Evidence-based Approaches to Preventing Alzheimer’s Disease, Part 1

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ABSTRACT

As a consequence of global aging, the occurrence of cognitive impairment and dementia is rapidly becoming a significant burden for medical care and public health systems. The worldwide prevalence of dementia, including Alzheimer’s disease, is estimated at 24.3 million people. This number is expected to increase ~4-fold by the year 2050 unless suitable interventions can be found. Current treatments have not been demonstrated to prevent the onset of Alzheimer’s disease; either they improve patients symptomatically or stabilize cognitive decline for periods ranging from months to a few years. Therefore, primary prevention remains the Holy Grail for this disease and reducing this imminent risk. We cannot control all risk factors for Alzheimer’s disease; we can, however, intervene relative to some Alzheimer’s disease risk factors. Mounting evidence points toward vascular disease as a major risk factor for both Alzheimer’s and vascular dementia. Controlling vascular risk factors such as lack of exercise, diabetes, hypertension, dietary fat intake, high cholesterol, and obesity have emerged as important influences relative to the risk of both vascular and Alzheimer’s dementia. However, the impact of these risk factors in causing dementia depends on the genetic makeup, environment, and lifestyle of the patient. There is insufficient evidence to make a firm recommendation for the primary prevention of dementia, and no primary prevention trial has successfully delayed the development of Alzheimer’s disease. Physicians may advocate for some actions which may reduce the effect of possible Alzheimer’s disease risk factors such as lowering cholesterol and homocysteine levels, lowering high blood pressure, controlling diabetes, increased consumption of fish, reducing consumption of dietary fat, and recommending moderate consumption of wine.

FOCUS POINTS

• Alzheimer’s disease is affected by numerous factors, which can be divided into modifiable and non-modifiable risk factors.
• The effect of risk factor modifications on any particular person will likely depend on his or her genetic makeup, environment, and lifestyle.
• Successful management of cardiovascular risk factors may decrease the risk of dementia in later life and links brain health to heart health.
• A possible relationship between dietary components and risk for Alzheimer’s disease has been found but no conclusive recommendations have been made.

INTRODUCTION

Alzheimer’s disease is a degenerative disorder which involves progressive and irreversible loss of neurons in regions of the brain characterized by impairment of memory and at least one other cognitive domain (aphasia, apraxia, agnosia, executive function). These must represent a decline from previous levels of functioning and be severe enough to interfere with daily function and independence.1,2 The incidence of Alzheimer’s disease ranges from 0.5% to ~4% per year depending on the age of the subjects studied.3,4 A meta-analysis of estimated prevalence of Alzheimer’s disease in the United States suggests...
an increase from 1% at 65–69 years of age, to 13% to 17% at 85–89 years of age, and 24% to 31% at 90–94 years of age. Worldwide prevalence of dementia, including Alzheimer’s disease, is estimated at 24.3 million people, with 4.6 million new cases occurring annually. This number is expected to increase over 4-fold by the year 2050 unless suitable interventions can be found. Available treatments either improve patients’ symptoms or, more frequently, stabilize cognitive decline for periods ranging from months to a few years. However, current treatments have not been demonstrated to prevent the onset of Alzheimer’s disease, a prerequisite for reducing the number of incident cases. Primary prevention, therefore, remains the ultimate goal relative to Alzheimer’s disease.

Alzheimer’s disease is affected by a number of factors. We do not have control over some of the risk factors for Alzheimer’s disease. We can do something about other possible Alzheimer’s disease risk factors. The effect of risk factor modifications on any particular person will likely depend on his or her genetic makeup, environment, and lifestyle.

In addition to the association of individual risk factors with dementia, the clustering of risk factors may be important as well. In one longitudinal cohort study, the risk of probable Alzheimer’s disease increased with the number of risk factors (diabetes, hypertension, heart disease, and smoking). Hazard ratios for one, two, and three or more risk factors were 1.8 (95% CI 1.1–3.0), 2.8 (95% CI 1.7–4.7), and 3.4 (95% CI 1.8–6.3), respectively, in a model adjusting for age, sex, the apolipoprotein E-ε4 (ApoE-e4) gene, and other confounders.

Three forms of prevention exist. Primary prevention aims at reducing disease incidence. Secondary prevention aims at preventing preclinical disease from progressing to clinical disease and depends on effective screening and early detection of dementia. Tertiary prevention is geared towards reducing disability, comorbidity, and further disease progression. If effective treatments exist, early detection can lead to modification of dementia risk. However, the US Preventive Services Task Force suggests there is insufficient evidence to support instituting such a universal screening policy.

## NON-MODIFIABLE RISK FACTORS

### Age

Age remains the strongest risk factor for dementia, particularly for Alzheimer’s disease. Alzheimer’s disease increased exponentially with age with no signs of leveling off. The risk of developing the disease doubles every 5 years in individuals >65 years of age. After 85 years of age, the risk reaches ~50%. Dementia incidence continued to increase with age after 85 years, but at a rate slower than the increase between 65–85 years of age.

### Family History

Family history is a risk factor for the development of Alzheimer’s disease. True familial Alzheimer’s disease accounts for <5% of cases. When diseases tend to run in families, either heredity (genetics) and/or environmental factors may play a role. Patients with a first-degree relative with dementia have a 10% to 30% increased risk of developing the disorder. The increased risk in first-degree relatives is lower if the patient develops Alzheimer’s disease late in life (≥85 years of age). The risk of Alzheimer’s disease in relatives of patients with early-onset disease is highest when the relatives are younger and diminishes as the relatives age. Asymptomatic family members of patients with familial Alzheimer’s disease have been found to show an increased prevalence of certain biomarkers and abnormal activation patterns on functional neuroimaging.

### Genetic Factors

There are genetic links to both the early- and late-onset Alzheimer’s disease. Early-onset Alzheimer’s disease is generally defined as occurring before 60 years of age. It accounts for only 6% to 7% of all cases of Alzheimer disease. From this small pool of patients, only 13% clearly exhibit autosomal dominant transmission over more than one generation. Three known causative gene mutations which lead to the early-onset form have been identified; 30% to 70% of mutations are in the presenilin-1 gene, 10% to 15% are in the amyloid precursor protein gene, and <5% are in the presenilin-2 gene.

For late-onset Alzheimer disease, at >65 years of age, the strongest evidence for a genetic risk factor in late-life nonfamilial Alzheimer’s disease exists for the ApoE-e4 gene. It mediates neuronal protection and repair and is believed to participate in early β-amyloid (Aβ) deposition. Three alleles of ApoE have been identified: e2, e3 and e4. The ApoE-e4 genotype has been linked to the development of Alzheimer’s disease and possibly to vascular dementia as well. In contrast, there is a possible protective effect for the e2 allele in Alzheimer’s disease. ApoE-e3, the most common form, plays a neutral role in the development of Alzheimer’s disease. The strength of the association between the ApoE-e4 allele and Alzheimer’s disease is stronger among women than men and also diminishes with age. Screening for the ApoE genotype is currently not recommended for clinically asymptomatic people as part of routine clinical practice.

Early-onset and familial Alzheimer’s disease are not synonymous. Sporadic cases of early-onset Alzheimer’s disease can occur with no family history and no genetic mutations, and familial late-onset pedigrees can occur with no responsible genes identified. All patients suspected of having familial early-onset Alzheimer’s disease should be referred to a specialty memory clinic or genetic clinic for further evaluation.
MODIFIABLE RISK FACTORS

Table 1 lists the probable modifiable risk factors for Alzheimer’s disease.

Cardiovascular Risk Factors

The risk of developing Alzheimer’s disease or vascular dementia appears to be increased by many conditions that damage the heart or blood vessels. Increasing evidence is emerging that vascular disease and its risk factors play important etiologic roles in both vascular dementia and Alzheimer’s dementia. Understanding the reasons for differences between populations in genetic vulnerability and environmental exposure may help to identify modifiable risk factors which may lead to effective prevention of vascular and Alzheimer’s dementia. Recent evidence suggests that the successful management of cardiovascular risk factors may decrease the risk of dementia in later life and links brain health to heart health.32

Hypertension

Although numerous studies have shown that high blood pressure33-38 is associated with an increased risk of both Alzheimer’s disease and all-cause dementia, curiously, some studies have shown that low blood pressure is also associated with an increased risk.39,40

The relationship between blood pressure and cognitive decline is not linear. There may be a U-shaped association between systolic and diastolic blood pressure at baseline and subsequent performance on mental status questionnaires.41 High diastolic pressure has been associated with hippocampal atrophy, whereas a low diastolic pressure may be associated with amygdala and hippocampal atrophy.42 Vascular disease may contribute to atrophy of structures linked with Alzheimer’s pathology. Elevated systolic blood pressure in midlife may be associated with incident dementia 20 years later.43 Young adults are as vulnerable as the elderly to blood pressure-related decline in at least one aspect of cognitive function.44

Studies45-48 have yielded conflicting data regarding the effect of antihypertensive therapy on dementia prevention. For example, the results of the Systolic Hypertension in Europe49 study among participants receiving antihypertensive treatment revealed a 53% reduction in vascular or mixed dementia and a 60% reduction in Alzheimer’s disease. The Perindopril Protection Against Recurrent Stroke Study,50 a clinical trial of prevention of recurrent stroke by treatment with antihypertensive medications, reported a 34% reduction in a composite measure of cognitive impairment and dementia. On the other hand, the results of the cognitive part of the Hypertension in the Very Elderly Trial51 found no statistical differences between treatment and placebo groups with regard to dementia or cognitive decline; there is neither improvement nor worsening of the cognitive function. Another study52 yielded mixed results, with hypertension being related to a worsening in executive function, but not memory or language scores.

Hyperlipidemia

Lipids metabolism are likely to be an important pathway in Aβ-protein deposition, tau phosphorylation, and disruption of synaptic plasticity and neurodegenerative endpoints.53-55 Hypercholesterolemia may increase the risk of dementia.33,56 Epidemiologic studies have established an association between cognitive decline and/or incident dementia, higher dietary intake of saturated fats, transunsaturated fats, or cholesterol,57,58 and vascular dementia.59-61 However, not all studies have confirmed this association.62-65 Some have even shown a lower risk of dementia with high cholesterol levels.66 Some longitudinal studies indicate that, as with body mass index, serum cholesterol levels may decrease in the early stages of dementia, limiting the ability to see an effect of hypercholesterolemia on dementia risk when the measurements are made later in life.67

This has led to studies measuring the effect of cholesterol-lowering therapies—specifically the statin drugs—on the risk of dementia, which have shown mixed results. The treatment of hypercholesterolemia with statins impedes large-vessel atherosclerosis and its consequences. In addition, it may trigger a variety of metabolic effects on the brain which may be related to Alzheimer’s disease pathogenesis.68 Some epidemiologic studies69 have shown a negative association between statins use and Alzheimer’s disease risk, and several mechanisms have been postulated.

Retrospective studies have suggested that statins may prevent the development of dementia.70,71 This potential effect could be a direct association between amyloid processing and cholesterol in the brain,72 or an indirect effect via decreasing the risk of stroke, since even small cerebral infarcts worsen the severity of Alzheimer’s disease.73

**TABLE 1**

**PROBABLE MODIFIABLE RISK FACTORS FOR ALZHEIMER’S DISEASE**

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Hypertension</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>Hyperlipidemia</td>
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<td>Smoking</td>
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<td>Alcohol</td>
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<td>Depression</td>
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<tr>
<td>Metabolic syndrome</td>
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<tr>
<td>Trace mineral, chemical, and environmental exposure</td>
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<tr>
<td>Head trauma</td>
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<tr>
<td>Elevated homocysteine; Vitamin B&lt;sub&gt;6&lt;/sub&gt;; Vitamin B&lt;sub&gt;12&lt;/sub&gt;; and folate deficiency</td>
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<tr>
<td>Chronic kidney disease</td>
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However, this efficacy in reducing the incidence of dementia, the degree of age-related cognitive decline, or the neuropathologic burden of Alzheimer pathology has been found in some studies,74,75 but is not consistent.76 Two large, randomized controlled trials75,77 failed to show that use of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins) reduced the incidence of dementia. A Cochrane review77 concluded that the evidence for a causal association was not yet present.

At present, even though there may be compelling reasons to treat hyperlipidemia, there is no definitive evidence that treatment of hyperlipidemia will reduce risk of subsequent Alzheimer’s disease.78

**Diabetes Mellitus**

Studies73,79-85 from various populations have consistently shown an association between diabetes and cognitive decline or dementia. Diabetes is associated with a 50% to 100% increase in risk of Alzheimer’s disease and of dementia overall and a 100% to 150% increased risk of vascular dementia.81 The relationship between diabetes and dementia of the Alzheimer’s type remains controversial.86 The mechanism by which diabetes may increase dementia risk is uncertain; it does not appear to be mediated entirely through vascular disease.87 Insulin resistance is present in most diabetic patients and is associated with compensatory hyperinsulinemia. The Honolulu-Asia Aging Study88 demonstrated that the effect of high levels of insulin on the risk of dementia was independent of diabetes and blood glucose. Increased peripheral insulin levels are associated with reduced brain atrophy and cognitive impairment in patients with early Alzheimer’s disease, suggesting a role for insulin signaling in the pathophysiology of Alzheimer’s disease.89 A possible relationship between insulin and AP metabolism90,91 is also being studied.

It is not clear that treating diabetes reduces the risk of dementia. Higher postprandial plasma glucose levels were associated with greater declines in cognitive performance.91 An inverse correlation has been noted between some cognitive measures and hemoglobin A1C levels, suggesting that worse glycemic control may be associated with greater cognitive decline.95 However, patients treated with insulin actually had the highest incidence of dementia.96

**Smoking**

Cigarette smoke contains numerous toxic compounds that may directly affect neuronal function and integrity, which may have implications for long-term neuronal function and survival.97 Acute nicotine and tobacco consumption is associated with increased blood flow and metabolism in some parts of the brain,98,99 but chronic smoking has been linked to decreased global cerebral blood flow100 as well as acceleration of cerebral atrophy and ventricular enlargement.101

Data regarding the impact of smoking on the risk of dementia are conflicting. Reported associations between cigarette smoking and Alzheimer’s disease have been varied.102-106 Some studies102,107,108 have suggested that smoking in middle aged and elderly people is associated with an increased risk of dementia. Stroke is one of the possible mechanisms by which smoking can lead to dementia.109,110 One study111 showed that current smokers, but not former smokers, were at increased risk for Alzheimer’s disease. However, other studies112 found no association. In addition, one report113 suggested that cigarette smoking may have a protective effect on Alzheimer’s disease by reducing senile plaque formation. However, even if smoking has a protective effect on Alzheimer’s disease, it could be completely or partially offset by an increased risk of lung cancer, chronic obstructive pulmonary disease, and vascular dementia.114

Effect modification by ApoE-e4 may explain, at least in part, the conflicting results. ApoE-e4 carriers have fewer nicotinic receptors, and nicotine may help increase the density of the receptors or assist in the release of neurotransmitters, suggesting that there may be a direct biologic modification of the effect of smoking by ApoE-e4.115 In two population-based cohorts,116-118 smoking was associated with either memory decline or Alzheimer’s disease in patients without, but not with, the ApoE-e4 allele.

**Metabolic Syndrome**

The metabolic syndrome is a cluster of cardiovascular risk factors, which include obesity, hypertension, insulin resistance, and dyslipidemia. In one study,119 the prevalence of Alzheimer’s disease was significantly higher in patients with metabolic syndrome. However, this association remains controversial. One case control study120 also found an association between the metabolic syndrome and Alzheimer’s disease (OR 3.2; 95% CI 1.2-8.4). However, in a cohort study,121 the metabolic syndrome was weakly associated with incident vascular dementia but not Alzheimer’s disease. Other longitudinal studies of the metabolic syndrome and cognitive decline in older patients have found either no association or increased cognitive decline only in patients who also had increased markers of inflammation such as serum C-reactive protein and interleukin-6.122

**Diet**

Nutritional factors have been investigated as potential modifiable risk factors for dementia. A possible relationship between dietary components and risk for Alzheimer’s disease and other dementias has been found but no conclusive recommendations have been made. Table 2 lists possible helpful agents to prevent Alzheimer’s disease.

**Antioxidant Vitamins**

The brains of patients with Alzheimer’s disease contain lesions that are typically associated with free radical exposure as well as elevated levels of endogenous antioxidants. Exogenous
antioxidants reduce the toxicity of Aβ in in vitro studies of brains of patients with Alzheimer’s disease.123,124 These findings have led to interest in assessing the role of antioxidants (eg, vitamin E, β-carotene, flavanoids, and vitamin C) for the prevention of Alzheimer’s disease. A case control study125 of patients with Alzheimer’s disease found that patients with Alzheimer’s disease had a lower level of β-carotene and vitamin A but not α-carotene when compared to controls.

A controlled, randomized, multicenter trial in patients with Alzheimer’s disease of moderate severity126 showed that a high dose of α-tocopherol (Vitamin E, 2,000 IU/day) or selegiline slows the progression of disease. While some studies127,128 have reported that higher dietary intake of antioxidants was associated with a lower risk of Alzheimer’s disease, these studies have had significant limitations.129 Other studies130-132 have not found an association between dietary antioxidant intake and the risk of development of Alzheimer’s disease or cognitive impairment. Randomized clinical trials133 have not found a benefit for vitamin E in improving cognitive outcomes. Furthermore, doses of vitamin E >400 IU/day have been shown to have negative cardiovascular effects and increased mortality.134

Some explanations have been proposed to explain the absence of cognitive improvement with vitamin E supplements. Vitamin E supplements have traditionally contained only α-tocopherol the more potent antioxidant; however, γ-tocopherol, the more abundant form in the US diet, also has anti-inflammatory properties.135 The combined intake of the eight different tocopherol forms reduces oxidative stress and inflammation to a greater degree than α-tocopherol alone.136

The lack of high-level evidence to support an association between cognitive benefits or decreased Alzheimer’s disease incidence with vitamin E use, combined with the potential for adverse cardiovascular outcomes and increased all-cause mortality, has led to the recommendation of immediately ceasing prophylactic, high-dose vitamin E supplementation in elderly patients for primary or secondary prevention of Alzheimer’s disease. Although the risks of taking high doses of vitamin C are lower than those with vitamin E, the lack of consistent efficacy data for vitamin C in preventing or treating Alzheimer’s disease may discourage its routine use for this purpose.137,138 Note that is a potential role of the curcumin curry spice in Alzheimer’s disease. Curcumin has antioxidant, anti-inflammatory, and anti-amyloid activity properties. Curcumin is a promising agent in the treatment and/or prevention of Alzheimer’s disease.139-142

Homocysteine, Vitamins B6, B12, and Folate
There is some evidence that elevated serum homocysteine and/or low serum levels of folate, vitamin B6, and vitamin B12 may be associated with impaired cognition and risk of dementia. However, there are no convincing data that vitamin supplementation prevents dementia.

Homocysteine is recognized as a risk factor for stroke and heart disease, and it could potentially play a role in vascular dementia through its association with large143 and small vessel disease.144 In addition, homocysteine may mediate cognitive decline and dementia by direct neurotoxicity.145-147 However, the evidence for elevated homocysteine as an independent risk factor for cognitive decline and dementia is conflicting.148-151

This association between Alzheimer’s disease and elevated homocysteine concentrations has been reported in case control studies.152,153 Several cross-sectional studies have also found significant associations between lower folate and hyperhomocysteinemia with dementia or cognitive impairment.154-156 However, the direction of cause and effect is not known. Moreover, in non-demented elderly populations, plasma homocysteine is inversely associated with poor performance and the relation was most marked for psychomotor speed.151,157,158 The results of longitudinal studies which investigated the relationship between hyperhomocysteinemia and risks of incident Alzheimer’s disease have been inconsistent. Some prospective cohort studies159,160 (eg, the Framingham Study159) reported a strong association, but others (eg, the Washington Heights–Inwood Columbia Ageing Project161) reported no association.

There is no conclusive evidence that homocysteine-lowering therapy using supplementation with folic acid or other B vitamins improves cognitive function or prevents cognitive decline. One study162 found no benefit of using homocysteine-lowering therapy after 2 years. Another study163 found that there is possible benefit from folate therapy.

Fish and Omega-3 Fatty Acids
Numerous studies158,127,132,148 have reported that high intakes of total fat, saturated fat, and total cholesterol increase the risk for incident dementia. A reduced level of omega-3 fatty acids has been linked to an increased risk of dementia in epidemiologic studies.164 There may be a benefit for higher fish consumption relative to the risk of dementia or cognitive decline,165-167 with some exceptions.62

### Table 2
**Possible Helpful Agents to Prevent Alzheimer’s Disease**

<table>
<thead>
<tr>
<th>Antioxidant vitamins</th>
<th>NSAID therapy</th>
<th>Fish and omega-3 fatty acids</th>
<th>Mediterranean diet</th>
<th>Fruit and vegetables</th>
<th>Homocysteine, vitamins B6, and B12, and folate</th>
<th>Alcohol</th>
<th>Caffeine</th>
<th>Hormone therapy</th>
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NSAID = non-steroid anti-inflammatory drug.


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Interest has focused on specific omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Several case control studies have reported lower biochemical levels of omega-3 fatty acids in the plasma and brain tissue of patients with Alzheimer’s disease compared with controls. In the Framingham study, 62 individuals with the top quartile levels of DHA measured at baseline had lower rates of incident dementia over 9 years of follow-up. These long-chain omega-3 fatty acids, a type of polyunsaturated fat (PUFAs) consumed almost exclusively from fish, and its precursor α-linoleic acid from vegetable oils and nuts have antiaggregatory, antithrombotic, and anti-inflammatory properties. A number of studies have found that omega-3 fatty acid rich diets resulted in better regulation of neuronal transmission, 28 and reduced oxidative damage. 171

Thus, increased intake of fish and omega-3 PUFAs, particularly EPA and DHA, might play a protective role against age-related cognitive decline. One fish meal per week was associated with a 60% reduction in the risk of developing Alzheimer’s disease in both the Rotterdam and Chicago studies. 62 The Chicago study also examined risk of disease according to intake of omega-3 fatty acids. Higher total intake of omega-3 fatty acids was significantly associated with a lower risk for Alzheimer’s disease. However, the Rotterdam study did not find an association between total intake of omega-3 fatty acids and risk of Alzheimer’s disease. 135

Results from cross-sectional studies have been inconsistent, showing either that a high intake of omega-3 PUFAs was associated with less cognitive decline, 168,172 or no association. 57,173,174 Longitudinal studies of fish or omega-3 PUFA intake and cognitive performance have also yielded contradictory results. In some studies, 62,164,165,175 high fish or omega-3 PUFAs consumption was protective against cognitive decline, whereas no association was found in other studies. 58,172 Most studies 176-178 of omega-3 PUFA concentrations in the blood showed high concentrations to be associated with a lower risk of cognitive decline. A very small number of randomized trials 179 with cognitive endpoints have been performed in elderly patients with established dementia.

Although these studies show promise that dietary intake of fish and omega-3 fatty acids may protect against Alzheimer’s disease, more research needs to be conducted before one can attribute a causal association with these findings. In the absence of evidence from randomized controlled trials, one cannot offer unequivocal advice regarding seafood or omega-3 fatty acid intake for the primary prevention of dementia.

**Mediterranean Diet**

The results of a recent community-based study 180 involving nondemented individuals showed that adherence to a traditional Mediterranean diet was associated with significant reduction in risk for incident Alzheimer disease. Longitudinal studies have also suggested that adherence to a Mediterranean-style diet is associated with a decreased risk of Alzheimer’s disease, as is consumption of fish. Adherence to the Mediterranean diet may affect not only risk for Alzheimer’s disease but also subsequent disease course with lower mortality in Alzheimer’s disease with a possible dose-response relationship. 184

**Fruits and Vegetables**

Both fruit and vegetable intake have been associated with improved cognitive performance in elderly subjects. 180,185 Consumption of fruits and vegetables has been associated with decreased incident dementia. 177,186 However, some studies 187,188 have found that only high consumption of vegetables but not fruits was associated with less cognitive decline.

**Alcohol**

Data on alcohol use and cognitive function in the elderly are mixed with inconsistent results. 189-191 The relationship between alcohol consumption and dementia is complex, mediated by dose and type of alcohol. Epidemiologic studies 192,193 have reported an association between alcohol consumption and the risk of dementia.

There is a U-shaped relationship between alcohol consumption and cognitive impairment. 194,195 Epidemiologic evidence has established that moderate consumption of wine (250–500 mL/day), compared with an intake of more or less than this amount, is associated with a reduced risk of subsequent all-cause dementia and of Alzheimer’s disease. 196 High levels of alcohol intake, which are usually associated with clinical problem drinking and alcoholism, can lead to cognitive decline. However, moderate alcohol consumption may be protective, 128,197,198 and it is associated with an ~50% reduced risk of combined probable dementia and mild cognitive impairment. 199

Some studies 193 have shown that wine consumption, but not other types of alcohol, reduce the risk of dementia. A recent randomized controlled trial 200 showed that drinking low to moderate amounts of alcohol may delay age-associated cognitive decline in older women (including slowing deterioration in global cognitive function), but these apparent benefits were not clearly seen in older men. One needs to note that alcohol-associated cognitive impairment may be confounded by other factors such as smoking, dietary deficiencies of vitamins and antioxidants, or head trauma.

The ApoE-e4 allele may modify the effect of alcohol, although the evidence is conflicting. The risk of dementia has been associated with increased alcohol consumption only in carriers of the e4 allele. 201 However, the risk of cognitive impairment was not associated with any interaction between alcohol consumption and the ApoE genotype among elderly women. 202

In the absence of evidence from randomized controlled trials, a firm recommendation for the use of alcohol to reduce the risk of Alzheimer’s disease cannot be offered; neither can one recommend that a nondrinker begin to drink alcohol.
CONCLUSION

Dementia is the result of a set of underlying pathologic processes at least some of which may be preventable or modifiable. Mounting evidence points toward vascular disease as a major culprit for both Alzheimer’s and vascular dementia. There is insufficient evidence to recommend for or against treating systolic hypertension, type 2 diabetes mellitus, hyperlipidemia, and hyperhomocysteinemia for the specific purpose of reducing the risk of dementia. Genetic vulnerability related to ApoE-e4 modifies many of these risks, and such interactions may increase the contribution of genetic factors in the context of exposure to higher-risk environments. Although there is insufficient evidence to make a firm recommendation for the primary prevention of dementia, physicians may advocate taking some actions to reduce the risk of possible Alzheimer's disease risk factors such as lowering cholesterol and homocysteine levels, lowering high blood pressure levels, and controlling diabetes.

The first part of this article reviewed the data relative to non-modifiable risk factors for Alzheimer’s disease and began to focus on two extremely important modifiable risk factors—cardiovascular and dietary. Part 2 of this article, to appear in the July issue of Primary Psychiatry, will discuss the role of lifestyle modification in possibly delaying the onset of or preventing Alzheimer’s disease. It will focus on the role of physical and mental exercise as well as other areas of concern including head trauma, hormone therapy, depression, and environmental exposure.

REFERENCES

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