

Can lifestyle modifications delay or prevent Alzheimer's disease?

Evidence suggests combining lifestyle modifications may yield better cognitive outcomes

Clinicians have devoted strenuous efforts to secondary prevention of Alzheimer's disease (AD) by diagnosing and treating patients as early as possible. Unfortunately, there is no cure for AD, and the field has witnessed recurrent failures of several pharmacotherapy candidates with either symptomatic or disease-modifying properties.¹ An estimated one-third of AD cases can be attributed to modifiable risk factors.² Thus, implementing primary prevention measures by addressing modifiable risk factors thought to contribute to the disease, with the goal of reducing the risk of developing AD, or at least delaying its onset, is a crucial public health strategy.

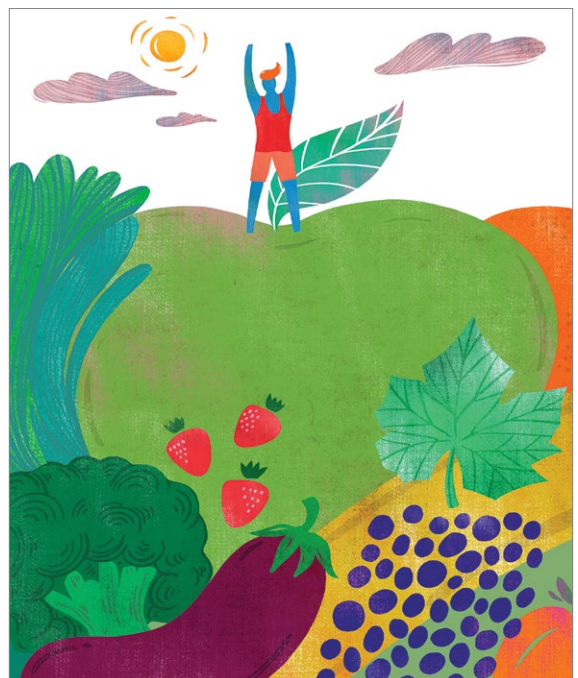
Cardiovascular risk factors, such as hypertension, hyperlipidemia, diabetes, hyperhomocysteinemia, obesity, and smoking, have emerged as substantive risk factors for AD.³ Optimal management of these major risk factors, especially in mid-life, may be a preventive approach against AD. Although detailing the evidence on the impact of managing cardiovascular risk factors to delay or prevent AD is beyond the scope of this article, it is becoming clear that "what is good for the heart is good for the brain."

Additional modifiable risk factors are related to lifestyle habits, such as physical exercise, mental and social activity, meditation/spiritual activity, and diet. This article reviews the importance of pursuing a healthy lifestyle in delaying AD, with the corresponding levels of evidence that support each specific lifestyle modification. The levels of evidence are defined in *Table 1*⁴ (page 31).

continued

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Higher levels of physical exercise in cognitively intact older adults are linked with reduced brain amyloid beta deposits



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Physical exercise

Twenty-one percent of AD cases in the United States are attributable to physical inactivity.⁵ In addition to its beneficial effect on metabolic syndrome, in animal and human research, regular exercise has been shown to have direct neuroprotective effects. High levels of physical activity increase hippocampal neurogenesis and neuroplasticity, increase vascular circulation in the brain regions implicated in AD, and modulate inflammatory mediators as well as brain growth factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1).⁶

The definition of regular physical exercise varies across the literature, but usually implies aerobic exercise—an ongoing activity sufficient to increase the heart rate and the need for oxygen, sustained for 20 to 30 minutes per session.⁷ Modalities include household activities and leisure-time activities. In a large prospective cohort study, Scarmeas et al⁸ categorized leisure-time activities into 3 types:

- light (walking, dancing, calisthenics, golfing, bowling, gardening, horseback riding)
- moderate (bicycling, swimming, hiking, playing tennis)
- vigorous (aerobic dancing, jogging, playing handball).

These types of physical exercise were weighed by the frequency of participation per week. Compared with being physically inactive, low levels of weekly physical activity (0.1 hours of vigorous, 0.8 hours of moderate, or 1.3 hours of light exercise) were associated with a 29% to 41% lower risk of developing AD, while higher weekly physical activity (1.3 hours of vigorous, 2.3 hours of moderate, or 3.8 hours of light exercise) were associated with a 37% to 50% lower risk (level III).⁸

In another 20-year cohort study, engaging in leisure-time physical activity at least twice a week in mid-life was significantly associated with a reduced risk of AD, after adjusting for age, sex, education, follow-up time, locomotor disorders, apolipoprotein E (ApoE) genotype, vascular disorders, smoking, and alcohol intake (level III).⁹ Moreover, a systematic review of 29 randomized

controlled trials (RCTs) showed that aerobic exercise training, such as brisk walking, jogging, and biking, was associated with improvements in attention, processing speed, executive function, and memory among healthy older adults and those with mild cognitive impairment (MCI; level IA).¹⁰

From a pathophysiological standpoint, higher levels of physical exercise in cognitively intact older adults have been associated with reduced brain amyloid beta deposits, especially in ApoE4 carriers.¹¹ This inverse relationship also has been demonstrated in patients who are presymptomatic who carry 1 of the 3 known autosomal dominant mutations for the familial forms of AD.¹²

Overall, physicians should recommend that patients—especially those with cardiovascular risk factors that increase their risk for AD—exercise regularly by following the guidelines of the American Heart Association or the American College of Sports Medicine.¹³ These include muscle-strengthening activities (legs, hips, back, abdomen, shoulders, and arms) at least 2 days/week, in addition to either 30 minutes/day of moderate-intensity aerobic activity such as brisk walking, 5 days/week; or 25 minutes of vigorous aerobic activity such as jogging and running, 3 days/week¹⁴ (level IA evidence for overall improvement in cognitive function; level III evidence for AD delay/risk reduction). Neuromotor exercise, such as yoga and tai chi, and flexibility exercise such as muscle stretching, especially after a hot bath, 2 to 3 days/week are also recommended (level III).¹⁵

Mental activity

Nineteen percent of AD cases worldwide and 7% in the United States. can be attributed to low educational attainment, which is associated with low brain cognitive reserve.⁵ Cognitive resilience in later life may be enhanced by building brain reserves through intellectual stimulation, which affects neuronal branching and plasticity.¹⁶ Higher levels of complex mental activities measured across the lifespan, such as education, occupation, reading, and writing, are correlated with significantly less hippocampal volume shrinkage over time.¹⁷ Frequent participation

Table 1

Practice guidelines levels of evidence

Level IA	Evidence from meta-analysis of randomized controlled trials
Level IB	Evidence from at least 1 randomized controlled trial
Level IIA	Evidence from at least 1 controlled study without randomization
Level IIB	Evidence from at least 1 other type of quasi-experimental study
Level III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
Level IV	Evidence from expert committee reports or opinions, or clinical experience of respected authorities, or both

Source: Reference 4

in mentally stimulating activities—such as listening to the radio; reading newspapers, magazines, or books; playing games (cards, checkers, crosswords or other puzzles); and visiting museums—was associated with an up to 64% reduction in the odds of developing AD in a cohort of cognitively intact older adults followed for 4 years.¹⁸ The correlation between mental activity and AD was found to be independent of physical activity, social activity, or baseline cognitive function.¹⁹

In a large cohort of cognitively intact older adults (mean age 70), engaging in a mentally stimulating activity (craft activities, computer use, or going to the theater/movies) once to twice a week was significantly associated with a reduced incidence of amnesic MCI.²⁰ Another prospective 21-year study demonstrated a significant reduction in AD risk in community-dwelling cognitively intact older adults (age 75 to 85) who participated in cognitively stimulating activities, such as reading books or newspapers, writing for pleasure, doing crossword puzzles, playing board games or cards, or playing musical instruments, several times/week.²¹

Growing scientific evidence also suggests that lifelong multilingualism can delay AD onset by 4 to 5 years.²² Multilingualism is associated with greater cognitive reserve, gray matter volume, functional connectivity and white matter density.²³

Physicians should encourage their patients to engage in intellectually stimulating activities and creative leisure-time activities several times/week to enhance their cognitive reserves and delay AD onset

(level III evidence with respect to AD risk reduction/delay).

Social activity

Social engagement may be an additional protective factor against AD. In a large 4-year prospective study, increased loneliness in cognitively intact older adults doubled the risk of AD.²⁴ Data from the large French cohort PAQUID (Personnes Agées QUID) emphasized the importance of a patient's social network as a protective factor against AD. In this cohort, the perception of reciprocity in relationships with others (the perception that a person had received more than he or she had given) was associated with a 53% reduction in AD risk (level III).²⁵ In another longitudinal cohort study, social activity was found to decrease the incidence of subjective cognitive decline, which is a prodromal syndrome for MCI and AD (level III).²⁶

A major confounder in studies assessing for social activity is the uncertainty if social withdrawal is a modifiable risk factor or an early manifestation of AD, since apathetic patients with AD tend to be socially withdrawn.²⁷ Another limitation of measuring the impact of social activity relative to AD risk is the difficulty in isolating social activities from activities that have physical and mental activity components, such as leisure-time activities.²⁸

Meditation/spiritual activity

Chronic psychological stress is believed to compromise limbic structures that regulate

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Mentally stimulating activities were found to be associated with a reduced risk of developing AD in a cohort of cognitively intact older adults



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RCTs have found that mindfulness-based interventions can modulate inflammatory processes implicated in AD

stress-related behaviors and the memory network, which might explain how being prone to psychological distress may be associated with MCI or AD.²⁹ Cognitive stress may increase the oxidative stress and telomere shortening implicated in the neurodegenerative processes of AD.³⁰ In one study, participants who were highly prone to psychological distress were found to be at 3 times increased risk for developing AD, after adjusting for depression symptoms and physical and mental activities (level III).³¹ By reducing chronic psychological stress, meditation techniques offer a promising preventive option against AD.

Mindfulness-based interventions (MBI) have gained increased attention in the past decade. They entail directing one's attention towards the present moment, thereby decreasing ruminative thoughts and stress arousal.³² Recent RCTs have shown that MBI may promote brain health in older adults not only by improving psychological well-being but also by improving attentional control³³ and functional connectivity in brain regions implicated in executive functioning,³⁴ as well as by modulating inflammatory processes implicated in AD.³⁵ Furthermore, an RCT of patients diagnosed with MCI found that compared with memory enhancement training, a weekly 60-minute yoga session improved memory and executive functioning.³⁶

Kirtan Kriya is a meditation technique that is easy to learn and practice by older adults and can improve memory in patients at risk for developing AD.³⁷ However, more rigorous RCTs conducted in larger samples of older adults are needed to better evaluate the effect of all meditation techniques for delaying or preventing AD (level IB with respect to improvement in cognitive functioning/level III for AD delay/risk reduction).³⁸

Spiritual activities, such as going to places of worship or religious meditation, have been associated with a lower prevalence of AD. Attending religious services, gatherings, or retreats involves a social component because these activities often are practiced in groups. They also confer a method of dealing with psychological distress and depression. Additionally, frequent readings

of religious texts represents a mentally stimulating activity that may also contribute to delaying/preventing AD (level III).³⁹

Diet

In the past decade, a growing body of evidence has linked diet to cognition. Individuals with a higher intake of calories and fat are at higher risk for developing AD.⁴⁰ The incidence of AD rose in Japan after the country transitioned to a more Westernized diet.⁴¹ A modern Western diet rich in saturated fatty acids and simple carbohydrates may negatively impact hippocampus-mediated functions such as memory and learning, and is associated with an increased risk of AD.⁴² In contrast with high-glycemic and fatty diets, a "healthy diet" is associated with a decrease in beta-amyloid burden, inflammation, and oxidative stress.^{43,44}

Studies focusing on dietary patterns rather than a single nutrient for delaying or preventing AD have yielded more robust and consistent results.⁴⁵ In a recent meta-analysis, adhering to a Mediterranean diet—which is rich in fruits and vegetables, whole grains, olive oil, and fish; moderate in some dairy products and wine; and low in red meat—was associated with a decreased risk of AD; this evidence was derived mostly from epidemiologic studies.⁴⁶ Scarmeas et al⁸ found that high adherence to the Mediterranean diet was associated with 32% to 40% reduced risk of AD. Combining this diet with physical exercise was associated with an up to 67% reduced risk (level III). The Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in total grains, fruits, vegetables, and dairy products, but low in sodium and sweets, correlated with neurocognitive improvement in patients with hypertension.⁴⁷ Both the Mediterranean and DASH diets have been associated with better cognitive function⁴⁸ and slower cognitive decline.⁴⁹ Thus, an attempt to combine the neuroprotective components from both diets led to the creation of the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet, which also has been associated with a lower incidence of AD.⁵⁰

Besides specific diets, some food groups have also been found to promote brain health and may help delay or prevent AD. Berries have the highest amount of antioxidants of all fruit. Among vegetables, tomatoes and green leafy vegetables have the highest amount of nutrients for the brain. Nuts, such as walnuts, which are rich in omega-3 fatty acids, are also considered “power foods” for the brain; however, they should be consumed in moderation because they are also rich in fat. Monounsaturated fatty acids, which are found in olives and olive oil, are also beneficial for the brain. Among the 3 types of omega-3 fatty acids, the most important for cognition is docosahexaenoic acid (DHA) because it constitutes 40% of all fatty acids in the brain. Mainly found in oily fish, DHA has antioxidant and anti-inflammatory properties that may delay or prevent AD. Low levels of DHA have been found in patients with AD.⁵¹

Curcumin, which is derived from the curry spice turmeric, is a polyphenol with anti-inflammatory, antioxidant, and anti-amyloid properties that may have a promising role in preventing AD in cognitively intact individuals. Initial trials with curcumin have yielded mixed results on cognition, which was partly related to the low solubility and bioavailability of its formulation.⁵² However, a recent 18-month double-blind randomized placebo-controlled trial found positive effects on memory and attention, as well as reduction of amyloid plaques and tau tangles deposition in the brain, in non-demented older adults age 51 to 84 who took Theracumin, a highly absorptive oral form of curcumin dispersed with colloidal nanoparticles.⁵³ A longer follow-up is required to determine if curcumin can delay or prevent AD.

Alcohol

The role of alcohol in AD prevention is controversial. Overall, data from prospective studies has shown that low to moderate alcohol consumption may be associated with a reduced risk of AD (level III).⁵⁴ Alcohol drinking in mid-life showed a U-shaped relationship with cognitive impairment; both abstainers and heavy

drinkers had an increased risk of cognitive decline compared with light to moderate drinkers (level III).⁵⁵ Binge drinking significantly increased the odds of cognitive decline, even after controlling for total alcohol consumption per week.⁵⁵

The definition of low-to-moderate drinking varies substantially among countries. In addition, the size and amount of alcohol contained in a standard drink may differ.⁵⁶ According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA),⁵⁷ moderate drinking is defined as up to 1 drink daily for women and 2 drinks daily for men. Binge drinking involves drinking >4 drinks for women and >5 drinks for men, in approximately 2 hours, at least monthly. In the United States, one standard drink contains 14 grams of pure alcohol, which is usually found in 12 ounces of regular beer, 5 ounces of wine, and 1.5 ounces of distilled spirits (vodka or whiskey).⁵⁸

In a 5-year prospective Canadian study, having 1 drink weekly (especially wine) was associated with an up to 50% reduced risk of AD (level III).⁵⁹ In the French cohort PAQUID, mild drinkers (<1 to 2 drinks/day) and moderate drinkers (3 to 4 drinks daily) had a reduced incidence of AD compared with non-drinkers. Wine was the most frequently consumed beverage in this study.⁶⁰ Other studies have found cognitive benefits from mild to moderate drinking regardless of beverage type.⁵⁴ However, a recent study that included a 30-year follow-up failed to find a significant protective effect of light drinking over abstinence in terms of hippocampal atrophy.⁶¹ Atrophy of the hippocampus was correlated with increasing alcohol amounts in a dose-dependent manner, starting at 7 to 14 drinks/week (level III).⁶¹

Research has shown that moderate and heavy alcohol use or misuse can directly induce microglial activation and inflammatory mediators’ release, which induce amyloid beta pathology and leads to brain atrophy.⁶² Hence, non-drinkers should not be advised to begin drinking, because of the lack of RCTs and the concern that beginning to drink may lead to heavy drinking. All drinkers should be advised to adhere to the NIAAA recommendations.¹³

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The Mediterranean and DASH diets are associated with better cognitive function and slower cognitive decline

continued



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Despite some evidence of the benefit of alcohol, non-drinkers should not be advised to begin drinking

Table 2

9 Recommendations for the prevention/delay of Alzheimer's disease

1. Daily physical exercise according to the AHA/ACSM recommendations
2. Adhering to a healthy nutritional regimen
3. Pursuing intellectually challenging and creative leisure activities
4. Maintaining optimal sleep and implementing stress-relieving strategies
5. Staying socially active
6. Education and counseling regarding the NIAAA recommendations for alcohol consumption in cognitively intact drinkers
7. Counseling about smoking cessation
8. Providing medical advice regarding optimal metabolic and cardiovascular risk factor control
9. Counseling about strategies to prevent head trauma and exposure to hazardous substances that may impair cognition

Source: Adapted from reference 13

ACSM: American College of Sports Medicine; AHA: American Heart Association; NIAAA: National Institute on Alcohol Abuse and Alcoholism

Coffee/tea

Although studies of caffeinated coffee have been heterogeneous and yielded mixed results (beneficial effect vs no effect on delaying cognitive decline), systematic reviews and meta-analyses of cross-sectional, case-control, and longitudinal cohort studies have found a general trend towards a favorable preventative role (level III).⁶³⁻⁶⁵ Caffeine exhibits its neuroprotective effect by increasing brain serotonin and acetylcholine, and by stabilizing blood-brain-barrier integrity.⁶⁶ Moreover, in an animal study, mice given caffeine in their drinking water from young adulthood into older age had lower amyloid beta plasma levels compared with those given decaffeinated water.⁶⁷ These findings suggest that in humans, 5 cups of regular caffeinated coffee daily, equivalent to 500 mg of caffeine, could be protective against cognitive impairment. Other caffeinated beverages, such as tea or soft drinks, contain up to 4 times less caffeine per serving; many more servings would therefore be required to reach the target amount

of 500 mg/d of caffeine.⁶⁷ Data from the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study demonstrate a 65% reduced risk of dementia/AD in individuals who consumed 3 to 5 cups of regular coffee daily in mid-life.⁶⁸

An Italian study showed that older adults who don't or rarely drink coffee (<1 cup daily) and those who recently increased their consumption pattern to >1 cup daily had a higher incidence of MCI than those who habitually consumed 1 to 2 cups daily.⁶⁹ Therefore, it is not recommended to advise a change in coffee drinking pattern in old age. Older adults who are coffee drinkers should, however, be educated about the association between heavier caffeine intake and anxiety, insomnia, and cardiac arrhythmias.⁷⁰

Despite its more modest caffeine levels, green tea is rich in polyphenols, which belong to the family of catechins and are characterized by antioxidant and anti-inflammatory properties.⁷¹ In a Japanese cohort, higher green tea consumption (up to 1 cup daily) was associated with a decreased incidence of MCI in older adults.⁷² More studies are needed to confirm its potential preventative role in AD.

Which lifestyle change is the most important?

Focusing on a single lifestyle change may be insufficient, especially because the bulk of evidence for individual interventions comes from population-based cohort studies (level III), rather than strong RCTs with a long follow-up. There is increasing evidence that combining multiple lifestyle modifications may yield better outcomes in maintaining or improving cognition.⁷³

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a large, 2-year RCT that included community-dwelling older adults (age 60 to 77) with no diagnosis of major neurocognitive disorder, found that compared with regular health advice, multi-domain interventions reduced cognitive decline and improved overall cognition, executive functioning, and processing speed. The interventions evaluated

in this study combined the following 4 modalities⁷⁴:

- a healthy diet according to the Finnish nutrition recommendations (eating vegetables, fruits, and berries [minimum: 500 g/d], whole grain cereals [several times a day], and fish [2 to 3 times/week]; using low-salt products; consuming fat-free or low-fat milk products; and limiting red meat consumption to <500 g/week

- regular physical exercise tailored for improving muscle strength (1 to 3 times/week) coupled with aerobic exercise (2 to 5 times/week)

- cognitive training, including group sessions that have a social activity component and computer-based individual sessions 3 times/week that target episodic and working memory and executive functioning

- optimal management of cardiovascular risk factors.

This multi-domain approach for lifestyle modification should be strongly recommended to cognitively intact older patients (level IB).

Modeled after the FINGER study, the Alzheimer's Association U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) is a 2-year, multicenter, controlled clinical trial aimed at testing the ability of a multi-dimensional lifestyle intervention to prevent AD in at-risk older adults (age 60 to 79, with established metabolic and cardiovascular risk factors). Interventions include a combination of physical exercise, nutritional counseling and management, cognitive and social stimulation, and improved management of cardiovascular risk factors. Recruitment for this large-scale trial was estimated to begin in January 2019 (NCT03688126).⁷⁵

On a practical basis, Desai et al¹³ have proposed a checklist (Table 2,¹³ page 34) that

Related Resources

- Anderson K, Grossberg GT. Brain games to slow cognitive decline in Alzheimer's disease. *J Am Med Dir Assoc.* 2014;15(8):536-537.
- Small G, Vorgan G. The memory prescription: Dr. Garry Small's 14-day plan to keep your brain and body young. New York, NY: Hyperion; 2004.
- Small G, Vorgan G. The Alzheimer's prevention program; keep your brain healthy for the rest of your life. New York, NY: Workman Publishing Company, Inc.; 2012.

Drug Brand Name

Curcumin • Theracurmin

physicians can use in their routine consultations to improve primary prevention of AD among their older patients.

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continued

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Studies of caffeinated coffee have been mixed, but some evidence suggests a preventive role

Bottom Line

Advise patients that pursuing a healthy lifestyle is a key to delaying or preventing Alzheimer's disease. This involves managing cardiovascular risk factors and a combination of staying physically, mentally, socially, and spiritually active, in addition to adhering to a healthy diet such as the Mediterranean diet.



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A multi-domain approach for lifestyle modification should be strongly recommended to cognitively intact older patients

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