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Review Article

Lowering the risk of Alzheimer's disease: Evidence-based practices emerge from new research

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Abstract

Background: The increasing prevalence of Alzheimer's disease (AD) and other aging-related dementias as the population ages will have a dramatic impact on both provision of health care and the economy if nothing is done to prevent or delay the onset of AD or to slow its progression.
Methods: A comprehensive review of the literature in several promising areas of inquiry, other than those representing Food and Drug Administration (FDA)–approved AD- or dementia-specific pharmacologic therapies, that may impact the risk or progression of AD and related dementias was undertaken.
Results: Results highlight a number of factors associated with AD and dementia. These include education and occupation, cognitive and leisure activities, exercise, cholesterol and statins, and head trauma.
Conclusions: Factors associated with AD and dementia may have potential as strategies useful in preventing or delaying AD and dementia or slowing its progression. Further research is needed to determine the validity and strength of the associations and to ascertain causality.

Keywords: Alzheimer's disease; Dementia; Education; Occupation; Cognitive activities; Exercise; Cholesterol; Statins; Head trauma; Prevention

1. Introduction

It has been well established that the prevalence of Alzheimer's disease (AD) will increase dramatically as the population ages [1]. As of 2000, 4.5 million individuals in the United States had AD. Given the rapid growth among the oldest age groups and the increasing incidence of AD with age, that number is projected to increase to 13.2 million by 2050 [2]. Further, it is well understood that this dramatic escalation of the number of people with AD will have a significant impact on the health care system in this country as well as a major economic impact [3].

However, if onset or progression of disease could be delayed, even by a few years, the prevalence of AD, along with the public health and economic burdens that accompany it, could be reduced dramatically. Delaying onset of AD by only 2 years would translate into 2 million fewer individuals with the disease after 50 years, and a 1-year delay would result in almost 800,000 fewer [1].

Evidence-based possibilities or practices for slowing the progression of AD and other aging-related neurodegenerative diseases that manifest clinically by cognitive impairments or for delaying the onset of these disorders definitely appear to exist today. Drugs that can slow the progression of AD are currently being prescribed, and AD drug discovery efforts are the subject of intense research [4,5].

This article reviews promising areas of inquiry, other than the Food and Drug Administration (FDA)–approved AD- and dementia-specific pharmacologic therapies noted above, that may reduce the risk of AD or slow its progression. It is important to emphasize that although this provides

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an up-to-date summary of the scientific literature on this subject, it by no means constitutes an endorsement or recommendation for any of the practices or interventions included here in this review.

2. Education and occupation

Educational level has shown a strong association with risk of AD or other aging-related dementias [6–8]. One study that explored this association used data from the Kungsholmen Project. For this community-based project, all dementia-free residents of Kungsholmen, a district in Stockholm, Sweden, age 75 and older in October 1987 were eligible for enrollment. A total of 1,810 residents completed the initial survey in 1987 to 1989; 1,296 subjects had no dementia at initial interview and are included in this analysis. Between initial assessment and follow-up, dementia developed in 147 subjects (109 had AD diagnosed). Study investigators initially included 3 categories of education: less than 8 years, 8 to 10 years, and $\geq$11 years. Initial analyses indicated no reliable difference between the 8 to 10 years group and the $\geq$11 years group for incidence of dementia, so these 2 groups were combined for subsequent analyses. Study subjects with less education (<8 years) were 2.6 (95% confidence interval [CI], 1.5 to 4.4) times more likely to have AD and 1.7 (95% CI, 1.1 to 2.6) times more likely to have dementia of any type when compared with subjects with more education ($\geq$8 years) [6].

Karp et al [7] used a subset of this same study population ($N = 931$) to examine the relationships among education, occupation, and risk of AD and other dementias. Both education and occupation were found to be risk factors when examined individually; however, when both education and occupation were included in the analysis at the same time, only education remained as a statistically significant risk factor.

Another study, conducted with subjects from the Nurses' Health Study, also found an association between educational level and cognitive function. Investigators included members of the all-female sample who were at least 70 years old, had no history of stroke, and had responded to the most recent survey that was mailed as part of the Nurses' Health Study. Of those eligible to participate, 19,319 completed a telephone interview (between 1995 and 2000) during which cognitive function was assessed and information about educational level attained was provided. Six different tests of cognitive function were combined to obtain a global cognitive function score. Women with an advanced (master's or doctoral) degree were 51% (odds ratio [OR], 0.49; 95% CI, 0.36 to 0.66) less likely to have a poor score on the global cognitive function measure, and women with a bachelor's degree were 17% (OR, 0.83; 95% CI, 0.72 to 0.96) less likely compared with women with a Registered Nurse diploma. Investigators also found a statistically significant association between higher levels of education and the odds of decreasing scores on all 6 cognitive tests. Other socioeconomic factors that were measured (ie, husband's level of education, household income) showed little or no association with cognitive function [8].

Wilson et al [9] examined the relationship between education and the rate of cognitive decline using a global cognitive function measure and a sample of 494 community-dwelling individuals with AD from the Chicago area. The global measure combined scores on 9 separate cognitive tests, and study subjects were followed up for about 3 years, on average, with reexaminations every 6 months. At baseline, those with higher levels of education scored higher on the global cognitive measure. Over time, the cognitive scores of those with higher levels of education decreased at a somewhat more rapid rate compared with those with less education.

Whalley et al [10] conducted a study that examined the association between a test of mental ability taken in childhood, the Moray House Test (MHT), and dementia in later life. All children in Scotland who were born in 1921 and were in school on June 1, 1932 were given the MHT. Whalley et al were able to link data from patients with dementia, and controls, without dementia, to these childhood scores. Although they found no association between MHT score and early-onset dementia, they did find an association between MHT score and late-onset dementia ($p<0.03$).

Regarding occupation and its link to AD and dementia, some studies have found an association [11], and others have not [12]. Using 2,950 subjects from the southwest of France who are part of the PAQUID study, investigators found no association between occupation and risk of AD. These investigators conclude that cognitive abilities earlier in life may have greater effect [12]. However, Smyth et al [11] undertook a case-control study in the Cleveland area with 122 cases of possible or probable AD and 235 controls. They broke occupations down into 4 categories of demands: mental, social, physical, and motor. They found that compared with controls, patients had lower mental demand scores ($p = 0.007$). Patients also had higher physical demand scores compared with controls ($p = 0.02$).

3. Cognitive and leisure activities

There is emerging evidence that leisure activities and, in particular, cognitively stimulating activities, may offer a strategy for prevention or treatment of AD and dementia [13–16]. In one recent study, Verghese et al [13] analyzed data from 469 adults, aged 75 to 85, enrolled in the Bronx Aging Study between 1980 to 1983. Study subjects were followed up until 2001. During that time, dementia developed in 124 study participants. Comparing the dementia group to the nondementia group, a number of baseline characteristics were associated with the development of dementia. Among these were the cognitive activity score,

with the nondementia group having greater cognitive activity ($p<0.001$). The overall physical activity score did not show a statistically significant association. Specific cognitive activities, from among those that were studied, that were associated with a lower risk of dementia were playing board games, playing a musical instrument, and reading. Dancing was the only physical activity associated with a lower risk of dementia. Increasing the cognitive activity score by 1 point resulted in a 7% lower risk of dementia, and subjects with greater than 11 cognitive activity days per week had a 63% lower risk of dementia development. It is important to note that these are associations, and that a causal effect was not established with this study [13].

Wilson et al [14] looked at subjects who were part of the Religious Orders Study, a sample of 733 Catholic nuns, priests, and brothers, all age 65 or older. Study participants were followed for up to 7 years. During that time, AD developed in 111. A comparison of baseline characteristics indicated that subjects in whom AD developed were more likely to have a lower cognitive activity score compared with those in whom AD did not develop ($p<0.02$). In fact, a 1-point increase in the cognitive activity score resulted in a 33% lower risk of AD development. There was no association identified between the physical activity score and risk of AD. Again, these data show an association and not a causal effect [14].

Another study focused on activity undertaken earlier in life and assessed its association with development of AD later in life. Cases included 193 patients with probable or possible AD, enrolled in the Research Registry of the University Alzheimer Center, University Hospitals of Cleveland, and there were 358 healthy controls. Via questionnaires, controls and surrogates for the cases were asked about 26 nonoccupational activities that might have been performed during early adulthood (20s and 30s) and middle adulthood (40s and 50s). Controls participated in more activities than cases ($p<0.001$) and, on average, spent more hours devoted to intellectual activities when compared with patients ($p\leq0.05$). Study subjects who increased their intellectual activities as they moved from early to middle adulthood were more likely to be in the control group [15].

Crowe et al [16] studied a sample of twins (107 same-sex pairs), with 1 twin diagnosed as having dementia and the other not having dementia. Participation in leisure activities over 20 years before they were evaluated for dementia was assessed. Participating in more activities resulted in a lower risk of dementia ($p\leq0.05$). Further analysis by gender indicated that more activities lowered the risk for women but not for men. Although the assessment of leisure activity participation occurred over 20 years before diagnosis, and it is therefore less likely that early symptoms of dementia were affecting leisure activity participation, this study still cannot definitively prove that participation in leisure activities leads to better cognitive skills. In fact, higher cognitive function may lead to increased activity [16].

A recently published study examined the effects of a cognitive motor intervention (CMI) on study subjects receiving cholinesterase inhibitor treatment and having mild cognitive impairment (MCI) or probable AD. Thirty subjects were assigned randomly to the experimental group, and 38 were assigned to the control group. Twice a week for 1 year, the experimental group participated in a CMI, which included reality orientation, cognitive exercises, activities of daily living (ADL) training, and psychomotor activities. Each session lasted 3 1/2 hours. Assessments occurred at baseline, 1 month, 3 months, 6 months, and 12 months. At the 1-month assessment, subjects in the experimental group showed cognitive improvement ($p = 0.05$), and the control group did not. At month 6, the experimental group maintained their cognitive status, whereas the cognitive status of the control group declined. Subjects in the experimental group with less education had a higher cognitive response at month 6, which persisted at month 12, indicating that perhaps those with less education would get the most benefit from an intervention such as this [17].

Basic science research findings add further support for the potential role of cognitively stimulating activity in decreasing the risk of AD and dementia. In a recent study, investigators were able to show that providing an enriched environment (ie, running wheels, toys) for transgenic mice that model AD-like Aβ brain amyloidosis, resulted in a remarkable decrease in amyloid deposition and Aβ levels when compared with mice from a standard environment [18].

4. Physical activity

Although several of the studies noted above did not find an association between physical activity and AD or dementia [13, 14], other studies have identified such a relationship [19, 20]. For example, results from the prospective, community-based Canadian Study of Health and Aging indicate an association between physical activity and dementia. A total of 721 cases and 3,894 controls were initially interviewed in 1991 and 1992. Follow-up interviews were completed in 1996 and 1997. More intense and more frequent exercise were related to a lower risk of AD ($p = 0.02$), cognitive impairment–no dementia ($p<0.001$), and other dementias, excluding vascular dementia ($p = 0.04$). Vascular dementia showed an association, but it was not significant ($p = 0.46$). Further analysis by gender indicated that significant associations may exist for women only. These data point to an association and cannot prove cause and effect [19].

Among the sample of women who were part of the Study of Osteoporotic Fractures, an association between physical activity and cognitive decline was also identified. Of the 5,925 women enrolled and interviewed in 1986 to 1988, 1,178 experienced cognitive decline 6 to 8 years later at follow-up, defined as a score on the modified Mini-Mental

State Examination at least 3 points lower at follow-up when compared with baseline. Physical activity was measured using a self report of distance walked and kilocalories used per week. For both distances and kilocalories, data were divided into quartiles, representing low to high activity levels. Twenty-four percent of women who walked the shortest distances weekly experienced cognitive decline compared with 17% in the group who walked the greatest distances ($p<0.001$). The same percentages emerged (24% vs 17%) when looking at kilocalories expended ($p<0.001$). Odds for experiencing a cognitive decline for women at the highest level of distances walked were 37% lower than women at the lowest level and 35% lower when examining quartiles for kilocalories used. Across quartiles for both distances and kilocalories, greater physical activity was associated with less risk of cognitive decline ($p<0.001$) [20].

Several possible explanations for the inconsistency of findings in the area of an association between cognitive function and physical activity have been put forth by Churchill et al [21]. First, they speculate that to be of the greatest benefit for cognitive function, exercise programs should be long range, undertaken over years and not months. Next, they suggest that different types of physical activity could produce differing results. Third, they propose that cognitive function as a measurement may be too broad. Perhaps some studies are evaluating a particular cognitive process, and an association is found between cognitive function, defined this specific way, and exercise. Other studies not showing an association may in fact be measuring a different cognitive process but still labeling the measurement as cognitive function [21].

A study by Kramer et al [22] illustrates the differential effects of various types of exercise on distinct cognitive processes. This study examined the disparate effects of aerobic and anaerobic exercise on various cognitive processes. A sample of 124 nonexercising adults, aged 60 to 75 years old, was assigned randomly to 1 of 2 groups: walking (aerobic) or stretching and toning (anaerobic). Various cognitive tests were given to study subjects before their engagement in their assigned exercise activity. After 6 months of exercise, subjects were retested. As hypothesized, the aerobic group improved their performance on tasks requiring greater executive control, and the anaerobic group did not. For tasks less dependent on executive control, there were no differences between performances of the aerobic and anaerobic groups [22].

Results of a meta-analysis of 18 longitudinal studies examining the relationship between exercise and cognitive improvement among nonexercising adults ($\geq$55 years of age) indicated that there is a relationship, with greater physical activity associated with greater cognitive improvement [23]. For all 18 studies, exercise was classified as either (1) aerobic or (2) combination, which included both aerobic and strength training. Cognitive processes were categorized as (1) speed, (2) visuospatial, (3) controlled processing, or (4) executive control. Noting the potential for overlap among the 4 categories, cognitive tasks could be assigned to multiple categories. A general comparison of exercise groups and control groups showed that although both groups improved in cognitive function between time1 and time 2, the exercise groups showed a greater, and statistically significant, improvement. The greatest benefit was realized for cognitive processes that involved executive control ($p<0.05$). Combination exercise programs were more beneficial than programs involving aerobic exercise alone ($p<0.05$). Interventions with exercise sessions of less than 30 minutes had no statistically significant effect on cognitive functioning [23].

Adlard et al [24] report results from their research on a transgenic mouse model of AD-like Aβ brain amyloidosis that support the potential of exercise as a possible strategy for lowering the risk of AD and dementia. Aβ was significantly reduced for mice provided with running wheels for a period of 5 months when compared with mice not provided with running wheels. Further, the mice with running wheels showed an increase in the speed with which they learned [24].

5. Estrogen

At one point, hormone replacement therapy (HRT), either estrogen alone or estrogen plus progestin, showed promise as a potential means of reducing risk of dementia or AD. A meta-analysis published in 1998, reports on 10 studies examining the relationship between HRT and risk of dementia or AD; 8 are case-control studies and 2 are prospective cohort studies. Results of the studies ranged from an association between HRT and a lower risk of dementia or AD through an association between HRT and a higher risk of dementia or AD and also included no association, thus, highlighting the lack of agreement among findings. Although after a meta-analysis of the studies resulted in identifying a 29% decrease in risk of dementia or AD for HRT users, the investigators noted weaknesses of the studies that were included [25].

In 2000, Hogervorst et al [26] published a rigorous and comprehensive meta-analysis of published studies and noted a slight positive effect, although it was not consistent [26]. Another meta-analysis published in 2002 concluded that given the methodologic problems with the studies that were identified and analyzed, the association between HRT use and a reduced risk of dementia was uncertain [27].

Results of several studies undertaken as part of the Women's Health Initiative Memory Study indicate that not only is HRT not associated with a lower risk of dementia, but, in fact, HRT use may be associated with an increased risk of dementia. In a study of a combined regimen of HRT (estrogen and progestin) and its association with probable dementia, Shumaker et al [28] found that HRT users were

about twice as likely to have probable dementia compared with the placebo group (hazard ratio, 2.05, 95% CI, 1.21 to 3.48). In a later study, which looked at use of estrogen alone for women who previously had a hysterectomy, Shumaker et al [29] found that those using HRT had a 49% higher incidence of probable dementia during follow-up, compared with the placebo group. However, this result was not statistically significant ($p = 0.18$). Both arms of this clinical trial have been terminated (estrogen and progestin in July 2002 and estrogen alone in February 2004) because of adverse events and concern over increases in health risks for study subjects [29].

6. Antioxidant vitamin supplements – vitamins E and C

The evidence regarding the association between the intake of vitamins E and C and AD or dementia is mixed. Several studies have found a reduced risk of AD or dementia [30, 31], whereas others have not [32].

Using a sample of 5,395 dementia-free subjects from the Rotterdam Study, a prospective, population-based study that included subjects from a suburb in the Netherlands, researchers followed up with participants from enrollment, 1990 through 1993, to 1997 through 1999. By the end of the study, 197 subjects had dementia and 146 of those had AD. Using a linear term for intake, investigators found that study subjects with high intakes of vitamin C had a 0.82 chance of having AD compared with subjects who did not have high intakes of vitamin C (95% CI, 0.68 to 0.99). The association with Vitamin E intake was of borderline significance. When they used tertiles to represent vitamin intake, use of vitamin E was associated with a lower risk of AD and vitamin C showed a borderline association [30].

Zandi et al [31] using data from the Cache County Study, another prospective study of older individuals in Utah, found reduced risk of AD among vitamin E and vitamin C supplement users. Of a total of 4,740 participants included in this analysis, 200 had AD diagnosed at the first assessment. They represented prevalent cases. At the 3-year follow up, 104 subjects had AD diagnosed . They represented incident cases. Examining prevalent cases at the first assessment, taking vitamin E was associated with a 0.44 (95% CI, 0.19 to 0.86) reduced risk of having AD. When analyses were performed on combinations of supplement use, taking both vitamin E and vitamin C supplements in combination reduced the risk of having AD to 0.22 (95% CI, 0.05 to 0.60). For incident cases of AD, using both vitamin E and vitamin C supplements in combination reduced the risk of AD to 0.36 (95% CI, 0.09 to 0.99) [31].

Investigators using data from the Washington Heights-Inwood Columbia Aging Project examined the association between vitamin E and vitamin C intake and risk of AD. From a total of 980 randomly selected Manhattan residents, age 65 and older and meeting the criteria for this analysis, 242 had AD diagnosed. They found no association between vitamin E and vitamin C intake, either through regular diet or supplement use, and risk of AD [32].

A meta-analysis examining the association between vitamin E supplementation and mortality published earlier this year found that high doses of vitamin E may increase risk for mortality [33]. This article sounds a note of caution for vitamin E supplementation as a preventative strategy and also emphasizes the need for more basic and clinical research on the role of oxidative stress as a risk factor or mediator of AD and other aging-related neurodegenerative dementias.

7. Cholesterol and statins

There is some evidence to suggest that high cholesterol may be associated with a higher risk of AD. For example, for one prospective study, 1,287 subjects were drawn from the North Karelia Project and the Finnish component of the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease. Subjects were enrolled from 1 of 4 independent samples surveyed in 1972, 1977, 1982, and 1987. Investigators found that higher total cholesterol levels at midlife were associated with a higher risk of AD at follow-up in 1998 when subjects were at least 65 years old. This association was independent of the association with the *APOE* ϵ4 allele and AD. However, the risk of AD for subjects with both the *APOE* ϵ4 allele and high cholesterol was greater than for subjects with either the *APOE* ϵ4 allele or high cholesterol alone [34].

Evidence suggests that high-density lipoproteins (HDL) may have a protective effect in its association with cognition. In a recent study of 139 adults 95 to 107 years old, researchers investigated the relationship between HDL levels and scores on the Mini-Mental State Examination (MMSE). They found a statistically significant correlation between HDL levels and MMSE scores ($p<.0001$). Interestingly, although not statistically significant, HDL was higher for women in the sample compared with men. The strength of the association between HDL and MMSE score was similar for both women and men [35].

Although not all research results are consistent in identifying this association [36], many studies have ascertained an association between use of statins, a class of drugs often prescribed to lower cholesterol, and a decreased risk of AD or dementia [37–39]. This association lends more evidence to the potential association between high cholesterol and AD and dementia.

An epidemiologic study, using data from the General Practice Research Database in the United Kingdom, included as a base population patients who were at least 50 years old and (1) had been given at least one prescription for a statin or other lipid-lowering agent, (2) had untreated hyperlipidemia, or (3) had neither hyperlipidemia nor a prescription for a lipid-lowering agent. Drawn from this

base population were 284 patients with dementia or AD diagnosed for the first time and 1,080 matched controls. Patients were followed up from 1992 to 1998. Analysis of the data showed that patients who were prescribed statins had a 71% (95% CI, 37% to 87%) lower risk of the development of dementia or AD ($p = 0.002$) [37].

Rockwood et al [38] conducted a case-control, secondary analysis of data from the Canadian Study of Health and Aging to see if there was an association between dementia and lipid-lowering agents (LLAs). Cases included 492 study participants who did not have dementia or AD when enrolled (1991 to1992), but had dementia or AD at follow-up (1996). There were 823 controls, those who did not have dementia or AD at enrollment or follow-up. They found that statin use was associated with a lower risk of dementia or AD for subjects less than 80 years of age. For those 80 and older, there was no significant association.

Another study used a chart review in an outpatient geriatrics practice to examine the association between statin use and AD and dementia. Included were all patients in the practice using statins or with a diagnosis of hypercholesterolemia or dementia. A total of 655 patients, 233 with dementia and 113 on statins, were included in the sample. At their initial office visit, patients on statins were less likely to have dementia ($p<0.001$), AD ($p<0.001$), or vascular dementia ($p<0.001$). After adjusting for covariates, the associations were still statistically significant. There were no differences relative to statin use for patients with Diffuse Lewy Body disease or mixed-type dementia. At a follow-up visit, on average 10 to 11 months after the initial visit, patients in the statin group increased their MMSE scores, whereas, scores for patients not taking statins decreased ($p = 0.025$). Even after adjusting for covariates, the statin group was more likely to improve or have no change on MMSE score ($p = 0.045$). Twenty-five percent of the sample was included in this follow-up. This association between statin use and increased MMSE score is important because it may point to the potential of statins to delay or arrest cognitive decline [39].

8. NSAIDS

NSAIDS or nonsteroidal antiinflammatory drugs were once touted as showing promising evidence that they may be useful in preventing or treating AD. Using data from the Rotterdam Study, undertaken with a population-based cohort of residents 55 years and older living in a suburb of Rotterdam, investigators identified an association between a lower risk of AD, but not vascular dementia, and the use of NSAIDS, if taken long term (2 years or longer) [40]. An earlier study, which also used data from the Rotterdam Study, found no association between using NSAIDS and a lower incident AD risk. However, long-term use was defined as more than 2 months for that analysis [41].

Using data from the Cache County Study, another population-based cohort, Anthony et al [42] reported that use of NSAIDS was associated with a reduced prevalence of AD. An analysis of data from the Cache County Study conducted several years later examined the association between incident AD and use of NSAIDS. The analysis indicated an inverse association for long-term users (>2 years). Also, comparing current and former users, the association held only for former users [43].

Etminan et al [44] conducted a meta-analysis, published in 2003, of 9 observational studies that examined the association between AD and NSAIDS. The results indicated an association. When they compared shorter- and longer-term usage, the association held for long-term users (most defined as >2 years).

A later meta-analysis of 25 studies examined and compared the pooled results of 3 types of studies: those that used prevalent dementia as the outcome, those that used incident dementia as the outcome, and those that used cognitive decline as the outcome. Results indicated a relative risk of 0.51 (95% CI, 0.37 to 0.70) for prevalent dementia, 0.79 (95% CI, 0.68 to 0.92) for incident dementia, and 1.23 (95% CI, 0.70 to 2.31) for studies that used cognitive decline as the outcome. DeCraen et al [45] concluded from these pooled findings, which showed a decline of the relative risks when comparing the three types of studies, that the associations identified between NSAID use and a lower risk of dementia were perhaps caused by several different kinds of bias, such as recall bias and publication bias.

A randomized trial of rofecoxib (a selective COX-2 inhibitor), naproxen, or placebo, which was undertaken with subjects having mild-to-moderate AD showed no effect of the NSAIDS on cognitive decline. The study included 351 subjects enrolled from centers affiliated with the Alzheimer's Disease Cooperative Study. Participants were treated for 1 year, and the investigators noted that a longer treatment period may be needed to show positive results of the drugs. At the time the results of this study were published, they also noted this trial does not address the potential for prevention of AD from NSAIDS [46]. The Alzheimer's Disease Antiinflammatory Prevention Trial (ADAPT) was designed to test the effectiveness of certain NSAIDS as a prevention strategy. In December 2004, the National Institute on Aging ended the ADAPT trial owing, in part, to safety concerns about naproxen [47].

9. Head trauma

A number of studies have found an association between head injury and AD and dementia [48–50]. Plassman et al [48] studied a cohort of male World War II veterans who had documented nonpenetrating head injury during their years of service. The sample included 548 veterans with head injury and 1,228 without. Those with a history of head

injury were 2.16 times more likely to have AD (95% CI, 1.10 to 4.23) and 2.46 times more likely to have dementia (95% CI, 1.43 to 4.24) when compared with those without head injury. Further, the risk increased as the severity of the injury increased (for AD, $p = 0.0013$ and for dementia, $p<0.0001$). For mild head injury, there was no statistically significant increased risk for either AD or dementia.

Using a sample that included 198 subjects with AD compared with 2 nonmatched control groups: one made up of 164 individuals with other dementias and another of 176 nondemented individuals, investigators assessed the risk of AD associated with head injury among patients seen at a psychogeriatric unit in Warrington, United Kingdom. Comparing those in the AD group with those without dementia, the OR was 2.4 (95% CI, 1.3 to 4.1), and comparing those with other dementias to those with no dementia, the OR was 2.36 (95% CI, 1.4 to 4.0). When they combined the AD and other dementia groups and compared them with the nondementia group, the OR was 2.4 (95% CI, 1.4 to 4.1) [49].

Fleminger et al [50] conducted a meta-analysis, reviewing case-control studies to examine the association between head injury and AD. They identified 15 studies that met their criteria for inclusion. Results indicated an association. The OR was 1.58 (95% CI, 1.21 to 2.06). When they compared men with women, the association held for men only (OR, 2.26; 95% CI, 1.13 to 4.53 for men and OR, 0.92; 95% CI, 0.53 to 1.59 for women) [50].

There are, however, studies that indicate no association between head injury and AD and dementia [51, 52]. For example, in an analysis of data from 6,645 subjects who were participating in the Rotterdam Study, a prospective study of persons older than 55 who were living in a suburb of Rotterdam when the study was initiated, 78% of those invited agreed to participate, researchers assessed the association between dementia and head trauma. After an average follow-up period of about 2 years, 129 subjects had dementia diagnosed, 91 of whom had AD. Investigators found no association between head injury and dementia (relative risk [RR], 1.0; 95% CI, 0.5 to 2.0) or AD (RR, 0.8; 95% CI, 0.4 to 1.9) [51].

Launer et al [52] assessed the risk of AD associated with head trauma by pooling data from 4 population-based studies conducted in Europe, including data from a subsample of subjects age 65 and older from the Rotterdam Study discussed above. From the pooled sample, there were 528 incident cases of dementia, and 352 cases were diagnosed as AD. They found no support for an association between dementia or AD and head trauma.

10. Summary

As outlined in this review of the literature to date, there are a number of strategies that may have the potential to decrease the risk of AD and dementia, several of which represent lifestyle practices (eg, cognitive activity, exercise, avoiding head trauma) and others of which represent "collateral benefits" of interventions designed for the treatment of disorders other than AD or dementia that appear to also reduce the risk for AD or dementia (eg, statins, NSAIDs). There are other possible risk factors not covered in this review, such as high blood pressure [34, 35], diabetes [53], and elevated homocysteine levels [54], the specific treatments for which also might have "collateral benefits" for reducing the risk of AD and dementia. However, further studies are needed to investigate these possibilities, and more research is needed on all of these strategies and factors summarized here to determine not only the validity and strength of their associations with AD and dementia but also to ascertain causality. Ultimately, primary prevention trials are needed to evaluate which among the possible practices or strategies reviewed here will indeed show a robust ability to prevent AD or dementia.

11. Research and health policy implications for the future

The most important conclusion or "take home" message of this review is that a number of promising strategies for minimizing or counteracting putative risk factors for AD or dementia have emerged from multiple lines of research recently; however, considerably more information is needed from additional studies before specific measures can be recommended to the general public or incorporated into health policy initiatives. Greater investment of resources will be essential to carry out the necessary research studies because they will be challenging to undertake. Large numbers of participants, in both intervention and control groups, will need to be enrolled in these studies and then followed for many years to distinguish between strategies that are merely associated with AD or dementia and those that can in fact prevent or delay its onset or progression. Further complicating the undertaking of studies of potentially effective risk-reducing best practices is the paucity of cost-effective measures for assessing small changes in disease progression. The identification of biomarkers of disease progression that can be obtained in a noninvasive, cost-effective manner (eg, blood, urine, saliva, nasal secretions, oral epithelial swabs, olfactory testing) will permit investigators to more readily identify early stages of the disease process, as well as the rate of its progression and will therefore make trials of possible prevention strategies more straightforward and somewhat less costly. Therefore, greater investment in studies to identify biomarkers for AD and other neurodegenerative dementias is also essential.

Focusing prevention trials on groups at highest risk, such as the "old-old" or those with mild cognitive impairment, would reduce the time and effort, and therefore the costs, of these trials, but results would not necessarily be applicable for the general population. Risk profiles may influence the effectiveness of any intervention that is tested. Younger

subjects may respond differently than older subjects. Carriers of the *APOE* ϵ4 allele may benefit from a certain intervention, whereas there may be no advantage for noncarriers. Teasing out the components of the strategies that have the potential for the greatest impact on AD and dementia (eg, specific cognitive activities with the greatest effect) also remains a challenge. Research dollars must be invested in areas showing the greatest promise. However, some interventions that exhibit only modest effects on an individual basis may prove to be relatively inexpensive, safe, and easy to carry out. Thus, they will be more likely to be widely adopted and when the individual effects are multiplied over large populations, the impact can be substantial.

Because the current findings from correlative studies of potential modifiers of risk factors for AD and dementia reviewed here do not prove cause and effect, it is imprudent to make recommendations for interventions or treatments based on these studies. However, many of the associations have been documented in multiple community-based studies, and many interventions based on these associations are low risk and beneficial in preventing other diseases like heart disease, diabetes, and hypertension. Exercise is an excellent example. There are proven health benefits to exercising at least 3 times a week. The evidence described above indicates that such a program of exercise may also be associated with a lower risk of AD and dementia. In other words, many of the strategies and interventions reviewed here have well-documented health-promoting effects, but none have been proven to prevent or delay AD or dementia. Having pondered the consequences of doing nothing to prevent or delay the onset of AD or dementia, paired with the demographic shift that has already begun, programs designed to promote healthy aging, including a number of the measures described above, should be implemented because they are likely to be beneficial throughout the lifespan of most people as they age. In fact, we at the University of Pennsylvania have initiated several "healthy brain aging" programs, including one funded by the MetLife Foundation, that will have local, statewide, and national impact. These "healthy brain aging" programs will provide preliminary data for the design of larger scale programs once the much needed research on prevention strategies has been accomplished.

As the demographics of the United States continue to undergo dramatic shifts in the coming decades, it is imperative that we make a major commitment of resources to researching the most promising strategies and interventions for preventing or delaying AD and dementia. The research described above has provided us with a map of many promising areas of inquiry. What is needed now is a greater investment of research dollars that will allow the necessary follow-up studies to be conducted in a timely manner.

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