes a potential beneficial intervention for AD. Multiple evidences suggested that exercise in general plays beneficial roles in improving brain function. Most common mechanisms of exercise-induced enhancement of brain function are including alteration of neurogenesis, neuron plasticity, neuronal signaling and receptors, as well as neuronal networks. This mini review includes most recent clinical studies and focuses on the effects of physical exercise, cognitive stimulation, and combination of both physical and cognitive training on protection and rescue cognitive decline in people with AD.

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1. Clinical trials on physical exercise/activity and Alzheimer's disease (AD)

Accumulated evidence shows that integrating a body movement, such as exercising or dancing, with learning improves memory retention. One of the most common exercises is aerobic exercise, which has been widely studied for its potential beneficial effects on cognition and brain function. In the healthy elderly, studies show that aerobic exercise has a potent impact on promoting the function of the hippocampus and stimulating neuroplasticity, an important feature in maintaining healthy aging.¹ Similar protective effects of physical exercise were also reported from a recent clinical study that included magnetic resonance image (MRI) analysis of both individuals who performed exercise (150 min of moderate-to-vigorous physical activity per week) and those who engaged in no exercise.² This study found that individuals at risk for AD had faster rates of brain atrophy and that physical exercise could attenuate the

brain atrophy. Although most studies have been focused on the importance of physical exercise in prevention of AD, a few recent clinical trials have investigated whether exercise can treat the AD itself. One multicenter single-blind randomized controlled trial of moderate- to high-intensity exercise in patients with AD has been well recognized.³ Participants ($n = 200$) were randomized to a control group (who received usual treatment without exercise) or an intervention group (who underwent 3 × 60 min of moderate- to high-intensity aerobic exercise per week for 16 weeks). The study showed that the 4 months of exercise not only demonstrated a potential action in preserving cognitive activity (better intellectual skills) but also reduced neuropsychiatric symptoms (less anxiety and depression) in patients with mild AD, particularly with a high rate of attendance and high-intensity exercise, suggesting that the level of exercise intensity is important in achieving cognitive improvement. One of the important aspects of studying exercise in AD is the follow-up period after an exercise program of short duration, during which one can observe the long-term effect on brain function. A very recent clinical trial followed a community-based elderly cohort for over 10 years to study the association of physical activity with the risk of incidental dementia and

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subclinical brain magnetic resonance imaging markers of dementia.⁴ The study found that physical activity affected the size of the hippocampus, which controls short-term memory. Moreover, the study demonstrated that the beneficial effect of regular physical exercise in protecting against dementia was strongest in people aged 75 years or older, because low physical activity is associated with a higher risk for dementia in older individuals. Tan et al.'s⁴ work suggested that it is never too late to start physical exercise. However, several other studies failed to find a beneficial association between physical exercise and reduction of dementia risk. This is possibly related to the lack of a good length of follow-up or to inadequate physical activity assessments, which might show a possible nonlinear relationship between physical activity and dementia.⁵

2. Clinical trials of cognitive stimulation in AD

There was consistent evidence from multiple trials that cognitive stimulation programs benefitted cognition in people with mild-to-moderate dementia. For example, a very recent clinical trial showed that people with moderate dementia who underwent 7 weeks of cognitive stimulation therapy showed better cognitive function in several cognitive measurements, such as the Mini-Mental State Examination score (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) subscale for narrative language, and mood measurements than patients with dementia in the control group.⁶ Another recent clinical study used computerized cognitive training of a large group of patients with early-stage AD.⁷ People with AD ($n = 80$) were randomized into 2 groups: the experimental group used computerized rehabilitative software 3 times a week for 12 weeks, and the control group underwent a control intervention. Cognitive functions were examined at 3 time points: before training, after training, and at the 6-month follow-up. Patients in the experimental group showed a significant improvement in memory, attention, executive function, and language skills, and their achievements were stable after 6 months. This study provided important evidence that computerized training in AD might be a good tool for improving patients' cognitive function. Another interesting study investigated the generalizability of trained skills to novel tasks and learned skill stability over time in patients with AD.⁸ Participants' performances on the Geographical Exercise for Cognitive Optimization Task, on a similar untrained task, and on a different untrained task were recorded before and after the intervention and at the 24-month follow-up. In the study, the trained patients showed a significant acquirement of procedural skills that were maintained over time, including acquiring and maintaining new skills on both a trained task and a similar untrained task.

It is also true that not everyone has same response to cognitive stimulation in dementia; some show the benefit of cognitive stimulation treatments in dementia and some do not. A retrospective observational study was conducted between 2004 and 2012 in 60 patients with AD who followed a 1-year cognitive stimulation program.⁹ A cognitive and functional assessment was performed before and after the intervention. The MMSE scores were used to distinguish good responders (higher cognitive performance) from nonresponders (poor cognitive perfor-

mance) at baseline. After 12 months of cognitive stimulation treatment, good responders had significantly better results than nonresponders on the MMSE in temporal orientation and category evocation and on the Philadelphia Geriatric Center Instrumental Activities of Daily Living scale, suggesting that cognitive stimulation is linked to cognitive and functional capacity. Therefore, further development of customized interventions in patients with AD patients is needed.

3. Clinical trials of combination of physical and cognitive training in AD

Increasing evidence indicates that nonpharmacologic interventions, specifically combining cognitive and physical training, may be effective in protecting against decline of cognitive and brain functions in healthy aging as well as in neurodegenerative diseases such as AD.

It is worth noting that there were several clinical trials investigating the effect of physical and cognitive training on AD in 2016. One of the studies investigated the different pathways between physical and cognitive training.¹⁰ Both types of training were carried out for 12 weeks (3 h/week), and neurocognitive, MRI, and physiological measures were assessed at baseline, during training, and after training. It is interesting to note that the study showed executive function improvement and increased cerebral blood flow within related brain regions in the cognitive training group, whereas enhanced memory was observed in the physical training group, in whom cerebral blood flow increased in the hippocampi of those who showed memory enhancement. Such a distinct benefit between the 2 types of trainings might suggest a better effectiveness of combined protocols to strengthen brain health. A recent controlled interventional clinical trial that included 10 weeks of physical and cognitive training and a lifestyle survey in 45 elderly individuals at risk of dementia showed that neither physical nor cognitive training interventions improved global cognition compared with the control group.¹¹ Instead, self-reported lifestyle showed significant benefits in global cognition and memory. Another recent clinical investigation of the effectiveness of long-term exercise training in improving cognitive function with a smaller sample size showed that 6 months of treadmill physical training and aerobic exercise training improved the executive function in persons with cognitive decline, particularly in those with objective cognitive impairment.¹² Another single-blind 6-month randomized controlled trial examined the effect of physical exercise in combination with a multicomponent cognitive program on the cognitive performance of aged individuals with moderate to severe AD.¹³ This study showed that physical exercise (60 min of supervised exercise sessions, 5 times a week for 6 months) plus a cognitive program (music, art, handicrafts, or laughing activities with therapists 2 × 60 min per day, 5 days per week for 6 months) showed no significant improvements in the baseline value after 6 months. However, the ADAS-cog score was significantly lower in those who participated in the PA plus cognitive program compared with individuals in the multicomponent cognitive program without exercise at adjusted baseline value, taking into account age, sex, and years of education.

4. Conclusion

In summary, the recent clinical trials of the effects of various exercises on prevention of AD suggested that long-term physical exercise with a multicomponent cognitive intervention might improve cognitive function in patients with AD.

Authors' contributions

YS participated in and carried out the initiation and preparation for this paper. RL carried out most of writing of the paper. Both authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

Competing interests

Neither of the authors declare competing financial interests.

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