

Lowering risk *of*



Medical, dietary, and lifestyle choices
may promote healthy brain aging

Alzheimer's disease

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Pharmacologic treatments for Alzheimer's disease (AD) may improve symptoms but have not been shown to prevent AD onset. Primary prevention therefore remains the goal. Although preventing AD by managing risk factors such as age or genetics is beyond our control (*Box 1, page 24*), we can do something about other factors.

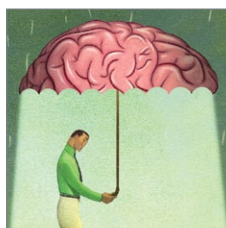
This article summarizes the findings of many studies that address AD prevention and includes an online-only bibliography for readers seeking an in-depth review. The evidence does not support a firm recommendation for any specific form of primary prevention and has revealed hazards associated with estrogen therapy and nonsteroidal anti-inflammatory drugs (*Box 2, page 25*). Most important, it suggests that you could reduce your patients' risk of developing AD by routinely supporting their mental, physical, and social health.

The potential benefits of modifying an individual's AD risk factors likely will depend on his or her genetic makeup, environment, and lifestyle. Even so, counseling patients to exercise more and improve their diets—such as by eating more fish, fruits, and vegetables and less saturated fat—might help protect the brain. Your ongoing efforts to manage hypertension, hypercholesterolemia, and diabetes also may reduce their AD risk.

Cardiovascular risk factors

The risk of developing AD or vascular dementia appears to be increased by conditions that damage the heart or blood vessels. Recent evidence suggests that successfully managing cardiovascular risk factors may decrease the likelihood of dementia in later life.

continued



Alzheimer's risk

Clinical Point

High serum cholesterol may contribute to AD development but lowering cholesterol with statins does not prevent it

Box 1

Nonmodifiable risk factors for Alzheimer's disease

Age remains the strongest risk factor for dementia, particularly for Alzheimer's disease (AD).^a The risk of developing AD doubles every 5 years after age 65 and approaches 50% after age 85.^b

Family history is a risk factor for AD, although true familial AD accounts for <5% of cases.^c When diseases show a familial pattern, either genetics, environmental factors, or both may play a role. Patients with a first-degree relative with dementia have a 10% to 30% increased risk of developing the disorder.^d

Genetic factors play a role in both early-onset and late-onset AD. Early-onset AD (before age 65) accounts for 6% to 7% of cases.^e From this small pool of patients, only 13% exhibit clear autosomal dominant transmission over >1 generation.^f Three gene mutations have been associated with early-onset AD:

- 30% to 70% are in the presenilin-1 gene
- 10% to 15% are in the amyloid precursor protein gene
- <5% are in the presenilin-2 gene.^{g,h}

For late-onset AD (after age 65), the strongest evidence for a genetic risk factor exists for the epsilon 4 allele of the apolipoprotein E gene (APOE ε4).ⁱ This genotype has been linked to the development of AD and possibly to vascular dementia.^{j,k} In contrast, the epsilon 2 allele of APOE may exert a protective effect in AD.^l APOE ε3, the most common allele, appears to play a neutral role in the development of AD.

Source: For reference citations, see this article at CurrentPsychiatry.com

Hypertension is associated with a higher risk of AD and all-cause dementia. Curiously, some studies have shown that *low* blood pressure also increases dementia risk, suggesting a U-shaped relationship between blood pressure and cognitive decline. Systolic hypertension in midlife may be associated with dementia 20 years later.

One might assume that antihypertensive therapy would help prevent dementia, but the data are conflicting. The Systolic Hypertension in Europe (SYST-EUR) study¹ showed a 53% reduction in vascular dementia or mixed dementia among patients receiving antihypertensive medication and a 60% reduction in AD. Similarly, the PROGRESS² clinical trial of prevention of recurrent stroke by antihypertensive treat-

ment reported a 34% reduction in a composite measure of cognitive impairment and dementia. On the other hand, cognitive function neither improved nor worsened in the Hypertension in the Very Elderly Trial (HYVET-COG),³ whether patients received blood pressure treatment or placebo.

Hyperlipidemia. Lipid metabolism likely is an important pathway in amyloid beta-protein deposition, tau phosphorylation, and disruption of synaptic plasticity and neurodegenerative endpoints. Cognitive decline and incident dementia have been associated with higher dietary intake of saturated fats, partially hydrogenated unsaturated fatty acids (trans fats), and cholesterol. Not all studies have found this association, however. This could be because serum cholesterol levels may decrease in early dementia, limiting the ability to detect an effect of hypercholesterolemia on dementia risk when measurements are made later in life.

Using statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) to treat hypercholesterolemia has been hypothesized to impede large vessel atherosclerosis and its consequences and to trigger metabolic effects in the brain related to AD pathogenesis. Mechanisms by which statins might help prevent dementia include:

- a direct association between amyloid processing and cholesterol in the brain
- an indirect effect by decreasing the risk of stroke, as even small cerebral infarcts worsen AD severity.

Nonrandomized epidemiologic studies such as the Cardiovascular Health Study⁴ and MRC/BHF Heart Protection Study⁵ suggested that statin treatment might reduce the incidence of dementia, the degree of age-related cognitive decline, and AD's neuropathologic burden. Large, randomized, controlled trials have not supported these observations, however. Statins failed to reduce the incidence of dementia in:

- the Heart Protection Study, testing simvastatin for 5 years in 20,536 subjects age 40 to 80⁵
- the 3-year Preventive Study of Pravastatin in the Elderly at Risk (PROSPER) of 5,800 subjects.⁶

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Estrogen and NSAIDs: Not recommended for AD protection

Estrogen. Before the Women's Health Initiative (WHI) study, various trials of the effects of estrogen therapy on the development of Alzheimer's disease (AD) in women age ≥ 65 showed inconsistent results. In the randomized, placebo-controlled WHI Memory Study, conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, did not prevent mild cognitive impairment or improve global cognitive function and was associated with an increased risk for probable dementia.⁸ Based on this evidence, conjugated equine estrogen with or without medroxyprogesterone is not recommended as therapy to protect cognitive function in older women.

NSAID therapy. Cytokine-mediated inflammation may play a role in neurodegenerative disorders and cognitive impairment in the elderly. Nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, have been studied for a possible protective effect against AD and cognitive decline,⁹ possibly

by lowering amyloidogenic proteins.⁶ A 1-year randomized controlled trial by the Alzheimer's Disease Cooperative Consortium found no significant differences in cognition scores of patients treated with once-daily rofecoxib, 25 mg, or twice-daily naproxen sodium, 220 mg, when compared with placebo.⁴ Similarly, naproxen and celecoxib did not prevent AD in the randomized, controlled Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT).⁶ Rofecoxib has been withdrawn from the market, and celecoxib labeling carries a warning of potential for increased risk of cardiovascular events and life-threatening gastrointestinal bleeding associated with its use.

NSAIDs and COX-2 inhibitors are not recommended for the treatment or prevention of dementia or cognitive impairment. Their use for AD prevention is not supported by randomized clinical trials^{4,6} and they may have serious adverse effects.

Source: For reference citations, see this article at CurrentPsychiatry.com

Similarly, patients receiving adjunctive atorvastatin or placebo showed no significant differences in cognition assessments after 72 weeks in the Lipitor's Effect in Alzheimer's Dementia (LEADe) study. This trial enrolled 640 subjects age 50 to 90 with mild-to-moderate dementia who were treated with donepezil.⁷ A recent Cochrane review concluded that high serum cholesterol may contribute to the development of AD and vascular dementia, but lowering cholesterol levels with statins does not prevent these problems.⁸

Diabetes mellitus. Diabetes and cognitive decline are closely associated. Diabetes is associated with a 50% to 100% increase in risk of AD and dementia overall and a 100% to 150% increased risk of vascular dementia. The mechanism by which diabetes increases dementia risk is uncertain but does not appear to be mediated entirely through vascular disease. High and low insulin levels may increase the risk of dementia, independent of diabetes and blood glucose. Increased peripheral insulin levels are associated with reduced brain atrophy and cognitive impairment in patients

with early AD, suggesting a role for insulin signaling in AD pathophysiology. A possible relationship between insulin and beta amyloid metabolism is being studied.

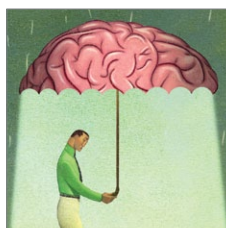
Elevated postprandial plasma glucose has been associated with accelerated declines in cognitive performance.⁹ An inverse correlation has been noted between some cognitive measures and hemoglobin A1C levels.¹⁰ It is not clear that treating diabetes reduces the risk of dementia. In addition, in the prospective, population-based Rotterdam study, elderly patients with type 2 diabetes treated with insulin had the highest incidence of dementia.¹¹

Tobacco smoke directly affects neuronal function, integrity, and survival. Chronic smoking has been linked to decreased global cerebral blood flow, accelerated cerebral atrophy, and ventricular enlargement.

Some studies suggest an increased risk of dementia in middle-aged and elderly smokers, possibly through a cerebrovascular mechanism such as stroke. Other studies found no association between smoking and dementia risk, and 1 suggested that nicotine may protect against AD by reduc-

Clinical Point

In 2 studies, smoking was linked to memory decline in patients without the APOE e4 genotype but not in those with this gene



Alzheimer's risk

Clinical Point

High adherence to the Mediterranean diet is associated with significantly lower risk for Alzheimer's disease

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Box 3

Is depression an independent risk factor for dementia?

Depression often occurs before or as a coexisting condition with Alzheimer's disease (AD).^a Although depression has been considered a response to cognitive decline or an early manifestation of dementia,^b it also could be an independent risk factor.^{c,d}

The pathologic mechanism linking depression and subsequent dementia is not well understood. Hypotheses include an indirect neurotoxic effect of depression mediated by cortisol-induced hippocampal atrophy or lowered brain-derived neurotrophic factor levels.^e Depression and dementia might share genetic links, although a cohort study of 404 individuals with AD detected no association between apolipoprotein E genotypes or alleles and depressive symptoms.^f

Source: For reference citations, see this article at CurrentPsychiatry.com

ing senile plaque formation. Any protective effect of smoking would be offset by increased risks of lung cancer, chronic obstructive pulmonary disease, and vascular dementia.

The apolipoprotein E epsilon 4 (APOE e4) gene may explain, at least in part, the conflicting results of these studies. In 2 population-based cohorts,^{12,13} smoking was associated with memory decline in patients without, but not with, the APOE e4 genotype.

Dietary factors

Antioxidants. The brains of patients with AD contain elevated levels of endogenous antioxidants. In vitro studies show exogenous antioxidants can reduce the toxicity of beta-amyloid in brain tissue of persons with AD. These findings have led to interest in assessing the role of dietary antioxidants such as vitamins E and C for AD prevention.

High-dose alpha-tocopherol (vitamin E, 2,000 IU/d) may slow disease progression in patients with AD, but this association is not consistently found. Furthermore, a meta-analysis of 19 randomized controlled trials (RCTs) totaling >135,000 patients found an association between vitamin E doses >400 IU/d and increased all-cause mortality.¹⁴ High-dose vitamin E supple-

mentation for primary or secondary prevention of AD may be dangerous and is not recommended.

The lack of consistent efficacy data for vitamin C in preventing or treating AD may discourage its routine use for this purpose.¹⁵

Homocysteine is a risk factor for stroke and heart disease. It also could play a role in vascular dementia through its association with large- and small-vessel disease.

Low folate and hyperhomocysteinemia have been associated with dementia or cognitive impairment, although a cause-effect relationship is not clear. In nondemented elderly populations, plasma homocysteine is inversely associated with poor performance in tests of global cognitive function, particularly in measures of psychomotor speed.

In a recent double-blind RCT, folic acid supplementation for 3 years significantly improved domains of cognitive function that tend to decline with age, especially information processing and sensorimotor speed.¹⁶ No other good evidence, however, has shown that homocysteine-lowering therapy using folic acid or other vitamin B supplements improves cognitive function or prevents cognitive decline.

Fish and omega-3 fatty acids. High total fat, saturated fat, and total cholesterol intake increases the risk for incident dementia. In epidemiologic studies, low omega-3 fatty acid serum levels have been linked to increased dementia risk.

Fish consumption may be beneficial in reducing the risk of dementia or cognitive decline. A prospective study of 815 elderly persons found 60% less risk of developing AD in those who ate ≥ 1 fish meal per week, compared with those who rarely or never ate fish.¹⁷ In the Framingham study, individuals who at baseline were in the top quartile of docosahexaenoic acid consumption had lower dementia rates over 9 years of follow-up.¹⁸ Results from cross-sectional and longitudinal studies have been inconsistent; some have shown that high intake of n-3 polyunsaturated fatty acids is associated with less cognitive decline,¹⁹ whereas others have not.²⁰

Although we cannot offer unequivocal advice regarding seafood or omega-3 fatty acid intake for primary prevention of dementia without evidence from RCTs, these uncontrolled studies show promise.

Mediterranean diet (MeDi) components include abundant fruits and vegetables, fish or shellfish at least twice weekly, very limited red meat, olive oil or canola oil instead of butter or margarine, tree nuts such as walnuts or pecans, red wine in moderation, and using herbs and spices instead of salt to season food. High adherence to the MeDi has been associated with a significantly lower risk for incident AD. The MeDi may affect the risk of developing AD²¹ as well as subsequent disease course, with a possible dose-response relationship in lower mortality.²²

Eating fruits and vegetables has been associated with improved cognitive performance²² and decreased incident dementia in elderly subjects.¹⁸

Table

Brain exercises to suggest to patients

Learn something new (how to play a musical instrument, a foreign language, or a new hobby)

Play memory games

Practice using the opposite hand to perform tasks you usually do with your dominant hand

Read, especially challenging material

Join a book discussion group

Write; if not a book or article, write a diary, letters, or emails or start your memoirs

Do crossword, Sudoku, or jigsaw puzzles

Play board games, card games, and other strategy games

Debate or discuss topics

Alcohol. A U-shaped relationship exists between alcohol consumption and dementia risk. High alcohol intake is associated with clinical problem drinking and alco-

Clinical Point

Physical exercise is believed to enhance brain neurotrophic factor and modify apoptosis, and can deter stroke

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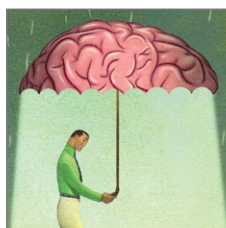
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Alzheimer's risk

Clinical Point

Higher levels of leisure activity and daily mentally stimulating activities are associated with decreased risk of Alzheimer's disease

holism and can lead to cognitive decline. Conversely, moderate wine consumption (250 to 500 mL/d) may be protective—compared with more or less than this amount—and is associated with approximately 50% less risk of dementia.

Alcohol use may increase the risk of dementia in persons carrying the APOE ε4 allele, according to the population-based Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study from Sweden.²³ After an average 21 years of follow-up of 1,449 individuals, researchers found that environmental factors—such as physical inactivity, dietary fat intake, alcohol consumption, and smoking at midlife—were associated with an increased risk of dementia at age 65 to 79 in APOE ε4 carriers compared with noncarriers. The study also found that physical inactivity, dietary fat intake, and smoking at midlife increase AD risk, especially among APOE ε4 carriers.

In the absence of evidence from RCTs, we cannot recommend alcohol to reduce the risk of AD.

Lifestyle and activity

Three components of lifestyle—social, mental, and physical activity—are inversely associated with the risk for dementia, AD, and cognitive impairment.

Physical exercise has been thought to enhance brain neurotrophic factor and modify apoptosis. Exercise can deter stroke and microvascular disease and improve regional cerebral blood flow. In the Cardiovascular Health Study, participants who expended the highest quartile of energy had a lower risk of all-cause dementia and AD compared with participants who expended the lowest quartile of energy.²⁴

Mental and social activity. Epidemiologic studies have shown associations between higher educational achievement and other socioeconomic factors and reduced AD risk. Advanced education is believed to represent a cognitive reserve that delays presentation of AD's effects on memory and cognitive function, rather than providing a protective effect against accumu-

lation of AD pathology. Higher-educated individuals appear to experience a somewhat more rapid rate of cognitive decline when AD does become apparent, perhaps because they have accumulated a greater degree of AD pathology at that point compared with less-educated persons.

Among 117 persons with dementia in the Bronx Aging Study, each additional year of formal education delayed the time of accelerated decline by 0.21 years. After accelerated decline began, each year of additional formal education was associated with a slightly faster rate of memory decline.²⁵

The longitudinal, population-based Kungsholmen Project in Stockholm, Sweden, found an association between daily mentally stimulating activities and decreased risk of all-cause dementia.²⁶ Similarly, higher levels of leisure activity were linked to reduced risk of all-cause dementia in a longitudinal study of 1,772 persons age ≥65 living in Manhattan, NY.²⁷ In a randomized, single-controlled study of the long-term effects of cognitive training, elderly individuals from 6 U.S. cities showed sustained improvement in specific cognitive performance up to 5 years after training sessions began, including memory, reasoning, and speed of processing.²⁸

It seems reasonable to encourage older patients to maintain or increase physical, cognitive, and leisure activities as well as social interaction. These interventions can improve the quality of life and lower the risk of depression, which may be a response to cognitive decline or an independent risk factor for dementia (**Box 3, page 26**). The **Table (page 27)** lists “brain exercises” you can suggest to patients to increase their mental and social activity.

Head trauma. The Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) project found an association between AD risk and a history of head trauma, especially in persons with APOE ε4 alleles.²⁹ Conversely, the Rotterdam Study showed no change in dementia risk for persons with a history of head trauma.³⁰

Even in the absence of conclusive evidence supporting AD prevention, protect-

continued on page 35

continued from page 28

ing the head by buckling seat belts while driving, wearing helmets when participating in sports, and “fall-proofing” the home is recommended.

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Related Resource

• For an extensive bibliography of literature on Alzheimer's disease risk factors and prevention, see this article at Current Psychiatry.com.

Drug Brand Names

Atorvastatin • Lipitor	Pravastatin • Pravachol
Celecoxib • Celebrex	Rofecoxib • Vioxx
Donepezil • Aricept	Simvastatin • Zocor
Medroxyprogesterone • Provera	

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Clinical Point

Evidence of a link between head trauma and AD risk is inconclusive

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Bottom Line

Some of dementia's pathologic processes may be preventable or modifiable, but evidence does not support using medications specifically to reduce Alzheimer's disease (AD) risk. Instead, tell patients that eating less fat and more fish, fruits, and vegetables; not smoking tobacco; exercising; and participating in social and intellectually stimulating activities may reduce the effect of AD risk factors.



Alzheimer's risk

Box 1

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Box 2

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Box 3

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