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WILL A HEALTHY LIFESTYLE HELP PREVENT ALZHEIMER'S DISEASE?

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■ **Abstract** Alzheimer's disease (AD) appears to resemble other chronic diseases, whereby a myriad of interconnected factors, including those associated with lifestyle, are involved in disease development. In this paper, we examine accepted and proposed risk factors for AD and explore health behaviors, including diet, exercise, prevention of injury, and cognitive stimulation, that may help prevent AD. Adherence to a healthy lifestyle may directly protect against AD or may prevent diseases associated with AD, such as vascular disease and diabetes. A healthy lifestyle to prevent AD may be important throughout life rather than after disease manifestation and may be particularly relevant if other factors, such as genetic predisposition, also increase risk of AD. If changes in lifestyle can help prevent AD by reducing modifiable risk factors, this knowledge can aid individuals who wish to take action to protect themselves and their families from the disease.

INTRODUCTION

Although scientists have made numerous advances in determining possible causes and mechanisms of Alzheimer's disease (AD), the disease remains enshrouded in mystery. Similar to other chronic diseases, some of the risk for AD may be due to our own actions, and therefore, personal and societal choices may influence AD development. If we do not discover ways to either delay the onset or slow the progression of the disease, projections indicate that the public health impact of AD over the next 50 years will be severe, with prevalence of AD increasing four times over current rates, afflicting between 8 to 13 million people in the United States alone by the year 2050 (20). This scenario is slightly brighter if successful prevention methods are identified, introduced, and utilized; but even with some successes, rates will probably greatly increase (79).

The current annual economic cost of AD for health care and lost wages in the United States is between $80 and $100 billion, making it the third most costly disease, behind heart disease and cancer (56). In addition to the increasing numbers

of individuals suffering with the disease, these projections point to much higher costs for patient care, increases in caregiver burden, and the need for more outpatient and institutional care (79). Emphasis on prevention, rather than treatment, can reduce disease incidence and avoid the costly consequences of this disease.

Originally, scientists believed that lifestyle factors did not affect AD. Ecological and cross-sectional studies indicated that AD prevalence and incidence rates differed in countries throughout the world (16), but methodological weaknesses in many of the earlier studies dampened interest in examining environmental risk factors. Over time, research methods have improved, yet international comparisons continue to show differential rates of AD, with lower rates in developing than in developed countries (31, 37). Additionally, longitudinal studies show increased rates of AD in populations that migrate to more developed countries (27, 90).

Another methodological issue that slowed interest in lifestyle factors was the exclusion of individuals at risk for vascular disease from early AD research (77). Historically, AD and vascular dementia were considered to be distinct diseases, with AD being the most prevalent subtype of dementia, followed by vascular dementia (37). However, the types of dementia appear to represent a continuum of diseases, with overlapping causes and mixed pathologies. Neuropathologic studies indicate that most individuals have either AD alone or a combination of AD and vascular dementia, with few pure cases of vascular dementia detected at autopsy (80). Although many writers use the terms AD and dementia interchangeably, we attempt to distinguish research on AD from research on other types of dementia.

The increasing acceptance of a relationship between vascular disease and AD, combined with recent research implicating environmental factors in development of cognitive decline and AD, has strengthened the possibility that healthy lifestyle choices may prevent AD. Similar to other chronic diseases, myriad interconnected factors, including those associated with lifestyle, appear to be involved in AD development. In this paper, we examine accepted and proposed risk factors for AD and then explore health behaviors that may help prevent AD. If studies determine that AD has modifiable risk factors and that changes in lifestyle can help prevent AD, this knowledge can aid individuals who wish to take personal action to help protect themselves and their families from the disease and support advocacy of community efforts to improve and maintain health behaviors.

OVERVIEW OF ALZHEIMER'S DISEASE

In the U.S. population, prevalence rates for all types of dementia, including AD, are 4%–11% for people >65 years and 24%–47% for those >85 years, the fastest growing sector of all age groups (87). Early-onset AD is rare and usually occurs in individuals younger than 60 years of age, whereas late-onset accounts for the vast majority of AD cases and generally develops after age 60 (83).

A growing body of literature supports AD as a syndrome with multiple brain abnormalities, including: (*a*) accumulation of abnormal materials, especially amyloid

plaques and neurofibrillary tangles, the two hallmark lesions in AD; (*b*) loss of brain substance, especially synapses, and reductions in neurotransmitters; (*c*) oxidative damage; and (*d*) inflammation (6). Whether these abnormalities fuel AD or result from cells working to combat the disease process is uncertain, but clearly the disease process is complex (6).

In general, AD research has focused on single risk factors, although more recent studies have examined combinations of risk factors and development of AD. As recently as 1997, the primary accepted risk factors for AD were old age, family history, *Apolipoprotein E* (*ApoE*) genotype, and Down's syndrome (36). Additional risk factors for AD are being identified and are categorized in this paper as non-modifiable and modifiable. Table 1 summarizes selected studies of AD that examine potentially modifiable lifestyle factors.

It is important to note, because we discuss risk factors for AD, that risk factors do not necessarily cause disease but rather are associated with increased likelihood of disease occurrence (45). Additionally, the research discussed below regarding risk factors for AD represents a broad range of study designs, study populations, outcome and exposure measures, data analysis, and result interpretation. Although some studies are randomized controlled intervention studies, many are longitudinal cohort studies of varying duration with individuals at differing baseline cognitive skills, as measured by various cognitive tests and clinical outcomes. Other studies are retrospective case-control studies, which are subject to numerous methodological biases, or cross-sectional studies, which provide information on relationships between risk factors and disease, but not on temporal sequence or causality. As research focuses on potential lifestyle risk factors for AD, the quality of studies will continue to strengthen, as is illustrated by the increased funding by the National Institutes of Health for randomized controlled trials and long-term longitudinal studies of lifestyle factors.

Non-Modifiable Risk Factors

ADVANCED AGE Although many people experience little or no decline in cognitive functioning as they age, the aging process generally slows down brain activity. Numerous age-related changes occur in the vasculature of the brain, including decreased capillary density, narrowed lumens, degenerated pericytes, and thickened basement membranes (17). In AD, these age-related changes are aggravated by further decreased capillary density and basement membrane thickening, together with other AD pathophysiologic processes such as twisted microvessels and mitochondrial losses (12). The risk of AD increases exponentially with age, doubling every five years for individuals over the age of 65 until at least the age of 90 years (37), and this age-associated increase persists in international studies (11).

FAMILY HISTORY OF AD Individuals have 3.5 times greater the risk of developing AD if they have a parent or sibling with the disease (83). This risk increases with age and is greater for relatives of individuals with early-onset rather than late-onset

TABLE 1 Selected longitudinal and clinical trials of lifestyle factors and AD

Name of study (Reference)	Study population	Type of study (sample size)	Outcome measure	Summary of major findings
ANTIOXIDANTS				
Honolulu aging study (50)	Japanese-American men living in Hawaii, aged 71–93	Longitudinal study: 3–13 years follow-up (N = 3496)	Incident and prevalent AD, VaD, mixed/other dementias	Vitamin C and E supplements protected against VaD and mixed/other dementias but not AD.
Rotterdam study (19)	Community-dwelling adults free of dementia at baseline, aged 55 and older	Longitudinal study: 6 years average follow-up (N = 5395)	Incident AD	Vitamin C and E intake from foods was associated with lower risk of AD and was most pronounced among smokers
Chicago health and aging (55)	Community-dwelling adults free of AD at baseline, aged 65 and older	Longitudinal study: 4 years average follow-up (N = 815)	Incident AD	Vitamin E intake from foods, but not supplements, associated with lower risk of AD but only among persons without ApoE e4 alleles.
Sano et al. study (75)	Patients with moderately-severe AD	Randomized controlled, multicenter trial (N = 341)	Death, institution-alization, loss of ADLs, severe dementia	Treatment with alpha-tocopherol, selegiline, or both delayed death, institutionalization, loss of ADLs, and disease progression
FATS				
Rotterdam study (40)	Community residents, aged 55 and older	Longitudinal study: 2.1 years average follow-up (N = 5386)	Incident dementia	High fish consumption inversely related to incident dementia and particularly to AD
HYPERTENSION				
Longitudinal population study in Sweden (78)	Systematic sample of 70-year old nondemented residents of Goteborg, Sweden	Longitudinal study: 15 years follow-up (N = 382)	Incident AD	Higher diastolic blood pressure at age 70 increased risk of AD at age 79–85

Honolulu-Asia aging study (46)	Cohort of Japanese-American men, aged 45–68 years at baseline	Longitudinal study: 26 years follow-up (N = 3703)	Incident AD	Higher systolic and diastolic blood pressure in midlife increased risk of AD never treated with antihypertensive meds
Populations in eastern Finland (42)	Random sample from population-based studies, aged 65–79 at follow-up	Longitudinal study: 21 years average follow-up (N = 1449)	Incident AD	Raised systolic blood pressure in midlife increased risk of AD in later life
CHOLESTEROL				
Finnish cohorts of seven countries study (62)	Community residents, men aged 40–59 years at baseline	Longitudinal study: 30 years follow-up (N = 444)	Prevalent AD	High serum cholesterol concentrations during middle age or early old age predicted AD prevalence
Populations in eastern Finland (42)	Random sample from population-based studies, aged 65–79 at follow-up	Longitudinal study: 21 years average follow-up (N = 1449)	Incident AD	High serum cholesterol concentration in midlife increased risk of AD in later life
HOMOCYSTEINE				
Framingham study (76)	Cohort of dementia-free adults, aged 68–97 at follow-up	Longitudinal study: 8 years median follow-up (N = 1092)	Incident AD	Strong, graded association of plasma homocysteine levels and risk of AD
COGNITIVE STIMULATION				
Religious Orders study (92)	Nuns, priests, and monks without dementia at baseline, 65 years or older at baseline	Longitudinal study: 4.5 years mean follow-up (N = 801)	Incident AD	Frequent participation in cognitively stimulating activities reduced risk of AD
DIABETES				
Honolulu-Asia aging study (68)	Cohort of Japanese-American men, aged 45–68 years at baseline	Longitudinal study: 26 years follow-up (N = 2574)	Incident AD	Type 2 diabetes increased risk of AD, particularly among carriers of the APOE e4 allele
PHYSICAL ACTIVITY				
Canadian study of health and aging (48)	Population-based, cognitively normal adults, aged 65 or older at baseline	Longitudinal study: 5 years follow-up(N = 4615)	Incident AD	Regular physical activity associated with reduced risk of AD

AD. The risk of AD by the age of 80 years for children whose parents both were afflicted with the disease is about 50% (36).

GENETIC PREDISPOSITION Several genetic mutations predispose to AD. Early-onset familial AD is partly the result of genetic mutations in chromosomes 21, 14, and 1 (30). Individuals with Down's syndrome have an extra copy of the beta-amyloid precursor gene on chromosome 21 and usually develop brain changes that resemble AD before 40 years of age, with about 50% developing dementia before 60 years of age (63).

Late-onset AD appears to result from multiple mutations that create a predisposition for the disease. The most widely studied mutation is the polymorphism for *ApoE*, a lipoprotein responsible for transporting and metabolizing cholesterol and other lipids to the neurons and for repairing injured neurons (62). Of the three major isoforms of *ApoE* (*ε2*, *ε3*, and *ε4*), *ε4* is a risk factor for both familial and late-onset AD (9). Approximately 15% to 30% of the general population has at least one *ApoE ε4* allele, and about 2% has two *ε4* alleles (43). Compared to individuals with no *ε4* alleles, individuals with one *ε4* allele are three to four times more likely and individuals with two *ε4* alleles are about eight to ten times more likely to develop AD. However, *ApoE ε4* alleles account for only about 13% to 20% of dementia cases (21).

Researchers are investigating other possible genetic risk factors for AD, such as polymorphisms for inflammatory cytokines, antioxidant enzymes, and oxidative stress enzymes (60, 71). Identifying genetic factors may provide valuable information for targeting prevention and treatment strategies to individuals at increased risk for AD (30).

Modifiable Risk Factors

HEAD INJURY Traumatic head injury with loss of consciousness has been associated with AD in numerous, but not all, studies (56), with risk being highest for injuries in adults over 70 years of age (53). Head injuries may reduce brain reserve or induce alterations in neuronal metabolism or circuitry (30). One study suggests that head trauma is only a risk factor for individuals who carry the ApoE ε4 allele, although the mechanism for this interaction is unclear (52). Animal studies suggest that repeated injuries, rather than single events, increase amyloid beta deposition (88), providing a possible explanation for the discordant findings of head injury and AD in humans.

LOW EDUCATION Cross-sectional and longitudinal research studies conducted in numerous countries have found an association between low education and AD (67). However, results are mixed, with some studies finding relationships with vascular dementia or AD only, and others, particularly in developing areas of the world, finding no relationship at all (26). The possible relationship between education and AD is complex, with four primary mechanisms speculated to account for these observed

associations: (*a*) cognitive reserve; (*b*) increased synaptic density through mental activity; (*c*) education as a proxy for other risk factors, such as health habits; and (*d*) diagnostic biases in neuropsychological tests (26). The positive correlations of low education with cognitive inactivity, poverty, and other demographic and health variables obscure a clear understanding of the role of education and AD.

COGNITIVE INACTIVITY Retrospective case-control and cross-sectional studies indicate that frequency of cognitive activity in midlife is associated with cognitive function in old age (24). The Religious Orders Study, a prospective study of over 800 nuns, priests, and monks who were healthy at baseline, found more frequent participation in cognitively stimulating activities was associated with reduced risk of AD. Cognitive activity may protect against AD through strengthening processing skills, making them more efficient and less vulnerable to age-related decline and damage by AD (92). However, when follow-up periods are relatively short, cognitive inactivity at baseline could simply reflect an early symptom of AD.

VASCULAR DISEASE Evidence implicates both cardiovascular and cerebrovascular disease as predispositions for AD (32). Both diseases cause decreased cerebral perfusion (oxygenation), which leads to lowered brain metabolism, brain lesions, and initiation of chronic pathophysiologic processes, all of which are implicated in AD (30). Cerebral infarcts, which result from strokes, are frequently detected in AD brains, and patients who have suffered a stroke experience reduced cognitive function, more rapid cognitive decline, and are more prone to develop AD (80). Additionally, cross-sectional studies show that patients with AD often have heart disease, and that nondemented patients with heart disease are at the same risk for formation of beta-amyloid plaques as are persons with AD (81).

Hypertension, a well-recognized risk factor for stroke and multi-infarct dementia, is now a suspected risk factor for AD (32). Indeed, the condition of the vasculature throughout one's life may be an important factor in the development of AD. Elevated blood pressure preceding development of AD was a risk factor in at least three longitudinal studies, including studies of Swedish adults followed for 9 to 15 years (78), Japanese-American men followed for an average of 25 years (46), and Finnish adults followed for an average of 21 years (42). However, once AD manifests, the disease appears to be associated with decreased blood pressure, which continues to decline as the disease progresses (78). This may, in part, explain the discrepant results regarding blood pressure and cognitive decline in cross-sectional research.

DIABETES Results of studies examining diabetes and AD are mixed; however, several large epidemiological studies of older adults have found higher rates of AD in adults with diabetes (68). Two population studies found that impaired glucose tolerance and hyperinsulinemia were associated with cognitive impairment and AD (44). The Honolulu-Asia Aging study found that diabetes was associated with development of AD and vascular dementia, and this association was strongest in

adults who also carried the ApoE $\varepsilon 4$ allele (68). This relationship is partly explained through the effect of diabetes on cerebral arteries and acetylcholine neurotransmitter function. Additionally, the advanced glycation end products associated with diabetes result in amyloid deposition, tau formation, and oxidative stress (58).

HIGH CHOLESTEROL High-serum cholesterol is strongly associated with vascular disease (82) and has recently become a suspected risk factor in AD research. Although results are conflicting in cross-sectional studies, longitudinal studies consistently implicate high cholesterol in AD development. Several Finnish studies have found that high serum cholesterol in midlife increased risk of AD in later life, independent of numerous demographic, behavioral, vascular, and genetic factors (42, 62). Further, a case-control study demonstrated reduced risk of AD in persons who are under 80 years of age and take statins or any lipid-lowering medication, providing further evidence of a high cholesterol and AD relationship (35).

HIGH HOMOCYSTEINE LEVELS Homocysteine is a substrate for several enzymes and is an important intermediate in the metabolic reactions of methionine, an essential amino acid. Intake of Vitamins B6 and B12 and folate are the major dietary determinants of plasma homocysteine levels, although other lifestyle factors, such as smoking, coffee, and alcohol consumption are also associated with high levels (18). High homocysteine is a major risk factor for vascular disease, and case-control studies have shown that patients with AD have higher homocysteine levels than controls (15). Although one prospective study of cognitive decline did not show an association (39), the Framingham Heart Study found a strong, graded association of homocysteine levels with risk for AD. In this study, high levels of homocysteine, measured up to eight years before dementia onset, nearly doubled the risk of developing AD (76).

ESTROGEN Estrogen has been widely researched for its potential protective role in numerous areas of women's health; however, study results have been mixed. Estrogen use was not associated with cognitive function in postmenopausal women in the Rancho Bernardo cohort (5), and both the Nurses' Health and the Women in the Atherosclerosis Risk in Communities studies did not find a protective effect for hormone replacement therapy (HRT) on cognitive function examined over time (2, 29). Although one small clinical trial of 12 women with AD indicated improved cognitive function for those treated with HRT (4), two larger trials of women with AD showed no improvement (57). A large federal study designed to examine the beneficial effects of a combined estrogen/progestin therapy was recently halted because of the increased risk of breast cancer, stroke, and heart disease observed in women taking HRT (93). Numerous possible mechanisms exist through which estrogen could protect against AD including its antioxidant properties (74), but with the latest clinical trial findings, research in this area will necessarily proceed with caution.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS Inflammation is one of the abnormalities detected in AD brains and is evidenced by the neurotoxic properties of prostaglandins, the cytokines that are released during inflammatory reactions. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins, and several case-control and cross-sectional studies have reported a lower risk of AD with reported NSAID use (8). In the Baltimore Longitudinal Study of Aging, use of NSAID was associated with reduced risk of AD, which was further decreased with increasing duration of NSAID use (84). However, the role of anti-inflammatory drugs in AD is unclear. A recent study found prednisone, another anti-inflammatory/immunosuppressive drug, ineffective in preventing cognitive decline in a randomized controlled trial of 138 people. Subjects in the prednisone treatment group showed a cognitive decline similar to subjects in the placebo group (1).

METAL EXPOSURE The neurotoxicity of iron, aluminum, and other metals and their role in catalyzing free radicals has led to research on the risk of exposure to metals for development of AD but with inconsistent results (14). Elevated concentrations of iron and aluminum in AD brains suggest that some alteration in the homeostasis of these metals could influence AD (14). However, studies examining relationships between aluminum in drinking water, aluminum powder, and other aluminum-containing products and AD are inconclusive, with some reporting negative and others showing positive associations (72).

INTERACTIONS OF RISK FACTORS Similar to results of studies on cardiovascular disease, recent research suggests that interactions between identified factors, particularly gene-environment interactions, are important in cognitive decline and development of dementia (13). One study found that women with an $\varepsilon 4$ allele were at much greater risk of AD compared to men with an $\varepsilon 4$ allele (9). Another study found that men, but not women, with variant genotypes for myeloperoxidase, an antimicrobial enzyme agent, and ApoE $\varepsilon 4$ had increased AD risk (71). Other studies have found that ApoE genotype interacts with several other risk factors to increase risk of AD, including ethnicity (85), diabetes (68), and several dietary factors (9, 55).

LIFESTYLE FACTORS THAT MAY HELP PREVENT AD

In general, health behaviors cluster together, and when an individual becomes aware of the effect that personal behaviors can have on health, that awareness may be reflected in numerous areas of living. For example, a person who increases physical activity may also improve other health behaviors, such as improving diet and reducing stress. Indeed, a healthy lifestyle may be the important factor, rather than specific behaviors, since these behaviors frequently work synergistically in maintaining health.

Studies on health behaviors have shown that adherence to healthy lifestyles, such as eating a vegetarian diet, eating fruits and vegetables, being physically active, not smoking, and maintaining optimum levels of blood pressure, blood cholesterol, and weight, reduces mortality (23). Further, evidence suggests that in people with healthy lifestyles, disability is delayed and compressed into fewer years at the end of life (89). Diseases positively influenced by health behaviors include vascular disease, coronary heart events, diabetes, and strokes, all of which are associated with AD. Therefore, adherence to a healthy lifestyle may affect AD directly or indirectly by preventing these diseases.

Research on healthy lifestyles is difficult. First, the health variables examined may be, in part, surrogates for other, unmeasured variables. Individuals who develop healthy habits may be different in numerous ways—physically, mentally, and perhaps spiritually—from those who do not develop healthy habits. Yet, the effect of the measured variables is often quite strong and therefore is unlikely to be due solely to confounding by other variables.

Second, diet features predominantly in the cascade of healthy lifestyle factors, and dietary measures are subject to numerous biases. Misclassifications in dietary assessments can be caused by an incomplete nutrient database, poor data quality, and deficits in the respondents' memories (91). Some of these shortcomings may be remedied as valid and reliable dietary biomarkers are identified, but many large cohort studies rely solely on self-report dietary data.

Third, much of the research in the area of healthy lifestyle factors is epidemiological, with few trials assessing long-term benefits of these behaviors. Primary prevention trials are especially cumbersome because of the long follow-up needed to detect disease incidence, the difficulty of implementing and maintaining behavioral lifestyle change, and the potential confounding by individual, community, and societal factors.

Some of the major aspects of a healthy lifestyle that we examine include diet, physical activity, and stress along with protection from head injuries and maintaining cognitive stimulation. Each of these factors has multiple components. For example, a healthy diet is comprised of numerous factors, including low intake of saturated fat and cholesterol; high intake of antioxidant-rich foods, fruits, vegetables, and whole grains; combined with adequate water consumption. Although examination of individual effects of each factor is limited since the behaviors likely occur in tandem, the following sections summarize some of these results.

Healthy Diet

Research supports diet as one of the most important factors in the incidence of several diseases and as a primary factor in increasing life expectancy (7). Improving dietary intake may affect AD prevalence directly, through intake of antioxidant-rich and low-cholesterol foods, and indirectly, through preventing other AD risk factors, such as high blood pressure, high cholesterol, and diabetes.

ANTIOXIDANTS Antioxidant nutrients include vitamin E, vitamin C, and beta-carotene. These nutrients help protect the body from oxidative damage by neutralizing free radicals, combining with the oxidative products and thereby breaking chain reactions, repairing or replacing molecules damaged by the radicals, and chelating transition metal catalysts (75). The oxidative damage observed in AD brains and the effects of antioxidant nutrients in decreasing oxidative damage in laboratory studies of brain tissue suggest that antioxidant intake could play a role in preventing AD (47).

Several cross-sectional studies have found lower serum levels of antioxidants, including alpha tocopherol (vitamin E) and ascorbic acid (vitamin C) in persons diagnosed with AD compared with control subjects (34). However, this may reflect, in part, reduced vitamin intake associated with the disease. Prospective studies provide somewhat stronger evidence, although many of these studies rely on self-report data. In the Rotterdam study cohort, adults who reported higher intake at baseline of foods rich in vitamins E and C had lower incidence of AD and other dementias (19). This relationship was most pronounced among smokers. The Chicago Health and Aging Project found that increased vitamin E intake from foods and not from supplements, was associated with decreased risk for developing AD, and this association occurred only in individuals who did not have an *ApoE ε4* allele (55). The Honolulu-Asia Aging study, which examined only supplemental and not dietary antioxidant intake, found that men who reported taking vitamin E and C supplements at baseline were less likely than those who did not take supplements to develop vascular dementia, but had no reduction in the risk of AD (50). An antioxidant intervention study found that for patients with moderately severe AD, vitamin E (1200 IU twice daily) intake and selegiline intake each delayed death, institutionalization, disease progression, or loss of daily living activities, but did not improve memory (75).

Studies of antioxidant intake are difficult for several reasons. First, antioxidant studies have variability in what they measure and how they measure it. Some studies measure antioxidants in serum, others measure amounts in plasma, and most have only self-report measures. Many studies do not assess both dietary and supplemental antioxidant intake, and studies with both types of data often do not analyze them separately. Second, intervention studies use different amounts and combinations of antioxidants, making comparisons across studies difficult. Third, many of the supplements taken by individuals and used in clinical trials differ in their ingredients. For example, the vitamin E supplements used in intervention studies have largely been made from synthetic vitamin E, which frequently includes only the alpha-tocopherol form of vitamin E. Other tocopherols may be more efficient in crossing the blood-brain barrier (70). Fourth, the older age and disease state of the subjects in many studies may be associated with neurologic damage that is too great for increases in antioxidant intake to stabilize or improve the condition.

The results of the laboratory studies showing oxidative stress in AD, the positive influence of antioxidants in reducing oxidative damage, and the studies showing

an association between varying components of antioxidant intake and AD support evaluation of the effectiveness of antioxidants on preventing AD. The National Institute on Aging is currently supporting several large clinical trials to examine the usefulness of vitamin E, vitamin C, selenium, beta-carotene, folate, multivitamins, and various combinations of these supplements in reducing the risk of cognitive decline and preventing AD.

GOOD FAT/BAD FAT The role of dietary fat in AD is complicated by lack of consensus among researchers regarding numerous aspects of the relationship between fat intake and health. For over 25 years, almost every national health organization has advocated low-fat diets yet much is unknown about the effects of fats versus carbohydrates, unsaturated versus saturated fat, good cholesterol (high-density lipoprotein) versus bad cholesterol (low-density lipoprotein), and cholesterol versus triglycerides on health outcomes. Fortunately, several large studies are under way to examine these areas. In the meantime, speculations abound regarding these effects on cognitive health.

Research studies have found that diets high in saturated and monosaturated fats (aka bad fat) are associated with worse cognitive decline (66), whereas diets high in unsaturated fat (aka good fat) and low in saturated fat are associated with better cognitive function (40). Animal studies show that membrane lipid composition can be altered by dietary fats, and bad fats increase levels of cholesterol in serum and the brain (64). Higher intakes of omega-3 long-chain polyunsaturated fatty acids (LCPUFA) appears to protect against thrombosis, inflammatory responses, high blood pressure, and insulin sensitivity (40). Two longitudinal cohort studies, the Zutphen Elderly Study and the Rotterdam Study, showed that high fish intake, which contains high levels of LCPUFA, was associated with reduced risk of dementia, particularly AD (Rotterdam) (40) and tended to be associated with reduced risk of cognitive decline (Zutphen) (38). LCPUFA intake may be associated with cognitive function and AD through prevention of vascular disease and diabetes or more directly through altering the lipid composition of the brain membrane, as has been seen in animal studies (61).

CHOLESTEROL A low-cholesterol diet is recommended to prevent numerous diseases, including heart disease, and may also prevent AD, through stopping the deleterious effect of high cholesterol on brain function, or through averting vascular disease. However, much of the early research may have missed the connection between cholesterol and AD because of a crossover effect described by Notkola et al. (62). In their research, high-serum cholesterol during midlife and early old age was associated with development of AD, but serum cholesterol levels dropped during the early stage of the disease, in most cases before manifestation of symptoms (62). This could explain the inconsistent findings in cross-sectional studies where all measurements occurred around the same time, possibly missing the increased and then decreased cholesterol levels as AD progresses. This crossover effect, whereby patients with AD actually had declining cholesterol levels, indicates that

recommendations for cholesterol-lowering diets or drugs for individuals who are already manifesting AD symptoms may be ill-advised. Although, to our knowledge, no clinical trials are exploring the effects of dietary cholesterol lowering on AD, several clinical studies are investigating the effects of cholesterol-lowering drugs on cognitive decline.

VITAMIN B AND FOLATE Speculations about the role of B vitamins and folate in AD have been fueled by the findings previously mentioned that high levels of homocysteine are associated with AD. Vitamin B6, vitamin B12, and folate are cofactors with homocysteine in enzymes, catalyze reactions, and recycle homocysteine back to methionine. Since vitamins B6 and B12 and folic acid can lower homocysteine levels, consuming more of these nutrients could possibly protect against AD (76). The AD Cooperative Study is conducting a clinical trial to determine the effect of folate and vitamins B6 and B12 supplementation on slowing cognitive decline in patients with AD. In addition to supplements, dietary approaches can also affect homocysteine levels, as evidenced by the DASH (Dietary Approaches to Stop Hypertension) study whereby consumption of a diet rich in fruits and vegetables, whole grains, beans, and low-fat dairy products lowered plasma homocysteine levels (51). Additional research examining the relationship between homocysteine, the B vitamins, and folate in AD is needed, along with studies examining the potential benefit of increasing folic acid and vitamin B intake through foods or supplements, on AD prevention.

Physical Activity

Increased physical activity is associated with reduced risk of numerous chronic diseases, including heart disease, stroke, and cancer of the breast and colon (61). Several large population studies have shown that higher physical activity increases life expectancy by 2 to 5 years (22), and a recent study found that older women with higher levels of physical activity during the 6 to 8 years of follow-up were less likely to develop cognitive impairment (94). Several case-control studies suggest that low physical activity is a risk factor for AD. In one case-control study, cases were more likely than controls to consider themselves less physically active than their same age peers for 10 or more years prior to enrollment in the study (10). A second case-control study determined that increased physical activities, such as participation in sports, exercising, and walking, during midlife were associated with reduced risk for AD (24). Recent support for a protective effect of physical activity on AD comes from the Canadian Study of Health and Aging, a longitudinal study that found that regular physical activity in cognitively-normal older adults was associated with reduced risk of AD at the 5-year follow-up assessment (48).

Direct and indirect mechanisms could explain a protective effect of physical activity on development of AD. Although in case-control studies, inactivity may reflect the early effects of the disease, longitudinal studies supporting a protective role suggest that other explanations merit consideration. Physical activity may

affect AD directly by increasing cerebral blood flow and stimulating neuronal growth or through affecting lipid, hormone, and insulin levels and the immune system (73). Additionally, physical activity is related to reduced risk for hypertension and obesity (24), two conditions implicated in AD. The large body of evidence verifying a protective role of physical activity in preventing chronic diseases suggests that explorations of biological mechanisms to explain this relationship are needed, along with examinations of physical activity variables in longitudinal studies.

Stress Management

Although the effects of stress have received little attention as a risk factor for AD, stress has a consistent negative effect on hypertension and heart disease (65). Several animal studies suggest that chronic stress may be a risk factor for cognitive decline and AD (54), and a small study of older men indicates that traumatic life events at early ages are associated with an increased incidence of AD (69).

Although research in this area is scant, numerous plausible biological mechanisms support a possible relationship between stress and AD. The sympathetic, neuroendocrine, and immune systems can over respond to chronic stress, which adversely affects brain function in animals (25). Elevated levels of cortisol, a hormone with augmented production in response to stress, have increased the risk of cognitive decline in humans (41), supported by the relationship observed between high cortisol levels and atrophy in the hippocampal area of the brain (49). Stress may cause this hippocampal damage or it may affect hormonal activities, immune functioning, or vascular factors, all of which are suspected of playing a role in AD. These mechanisms, combined with the growing interest in similarities between AD and other chronic diseases, indicate the need for further research into the role of chronic stress in development of AD.

Protection from Head Injury

Traumatic brain injury (TBI) is highest in adolescents and young adults (15–24 years) and older adults (>75 years) (33). The primary causes of all TBIs are motor vehicle, bicycle, or pedestrian-vehicle accidents; however, among the frail elderly, the second most frequent cause of TBI is falls (3). Head injury prevention strategies for adolescents and young adults, such as mandated motorcycle helmet use; promotion of helmet use in bicycling, skateboarding, and skiing; and efforts to alert sports participants of the dangers of boxing and heading the ball in soccer may help prevent AD in later life (3).

Cognitive Activity

The Religious Orders Study, a longitudinal study that examined the effects of cognitive activity on development of AD, found that compared with nuns, priests, and monks in the lowest 10% of cognitive activity, those who were in the upper 10% of cognitive activity were 47% less likely to develop AD. This study suggests

that individuals can directly affect their ability to retain their thinking capacity into old age by engaging in intellectual activities throughout life (92). However, these results need to be replicated in other longitudinal studies. Although research in this area is still preliminary, the Institute for the Study of Aging recommends that education begin early and that learning continue into old age to maintain cognitive health (33).

NO EASY ANSWERS

Research indicates that there are no easy answers to determining how to prevent AD. In addition to the questions mentioned in the discussion above of risk factors and potential prevention factors for AD, studies up to this point allow us to speculate on a few questions:

Will AD Prevention be Multifaceted?

Similar to what is known about risk for stroke, cardiovascular disease, and cancer, prevention of AD will likely require modifications in numerous aspect of life, including diet, physical and cognitive activity, and other behavioral factors. Studies of populations who have healthy lifestyles, such as the Amish and Seventh-Day Adventists, show lower rates of all chronic diseases, and interventions to improve lifestyle behaviors are effective in reversing heart disease (65). However, we have no definitive evidence yet of the role of lifestyle behaviors and AD. Although several clinical trials are under way to examine the benefit of pharmacologically treating conditions and diseases associated with AD, such as high cholesterol, high blood pressure, and heart disease, no trials on dietary interventions, to our knowledge, are being conducted. Further, it is possible that without changing dietary patterns underlying the conditions associated with AD, pharmacological treatments may have less effect than if coupled with improved dietary intake.

When Should AD Prevention Begin?

Although dietary factors in very early life are difficult to ascertain, recent longitudinal studies that collected risk factor data decades prior to disease onset support the hypothesis that risk factors in midlife and earlier, including hypertension, high cholesterol, low cognitive activities, and diabetes, are associated with subsequent development of AD (62, 78, 92). A few studies suggest that exposure to risk factors as early as the prenatal period and early childhood may affect AD outcome (28). Because the neurodegenerative processes in AD appear to begin long before cognitive decline is evident, effective preventive efforts, such as practicing good dietary habits and staying physically and cognitively active, will probably need to begin early in life.

Several of the lifestyle factors examined in this paper may have long-term, rather than short-term, protective effects on AD. For example, if the protective effects of physical activity are operating indirectly through prevention of cardiovascular or

cerebrovascular disease, participation in a short-term intervention may be ineffective. Similarly, interventions started after the disease process has manifested may be less effective than those initiated early in life. However, research in heart disease prevention provides some optimism in the utility of changing lifestyle behaviors after disease onset, since intensive lifestyle changes adapted by participants in the Lifestyle Heart Trial resulted in regression of coronary atherosclerosis and fewer cardiac events, compared to the controls (65).

Should AD Preventive Efforts be Targeted to Specific High-Risk Groups?

The diversity and heterogeneity of the world's population support the probability that risk factors will not operate in the same manner in different high-risk groups. Although research examining risk-factor interactions for AD is still preliminary, some of the observed interactions suggest that prevention interventions may be most effective in individuals at high risk for the disease. For example, although a particular aspect of a healthy lifestyle may not reduce risk of AD in all people, individuals who possess additional risk factors, such as the *ε4* allele, or who have other chronic diseases, such as diabetes or vascular disease, may receive increased protection from preventive efforts.

Even If a Healthy Lifestyle Helps Prevent AD, How Do We Change Behavior and Maintain This Change?

Initiating and maintaining behavior change is difficult. Even with diseases that have devastating and immediate results, such as AIDS, where specific behaviors are associated with disease, efforts to change behavior have been challenging. After identifying modifiable risk factors for AD, such as those involved in a healthy lifestyle, how do we get people to change their behaviors? What individual, family, community, and societal factors influence individual change, and how are these factors influenced? Understanding this extremely important area is pivotal to developing and implementing effective disease prevention programs.

The Task Force on Community Prevention Services has published a guide that reviews and recommends interventions designed to promote health and prevent disease (86); their website (http://www.thecommunityguide.org) provides systematic reviews and evidenced-based recommentations. As results are published from the studies currently examining interventions for AD, this guide may be valuable in developing successful community health programs, products, and services that are specific to AD prevention.

CONCLUSION

Much of what is proposed in this paper uses the public health paradigm of expanding risk factors research from one chronic disease to another, building on studies to date. AD research has greatly expanded our knowledge of the disease, its causes,

and possible preventative approaches; however, more research is clearly needed in these areas. We have posed questions and offered hypotheses for lifestyle factors that may be associated with AD and advocate for promotion of healthy lifestyle, which may directly reduce AD incidence and will positively influence numerous other chronic disease, including several that are associated with AD.

The large number of modifiable risk factors for AD indicates that even if several risk factors are not modifiable, individuals can reduce their risk of the disease through improving lifestyle behaviors. Similarly, the probable interactions between genetic and environmental factors suggest that individuals who are at high risk for disease owing to one risk factor may modify behaviors, such as dietary intake and exercise, to counter those risks. Because it appears that prevention of AD is a lifelong process, these health behaviors need to be maintained throughout life, rather than adopted after the disease begins to manifest. Educational interventions on the effects of healthy lifestyle on AD will need to stimulate behavioral change to reduce an individual's risk for AD; however, they will also need to raise awareness among parents and grandparents about the importance of healthy lifestyles, so that children develop and maintain healthy behaviors throughout life.

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LITERATURE CITED

1. Aisen PS. 2000. Anti-inflammatory therapy for Alzheimer's disease: implications of the prednisone trial. *Acta Neurol. Scand.* 176:85–89
2. Alves de Moraes S, Szklo M, Knopman D, Park E. 2001. Prospective assessment of estrogen replacement therapy and cognitive function. *Am. J. Epidemiol.* 154:733–39
3. NIH Consensus Development Panel. 1999. Rehabilitation of persons with traumatic brain injury. *JAMA* 282:974–83
4. Asthana S, Baker LD, Craft S, Stanczyk FZ, Veith RC, et al. 2001. High-dose estradiol improves cognition for women with AD: results of a randomized study. *Neurology* 57:605–12
5. Barrett-Connor E, Kritz-Silverstein D. 1993. Estrogen replacement therapy and cognitive function in older women. *JAMA* 269:2637–41
6. Behl C. 1999. Alzheimer's disease and oxidative stress: implications for novel therapeutic approaches. *Prog. Neurobiol.* 57:301–23
7. Bowen DJ, Beresford SAA. 2002. Dietary interventions to prevent disease. *Annu. Rev. Public Health* 23:255–86
8. Breitner JCS, Welsh KA, Helms MJ, Gaskell PC, Gua BA, et al. 1995. Delayed onset of Alzheimer's disease with nonsteriodal anti-inflammatory and histamine H2 blocking drugs. *Neurobiol. Aging* 16:523–30
9. Bretsky PM, Buckwalter JG, Seeman TE, Miller CA, Poirier J, et al. 1999. Evidence for an interaction between apolipoprotein E genotype, gender, and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 13:216–21
10. Broe GA, Henderson AS, Creasey H, McCusker E, Korten AE, et al. 1990. A case-control study of Alzheimer's disease in Australia. *Neurology* 40:1698–707
11. Canadian Study of Health and Aging. 1994. Canadian study of health and aging-study

methods and prevalence of dementia. *Can. Med. Assoc. J.* 150:899–913
12. Carr DB, Goate A, Phil D, Morris JC. 1997. Current concepts in the pathogenesis of Alzheimer's disease. *Am. J. Med.* 103:3S–10S
13. Chandra V, Pandav R. 1998. Gene-environment interaction in Alzheimer's disease: a potential role for cholesterol. *Neuroepidemiology* 17:225–32
14. Christen Y. 2000. Oxidative stress and Alzheimer disease. *Am. J. Clin. Nutr.* 71: 621S–9S
15. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. 1998. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer's disease. *Arch. Neurol.* 55:1449–55
16. Corrada M, Brookmeyer R, Kawas C. 1995. Sources of variability in prevalence rates of Alzheimer's disease. *Int. J. Epidemiol.* 24:1000–5
17. Cummings JL, Vinters HV, Cole GM, Khachaturian ZS. 1998. Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology* 51:S2–17
18. de Bree A, Verschuren WMM, Blom HJ, Kromhout D. 2001. Lifestyle factors and plasma homocysteine concentrations in a general population sample. *Am. J. Epidemiol.* 154:150–54
19. Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, et al. 2002. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* 287:3223–29
20. Evans DA. 1990. Estimated prevalence of Alzheimer's disease in the United States. *Milbank Q.* 68:267–89
21. Evans DA, Beckett LA, Field TS, Feng L, Albert MS, et al. 1997. Apolipoprotein E epsilon 4 and incidence of Alzheimer disease in a community population of older persons. *JAMA* 277:822–24
22. Ferrucci L, Izmirlian G, Leveille S, Phillips CL, Corti MC, et al. 1999. Smoking, physical activity, and active life expectancy. *Am. J. Epidemiol.* 149:645–53
23. Fraser GE, Shavlik DJ. 2001. Ten years of life: Is it a matter of choice? *Arch. Intern. Med.* 161:1645–52
24. Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, et al. 2001. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc. Natl. Acad. Sci. USA* 98:3440–45
25. Fuchs E, Uno H, Flugge G. 1995. Chronic psychosocial stress induces morphological alterations in hippocampal pyramidal neurons of the tree shrew. *Brain Res.* 673:275–82
26. Gatz M, Svedberg P, Pederson NL, Mortimer JA, Berg S, et al. 2001. Education and the risk of Alzheimer's disease: findings from the study of dementia in Swedish twins. *J. Gerontol. B Psychol. Sci. Soc.* 56B:P292–300
27. Graves AB, Larson EB, Edland SD, Bowen JD, McCormick WC, et al. 1996. Prevalence of dementia and its subtypes in the Japanese American population of King County, Washington State. *Am. J. Epidemiol.* 144:760–71
28. Graves AB, Mortimer JA, Bowen JD, McCormick WC, McCurry SM, et al. 2001. Head circumference and incident Alzheimer's disease. *Neurology* 57:1453–60
29. Grodstein F, Manson JE, Stampfer MJ. 2001. Postmenopausal hormone use and secondary prevention of coronary events in the nurses' health study. A prospective, observational study. *Ann. Intern. Med.* 135:1–8
30. Heininger K. 2000. A unifying hypothesis of Alzheimer's disease. III. Risk factors. *Hum. Psychopharmacol. Clin. Exp.* 15:1–70
31. Hendrie HC, Ogunniyi AO, Hall KS, Baiyewu O, Unverzagt FW, et al. 2001. Incidence of dementia and Alzheimer disease in 2 communities. Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. *JAMA* 285:739–47

32. Hofman A, Ott A, Breteler MMB, Bots ML, Slooter AJC, et al. 1997. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam study. *Lancet* 349:151–54
33. Institute for the Study of Aging. 2001. *Achieving and maintaining cognitive vitality with aging*. *Rep. A Workshop Report*, New York
34. Jeandel C, Nicolas MB, Nabet-Belleville F, Penin F, Cuny G. 1989. Lipid peroxidation and free radical scavengers in Alzheimer's disease. *Gerontology* 35:275–82
35. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman PA. 2000. Statins and the risk of dementia. *Lancet* 356:1627–31
36. Jorm AF. 1997. Alzheimer's disease: risk and protection. *Med. J. Aust.* 167:443–46
37. Jorm AF, Jolley D. 1998. The incidence of dementia. *Neurology* Sept.:728–33
38. Kalmijn S, Feskens EJM, Launer LJ, Kromhout D. 1997. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *Am. J. Epidemiol.* 145:33–41
39. Kalmijn S, Launer LJ, Lindemans J, Bots ML, Hofman A, et al. 1999. Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam study. *Am. J. Epidemiol.* 150:283–89
40. Kalmijn S, Launer LJ, Ott A, Witteman JCM, Hofman A, et al. 1997. Dietary fat intake and the risk of incident dementia in the Rotterdam study. *Ann. Neurol.* 42:776–82
41. Kalmijn S, Launer LJ, Stolk RP, de Jong FH, Pols HAP, et al. 1998. A prospective study in cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. *J. Clin. Endocrinol. Metab.* 83:3487–92
42. Kivipelto M, Helkala EL, Laakso MP, Hanninen T. 2001. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 322:1447–51
43. Kuller LH, Shemanski L, Manolio T. 1998. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke* 29:388–98
44. Kuusisto J, Koivisto K, Mykkanen L, Helkala EL, Vanhanen M, et al. 1997. Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. *BMJ* 315:1045–49
45. Last JM, ed. 1983. *A Dictionary of Epidemiology*. Oxford Univ. Press
46. Launer LJ, Ross GW, Petrovich H, Masaki K, Foley D, et al. 2000. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol. Aging* 21(1):49–55
47. Launer LJ, Kalmijn S. 1998. Anti-oxidants and cognitive function: a review of clinical and epidemiologic studies. *J. Neural Transm. Suppl.* 53:1–8
48. Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, et al. 2002. Risk factors for Alzheimer's Disease: a prospective analysis from the Canadian study of health and aging. *Am. J. Epidemiol.* 156(5):445–53
49. Lupien SJ, de Leon M, de Santi S. 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat. Neurosci.* 1:69–73
50. Masaki KH, Losonczy KG, Izmirlian G, Foley DJ, Ross GW, et al. 2000. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology* 54:1265–72
51. Massey LK. 2001. Dairy food consumption, blood pressure and stroke. *J. Nutr.* 131:1875–78
52. Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, et al. 1996. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. *Neurology* 45:555–57
53. Mayeux R, Ottman R, Tang MX, Noboa-Bauza L, Marder K, et al. 1993. Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and

their first-degree relatives. *Ann. Neurol.* 33:494–501

54. Meaney MJ, Aitken DH, van Berkel C, Bhatnagar S, Sapolsky RM. 1988. Effect of neonatal handling on age-related impairments associated with the hippocampus. *Science* 239:766–68
55. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, et al. 2002. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 287:3230–37
56. Mortimer JA, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, et al. 1991. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int. J. Epidemiol.* 20:S28–35
57. Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, et al. 2000. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. *JAMA* 283:1007–15
58. Munch G, Schinzel R, Loske C, Wong A, Durany N, et al. 1998. Alzheimer's disease-synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. *J. Neural Transm.* 105:439–61
59. National Institute on Aging/National Institutes of Health. 1997. *NIA: Progress Report on Alzheimer's Disease.* Washington, DC: NlA/NIH
60. Nicoll JAR, Mrak RE, Graham DI, Stewart J, Wilcock G, et al. 2000. Association of interleukin-1 gene polymorphisms with Alzheimer's disease. *Ann. Neurol.* 47:365–68
61. NIH Consensus Dev. Panel. 1996. Physical activity and cardiovascular health. *JAMA* 276(3):241–46
62. Notkola I, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, et al. 1998. Serum total cholestrol, apolipoprotein E&4 allele, and Alzheimer's disease. *Neuroepidemiology* 17:14–20
63. Oliver C, Crayton L, Holland A, Hall S, Bradbury J. 1998. A four year prospective study of age-related cognitive change in adults with Down's syndrome. *Psychol. Med.* 28:1365–77
64. Oner P, Bekpinar S, Oz B. 1991. Alterations in some lipid components and Ca^{2+} ATPase activity in brain of rats fed an atherogenic diet. *Res. Commun. Chem. Pathol. Pharmacol.* 72:337–45
65. Ornish D, Scherwitz LW, Billings JH, Gould KL, Merritt TA, et al. 1998. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* 280:2001–7
66. Ortega RM, Requejo AM, Andres P, Lopez-Sobaler AM, Quintas ME, et al. 1997. Dietary intake and cognitive function in a group of elderly people. *Am. J. Clin. Nutr.* 66:803–9
67. Ott A, van Rossum CT, van Harskamp F, van de Mheen H, Hofman A, et al. 1999. Education and the incidence of dementia in a large population-based study: The Rotterdam Study. *Neurology* 52:663–66
68. Peila R, Rodriguez BL, Launer LJ. 2002. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia aging study. *Diabetes* 51:1256–62
69. Persson G, Skoog I. 1996. A prospective population study of psychosocial risk factors for late-onset dementia. *J. Geriatr. Psychiatry* 11:15–22
70. Prasad KN, Cole WC, Hovland AR, Prasad KC, Nahreini P, et al. 1999. Multiple antioxidants in the prevention and treatment of neurodegenerative disease: analysis of biologic rationale. *Curr. Opin. Neurol.* 12:761–70
71. Reynolds WF, Hiltunen M, Pirskanen M, Mannermaa A, Helisalmi S, et al. 2000. MPO and APOEe4 polymorphisms interact to increase risk for AD in Finnish males. *Neurology* 55:1284–90
72. Rondeau V, Commenges D, Jacqmin-Gadda H, Dartigues JF. 2000. Relation between aluminum concentrations in drinking water and Alzheimer's disease: an

8-year follow-up study. *Am. J. Epidemiol.* 152:59–66

73. Ross GW, Petrovich H, White LR, Masaki KH, Li CY, et al. 1999. Characterization of risk factors for vascular dementia: the Honolulu-Asia aging study. *Neurology* 53:337–43
74. Rottkamp CA, Nunomura A, Hirai K, Syre LM, Perry G, et al. 2000. Will antioxidants fulfill their expectations for the treatment of Alzheimer's disease? *Mech. Ageing Dev.* 116:169–79
75. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, et al. 1997. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N. Engl. J. Med.* 336:1216–22
76. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, et al. 2002. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N. Engl. J. Med.* 346:476–83
77. Skoog I, Kalaria RN, Breteler MBM. 1999. Vascular factors and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 13:S106–114
78. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, et al. 1996. 15-year longitudinal study of blood pressure and dementia. *Lancet* 347:1141–45
79. Sloan PD, Zimmerman S, Suchindran C, Reed P, Wang L, et al. 2002. The public health impact of Alzheimer's disease, 2000–2050: potential implication of treatment advances. *Annu. Rev. Public Health* 23:213–31
80. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, et al. 1997. Brain infarction and the clinical expression of Alzheimer disease. The Nun study. *JAMA* 277:813–17
81. Sparks DL, Martin TA, Gross DR, Hunsaker JCI. 2000. Link between heart disease, cholesterol, and Alzheimer's disease: a review. *Microsc. Res. Tech.* 50:287–90
82. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, et al. 2000. Relationship of baseline serum cholestrol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA* 284:311–18
83. Stewart R. 2000. Risk factors for dementia. *Alzheimer's Dis. Int. Fact Sheet* 9:1–2
84. Stewart WF, Kawas C, Corrada M, Metter EJ. 1997. Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 48:626–32
85. Tang M, Stern Y, Marder K, Bell K, Gurland B, et al. 1998. The APOE-e4 Allele and the risk of Alzheimer disease among African Americans, Whites, and Hispanics. *JAMA* 279:751–55
86. Truman BI, Smith-Akin CK, Hinman AR, Gebbie KM, Brownson R, et al. 2000. Developing the guide to community preventive services—overview and rationale. *Am. J. Prev. Med.* 18(1S):18–26
87. U.S. Dep. Health Hum. Serv. 1996. Characteristics, epidemiology, and costs. In *Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias*, pp. 17–30. Rockville, MD: Agency for Health Care Policy Res.
88. Uryu K, Laurer H, McIntosh T, Pratico D, Martinez D, et al. 2002. Repetitive mild brain trauma accelerates Abeta deposition, lipid peroxidation, and cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis. *J. Neurosci.* 22:446–54
89. Vita AJ, Terry RB, Hubert HB, Fries JF. 1998. Aging, health risks, and cumulative disability. *N. Engl. J. Med.* 338:1035–41
90. White L, Petrovich H, Ross GW, Masaki KH, Abbott RD, et al. 1996. Prevalence of dementia in older Japanese-American men in Hawaii. *JAMA* 276:955–60
91. Willett W. 1998. Food-frequency methods. In *Nutritional Epidemiology*, pp. 74–94. New York: Oxford Univ. Press
92. Wilson RS, Mendes de Leon CF, Barnes LL, Schneider JA, Bienias JL, et al. 2002. Participation in cognitively stimulating

activities and risk of incident Alzheimer disease. *JAMA* 287:742–48

93. Writing Group for the Women's Health Initiative Investigators. 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized controlled trial. *JAMA* 288:321–33
94. Yaffe K, Barnes D, Nevitt M, Lui L, Covinsky K. 2001. A prospective study of physical activity and cognitive decline in elderly women. *Arch. Intern. Med.* 161:1703–8

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