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Prevention Strategies for Alzheimer's Disease

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PUBLIC HEALTH IMPORTANCE AND PREVENTION

In the past century, life expectancy has increased more than 27 years. As the number of elderly persons has dramatically increased, Alzheimer's disease (AD) has become one of the major public health problems in the United States and the entire developed world. The "prevalence and malignancy of AD," as described in a two-page editorial written in 1976 by Dr. Robert Katzman (1), has become well known to physicians as well as the lay public. In the editorial, Katzman estimated the prevalence and mortality due to AD, and placed AD as a leading cause of death in the United States. Hebert has shown that the impact of AD will be ever more dramatic over the next 50 years as the numbers of very elderly in the population rise at an accelerated rate (2). Projecting age-specific prevalence data for AD to the population distributions obtained from the U.S. Census Bureau, there were 4.5 million cases of AD in the United States in the year 2000 and there will be 13.2 million in the year 2050.

At present, AD is the third most expensive disease in the United States costing approximately $100 billion each year (3). Patients suffering from AD eventually become completely dependent and rely on relatives for care or are placed in nursing homes. Costs for the disease thus include direct (nursing home care, hospitalizations, physician visits, social services including adult day care, and medications) as well as indirect costs (loss of productivity and premature death). Given the increasingly aging population, the costs associated with the disease will certainly grow and will very likely make AD the most expensive disease in the United States within the next decades. Preventing or even delaying the onset of the disease will certainly have an enormous impact on society.

Considerable attention has been given to primary prevention strategies such as the so-called "vaccinations" for AD that rely on antibodies to amyloid β (Aβ), or drugs that act as inhibitors of β- and γ- secretase (anti-amyloid therapies, see Chap. 25 by Dr. D. Selkoe). However, despite potential promise for the future with these approaches, it may be that compounds already in existence can also serve to significantly reduce the age-associated incidence of AD. This chapter summarizes some of these promising approaches, including several that are currently being investigated in randomized clinical trials.

TYPES OF PREVENTION

Opportunities for prevention of AD can be illustrated within a model of AD as a chronic disease (Fig. 1) (4). Although this model describes a continuous process, three stages can be identified that explain conceptually different events throughout the disease process. In a chronic disease, there is typically an initial latent period, which may even last for several decades, before any clinical symptoms are evident. During this stage the pathologic process is initiated, likely due to one or more initiating factors. In AD, diffuse and neuritic plaques may begin to appear during this early stage of the disease (5). In the later prodromal (or preclinical) stage, mild clinical symptoms begin to appear as the disease process continues. During this stage, events leading to the development of neuritic degeneration, neurofibrillary tangles, and synaptic loss also begin. In the final expression (or clinical) stage, damage to the brain accumulates to such a degree that clinical symptoms are clearly evident in the form of cognitive and functional disability severe enough to warrant a diagnosis of Alzheimer's Dementia.

These different stages of the Alzheimer's disease process provide a variety of opportunities for intervention in the hopes of halting or altering the natural progression of the disease. *Primary prevention* strategies would act during the early latent stage to eliminate or reduce exposure to factors in order to prevent the transition into the pathologic process. *Secondary prevention* would act during the prodromal stage to delay the clinical manifestation of the disease. Finally, *tertiary prevention* would be applied during the expression stage of the disease in hopes of slowing or halting the progression of the dementia severity. When considering the utility of compounds for the "prevention" of AD in this model, it is crucial to remember that drugs or interventions that have a role in one stage of prevention may have no effect on other stages. For example, approaches that are useful for preventing the occurrence of strokes (anti-hypertensive drugs, cholesterol lowering agents, etc.) are of little utility for the tertiary prevention or treatment of the stroke once it has occurred. Similarly, it is likely that the primary and secondary prevention of AD will require different strategies than ones that may be useful for tertiary prevention (treatment). Studies that have suggested that certain compounds may be useful for the treatment of AD (6–16), do not give us clues regarding the potential utility in primary prevention. The biological processes that are targeted by any particular agent may no longer be operative once the disease process has reached these later stages.

Current available treatments for AD act only during the expression phase, and thus deal with tertiary prevention. The only FDA-approved drugs that are currently available for treating the primary symptoms of AD are aimed at symptomatically improving cognition or functional

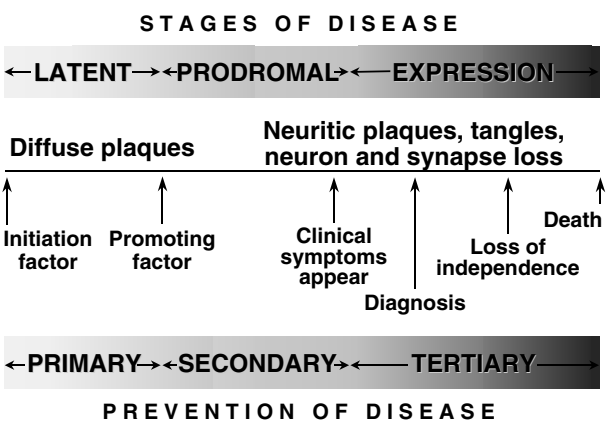

Figure 1 Alzheimer's disease as a chronic disease. *Source*: Adapted from Ref. 4.

ability (see Chap. 23 by Dr. M. Farlow). It is not known whether these drugs may also slow down the pathological progression of the disease. Moreover, the demonstrated effects of these drugs have been modest. This symptomatic approach may help maintain the overall intellectual ability of the patient for a period of time, however, if these drugs do indeed affect disease progression and mortality, they may in the long run extend the duration of the disease, thus increasing its prevalence. The other available treatments for AD deal with relief of behavioral symptoms such as aggression, hallucinations, depression, irritability, and delusions (see Chap. 24). This type of therapy is beneficial in terms of maintaining the quality of life of patients and caregivers, but again, acts only after the disease is clinically evident. Secondary prevention is also not ideal because it, too, is based on altering a disease process already established. In the long run, the opportunity for primary prevention of AD is considerably more appealing to the individual and to public health than are symptomatic therapies that may prolong the illness and hence actually increase the burden of disease. Primary prevention thus seems like the most effective course of action since it deals with preventing or slowing down the pathological process that will lead to expression of clinical symptoms.

There are three main types of observational study designs that are traditionally used in epidemiologic research when attempting to identify risk and protective factors in the development of a disease: case-control, cross-sectional, and cohort studies. Case-control studies are generally the first studies to be performed for the purpose of identifying risk or protective factors because they are generally conducted quickly and are relatively inexpensive. In cross-sectional studies, information about disease and exposure is obtained at a single point in time. Case-control studies and cross-sectional studies have similar disadvantages with respect to AD. While cost- and labor-efficient, these studies rely on recall of lifetime exposures. In the case of AD, this information is generally dependent on surrogate informants, such as spouses or children, who may not know the information of interest. Since case-control and cross-sectional studies consist of existing cases (prevalent cases), it is often difficult to interpret the results of these studies as it is unclear whether the exposure or the disease occurred first. A further complication may arise if physicians tend to prescribe certain medications more frequently if a subject is demented, which would result in an apparent increase in risk. Conversely, physicians may stop or not prescribe medications because a patient has dementia, which would result in an apparent decreased risk. To circumvent these problems, case-control or cross-sectional studies are generally followed by cohort studies. These investigations begin with participants that do not have the disease of interest and are followed up over time to identify newly diagnosed cases (incident cases). In these studies, exposure information is collected prospectively before the development of disease and is generally obtained uniformly for all members of the cohort and directly from the subjects themselves. These investigations provide invaluable information regarding potential agents, which can then be tested in clinical trials as preventive strategies against AD. In the following sections, we review these three types of studies but we concentrate on prospective investigations, that provide the strongest evidence short of a randomized clinical trial.

POTENTIAL PREVENTIVE INTERVENTIONS

Pharmacological Interventions

Over the past several years, certain factors have been described in numerous observational studies that may protect against the development of AD or may delay its onset. These potentially neuroprotective agents have been suggested as possible strategies that may be useful to delay or prevent the onset of AD. Potential agents have included hormonal replacement therapy, nonsteroidal anti-inflammatory drugs, antioxidants, folate, *Ginkgo biloba* and cholesterol-lowering agents. The evidence for each of these approaches is discussed below.

Estrogens

Potential mechanisms: Estrogens affect numerous biological processes relevant for brain health and for AD. Among other activities, they are known to affect regulation of acetylcholine and nerve growth factor, to exhibit antioxidant activity, to inhibit apolipoprotein E levels in plasma, and to affect vasculature. These potential mechanisms have been reviewed in several publications (17–19). Estrogens occur naturally in several forms, including estradiol, estrone, and estriol. Of these, estradiol has the highest potency at the receptor and may possibly be the most relevant for brain functioning. In the past, the most commonly prescribed form of estrogen replacement therapy consisted of conjugated equine estrogens (a mixture of numerous estrogens) without progestin. More recently, women with a uterus have been prescribed estrogen in combination with progestin. The effect of each of these preparations, however, may not be the same. The observational studies cited below generally grouped together all forms of estrogen.

Evidence from observational studies: Figure 2 shows the results from observational studies of estrogen use and AD that have been published to date. The results from many retrospective studies of estrogen and AD have been inconclusive. Two studies (20,21) found a statistically significant decrease in risk of AD with the use of estrogen replacement therapy. Other retrospective studies, however, have found a non-significant decrease in risk (22,23), no association (24,25) or a non-significant increase in risk (26,27). A cross-sectional study (28) has also looked at the association between use of estrogen and AD with results suggesting a protective effect of estrogen on AD.

In 1994, Paganini-Hill and Henderson (29) published the first study of estrogen and AD where information of estrogen use was collected prospectively. The authors studied a large cohort of women from the Leisure World retirement community and, using a nested case-control design, found that AD and related dementias in these women occurred less often in estrogen users relative to nonusers. Moreover, their study demonstrated both a dose and a duration effect, with the risk of AD decreasing with increasing dose and duration of estrogen use. Subsequently, several other prospective studies have found similar results. Greater protective effects of estrogen in postmenopausal women were also found in the North Manhattan Study (30), in the Baltimore Longitudinal Study of Aging (31), in studies performed with patients at the Mayo clinic (32), and in the Cache-County Study (33). Data from this last study also showed that increased duration of use afforded greater protection primarily in women with prior, rather than current, use. Not all prospective studies, however, have found the use of estrogens to be protective. Studies in the United Kingdom (34) and Canada (35) have failed to find an association.

In 1998, Yaffe and colleagues (17) performed a meta-analysis of all studies of ERT and AD that had been published up to that date. The authors did not find a significant reduction in risk when combining eight case-control studies [odds ratio (OR) = 0.80, 95% confidence interval (CI) = 0.5–1.28] but found a 52% reduction in risk of AD among estrogen users when they combined the results of two prospective studies (OR = 0.48, 95% CI = 0.29–0.81).

Although outside the scope of this chapter, estrogen has also been studied intensively in regards to cognitive performance (36–42), with several observational studies suggesting that it may enhance cognitive, particularly verbal abilities. Moreover, the improvement in cognition found in observational studies has been supported by a number of randomized clinical trials where the use of estrogens appeared to show improvements in certain cognitive abilities (43–45). Some observational studies (36,42) as well as randomized trials, however, (46–48) have failed to replicate the findings.

Anti-Inflammatory Drugs

Potential mechanisms: Neuritic plaques, a hallmark of AD pathology, have been associated with a host of proteins and acute-phase reactants, activated microglia, and complement

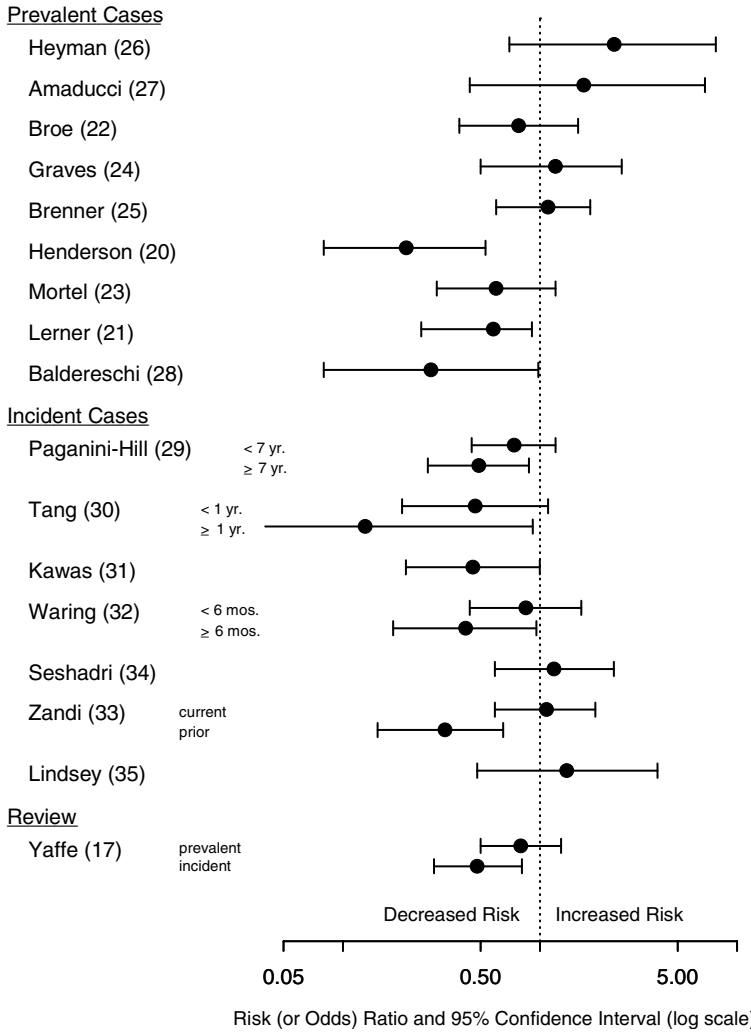

Figure 2 Observational studies of the effect of estrogen use on the risk of AD. *Abbreviations*: yr, year; mos, months.

activation, which are evidence of local inflammation. McGeer and colleagues (49,50) have extensively reviewed the biological mechanisms that link AD to inflammatory processes. From these observations, it follows that pharmacological suppression of inflammation may slow the rate of AD pathology. Anti-inflammatory drugs are inhibitors of the cyclooxygenase (COX) enzymes. Both isoforms of COX, COX1, and COX2, have been identified in the brain and have been suggested as potential targets for suppressing inflammatory reactions associated with AD. COX 1 is constitutive and its inhibition most likely mediates gastric and renal toxicities. COX 2 in most of the body is inducible, but appears to be constitutive in neurons. In addition, it has been noted to be upregulated in neurodegenerative models and in AD. It is not yet clear which of these isoforms is most relevant for the pathology associated with AD. Most anti-inflammatory drugs that have been available to date are non-selective inhibitors of both isoforms of the COX enzymes. However, selective COX 2 inhibitors have been developed recently and are also being tested in AD. More recently, an in vitro study observed that a subset of NSAIDs (ibuprofen, sulindac, and

indomethacin) were able to decrease levels of amyloidogenic Aβ-42 peptide in cultured cells, and that this effect was not mediated by COX activity inhibition (51). Subsequently, researchers from the Rotterdam study reported that the observed decrease in AD risk among NSAID users was restricted to that same subset of NSAIDs (52).

Evidence from observational studies: Since an initial observation by Jenkinson and colleagues (53), numerous epidemiological studies have reported a reduced risk of AD in patients with inflammatory diseases such as arthritis (22,54–56). It is not clear, however, whether these patients have a reduced risk because of the anti-inflammatory treatments taken for these conditions or whether persons with a predisposition, either genetic or environmental, to inflammatory diseases also have a predisposition toward a reduced risk of AD.

Many case-control and cross-sectional studies have looked at the association between use of steroids (24,55–57) or NSAIDs (56–60) and the risk of AD. In a review article by McGeer and colleagues (61), the combined odd ratios were estimated for case-control studies that looked at steroids or NSAIDs as protective factors for AD. For both types of studies the combined odds ratio indicated a significantly reduced risk among users of either steroids (combined OR = 0.66, 95% CI = 0.43–0.999) or among users of NSAIDs (combined OR = 0.50, 95% CI = 0.34–0.72). Figure 3 shows results from observational studies that have investigated AD and NSAID use.

Several prospective studies have also explored this association but not all have found a protective effect of NSAIDs against dementia or AD. In a population sample in southwest France, there was no difference in the risk of dementia between users and non-users of NSAIDs after a 2-year follow-up (62). Similarly, in a community survey conducted in Australia, no association was found between NSAID use and development of dementia after an average of 3.6 years of follow-up (63). A nested case-control study done at the Mayo clinic found a non-significant protective effect of NSAIDs among men and no effect among women (64).

Nonetheless, prospective studies with longer follow-up and larger numbers of subjects have tended to suggest a protective effect. Most studies that show an effect of NSAIDs on the risk of AD generally report about a 50% reduction in risk. In addition, most prospective studies have found increased protection against AD with increased duration of use. Subjects in the Baltimore Longitudinal Study of Aging (65) who had two or more years of exposure to NSAIDs, had approximately one-half the risk of AD than did subjects who reported no exposure, while subjects with less than two years of exposure had a non-significant reduced risk. This result was also demonstrated in a large population sample in the Netherlands, where exposure to NSAIDs was determined by pharmacy records (66). Subjects in this study who had taken NSAIDs for two or more years appeared to have a reduction in the incidence of AD while those who had used these drugs for less time did not show a reduction. Similar results with duration of use were found in the Cache County Study (67), where in addition former use was associated with a reduced risk of AD while current use was not. In 2003, Etminan and colleagues (68) performed a meta-analysis of nine observational studies of the effect of NSAIDs on AD published up to that date. The study found greater protection against AD with long term use [>2 years, relative risk (RR) = 0.27, 95% CI = 0.13–0.58] rather than intermediate use (<2 years, RR = 0.83, 95% CI = 0.65–1.06).

The effect of NSAIDs has also been examined in relation to cognitive decline in older persons. Some studies have reported an improvement in cognition with NSAID use (69,70) while others have found a significant worsening in cognition among users of NSAIDs (62,71).

Vitamins

B Vitamins

Potential mechanisms: Several potential mechanisms, some of which may be related to homocysteine, have been suggested to link the intake of B-vitamins, particularly folate, to the

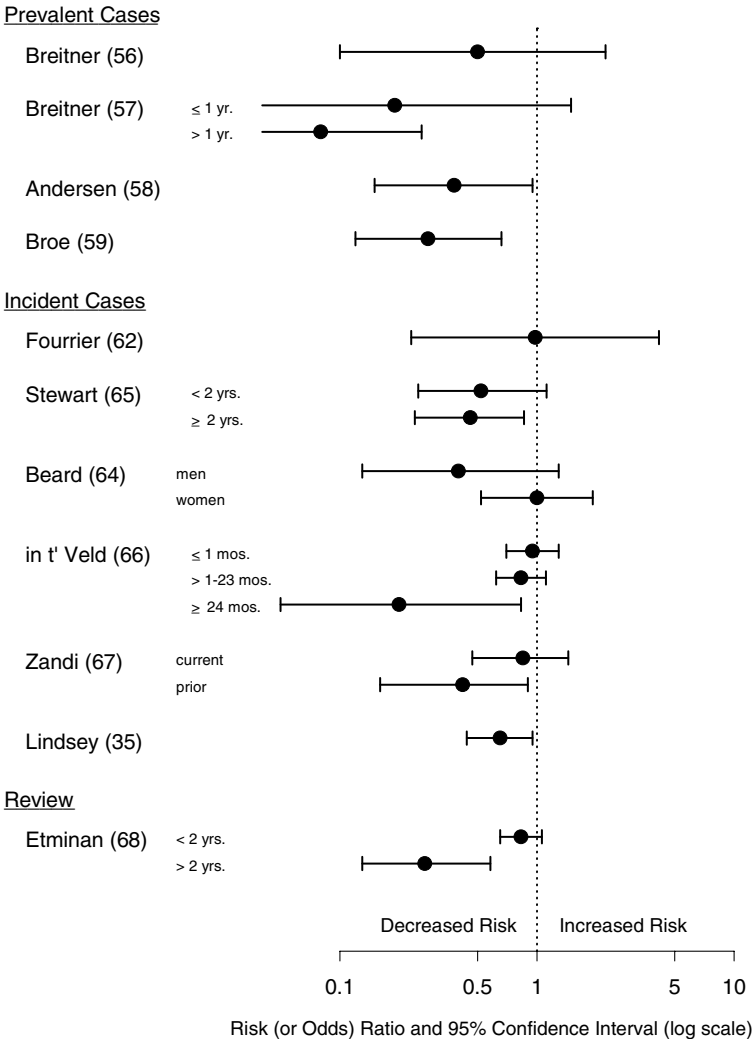

Figure 3 Observational studies of the effect of nonsteroidal anti-inflammatory drug use on the risk of AD. *Abbreviations*: yr, year; mos, months.

development of AD. Intake of folate and other B-vitamins is associated to homocysteine levels, a well-known risk factor for vascular disease (72–77). Studies that show a relation between vascular disease and AD (78–80) support the notion that homocysteine levels may contribute to vascular disease through a direct effect on vascular endothelial cells (81). However, even in the absence of significant cerebrovascular disease or atherosclerosis, homocysteine has been shown to be a risk factor in patients with neuropathologically confirmed AD (82). Non-vascular mechanisms have also been suggested to explain the link between folate intake and AD. Animal studies provide evidence that folic acid deficiency and homocysteine may be directly related to amyloid toxicity (83) or may cause direct toxicity to neuronal cells (84). Non-homocysteine mechanisms involving methylation reactions in the brain (85) have also been postulated to explain the association between folate intake and AD development. Of interest, two studies have associated atrophy in different areas of the brain to serum folate levels (86) or homocysteine levels, (82) but the mechanisms for these results are not known.

Evidence from observational studies: Most studies reporting on the association between AD and B-vitamins have looked at plasma or serum levels of the vitamins or homocysteine. In particular, one prospective study showed increased levels of plasma homocysteine as a strong risk factor for AD (87) and another smaller prospective study (88) found that subjects with low serum levels of folate or vitamin B12 had double the risk of an AD diagnosis 3 years later. Several small case-control studies (82,89–92) have also looked at this association. One of these studies reported a lower intake of folate in AD cases as compared to controls (92). To our knowledge, the only prospective study of the association between folate intake and AD is our own investigation in the Baltimore Longitudinal Study of Aging (93). In that study, subjects with a total folate intake (diet plus supplements) above the recommended dietary allowance (RDA) of 400 μg had a 55% decrease in risk compared to those below the RDA after an average follow-up of 9.3 years.

Antioxidants

Potential mechanisms: Free radicals are chemical species that play normal roles in the body's metabolism but can cause damage to the cell when present in excess. Antioxidants such as vitamin E, vitamin C, β-carotene, selenium, and α-lipoic acid, among others, can protect cells from damage by scavenging free radicals. When the balance between antioxidants and free radicals is broken in favor of free radicals, oxidative stress occurs. The effects of oxidative stress can accumulate over the years and could account in part for the late-life onset and the slowly progressive nature of AD and other neurodegenerative diseases. Moreover, aging itself is associated with a decreased ability to defend against the accumulation of free radicals (94). Experiments suggest that oxidative processes may be related to Aβ aggregation, microglial stimulation, damage to mitochondrial and nuclear DNA, as well as protein and lipid peroxidation. Evidence for the oxidative stress hypothesis in AD has been thoroughly reviewed by Markesbery (95) and more recently by Christen (96).

Evidence from observational studies: A few case-control studies have reported that antioxidant levels are significantly lower in AD patients compared to controls. These studies have observed that, compared to controls, AD patients may have lower vitamin C plasma levels (97), lower vitamin E serum levels (98,99), or lower vitamin E CSF levels (99). However, not all studies have been able to replicate these results (97,100).

Figures 4 and 5 shows results from prospective studies of vitamins E and C and risk of AD. Summarizing the results from these prospective studies is difficult because of the different sources of antioxidants (supplements, dietary, dietary plus supplements) in each study. Results have been conflicting, with a protective effect against AD in some (101,102) but not all studies (103,104). In the East Boston Study (101), data obtained from a medication questionnaire showed that none of the vitamin E or vitamin C supplement users developed AD after an average follow-up period of 4.3 years. In the Cache County Study, (102) use of vitamin E and vitamin C supplements in combination, but not individually, was associated with a lower incidence of AD. In contrast, the Honolulu Asian Aging Study did not find an association between use of vitamin E or C supplements after 3 to 5 years of follow-up (103). These antioxidants, however, were found to be protective against vascular dementia and mixed or other dementias. Finally, the Washington Heights-Inwood Columbia Aging Project (WHICAP) in northern Manhattan (104) found no association between supplement intake of vitamin C, or vitamin E and the incidence of AD after a 4-year follow-up.

Studies of dietary intake have also produced conflicting evidence. The Rotterdam Study (105) followed 5,395 subjects for an average of 6 years and found a significant decrease in AD risk in subjects with a high daily dietary intake of vitamin E and vitamin C. The Chicago Health and Aging project (CHAP) (106) reported on 815 subjects who were followed for an average of 3.9 years. The authors found that higher vitamin E intake from diet was associated with a reduced risk of AD but found no association with total intake of vitamin E (diet plus supplements), or with vitamin C

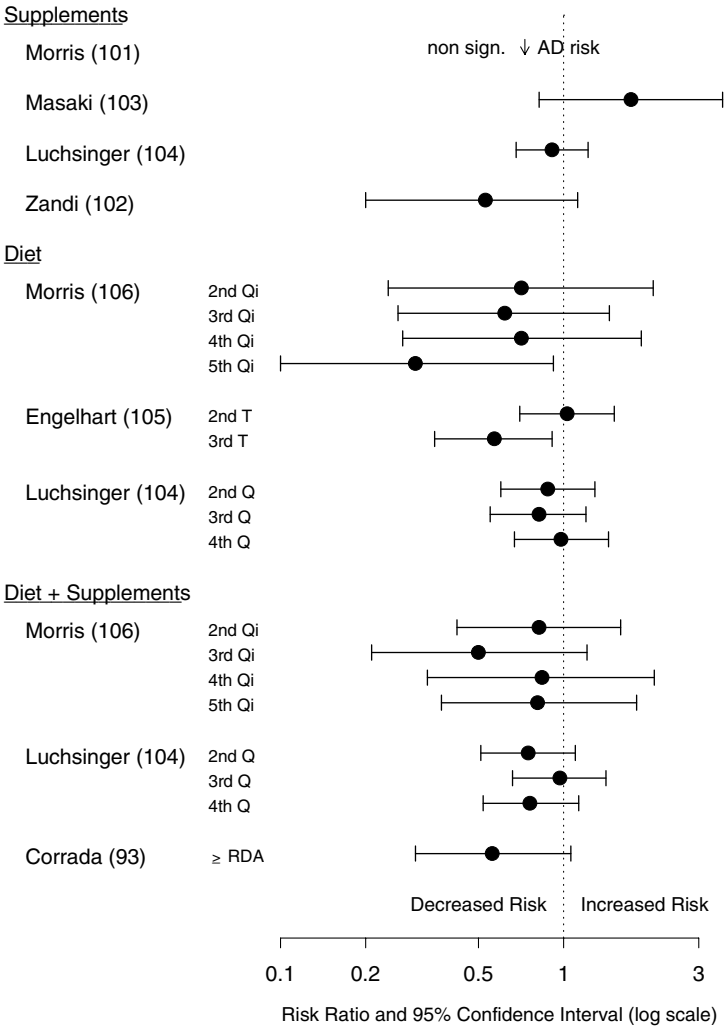

Figure 4 Observational studies of the effect of vitamin E on the risk of AD. *Abbreviations*: T, tertile; Q, quartile; Qi, quintile; sign, significant; RDA, recommended dietary allowance.

(diet or total intake). Last, the WHICAP study reported no association between dietary or total (diet plus supplements) intake of vitamin C or vitamin E and the incidence of AD in 980 subjects followed for an average of 4 years (104). In our studies in the Baltimore Longitudinal Study of Aging, total intake of vitamin E appeared to reduce the risk of AD. However, when vitamin E total intake was simultaneously analyzed with other vitamins, only total folate intake was significantly related to a decrease in risk of AD (93).

Many studies have also reported on the association between scores in cognitive tests and antioxidants, either from plasma levels, dietary intake, or supplement use. There is much literature on this association between antioxidants and cognitive performance in the elderly, but the evidence has yielded contradictory results (103,107–112).

Ginkgo Biloba

Potential mechanisms: The extract of the leaves of this ancient tree has long been used for medicinal purposes particularly in Asia, and more recently, in Europe (especially Germany).

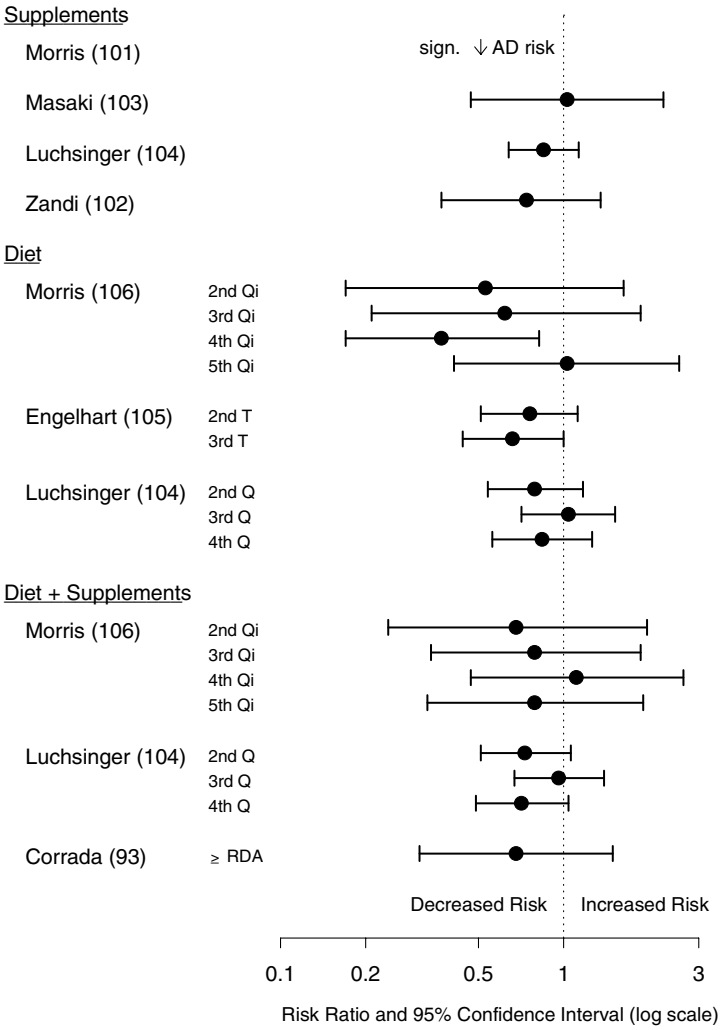

Figure 5 Observational studies of the effect of vitamin C on the risk of AD. *Abbreviations*: T, tertile; Q, quartile; Qi, quintile; sign, significant; RDA, recommended dietary allowance.

Considered a dietary supplement, it is available in the United States without prescription in a variety of formulations. *Ginkgo biloba* extracts are, besides vitamins, the most widely used form of alternative medicine to improve patients' memory (113,114). Although, there is little evidence that gingko can delay or prevent the onset of AD, it has been heavily promoted through the media and appears to be in wide usage in the United States for this purpose. *G. biloba* is often prescribed as an agent to treat memory disorders including AD, vascular, and mixed dementias in several European countries (115).

The effect of *G. biloba* as a preventive agent seems biologically plausible due to the properties of several of its components. The currently used extracts, the most common being "Egb 761" contains organic acids, flavonoids, and terpenoids (bilobilide and ginkolides). *G. biloba* components have antagonistic effects on platelet-activating factor, anti-inflammatory effects, impact on the cholinergic neurotransmitter system, and antioxidant and free radical scavenger properties (116). *G. biloba* has also been observed to inhibit neuronal death induced by Aβ (117) as well as inhibit Aβ aggregation (118).

Evidence from observational studies: Most of the evidence for the association between *G. biloba* and AD has come from animal laboratory studies, and treatment trials of demented patients. Most of the research on the effect of *G. biloba* has been published in European countries, particularly Germany, where *G. biloba* is frequently prescribed to treat memory disorders. To our knowledge, only one observational study has explored the association between *G. biloba* and the risk of AD. A report from a nested case-control study in France with a 7-year follow-up reported a non-significant decreasing risk of AD with increasing number of exposures to *G. biloba* (119).

Statins

Potential mechanisms: Statins are a type of drug prescribed for the lowering of serum cholesterol levels. These drugs work by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), the rate-limiting enzyme in cholesterol synthesis. There is increasing evidence linking cholesterol levels (120,121) and atherosclerotic cardiovascular disease (79,122) to AD pathogenesis. Proposed mechanisms include that elevations in cholesterol may reduce the levels of the soluble form of Aβ in the brain or somehow be linked through the role of apolipoprotein E in regulating cholesterol supply to neurons that produce Aβ. It is postulated that statins may help prevent against AD directly by reducing high cholesterol levels or indirectly by reducing cardiovascular disease. It is also possible that statins have effects on AD due to their anti-inflammatory properties.

Evidence from observational studies: Only a handful of observational studies have looked at risk of AD and statins. In a cross-sectional study, Wolozin and colleagues (123) found that users of statins identified from hospital records had a lower prevalence of AD (60% to 73% lower) than non-users. The reduction was apparent only with two types of statins (lovastatin and pravastatin) but not with a third type (simvastatin). Jick and colleagues (124) found similar results for all dementias combined in a study from the General Practice Research Database in the United Kingdom. In the Canadian Study of Health and Aging (125) the use of statins was also noted to be more common among controls than among cases of AD but only in subjects younger than 80 years of age.

Non-Pharmacological Interventions

Other factors, besides the pharmacological agents described in the previous sections, have been implicated as potentially beneficial against the development of dementia and AD. Among these are participation in physical activities and in cognitively demanding activities. Below we describe the available evidence for each of these.

Exercise

Potential mechanisms: Physical activity and exercise may be beneficial in reducing the risk of AD through a variety, or perhaps combination, of mechanisms. These mechanisms include lowering of blood pressure and serum lipids, as well as effects on cerebral blood flow and platelet aggregation (126–128). Alternatively, increased physical activity may affect AD indirectly by resulting in improved cardiovascular and cerebrovascular health, both of which have been associated with the clinical expression of AD (78,129).

Evidence from observational studies: Several case-control studies have explored the association between physical activity and AD. Some studies found a reduction in risk with increased activity (22,127,130), while others were not able to replicate the results (131). Prospective studies have also looked at the association, also with conflicting results. Studies from the Leisure World Retirement Community (29,132), a small prospective study in Australia (Sydney Older Persons Study) (133), a prospective study of dementia in the elderly of Shanghai (134), and a

recent report from the Chicago Health and Aging Study (135) have all failed to find an association between physical exercise and risk of dementia or AD.

Other prospective studies have found a significant reduction in risk with increased physical activity. A 3-year follow-up study in China (136) reported that subjects limited to indoor activities were at an increased risk of dementia compared to those without such limitations. The association was corroborated in a prospective study of residents of Hisayama, Japan (126), where after 7 years of follow-up, regular moderate physical activity was protective against AD but not vascular dementia. In the Canadian Study of Health and Aging (128) an association was observed between moderate or high levels of physical activity and a decreased risk of AD and dementia of any type. In addition, the authors observed a significant decreasing risk with increasing level of physical activity. In a community-based cohort study of Northern Manhattan residents, participation in physical activities such as walking for pleasure, going on an excursion, and physical conditioning, was associated with a 20% reduction in the risk of dementia (137). An association has also been found between increased physical activity and slower cognitive decline (128,138).

Social and Leisure Activities

Potential mechanisms: It is hypothesized that involvement in cognitively stimulating activities might delay the onset of dementia by increasing or maintaining brain reserve (139). In this hypothesis, the number of synapses between neurons increases due to increased cognitive stimulation. Therefore, an individual with higher cognitive reserve will cross the threshold at which dementia would be diagnosed at a later time than would an individual with lower cognitive reserve. It is possible, however, that decreased participation in leisure activities is a sign of early disease rather than a risk factor. If this is the case, subjects in early stages of dementia, even if not clinically apparent, would tend to participate less in these activities because of their incipient cognitive impairment. It is hard to distinguish between these two hypotheses especially when we consider the evidence that describes AD as a disease that may begin many years before symptoms are clinically apparent (140–142). Randomized trials would be the only way to obtain the information necessary to definitively distinguish between these two competing hypotheses.

Evidence from observational studies: Cross-sectional studies have reported an association between participation in social or leisure activities and development of dementia or AD (127,143) but the most compelling evidence comes from prospective studies. In a population-based cohort in France (PAQUID Study) (144) after a follow-up of at least 3 years a significant decrease in risk (about 50%) was observed among subjects participating in activities like traveling, odd jobs, knitting, or gardening. A study in Shanghai (134) observed that after 5 and 10 years of follow-up a lack of participation in leisure activities such as gardening, touring, or group activities increased the risk for AD. In a community-based cohort study of Northern Manhattan residents (137), risk of dementia decreased (about 40%) in subjects with high participation in leisure activities. The leisure activities most strongly associated with a decreased risk were reading, visiting friends or relatives, going to movies or restaurants, walking for pleasure, or going for an excursion. In two separate studies conducted by the same group of researchers, the Religious Orders Study (135) and the CHAP (145), the risk of developing AD decreased with increased participation in common cognitive activities, such as watching television, reading newspapers, and playing games. More recently, in a prospective study of twins from the Swedish Twin Registry (146) who were followed for at least 30 years, participation in a greater overall number of activities was protective against AD. When stratified by gender, however, overall activity as well as participation in intellectual-cultural activities was protective for women but not men.

1 Temporal Relationship
2 Biological Plausibility
3 Consistency or Replication of Findings
4 Absence of Confounding or Alternate Explanations
5 Dose-Response Relationship
6 Strength of the Association
7 Cessation of Exposure
8 Specificity of the Association

Figure 6 Criteria for judging whether an association is causal. *Source*: Adapted from Ref. 147.

CAUSALITY

All of the evidence presented above is encouraging for a potential causal relationship between these protective factors and the development of AD. The real issue is: can these agents or interventions, if used, prevent the development of AD? In the long run, a causal relationship between these and AD will depend on the demonstration of several criteria (Fig. 6). While there is evidence for many of the criteria for causality in the prospective studies conducted to date, randomized clinical trials are critical to complete the story. This is particularly important when trying to ensure the absence of potential confounders, many of which are likely to be unknown. The evidence from prospective observational studies although strong, is not conclusive, alternative explanations are still possible. In randomized trials, however, randomization assures that on average, known and unknown confounding factors are equally distributed between intervention and non-intervention groups, so any effect seen on the intervention group is attributed to the intervention itself and not to other factors. Fortunately, several randomized prevention trials are currently underway, which will help establish these causal relationships. (For a discussion of causal criteria see Gordis, 2000 (147) or Rothman and Greenland, 1998 (148).

PRIMARY AND SECONDARY PREVENTION TRIALS

In the model of AD as a chronic disease, interventions done in subjects with mild cognitive impairment (MCI) (149) can be considered a form of secondary prevention. Subjects with MCI have cognitive deficits that are not severe enough to meet the clinical criteria for AD. These subjects are at a higher risk of developing AD and are often at the initial pathological stages of the disease. Prevention trials done at this stage are important because of the benefits of potentially halting the disease process at a stage when people have mild symptoms and signs. It is also possible that if MCI precedes AD in the disease process, trials can be done at this stage that will require fewer subjects, would be done faster, and would be less costly than primary prevention trials (150). However, an intervention that works at this stage may not work at an earlier stage when the disease process is not as far along. Biological processes may change between the latent and prodromal stages. Thus, although important in their own right, secondary prevention trials would still not answer the question of primary prevention or vice versa.

In the long run, primary prevention trials would be expected to have the most public health impact. As we discussed above, randomized trials of primary prevention are crucial to determine if the use of putative protective agents will, in fact, prevent AD. Starting long after the initiation of primary prevention trials for heart disease and cancer, the first prevention trials in AD began only in the past few years. These landmark studies are presently underway and others are being proposed.

Hopefully the success of these studies will usher in a new era of prevention trials in AD. Many questions remain to be answered and ultimately primary trials are the only scientifically plausible way to demonstrate utility of putative protective factors in the prevention of AD and other dementias.

Primary Prevention Trials in AD

Success of primary prevention trials in AD depends on building a successful infrastructure for the recruitment and follow-up of normally aging individuals. In general these studies require thousands of subjects who are followed for several years. These studies are labor intensive and costly, but the potential savings to society would be substantial should one of the studies prove effective in the delay in onset or prevention of AD. For information about active trials in your area check the ADEAR (AD Education and Research) Web site (http://www.alzheimers.org/trials/index.html).

Estrogens

In the United States, two clinical trials were initiated to examine estrogens for the prevention of AD: the Women's Health Initiative Memory Study (WHIMS) and the Preventing Postmenopausal Memory Loss and Alzheimer's with Replacement Estrogens study (PREPARE). WHIMS is a component of the NIH-funded Women's Health Initiative. In this study, over 7000 women aged 65–79 were randomized to estrogen alone, estrogen plus progestin, or to placebo and followed for the development of dementia, memory loss, and other outcomes. In 2003 the study reported that women in the estrogen plus progestin group had twice the risk of developing dementia when compared to the placebo group. AD was the most common type of dementia diagnosed in that study. Early in 2004, the estrogen-only arm of the study was prematurely discontinued because of an increase in the risk of stroke as compared to the placebo group. Preliminary results suggested no difference in the two groups with respect to development of dementia. WHIMS thus provided data to suggest that estrogen in combination with progestin (or perhaps progestin alone) may increase the risk of AD. It did not, however, answer if estrogens alone are related to the risk.

The PREPARE study was also designed to examine the utility of conjugated estrogens, with or without progestin, to delay AD and memory loss in women 65 years or older with a family history of AD in a first-degree relative. Due to the findings in WHIMS, the trial was prematurely halted, but it is following the enrolled participants without revealing the treatment assignment in order to determine if there is a benefit with remote exposure.

Reconciling the results from observational studies and randomized trials of estrogen has been difficult. Numerous observational trials of estrogen have suggested a protective effect against AD. These studies investigated different populations, different types of estrogen preparations (conjugated estrogens, estrogen with and without progestin, estradiol, etc.), and involved different ages of exposure. It should be noted that most of the observational studies involved women on unopposed estrogens (i.e., no progestin). The results from a randomized trial of estrogen, however, suggested that, at least in combination with progestin, estrogen might actually increase the risk of dementia. It is possible that the positive association between estrogen and the development of AD applies only to unopposed estrogens or, alternatively that it was confounded in the observational studies. Self-selection of estrogen therapy by women and their physicians is not random and may identify individuals who are, in fact, protected in other ways. Alternatively, certain forms of estrogen at certain times may have value in the protection against AD and further research in the laboratory may yield additional clues to ways in which hormone replacement may be useful. At this time, however, estrogen cannot be recommended in the context of AD prevention.

Nonsteroidal Anti-Inflammatory Drugs

The National Institute on Aging funded the first primary prevention trial in AD to examine nonsteroidal anti-inflammatory drugs in 1999. The AD Anti-inflammatory Prevention Trial is being conducted at Johns Hopkins University, Sun Health Research Institute, Boston University, University of Rochester, and the University of Washington. This study is investigating the utility of naproxen as well as the selective COX2 inhibitor, celecoxib for the prevention of AD and cognitive decline in about 1000 subjects 70 years or older with a family history of dementia. This trial no longer gives mediation to subjects because of safety concerns, but subjects continue to be followed. More information about the study can be obtained by calling their toll free number 1-866-2STOPAD (1-866-278-6723) or on their Web site (http://www.2stopad.org).

Ginkgo Biloba

In 1999, the National Center for Complementary and Alternative Medicine in collaboration with the National Institute on Aging requested applications to study the potential efficacy of *G. biloba* for the prevention of AD in subjects aged 75 or older. The funding for this study, which has been named GEM (Ginkgo Evaluation of Memory Study), was awarded to a consortium of sites in Pennsylvania, Maryland, North Carolina, and California. In 2002, this placebo-controlled trial completed recruitment of over 3000 subjects who were randomized to 240 mg/day of *G. biloba* or placebo. In addition to the development of dementia, participants are monitored for other outcomes, including mortality, functional disability, and hospitalizations. Potential modifiers such as *APOE* genotype, education, depression, cardiovascular, and cerebrovascular disease are also being considered. It is anticipated that completion of the study will be in 2009. More information can be found on the study's Web site (http://nccam-ginkgo.org/aboutginkgo.aspx).

Potential Future Trials

As we continue the search for strategies to delay or prevent AD and other dementias, additional trials will undoubtedly be initiated. At present antioxidants (of various types), folic acid, and statins are among the more promising agents for further investigation in a primary prevention trial.

Secondary Prevention Trials

Antioxidants, cholinergic agents, and nonsteroidal anti-inflammatory drugs are among the agents currently under investigation for the secondary prevention of AD. These studies typically involve subjects with MCI. The Alzheimer's Disease Cooperative Study (ADCS), an NIH-funded consortium of investigators, recently completed a randomized, double-blind, placebo-control trial that evaluated the safety and efficacy of vitamin E and donepezil, a cholinesterase inhibitor, to delay clinical progression of elderly subjects from MCI to AD. Results from the trial, which enrolled approximately 720 participants aged 55 to 90 across the United States and Canada, were published in the *New England Journal of Medicine* in 2005 (www.nejm.org 10.1056/NEJMoa050151).

PUBLIC HEALTH IMPACT OF DELAYING THE ONSET OF AD

Primary prevention trials are costly, complex, and require a long time before completion. The cost and labor involved, however, are justified given the impact that those interventions could have in reducing the overall burden of the disease. Several authors have considered the potential impact of interventions to prevent or delay the onset of AD (151,152). Since the incidence of AD doubles with every five years of age after 65 years, a delay in onset of 5 years would reduce the age-specific incidence of AD by half. In 1998 Brookmeyer and colleagues (152) quantified the reduction in the number of cases of AD and the monetary savings associated with various delays in the onset of AD

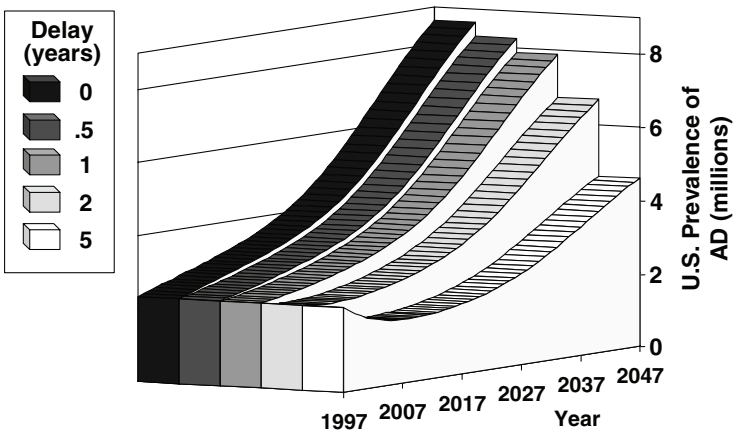

Figure 7 Potential impact of interventions to delay onset of AD. *Source*: Adapted from Ref. 152.

(Fig. 7). The number of people suffering from AD was conservatively estimated at 8 million by the year 2047. An intervention that would delay the onset of AD by 5 years would result in a 50% reduction in age-adjusted risk. Such a delay would reduce the number of prevalent cases by 1.15 million and 4.04 million respectively after 10 and 50 years. Even a modest delay in onset of 6 months would decrease the number of affected people by 100,000 and 380,000 after 10 and 50 years respectively. This modest delay would translate to annual savings of $4.7 billion (10 years) and $18 billion (50 years). Delays of 2 to 3 years, consistent with the observational reduction of AD by estrogens and nonsteroidals, would have even a greater effect. If any of the ongoing studies described above have positive results, the goal of reducing the incidence and delaying the onset of AD by several years may be realistic and could have significant public health impact.

SUMMARY

At present, no approach has been proven to prevent or delay the development of dementia or AD. Observational studies, however, have identified numerous putative protective factors in recent years. These potentially modifiable factors include hormonal replacement therapies, anti-inflammatory compounds, cholesterol-lowering agents, ginkgo biloba, antioxidants, such as Vitamins E and C, and folic acid. Non-pharmacologic approaches under investigation include physical exercise and involvement in cognitively demanding activities. Primary prevention trials are necessary to determine if any of these strategies have a role in the prevention of AD. WHIMS, the only trial completed to date, showed that hormonal replacement with estrogen and progestin appeared to increase the risk of dementia. Randomized trials of non-steroidal anti-inflammatory drugs and gingko biloba are currently in progress. Hopefully, additional trials will soon follow for other potentially promising agents, including antioxidants, folic acid and statins. Although it is costly to conduct primary prevention studies, the public health impact of even modest delays can be substantial. The exciting progress of the past few years will hopefully translate during the coming decade into proven prevention strategies.

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