

Review

Physical exercise in the prevention and treatment of Alzheimer's disease

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Abstract

Dementia is one of the greatest global challenges for health and social care in the 21st century. Alzheimer's disease (AD), the most common type of dementia, is by no means an inevitable consequence of growing old. Several lifestyle factors may increase, or reduce, an individual's risk of developing AD. Much has been written over the ages about the benefits of exercise and physical activity. Among the risk factors associated with AD is a low level of physical activity. The relationship between physical and mental health was established several years ago. In this review, we discuss the role of exercise (aerobic and resistance) training as a therapeutic strategy for the treatment and prevention of AD. Older adults who exercise are more likely to maintain cognition. We address the main protective mechanism on brain function modulated by physical exercise by examining both human and animal studies. We will pay especial attention to the potential role of exercise in the modulation of amyloid β turnover, inflammation, synthesis and release of neurotrophins, and improvements in cerebral blood flow. Promoting changes in lifestyle in pre-symptomatic and predementia disease stages may have the potential for delaying one-third of dementias worldwide. Multimodal interventions that include the adoption of an active lifestyle should be recommended for older populations.

Keywords: Aerobic exercise; Dementia; Exercise training; Lifestyle factors; Multidomain interventions; Resistance exercise

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and one of the most frequent neurodegenerative pathologies in elderly people, constituting about 90% of the cases of dementia in this population. AD is characterized by its irreversibility and progressive functional, cognitive, and behavioral loss. It is usually accompanied by various brain disorders such as amnesia, agnosia, apraxia, and aphasia.¹

Twenty-four million people in the world suffer from AD, and it is expected that by 2050 this number will be 4 times

greater.² These alarming numbers are explained by the fact that the main risk factor for this disease is age,³ and by 2050 it is estimated that the population over 65 years will be 3 times larger than it was in 2010, reaching close to 1.5 billion people.

AD is a devastating disease. The social and human cost for patients and caregivers is overwhelming, and the economic cost of AD is unaffordable. For instance, in the United States in 2017, the annual cost of care per patient over 65 with AD or another type of dementia was USD 48,000, or 3.5 times more than for a person without any type of dementia.^{4,5}

AD is characterized by the loss of neuronal synapses and pyramidal neurons accompanied by progressive cognitive neurodegeneration.⁶ The regions associated with more complex brain functions, such as the hippocampus and the neocortex, are the most affected.

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Although there are several hypotheses to explain the origin of AD, the 2 main neuropathological features include the extracellular accumulation of senile plaques around the neurons and the glia, and the intracellular formation of neurofibrillary tangles (NFTs). Senile plaques are formed mainly by the accumulation of insoluble amyloid β ($A\beta$) protein, especially its isoform $A\beta_{42}$, which is formed by the enzymatic cleavage of the transmembrane amyloid precursor protein (APP).^{7,8} NFTs are formed from the hyperphosphorylation of the tau protein. The main function of this protein is to stabilize the microtubules so that they connect with other elements of the neuronal cytoskeleton, such as neurofilaments and actin.⁹

Another feature in AD is the inflammatory response at the brain level. In the early stages of the disease, the immune response results in a removal of $A\beta$, ameliorating its symptoms.^{10,11} To generate a balance between the deposition and the clearance of $A\beta$, microglia plays a fundamental role by engulfing insoluble deposits of this peptide through the activation of receptors that promote phagocytic action, such as cluster of differentiation 36 (CD36), and receptors for advanced-glycosylation end products.^{12,13} Microglia also activates extracellular proteases such as neprilysin, the insulin degrading enzyme, endothelin converting enzyme 1, angiotensin converting enzyme, matrix metalloprotease, and the presequence peptidase.^{14–16} During advanced stages of the disease there is a prolonged stimulation of the immune response caused by $A\beta$, which leads to a decrease in the efficiency of the microglia to degrade it.¹⁷ In turn, this leads to the release of several proinflammatory products, such as cytokines, reactive oxygen, and nitrogen species, leading to an increase in the production of $A\beta$ and the hyperphosphorylation of tau, generating more damage and neuronal death.^{18–20} This state contributes to an increase in cognitive decline and the development of the disease.

The risk factors associated with AD, apart from age, are low educational level, diabetes, genetics, belonging to certain minority ethnic groups (prevalence of dementia is higher in British African–Caribbean people),²¹ diet, previous brain injuries, sleep disorders, hypertension, hearing loss, and low levels of physical activity.²² Physical activity (“any movement of the body”) and exercise (“physical activity that is typified by specific and purposeful training”) constitute 2 different concepts.²³ However, for the sake of clarity we refer to both these concepts interchangeably since some of the reports we refer to in this review use these expressions as synonyms. Older adults are considered physically active when they perform moderate-intensity aerobic physical activities for a minimum of 30 min, 5 days/week, or vigorous-intensity aerobic activity for a minimum of 20 min, 3 days/week.²³ Also, combinations of moderate- and vigorous-intensity activity can be performed to meet this recommendation. Moderate-intensity aerobic activity involves a moderate level of effort relative to an individual's aerobic fitness. On a 10-point scale, where sitting is 0 and all-out effort is 10, moderate-intensity activity is rated as a 5 or 6 and produces noticeable increases in heart rate and breathing. Using the same scale, vigorous-intensity activity is rated as a 7 or 8 and produces large increases in heart rate and breathing. Thus, physical inactivity, a concept that has also been included

in this review, is defined as *not* meeting any of the following 2 criteria: 30 min of moderate-intensity physical activity on at least 5 days/week or 20 min of vigorous-intensity physical activity on at least 3 days/week.

Gender is also considered a risk factor for AD; two-thirds of AD patients are women.⁵ This proportion is mainly attributed to the greater longevity of women over men, which makes them more susceptible to this and other age-associated diseases and syndromes.²⁴ Apart from this fact, if there is a real relationship between sex and AD risk, it is not clear. In the literature, epidemiological studies with controversial results can be found.^{25–27} Several results point to sex hormones as responsible, at least partially, for the higher incidence of AD in women. The important changes in sex hormone concentrations associated with a woman's age, the role of sexual dimorphism in the neuronal structures development, the gene-by-sex interactions, and the increased specific immune response of women, have all been associated with an increased risk of AD.²⁶

In this review, we mainly discuss the role of physical exercise as a therapeutic strategy for the treatment and prevention of AD.

2. Physical exercise and physiologic brain aging

Physical inactivity contributes to about 5 million deaths in the world each year from noncommunicable diseases.²⁸ The inverse relationship between a physically active life and the risk of suffering cognitive decline is widely documented,²⁹ and aerobic exercise training has been the most extensively used option for the study of the effect of physical activity in alleviating the negative impact of aging in cognitive function.^{29,30} The first evidence was published in the 1970s, when it was shown that middle-aged sports practitioners had better response in cognitive tasks that involved a psychomotor component when compared with sedentary aged-matched subjects.³¹ More recently, 1 study found a significant improvement in memory among middle-aged trained individuals, compared to sedentary subjects, when the Free and Cued Immediate Recall test was administered to both groups.³² The positive impact of long-term exercise training by delaying the onset of physiologic memory loss suggests the effectiveness of exercise as a preventive strategy against age-related memory loss and neurodegeneration. However, it is worth mentioning that late-onset exercise interventions have also shown positive results in the delay of brain aging. For example, in a groundbreaking paper published in 2011, the authors found that 1 year of moderate-intensity exercise (40 min duration, 3 days/week) increased the size of the hippocampus, as well as increasing spatial memory, in healthy older individuals.³³ The anatomic changes induced by aerobic exercise have also been confirmed by other research groups. For instance, it has been found that 6 months of exercise (60 min duration, 3 days/week) is sufficient to increase both the gray and white matter in the anterior cingulate cortex, as measured by magnetic resonance imaging, in older, cognitively healthy subjects.³⁴ Longer aerobic exercise training protocols (3 years' duration) in

sedentary older women have shown improvements in reaction time, motor function, and cognitive processing speed, indicating that exercise is effective in reversing or at least slowing the age-related declines in motor performance and in speed of cognitive processing.³⁵ However, some evidence shows that aerobic exercise interventions do not always induce improvements in cognitive function in older subjects (60–80 years).^{36–38} These contradictory results may be explained by the training duration, frequency, and/or intensity of the interventions.

The impact of resistance exercise on cognitive function has gained notice in the past few years. In a recent meta-analysis, more than 24 studies were reviewed that investigated the effects of weight lifting on different cognitive outcomes in older individuals. According to the results, resistance training has positive effects on measurements related to the detection of cognitive impairment and executive functions. However, resistance training has no effect on working memory measurements.³⁹ Although a high heterogeneity was observed in all analyses, the authors concluded that resistance training seemed to have positive effects on cognition. However, future research will need to determine why the effects are so variable.

From this first part of the review, we can conclude that exercise programs with components of both aerobic and resistance training, of moderate intensity, and lasting at least 45 min per session on as many days of the week as possible, are beneficial in terms of cognitive function in older healthy adults.⁴⁰

3. Physical exercise and multimodal interventions for the treatment and prevention of AD

Dementia is by no means an inevitable consequence of reaching retirement age. There are lifestyle factors that may decrease, or increase, an individual's risk of developing dementia.²² Around 35% of dementia is attributable to a combination of 9 risk factors: low education level, midlife hypertension, midlife obesity, hearing loss, later-life depression, diabetes, smoking, social isolation, and, of course, low physical activity.⁴¹

A meta-analysis that included 16 studies with more than 160,000 participants found a 45% reduction in the risk of developing AD due to the regular practice of physical activity (hazard ratio = 0.55, 95% confidence interval: 0.36–0.84, $p = 0.006$).⁴² In a sample of 716 older subjects followed for 3.5 years, similar results were found when assessing the risk of suffering AD. Those individuals with low daily physical activity levels were 53% more likely to suffer AD than those who reported more active lives (hazard ratio = 0.477, 95% confidence interval: 0.273–0.832).⁴³

Although there are discrepancies,^{36,44–49} the benefits of engaging in physical activities have also been seen in populations diagnosed with mild cognitive impairment (MCI) and AD. Several studies have found improvements in executive functions, memory, and cognitive tests in individuals with MCI who engaged in an aerobic exercise program.^{50–55} Improvements in the cognitive

function of individuals with MCI through physical activity are important in preventing the progression of the disease and in decreasing the number of AD in older people. In individuals diagnosed with AD, and, in general, at early stages of the disease, aerobic exercise alone, or accompanied with cognitive stimulation, induces improvements in some aspects of brain function,^{56–65} although in some studies exercise was accompanied with cognitive situation.

Few studies have been published on the effects of resistance training in people with MCI or AD.^{44,66–68} Prominent among them is the randomized, double-blind trial that included 100 people between 55 and 86 years of age with MCI.⁶⁹ In this study it was shown that 6 months of resistance exercise induced improvements in memory, attention, and executive functions. Moreover, those benefits persisted 12 months after the end of the intervention period.

Prevention through the promotion of changes in lifestyle in presymptomatic and predementia disease stages may have the potential for delaying one-third of dementias.⁷⁰ Engaging in physical exercise programs seems to be effective, but it is clearly not enough. Studies that examine multimodal interventions hypothesize that an integrated approach to addressing multiple risk factors for AD may be more successful than single-component interventions in producing benefits. Multimodal interventions often include changes in diet, physical activity, and cognitive training (Fig. 1).

Several studies attribute to the diet a key role in delaying the progression of AD. Some of these studies have tested diets considered as heart-healthy, such as the Dietary Approaches to Stop Hypertension diet (DASH), Mediterranean–DASH Intervention for Neurodegenerative Delay diet (MIND), or the Mediterranean diet.⁷¹ The inflammatory component of AD has been treated by supplementation with fatty acids, vitamins, flavonoids, polyphenols, probiotics, and dietary advanced glycation end products.⁷² Ketogenic diets, which are protective in other neurological disorders, also seem to have great potential in the prevention and treatment of the disease.⁷³ In humans,

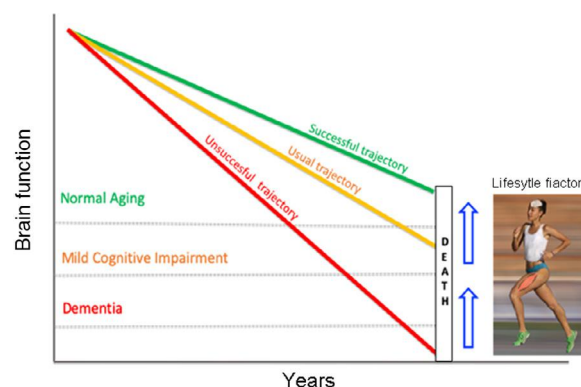


Fig. 1. Brain function in normal aging and Alzheimer's disease is influenced by lifestyle factors. The usual trajectory for brain aging (orange line) indicates that, years before death, an individual shows signs of mild cognitive impairment. In some cases, that cognitive damage takes place many years before death and even leads to dementia (red line). By modifying lifestyle factors through multimodal interventions, an individual can delay the onset of cognitive impairment until a very advanced age (green line).

few clinical trials have been carried out using ketogenic diets; instead, ketogenic agents have been used.⁷⁴ In animal models of AD, the increase in ketone levels in the body through intermittent fasting or supplementation with ketone esters have shown promising results.^{75,76}

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a multidomain intervention consisting of diet, exercise, cognitive training, and vascular risk monitoring, resulted in an improvement or maintenance of cognitive functioning in at-risk elderly people from the general population.⁷⁷ This trial was the first methodologically robust study showing that with a 2-year intervention, it was possible to reduce the risk of cognitive decline among the general elderly population, rather than solely with patients in a clinical setting. More recently, it has been found that engaging in physical activity and lowering vascular risk may have additive protective effects on delaying the progression of AD.²² Greater physical activity and lower vascular risk independently attenuated the negative association of A β burden with cognitive decline and neurodegeneration in asymptomatic individuals.⁷⁸

4. Potential protective mechanisms of physical exercise on brain aging, from mice to humans

The beneficial effects of physical activity go beyond skeletal muscle and involve adaptations in other organs. Exercise causes changes in the brain at the anatomic, cellular, and molecular levels by inducing a cascade of cellular and molecular processes that promote different physiologic phenomena, including angiogenesis, neurogenesis, synaptogenesis, and stimulation of neurotrophic factors that enhance learning, memory, and brain plasticity (Fig. 2).^{53,60,79–84} The availability of transgenic murine models that simulate the main neuropathologic characteristics of AD has enabled the study of the main protective mechanisms of exercise on brain aging. Among these mechanisms is an increase in cerebral blood flow

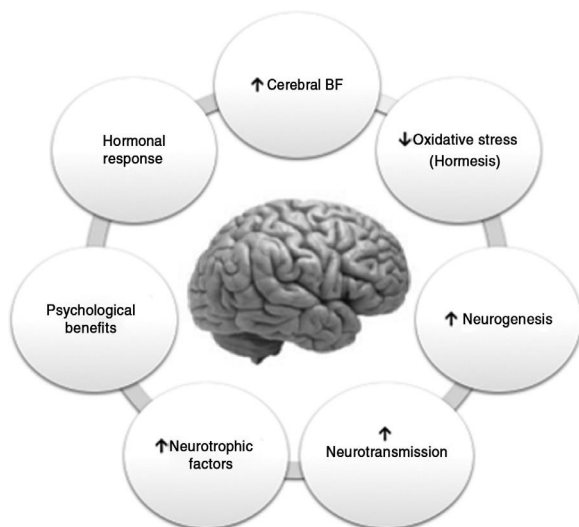


Fig. 2. Potential protective mechanisms of exercise on brain aging.

(CBF) in several cortical and subcortical areas,⁸⁵ together with the decrease in the formation of A β and the phosphorylation of the tau protein.^{86,87}

5. Summary of the main mechanisms that exercise can activate at the brain level

5.1. β -Amyloid peptide, tau protein, and exercise

In transgenic mice models for AD, a decrease in A β plaques and NFTs after both voluntary and forced exercise interventions has been found. In some cases, these findings have been accompanied by improvements in learning and memory.^{86–89} APP/PS1 are double transgenic mice expressing a chimeric mouse/human amyloid precursor protein (APP) (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9), both directed to central nervous system (CNS) neurons. In a recent study in double transgenic APPswe/PSEN1 Δ E9 mice, 10 weeks of voluntary exercise decreased both the load and the size of the A β plaques, as well as the phosphorylation of tau in the hippocampus. Improvements in spatial memory, a decrease in hippocampal neuronal loss, and an increase in neurogenesis in the Cornu Ammonis 3 (CA3) zone and the dentate gyrus were also reported in the study.⁹⁰ These results have been supported by studies in other AD transgenic mice models such as hPS2m (overexpress human Presenilin 2 mutant),⁸⁹ Tg-NSE/htau23 (overexpress human tau23 under the control of the NSE promoter),⁸⁸ Thy-Tau22 (human 4-repeat tau mutated at sites G272V and P301S under the control of Thy1.2 promoter),⁹¹ P301S-tau (overexpress the P301S-mutant human tau gene),⁸⁷ and Tg2576 (overexpress human APP 695).⁹² It is assumed that a successful therapy for AD would both remove the pathologic hallmarks of the disease and provide some functional recovery. However, there are studies that have not found a decrease in A β load and/or tau phosphorylation despite improvements in learning tasks and/or memory in the exercised mice.^{93–95} A key factor with exercise interventions is to start them in an early pathologic state. Exercise cannot counteract the formation of plaques and the cognitive deterioration if the intervention is carried out after their appearance.⁸⁶ Moreover, it has been shown in mice models that voluntary exercise may be superior to forced exercise if certain aspects of the disease, such as plaque deposition and memory impairment, are to be reduced.⁹²

Studies in humans have also found an inverse correlation between physical activity levels and the plasma and brain A β load in elderly people without cognitive disorders.^{96,97} Moreover, it has been found that a 6-month aerobic exercise intervention in individuals with MCI induced a 24% decrease in the plasma A β _{1–42} levels when compared with the levels found in the control group.⁵⁰ Jointly, all of these results indicate a potential role of exercise in modulating the A β turnover.

5.2. Exercise and inflammation

The term “inflammaging” characterizes a widely accepted hypothesis that aging is accompanied by a low-grade chronic upregulation of certain proinflammatory responses. It is

characterized by a relative decline in adaptive immunity and T-helper 2 responses and is associated with increased cell-mediated responses.⁹⁸ Inflammaging has been considered to be a “prodrome” to AD and microglial malfunction, a common feature during aging.⁹⁹

Exercise has important modulatory effects on immune function.¹⁰⁰ Systemically, physical exercise has been shown to have a positive effect on markers of inflammation, and recently those effects have been extended to the CNS.¹⁰¹

In the Tg2576 AD animal model, it was shown that 3 weeks of voluntary exercise were sufficient to decrease the concentration of A β and the proinflammatory cytokines interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α). These changes were accompanied by an increase in proteins related to the immune response, such as interferon- γ and macrophage inflammatory protein-1 α , in the hippocampus.¹⁰²

The anti-inflammatory effects of exercise on the CNS have also been evaluated in older animals. Higher levels of hippocampal IL-10 (the main anti-inflammatory cytokine) and lower IL-1 β /IL-10, IL-6/IL-10, and TNF- α /IL-10 ratios have been found in rats exercised for 10 days.¹⁰³ Barrientos et al.¹⁰⁴ found that the long-term memory impairment in older rats injected with *Escherichia coli* (*E. coli*) intraperitoneally could be prevented when they had free access to running wheels. Along with these findings, voluntary exercise also prevented the reduction in brain-derived neurotrophic factor (BDNF) expression in the CA1 zone of the hippocampus. Finally, the microglia of the exercised rats had a lower inflammatory response than the control rats, as measured by the expression of TNF- α , IL-1 β , and IL-6. These findings highlight the capacity of exercise to modulate inflammatory responses on CNS and reinforce its potential in minimizing the risk of suffering diseases related to neuroinflammation, such as AD.

Particularly in elderly people, regular physical activity has been shown to have a positive effect in the reduction of inflammatory markers such as C-reactive protein, IL-6, and TNF- α ^{105–110} at the systemic level. In many cases, this has been associated with better performance in cognitive tests in both cross-sectional^{111–113} and longitudinal studies.^{114–117}

Aerobic exercise lasting more than 2 weeks^{118–121} has been shown to improve the immune system in healthy elderly people by increasing the activity of the natural killer cells, the proliferation of T lymphocytes, hematopoietic stem cells, and endothelial progenitor cells. However, it is noteworthy that the results achieved with resistance exercise interventions have been more heterogeneous.¹²²

5.3. Neurotrophins, cognitive function, and exercise

Neurotrophins are growth factors belonging to the family of neurotrophic factors, which regulate axonal growth, synaptic plasticity, neurotransmission, hippocampal neurogenesis, synaptic protein expression, and long-term potentiation.^{123–128}

Among neurotrophins, BDNF has been extensively studied, and its relationship with exercise and cognitive function has been widely established.^{32,50,129–135} The brain synthesizes

about 75% of BDNF under normal conditions. During prolonged exercise, this synthesis is increased by 2- to 3-fold, and there is evidence indicating that circulating BDNF levels correlate with brain tissue BDNF levels.^{132,136}

Exercise provides cognitive benefit in 5xFAD mice (express human APP and PSEN1 transgenes with a total of 5 AD-linked mutations: the Swedish (K670N/M671L), Florida (I716V), and London (V717I) mutations in APP, and the M146L and L286V mutations in PSEN1), a mouse model of AD, by inducing both adult hippocampal neurogenesis and by elevating the levels of BDNF.¹³⁷ This combination seems to generate an adequate brain environment for the maintenance and survival of the new neurons in regions of the brain affected by AD. The induction of adult hippocampal neurogenesis in combination with the elevation of BDNF levels successfully mimic the beneficial effects of exercise in AD mice.¹³⁷ However, the induction of hippocampal neurogenesis alone did not benefit cognition or AD markers. Exercise has also shown its effectiveness on cognitive function and BDNF levels in mice models of accelerated aging.¹³⁰ Four weeks of moderate exercise were sufficient to improve recognition memory and increased hippocampal BDNF expression in 13-month-old mice.

Low levels of BDNF have been found in brains of people with AD,^{138,139} which supports the hypothesis that improving its production may be an effective alternative that delays the onset of the disease. In humans, several studies indicate that both acute and chronic exercise^{140–146} contribute to an increase in the peripheral levels of BDNF, and, in some cases, it is related to gains in cognitive function.^{131,147–149} Moreover, aerobic exercise-induced increments in hippocampal volume are associated with greater serum levels of BDNF in cognitively healthy older individuals,³³ and high serum levels of BDNF have been associated with low risk of AD.¹⁵⁰

The pathways responsible for the synthesis and release of BDNF in AD patients seem to be susceptible to stimulation with exercise. In fact, one bout of acute aerobic exercise increased the BDNF plasma levels in patients with AD and in healthy controls. Additionally, BDNF was associated with their physical activity levels.¹⁵¹

5.4. AD, CBF, and exercise

Aging has been associated with progressive losses in cognitive function and CBF.^{152–156} It has been shown that the rate of decrease with age of the CBF is 0.35%–0.45% per year in middle-aged and elderly subjects (Fig. 3).^{157,158} This leads to an accelerated decline in cognitive function and an increased risk of suffering dementia in the general population.¹⁵⁹

Although the cause of the CBF decrease in aging is not entirely clear, it has been postulated that changes in the density and elasticity of cerebral blood vessels, as well as the degeneration of pericytes and a reduction in the activity and number of neurons, could explain it.^{161,162}

Compared with healthy people, individuals with AD show a decrease of up to 40% in the CBF. Regions such as the precuneus, the hippocampus, the posterior cingulate gyrus,

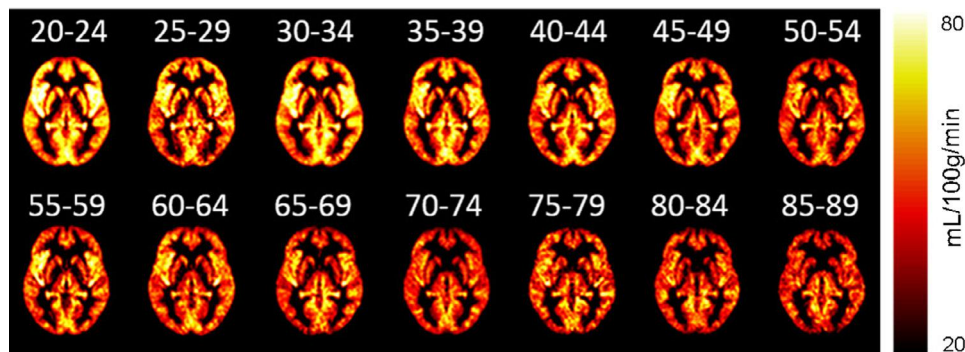


Fig. 3. CBF by age groups (at an interval of 5 years), measured by MRI (De Vis et al.,¹⁶⁰ used with permission of John Wiley and Sons). CBF = cerebral blood flow; MRI = magnetic resonance imaging.

and the temporal, occipital, and parietal lobes are mainly affected.^{163–167}

In animal models, it has been shown that the soluble form of A β protein can accumulate in cerebral blood vessels (which is known as amyloid angiopathy), generating a decrease in CBF and a vasoconstriction effect, possibly affecting neuronal activity.^{168,169} Intra-arterially injected solubilized A β_{1-40} in rats of 7–8 months of age decreased CBF and increased vascular resistance in the cerebral cortex of the animals, indicating that A β could contribute to the hypoperfusion observed during AD.¹⁷⁰

In older adults, the regular practice of exercise has a positive effect both on peripheral endothelial function¹⁷¹ and on the increase of CBF in areas such as the hippocampus.^{156,172,173} In middle-aged, cognitively healthy subjects, even short-term exercise programs, such as 3 h of aerobic exercise per week for 12 weeks, are sufficient to improve CBF at rest in regions such as the anterior cingulate and the hippocampus.^{174,175} However, even in physically active people, short periods of inactivity can decrease CBF in up to 8 regions of the brain, including the hippocampus.¹⁷⁶ Thus, CBF is sensitive to small changes in people's lifestyle, thus making it necessary to maintain a regular practice of exercise to preserve brain health.

Regarding AD patients and exercise, the results from studies have not been consistent.¹⁷⁷ For instance, in a study, exercise did not lead to any improvements in CBF,¹⁷⁸ concentrations of A β , total tau, or phosphorylated tau in the cerebrospinal fluid of people with AD.¹⁷⁹ This indicates that, although functional parameters are still likely to be positively affected in people with AD, changes in brain function may require an adjustment in the different components of the load, such as the duration of exercise sessions and the frequency, intensity, and type of exercise during the intervention.

Finding mimetics of physical exercise for those patients who have very compromised functionality is not easy, because physical exercise is a very systemic intervention and targets at several potential causes of AD. The possibility of using molecular mimetics, such as 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), is known to only improve brain function transiently¹⁸⁰ and does not achieve the same positive effects as, for instance, running. Another option would be to use neuromuscular electrical stimulation or vibration in people who

are unable to perform physical exercise, but this has not yet been tested in AD patients.¹⁸¹

6. Conclusion

Promoting changes in lifestyle in presymptomatic and pre-dementia disease stages may have the potential for delaying one-third of dementias worldwide. Exercise modulates A β turnover, inflammation, the synthesis and release of neurotrophins, and CBF. Multimodal interventions that include the adoption of an active lifestyle should be recommended for older populations.

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Authors' contributions

ADR and GOG performed the literature search and review and wrote the manuscript; ASP, CAC, FM, CGL, AGC, CBL, AC, and EGD analyzed and discussed the data and reviewed the manuscript; MCGC and JV designed and supervised the review, secured funding, and wrote the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

References

1. Yesavage JA, Brooks JO, Taylor J, Tinklenberg J. Development of aphasia, apraxia, and agnosia and decline in Alzheimer's disease. *Am J Psychiatry* 1993;**150**:742–7.

2. Dos Santos Picanco LC, Ozela PF, de Fatima de Brito Brito M, Pinheiro AA, Padilha EC, Braga FS, et al. Alzheimer's disease: a review from the pathophysiology to diagnosis, new perspectives for pharmacological treatment. *Curr Med Chem* 2018;**25**:3141–59.
3. World Health Organization. *Global health and aging*. Available at: https://www.who.int/ageing/publications/global_health.pdf. [accessed 15.01.2019].
4. Alzheimer's Association. *2018 Alzheimer's disease facts and figures: includes a special report on the financial and personal benefits of early diagnosis*. Available at: <https://www.alz.org/media/HomeOffice/FactsandFigures/facts-and-figures.pdf>. [accessed 18.11.2018].
5. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology* 2013;**80**:1778–83.
6. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry* 1999;**66**:137–47.
7. Sun X, Jin L, Ling P. Review of drugs for Alzheimer's disease. *Drug Discov Ther* 2012;**6**:285–90.
8. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science* 1992;**256**:184–5.
9. Aamodt EJ, Williams Jr. RC. Microtubule-associated proteins connect microtubules and neurofilaments *in vitro*. *Biochemistry* 1984;**23**:6023–31.
10. Chakrabarty P, Jansen-West K, Beccard A, Ceballos-Diaz C, Levites Y, Verbeeck C, et al. Massive gliosis induced by interleukin-6 suppresses A β deposition *in vivo*: evidence against inflammation as a driving force for amyloid deposition. *FASEB J* 2010;**24**:548–59.
11. Shafte SS, Kyrkanides S, Olschowka JA, Miller JN, Johnson RE, O'Banion MK. Sustained hippocampal IL-1 β overexpression mediates chronic neuroinflammation and ameliorates Alzheimer plaque pathology. *J Clin Invest* 2007;**117**:1595–604.
12. El Khoury J, Hickman SE, Thomas CA, Loike JD, Silverstein SC. Microglia, scavenger receptors, and the pathogenesis of Alzheimer's disease. *Neurobiol Aging* 1998;**19**(Suppl. 1):S81–4.
13. Yan SD, Chen X, Fu J, Chen M, Zhu H, Roher A, et al. RAGE and amyloid- β peptide neurotoxicity in Alzheimer's disease. *Nature* 1996;**382**:685–91.
14. Marr RA, Hafez DM. Amyloid-beta and Alzheimer's disease: the role of neprilysin-2 in amyloid-beta clearance. *Front Aging Neurosci* 2014;**6**:187. doi:10.3389/fnagi.2014.00187.
15. Vitek MP, Bhattacharya K, Glendening JM, Stopa E, Vlassara H, Bucala R, et al. Advanced glycation end products contribute to amyloidosis in Alzheimer disease. *Proc Natl Acad Sci U S A* 1994;**91**:4766–70.
16. Lee CY, Landreth GE. The role of microglia in amyloid clearance from the AD brain. *J Neural Transm (Vienna)* 2010;**117**:949–60.
17. Hickman SE, Allison EK, El Khoury J. Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *J Neurosci* 2008;**28**:8354–60.
18. Hsieh HL, Yang CM. Role of redox signaling in neuroinflammation and neurodegenerative diseases. *Biomed Res Int* 2013;**2013**: 484613. doi:10.1155/2013/484613.
19. Wee Yong V. Inflammation in neurological disorders: a help or a hindrance? *Neuroscientist* 2010;**16**:408–20.
20. Meda L, Cassatella MA, Szendrei GI, Otvos Jr. L, Baron P, Villalba M, et al. Activation of microglial cells by β -amyloid protein and interferon- γ . *Nature* 1995;**374**:647–50.
21. Adelman S, Blanchard M, Livingston G. A systematic review of the prevalence and covariates of dementia or relative cognitive impairment in the older African-Caribbean population in Britain. *Int J Geriatr Psychiatry* 2009;**24**:657–65.
22. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *The Lancet* 2017;**390**:2673–734.
23. Vina J, Borras C, Sanchis-Gomar F, Martinez-Bello VE, Olaso-Gonzalez G, Gambini J, et al. Pharmacological properties of physical exercise in the elderly. *Curr Pharm Des* 2014;**20**:3019–29.
24. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 2007;**29**:125–32.
25. Fisher DW, Bennett DA, Dong H. Sexual dimorphism in predisposition to Alzheimer's disease. *Neurobiol Aging* 2018;**70**:308–24.
26. Fiest KM, Roberts JI, Maxwell CJ, Hogan DB, Smith EE, Frolkis A, et al. The prevalence and incidence of dementia due to Alzheimer's disease: a systematic review and meta-analysis. *Can J Neurol Sci* 2016;**43** (Suppl. 1):S51–82.
27. Irvine K, Laws KR, Gale TM, Kondel TK. Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. *J Clin Exp Neuropsychol* 2012;**34**:989–98.
28. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *The Lancet* 2012;**380**:219–29.
29. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* 2001;**58**:127–44.
30. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med* 2011;**269**:107–17.
31. Spirduso WW, Clifford P. Replication of age and physical activity effects on reaction and movement time. *J Gerontol* 1978;**33**:26–30.
32. De la Rosa A, Solana E, Corpas R, Bartrés-Faz D, Pallàs M, Vina J, et al. Long-term exercise training improves memory in middle-aged men and modulates peripheral levels of BDNF and Cathepsin B. *Sci Rep* 2019;**9**:3337. doi:10.1038/s41598-019-40040-8.
33. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A* 2011;**108**:3017–22.
34. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* 2006;**61**:1166–70.
35. Rikli RE, Edwards DJ. Effects of a three-year exercise program on motor function and cognitive processing speed in older women. *Res Q Exerc Sport* 1991;**62**:61–7.
36. Blumenthal JA, Emery CF, Madden DJ, Schniebolck S, Walsh-Riddle M, George LK, et al. Long-term effects of exercise on psychological functioning in older men and women. *J Gerontol* 1991;**46**:P352–61.
37. Hill RD, Storandt M, Malley M. The impact of long-term exercise training on psychological function in older adults. *J Gerontol* 1993;**48**:P12–7.
38. Panton LB, Graves JE, Pollock ML, Hagberg JM, Chen W. Effect of aerobic and resistance training on fractionated reaction time and speed of movement. *J Gerontol* 1990;**45**:M26–31.
39. Landrigan JF, Bell T, Crowe M, Clay OJ, Mirman D. Lifting cognition: a meta-analysis of effects of resistance exercise on cognition. *Psychol Res* 2020;**84**:1167–83.
40. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sport Med* 2018;**52**:154–60.
41. Orgeta V, Mukadam N, Sommerlad A, Livingston G. The Lancet Commission on dementia prevention, intervention, and care: a call for action. *Ir J Psychol Med* 2019;**36**:85–8.
42. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med* 2009;**39**:3–11.
43. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology* 2012;**78**:1323–9.
44. Vital TM, Hernández SSS, Pedrosa RV, Teixeira CVL, Garuffi M, Stein AM, et al. Effects of weight training on cognitive functions in elderly with Alzheimer's disease. *Dement Neuropsychol* 2012;**6**:253–9.
45. Cott CA, Dawson P, Sidani S, Wells D. The effects of a walking/talking program on communication, ambulation, and functional status in residents with Alzheimer disease. *Alzheimer Dis Assoc Disord* 2002;**16**:81–7.
46. Toots A, Littbrand H, Bostrom G, Hornsten C, Holmberg H, Lundin-Olsson L, et al. Effects of exercise on cognitive function in older people with dementia: a randomized controlled trial. *J Alzheimers Dis* 2017;**60**:323–32.

47. Oken BS, Zajdel D, Kishiyama S, Flegal K, Dehen C, Haas M, et al. Randomized, controlled, six-month trial of yoga in healthy seniors: effects on cognition and quality of life. *Altern Ther Health Med* 2006;**12**:40–7.
48. Madden DJ, Blumenthal JA, Allen PA, Emery CF. Improving aerobic capacity in healthy older adults does not necessarily lead to improved cognitive performance. *Psychol Aging* 1989;**4**:307–20.
49. van Uffelen JGZ, Chin A, Paw MJM, Hopman-Rock M, van Mechelen W. The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. *Clin J Sport Med* 2008;**18**:486–500.
50. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 2010;**67**:71–9.
51. Nagamatsu LS, Handy TC, Hsu CL, Voss M, Liu-Ambrose T. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. *Arch Intern Med* 2012;**172**:666–8.
52. Blumenthal JA, Smith PJ, Mabe S, Hinderliter A, Lin PH, Liao L, et al. Lifestyle and neurocognition in older adults with cognitive impairments: a randomized trial. *Neurology* 2019;**92**:e212–23.
53. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *JAMA* 2004;**292**:1454–61.
54. Zheng G, Xia R, Zhou W, Tao J, Chen L. Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med* 2016;**50**:1443–50.
55. Scherder EJ, Van Paasschen J, Deijen JB, Van Der Knokke S, Orlebeke JF, Burgers I, et al. Physical activity and executive functions in the elderly with mild cognitive impairment. *Aging Ment Health* 2005;**9**:272–80.
56. Coelho FG, Santos-Galduroz RF, Gobbi S, Stella F. Systematized physical activity and cognitive performance in elderly with Alzheimer's dementia: a systematic review. *Braz J Psychiatry* 2009;**31**:163–70. [in Portuguese].
57. Friedman R, Tappen RM. The effect of planned walking on communication in Alzheimer's disease. *J Am Geriatr Soc* 1991;**39**:650–4.
58. Rolland Y, Rival L, Pillard F, Lafont C, Rivère D, Albarède J, et al. Feasibility [corrected] of regular physical exercise for patients with moderate to severe Alzheimer disease. *J Nutr Health Aging* 2000;**4**:109–13.
59. Öhman H, Savikko N, Strandberg TE, Kautiainen H, Raivio MM, Laakkonen ML, et al. Effects of exercise on cognition: the Finnish Alzheimer Disease Exercise Trial: a randomized, controlled trial. *J Am Geriatr Soc* 2016;**64**:731–8.
60. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Arch Phys Med Rehabil* 2004;**85**:1694–704.
61. Yu F, Kolanowski AM, Strumpf NE, Eslinger PJ. Improving cognition and function through exercise intervention in Alzheimer's disease. *J Nurs Scholarsh* 2006;**38**:358–65.
62. Vreugdenhil A, Cannell J, Davies A, Razay G. A community-based exercise programme to improve functional ability in people with Alzheimer's disease: a randomized controlled trial. *Scand J Caring Sci* 2012;**26**:12–9.
63. Panza GA, Taylor BA, MacDonald H V, Johnson BT, Zaleski AL, Livingston J, et al. Can exercise improve cognitive symptoms of Alzheimer's disease? *J Am Geriatr Soc* 2018;**66**:487–95.
64. Morris JK, Vidoni ED, Johnson DK, Van Sciver A, Mahnken JD, Honea RA, et al. Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial. *PLoS One* 2017;**12**: e0170547. doi:10.1371/journal.pone.0170547.
65. Palleschi L, Vetta F, De Gennaro E, Idone G, Sottosanti G, Gianni W, et al. Effect of aerobic training on the cognitive performance of elderly patients with senile dementia of Alzheimer type. *Arch Gerontol Geriatr* 1996;**22**(Suppl. 1):S47–50.
66. Hong SG, Kim JH, Jun TW. Effects of 12-Week resistance exercise on electroencephalogram patterns and cognitive function in the elderly with mild cognitive impairment: a randomized controlled trial. *Clin J Sport Med* 2018;**28**:500–8.
67. Yoon DH, Kang D, Kim H, Kim JS, Song HS, Song W. Effect of elastic band-based high-speed power training on cognitive function, physical performance and muscle strength in older women with mild cognitive impairment. *Geriatr Gerontol Int* 2017;**17**:765–72.
68. Garuffi M, Costa JL, Hernández SS, Vital TM, Stein AM, dos Santos JG, et al. Effects of resistance training on the performance of activities of daily living in patients with Alzheimer's disease. *Geriatr Gerontol Int* 2013;**13**:322–8.
69. Fiatarone Singh MA, Gates N, Saigal N, Wilson GC, Meiklejohn J, Brodaty H, et al. The study of mental and resistance training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *J Am Med Dir Assoc* 2014;**15**:873–80.
70. Viña J, Sanz-Ros J. Alzheimer's disease: only prevention makes sense. *Eur J Clin Invest* 2018;**48**:e13005. doi:10.1111/eci.13005.
71. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement* 2015;**11**:1007–14.
72. Szczechowiak K, Diniz BS, Leszek J. Diet and Alzheimer's dementia – nutritional approach to modulate inflammation. *Pharmacol Biochem Behav* 2019;**184**: 172743. doi:10.1016/j.pbb.2019.172743.
73. Broom GM, Shaw IC, Rucklidge JJ. The ketogenic diet as a potential treatment and prevention strategy for Alzheimer's disease. *Nutrition* 2019;**60**:118–21.
74. Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond)* 2009;**6**:31. doi:10.1186/1743-7075-6-31.
75. Pawlosky RJ, Kemper MF, Kashiwaya Y, King MT, Mattson MP, Veech RL. Effects of a dietary ketone ester on hippocampal glycolytic and tricarboxylic acid cycle intermediates and amino acids in a 3xTgAD mouse model of Alzheimer's disease. *J Neurochem* 2017;**141**:195–207.
76. Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, Laferla FM, et al. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. *Neurobiol Dis* 2007;**26**:212–20.
77. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *The Lancet* 2015;**385**:2255–63.
78. Rabin JS, Klein H, Kirn DR, Schultz AP, Yang HS, Hampton O, et al. Associations of physical activity and β -amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. *JAMA Neurol* 2019;**76**:1203–10.
79. Deslandes A, Moraes H, Ferreira C, Veiga H, Silveira H, Mouta R, et al. Exercise and mental health: many reasons to move. *Neuropsychobiology* 2009;**59**:191–8.
80. Eggermont L, Swaab D, Luiten P, Scherder E. Exercise, cognition and Alzheimer's disease: more is not necessarily better. *Neurosci Biobehav Rev* 2006;**30**:562–75.
81. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA* 1999;**96**:13427–31.
82. Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats *in vivo*. *Neuroscience* 2004;**124**:71–9.
83. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 2002;**25**:295–301.
84. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci* 2003;**14**:125–30.
85. Gligoroska JP, Manchevska S. The effect of physical activity on cognition—physiological mechanisms. *Mater Sociomed* 2012;**24**:198–202.
86. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *J Neurosci* 2005;**25**:4217–21.
87. Ohia-Nwoko O, Montazari S, Lau YS, Eriksen JL. Long-term treadmill exercise attenuates tau pathology in P301S tau transgenic mice. *Mol Neurodegener* 2014;**9**:54. doi:10.1186/1750-1326-9-54.

88. Leem YH, Lim HJ, Shim SB, Cho JY, Kim BS, Han PL. Repression of tau hyperphosphorylation by chronic endurance exercise in aged transgenic mouse model of tauopathies. *J Neurosci Res* 2009;**87**:2561–70.
89. Um HS, Kang EB, Koo JH, Kim HT, Lee Jin, Kim EJ, et al. Treadmill exercise represses neuronal cell death in an aged transgenic mouse model of Alzheimer's disease. *Neurosci Res* 2011;**69**:161–73.
90. Tapia-Rojas C, Aranguiz F, Varela-Nallar L, Inestrosa NC. Voluntary running attenuates memory loss, decreases neuropathological changes and induces neurogenesis in a mouse model of Alzheimer's disease. *Brain Pathol* 2016;**26**:62–74.
91. Belarbi K, Burnouf S, Fernandez-Gomez FJ, Laurent C, Lestavel S, Figeac M, et al. Beneficial effects of exercise in a transgenic mouse model of Alzheimer's disease-like Tau pathology. *Neurobiol Dis* 2011;**43**:486–94.
92. Yuede CM, Zimmerman SD, Dong H, Kling MJ, Bero AW, Holtzman DM, et al. Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. *Neurobiol Dis* 2009;**35**:426–32.
93. Richter H, Ambrée O, Lewejohann L, Herring A, Keyvani K, Paulus W, et al. Wheel-running in a transgenic mouse model of Alzheimer's disease: protection or symptom? *Behav Brain Res* 2008;**190**:74–84.
94. García-Mesa Y, López-Ramos JC, Giménez-Llort L, Revilla S, Guerra R, Gruart A, et al. Physical exercise protects against Alzheimer's disease in 3xTg-AD mice. *J Alzheimer's Dis* 2011;**24**:421–54.
95. Wolf SA, Kronenberg G, Lehmann K, Blankenship A, Overall R, Stautfenbiel M, et al. Cognitive and physical activity differently modulate disease progression in the amyloid precursor protein (APP)-23 model of Alzheimer's disease. *Biol Psychiatry* 2006;**60**:1314–23.
96. Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol* 2010;**68**:311–8.
97. Stillman CM, Lopez OL, Becker JT, Kuller LH, Mehta PD, Tracy RP, et al. Physical activity predicts reduced plasma β amyloid in the Cardiovascular Health Study. *Ann Clin Transl Neurol* 2017;**4**:284–91.
98. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* 2007;**128**:92–105.
99. Giunta B, Fernandez F, Nikolic WV, Obregon D, Rrapo E, Town T, et al. Inflammaging as a prodrome to Alzheimer's disease. *J Neuroinflammation* 2008;**5**:51. doi:10.1186/1742-2094-5-51.
100. Gomez-Cabrera MC, Viña J, Ji LL. Role of redox signaling and inflammation in skeletal muscle adaptations to training. *Antioxidants(Basel)* 2016;**5**:E48. doi:10.3390/antiox5040048.
101. Jensen CS, Bahl JM, Østergaard LB, Høgh P, Wermuth L, Heslegrave A, et al. Exercise as a potential modulator of inflammation in patients with Alzheimer's disease measured in cerebrospinal fluid and plasma. *Exp Gerontol* 2019;**121**:91–8.
102. Nichol KE, Poon WW, Parachikova AI, Cribbs DH, Glabe CG, Cotman CW. Exercise alters the immune profile in Tg2576 Alzheimer mice toward a response coincident with improved cognitive performance and decreased amyloid. *J Neuroinflammation* 2008;**5**:13. doi:10.1186/1742-2094-5-13.
103. Gomes da Silva S, Simões PSR, Mortara RA, Scorza FA, Cavalheiro EA, da Graça Naffah-Mazzacoratti M, et al. Exercise-induced hippocampal anti-inflammatory response in aged rats. *J Neuroinflammation* 2013;**10**:61. doi:10.1186/1742-2094-10-61.
104. Barrientos RM, Frank MG, Crysdale NY, Chapman TR, Ahrendsen JT, Day HE, et al. Little exercise, big effects: reversing aging and infection-induced memory deficits, and underlying processes. *J Neurosci* 2011;**31**:11578–86.
105. Yu Z, Ye X, Wang J, Qi Q, Franco OH, Rennie KL, et al. Associations of physical activity with inflammatory factors, adipocytokines, and metabolic syndrome in middle-aged and older Chinese people. *Circulation* 2009;**119**:2969–77.
106. Reuben DB, Judd-Hamilton L, Harris TB, Seeman TE. The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur studies of successful aging. *J Am Geriatr Soc* 2003;**51**:1125–30.
107. Colbert LH, Visser M, Simonsick EM, Tracy RP, Newman AB, Kritchevsky SB, et al. Physical activity, exercise, and inflammatory markers in older adults: findings from the Health, Aging and Body Composition Study. *J Am Geriatr Soc* 2004;**52**:1098–104.
108. Wannamethee SG, Lowe GD, Whincup PH, Rumley A, Walker M, Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation* 2002;**105**:1785–90.
109. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. *J Gerontol A Biol Sci Med Sci* 2000;**55**:M709–15.
110. Elosua R, Bartali B, Ordovas JM, Corsi AM, Lauretani F, Ferrucci L. Association between physical activity, physical performance, and inflammatory biomarkers in an elderly population: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2005;**60**:760–7.
111. Ravaglia G, Forti P, Maioli F, Arnone G, Pantieri G, Cocci C, et al. The clock-drawing test in elderly Italian community dwellers: associations with sociodemographic status and risk factors for vascular cognitive impairment. *Dement Geriatr Cogn Disord* 2003;**16**:287–95.
112. Baune BT, Ponath G, Golledge J, Varga G, Arolt V, Rothermundt M, et al. Association between IL-8 cytokine and cognitive performance in an elderly general population—the MEMO-Study. *Neurobiol Aging* 2008;**29**:937–44.
113. Alley DE, Crimmins EM, Karlamangla A, Hu P, Seeman TE. Inflammation and rate of cognitive change in high-functioning older adults. *J Gerontol A Biol Sci Med Sci* 2008;**63**:50–5.
114. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 2003;**61**:76–80.
115. Teunissen CE, van Boxtel MP, Bosma H, Bosmans E, Delanghe J, De Bruijn C, et al. Inflammation markers in relation to cognition in a healthy aging population. *J Neuroimmunol* 2003;**134**:142–50.
116. Weaver JD, Huang MH, Albert M, Harris T, Rowe JW, Seeman TE. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. *Neurology* 2002;**59**:371–8.
117. Cobb JL, Wolf PA, Au R, White R, D'Agostino RB. The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. *Neurology* 1995;**45**:1707–12.
118. Yan H, Kuroiwa A, Tanaka H, Shindo M, Kiyonaga A, Nagayama A. Effect of moderate exercise on immune senescence in men. *Eur J Appl Physiol* 2001;**86**:105–11.
119. Thijssen DHJ, Vos JB, Verseyden C, van Zonneveld AJ, Smits P, Sweep FC, et al. Haematopoietic stem cells and endothelial progenitor cells in healthy men: effect of aging and training. *Ageing Cell* 2006;**5**:495–503.
120. Woods JA, Coddia MA, Wolters BW, Evans JK, Lu Q, McAuley E. Effects of 6 months of moderate aerobic exercise training on immune function in the elderly. *Mech Ageing Dev* 1999;**109**:1–19.
121. Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Mackey JR. Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. *J Appl Physiol* 2005;**98**:1534–40.
122. Sellami M, Gasmi M, Denham J, Hayes LD, Stratton D, Padulo J, et al. Effects of acute and chronic exercise on immunological parameters in the elderly aged: can physical activity counteract the effects of aging? *Front Immunol* 2018;**9**:2187. doi:10.3389/fimmu.2018.02187.
123. Birling MC, Price J. Influence of growth factors on neuronal differentiation. *Curr Opin Cell Biol* 1995;**7**:878–84.
124. Thoenen H. Neurotrophins and neuronal plasticity. *Science* 1995;**270**:593–8.
125. Lewin GR, Barde YA. Physiology of the neurotrophins. *Annu Rev Neurosci* 1996;**19**:289–317.
126. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci* 2001;**24**:677–736.
127. Tartaglia N, Du J, Tyler WJ, Neale E, Pozzo-Miller L, Lu B. Protein synthesis-dependent and -independent regulation of hippocampal synapses by brain-derived neurotrophic factor. *J Biol Chem* 2001;**276**:37585–93.

128. Dinoff A, Herrmann N, Swardfager W, Liu CS, Sherman C, Chan S, et al. The effect of exercise training on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF): a meta-analysis. *PLoS One* 2016;**11**: e0163037. doi:10.1371/journal.pone.0163037.
129. Berchtold NC, Chinn G, Chou M, Kesslak JP, Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience* 2005;**133**: 853–61.
130. Maejima H, Kanemura N, Kokubun T, Murata K, Takayanagi K. Exercise enhances cognitive function and neurotrophin expression in the hippocampus accompanied by changes in epigenetic programming in senescence-accelerated mice. *Neurosci Lett* 2018;**665**:67–73.
131. Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, et al. High impact running improves learning. *Neurobiol Learn Mem* 2007;**87**:597–609.
132. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol* 2009;**94**:1062–9.
133. Kim TW, Choi HH, Chung YR. Treadmill exercise alleviates impairment of cognitive function by enhancing hippocampal neuroplasticity in the high-fat diet-induced obese mice. *J Exerc Rehabil* 2016;**12**:156–62.
134. García-Mesa Y, Pareja-Galeano H, Bonet-Costa V, Revilla S, Gómez-Cabrera MC, Gambini J, et al. Physical exercise neuroprotects ovariectomized 3xTg-AD mice through BDNF mechanisms. *Psychoneuroendocrinology* 2014;**45**:154–66.
135. Pareja-Galeano H, Brioché T, Sanchis-Gomar F, Montal A, Jovaní C, Martínez-Costa C, et al. Impact of exercise training on neuroplasticity-related growth factors in adolescents. *J Musculoskelet Neuronal Interact* 2013;**13**:368–71.
136. Klein AB, Williamson R, Santini MA, Clemmensen C, Ettrup A, Rios M, et al. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. *Int J Neuropsychopharmacol* 2011;**14**:347–53.
137. Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, Clemenson GD, et al. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science* 2018;**361**:eaan8821. doi:10.1126/science.aan8821.
138. Holsinger RM, Schnarr J, Henry P, Castelo VT, Fahnestock M. Quantitation of BDNF mRNA in human parietal cortex by competitive reverse transcription-polymerase chain reaction: decreased levels in Alzheimer's disease. *Brain Res Mol Brain Res* 2000;**76**:347–54.
139. Phillips HS, Hains JM, Armanini M, Laramée GR, Johnson SA, Winslow JW. BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. *Neuron* 1991;**7**:695–702.
140. Gold SM, Schulz KH, Hartmann S, Mladek M, Lang UE, Hellweg R, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *J Neuroimmunol* 2003;**138**:99–105.
141. Zoladz JA, Pilc A, Majerczak J, Grandys M, Zapart-Bukowska J, Duda K. Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. *J Physiol Pharmacol* 2008;**59** (Suppl. 7):S119–32.
142. Tang SW, Chu E, Hui T, Helmeste D, Law C. Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. *Neurosci Lett* 2008;**431**:62–5.
143. Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, et al. Endurance training enhances BDNF release from the human brain. *Am J Physiol Regul Integr Comp Physiol* 2010;**298**:R372–7.
144. Rojas Vega S, Strüder HK, Vera Wahrmann B, Schmidt A, Bloch W, Hollmann W. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Res* 2006;**1121**:59–65.
145. Cho HC, Kim J, Kim S, Son YH, Lee N, Jung SH. The concentrations of serum, plasma and platelet BDNF are all increased by treadmill VO₂max performance in healthy college men. *Neurosci Lett* 2012;**519**:78–83.
146. Brunelli A, Dimauro I, Sgrò P, Emerenziani GP, Magi F, Baldari C, et al. Acute exercise modulates BDNF and pro-BDNF protein content in immune cells. *Med Sci Sport Exerc* 2012;**44**:1871–80.
147. Griffin EW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav* 2011;**104**:934–41.
148. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med Sci Sports Exerc* 2007;**39**:728–34.
149. Vaughan S, Wallis M, Polit D, Steele M, Shum D, Morris N. The effects of multimodal exercise on cognitive and physical functioning and brain-derived neurotrophic factor in older women: a randomised controlled trial. *Age Ageing* 2014;**43**:623–9.
150. Weinstein G, Beiser AS, Choi SH, Preis SR, Chen TC, Vorgas D, et al. Serum brain-derived neurotrophic factor and the risk for dementia: the Framingham heart study. *JAMA Neurol* 2014;**71**:55. doi:10.1001/jama-neurol.2013.4781.
151. Coelho FG, Vital TM, Stein AM, Arantes FJ, Rueda AV, Camarini R, et al. Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *J Alzheimers Dis* 2014;**39**:401–8.
152. Bertsch K, Hagemann D, Hermes M, Walter C, Khan R, Naumann E. Resting cerebral blood flow, attention, and aging. *Brain Res* 2009;**1267**:77–88.
153. Hagstadus S, Risberg J. Regional cerebral blood flow characteristics and variations with age in resting normal subjects. *Brain Cogn* 1989;**10**:28–43.
154. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med* 2013;**29**:737–52.
155. Park DC, Polk TA, Mikels JA, Taylor SF, Marshuetz C. Cerebral aging: integration of brain and behavioral models of cognitive function. *Dialogues Clin Neurosci* 2001;**3**:151–65.
156. Heo S, Prakash RS, Voss MW, Erickson KI, Ouyang C, Sutton BP, et al. Resting hippocampal blood flow, spatial memory and aging. *Brain Res* 2010;**1315**:119–27.
157. Parkes LM, Rashid W, Chard DT, Tofts PS. Normal cerebral perfusion measurements using arterial spin labeling: reproducibility, stability, and age and gender effects. *Magn Reson Med* 2004;**51**:736–43.
158. Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJ, et al. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain* 1990;**113**:27–47.
159. Wolters FJ, Zonneveld HI, Hofman A, van der Lugt A, Koudstaal PJ, Vernooij MW, et al. Cerebral perfusion and the risk of dementia: a population-based study. *Circulation* 2017;**136**:719–28.
160. De Vis JB, Peng SL, Chen X, Li Y, Liu P, Sur S, et al. Arterial-spin-labeling (ASL) perfusion MRI predicts cognitive function in elderly individuals: a 4-year longitudinal study. *J Magn Reson Imaging* 2018;**48**:449–58.
161. Zhang N, Gordon ML, Goldberg TE. Cerebral blood flow measured by arterial spin labeling MRI at resting state in normal aging and Alzheimer's disease. *Neurosci Biobehav Rev* 2017;**72**:168–75.
162. Kalaria RN. Cerebral vessels in ageing and Alzheimer's disease. *Pharmacol Ther* 1996;**72**:193–214.
163. Austin BP, Nair VA, Meier TB, Xu G, Rowley HA, Carlsson CM, et al. Effects of hypoperfusion in Alzheimer's disease. *J Alzheimers Dis* 2011;**26**:123–33.
164. Du AT, Jahng GH, Hayasaka S, Kramer JH, Rosen HJ, Gorno-Tempini ML, et al. Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI. *Neurology* 2006;**67**:1215–20.
165. Aslani I, Habeck C, Scarmeas N, Borogovac A, Brown TR, Stern Y. Multivariate and univariate analysis of continuous arterial spin labeling perfusion MRI in Alzheimer's disease. *J Cereb Blood Flow Metab* 2008;**28**:725–36.
166. Binnewijzend MA, Kuijer JP, Benedictus MR, van der Flier WM, Wink AM, Wattjes MP, et al. Cerebral blood flow measured with 3D pseudo-continuous arterial spin-labeling MR imaging in Alzheimer disease and mild cognitive impairment: a marker for disease severity. *Radiology* 2013;**267**:221–30.
167. Johnson NA, Jahng GH, Weiner MW, Miller BL, Chui HC, Jagust WJ, et al. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. *Radiology* 2005;**234**:851–9.

168. Dietrich HH, Xiang C, Han BH, Zipfel GJ, Holtzman DM. Soluble amyloid-beta, effect on cerebral arteriolar regulation and vascular cells. *Mol Neurodegener* 2010;**5**:15. doi:10.1186/1750-1326-5-15.
169. Niwa K, Younkin L, Ebeling C, Turner SK, Westaway D, Younkin S, et al. Aβ1-40-related reduction in functional hyperemia in mouse neocortex during somatosensory activation. *Proc Natl Acad Sci U S A* 2000;**97**:9735–40.
170. Suo Z, Humphrey J, Kundtz A, Sethi F, Placzek A, Crawford F, et al. Soluble Alzheimers β-amyloid constricts the cerebral vasculature *in vivo*. *Neurosci Lett* 1998;**257**:77–80.
171. Taddei S, Galetta F, Virdis A, Ghiadoni L, Salvetti G, Franzoni F, et al. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. *Circulation* 2000;**101**:2896–901.
172. Burdette JH, Laurienti PJ, Espeland MA, Morgan A, Telesford Q, Vechlekar CD, et al. Using network science to evaluate exercise-associated brain changes in older adults. *Front Aging Neurosci* 2010;**2**:23. doi:10.3389/fnagi.2010.00023.
173. Ainslie PN, Cotter JD, George KP, Lucas S, Murrell C, Shave R, et al. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *J Physiol* 2008;**586**:4005–10.
174. Chapman SB, Aslan S, Spence JS, Defina LF, Keebler MW, Didehbani N, et al. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. *Front Aging Neurosci* 2013;**5**:75. doi:10.3389/fnagi.2013.00075.
175. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, et al. An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci U S A* 2007;**104**:5638–43.
176. Alfini AJ, Weiss LR, Leitner BP, Smith TJ, Hagberg JM, Smith JC. Hippocampal and cerebral blood flow after exercise cessation in master athletes. *Front Aging Neurosci* 2016;**8**:184. doi:10.3389/fnagi.2016.00184.
177. Sobol NA, Hoffmann K, Frederiksen KS, Vogel A, Vestergaard K, Brændgaard H, et al. Effect of aerobic exercise on physical performance in patients with Alzheimer's disease. *Alzheimer's Dement* 2016;**12**:1207–15.
178. van der Kleij LA, Petersen ET, Siebner HR, Hendrikse J, Frederiksen KS, Sobol NA, et al. The effect of physical exercise on cerebral blood flow in Alzheimer's disease. *NeuroImage Clin* 2018;**20**:650–4.
179. Steen Jensen C, Portelius E, Siersma V, Høgh P, Wermuth L, Blennow K, et al. Cerebrospinal fluid amyloid Beta and tau concentrations are not modulated by 16 weeks of moderate- to high-intensity physical exercise in patients with Alzheimer disease. *Dement Geriatr Cogn Disord* 2016;**42**:146–58.
180. Guerrieri D, van Praag H. Exercise-mimetic AICAR transiently benefits brain function. *Oncotarget* 2015;**6**:18293–313.
181. Valenzuela PL, Castillo-García A, Morales JS, Izquierdo M, Serra-Rexach JA, Santos-Lozano A, et al. Physical exercise in the oldest old. *Compr Physiol* 2019;**9**:1281–304.