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Risk Factors and Preventive Interventions for Alzheimer Disease

State of the Science

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Background: Numerous studies have investigated risk factors for Alzheimer disease (AD). However, at a recent National Institutes of Health State-of-the-Science Conference, an independent panel found insufficient evidence to support the association of any modifiable factor with risk of cognitive decline or AD.

Objective: To present key findings for selected factors and AD risk that led the panel to their conclusion.

Data Sources: An evidence report was commissioned by the Agency for Healthcare Research and Quality. It included English-language publications in MEDLINE and the Cochrane Database of Systematic Reviews from 1984 through October 27, 2009. Expert presentations and public discussions were considered.

Study Selection: Study inclusion criteria for the evidence report were participants aged 50 years and older from general populations in developed countries; minimum sample sizes of 300 for cohort studies and 50 for randomized controlled trials; at least 2 years between exposure and outcome assessment; and use of well-accepted diagnostic criteria for AD.

Data Extraction: Included studies were evaluated for eligibility and data were abstracted. Quality of overall evidence for each factor was summarized as low, moderate, or high.

Data Synthesis: Diabetes mellitus, hyperlipidemia in midlife, and current tobacco use were associated with increased risk of AD, and Mediterranean-type diet, folic acid intake, low or moderate alcohol intake, cognitive activities, and physical activity were associated with decreased risk. The quality of evidence was low for all of these associations.

Conclusion: Currently, insufficient evidence exists to draw firm conclusions on the association of any modifiable factors with risk of AD.

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ALZHEIMER DISEASE (AD) IS the most common cause of dementia, accounting for an estimated 60% to 80% of all dementia cases.[1] It is characterized by pathological hallmarks in the brain, ie, abnormal protein deposits (β-amyloid plaques) and tangled protein fibers (neurofibrillary tangles). Up to 5.3 million Americans may currently have AD,[1] and these numbers are expected to increase significantly with the aging of the baby boom generation.

Age is currently the strongest known risk factor for AD; there is also strong evidence that apolipoprotein E (*APOE*) gene variation is associated with higher risk of AD. To date, numerous studies have attempted to delineate risk factors for the development and progression of AD, generating abundant theories on potential risk factors, preventive measures, and therapies. However, at the State-of-the-Science Conference convened by the National Institutes of Health (NIH),[2] an independent panel concluded that currently there is no evidence of even moderate scientific quality supporting the association of any modifiable factor with reduced risk of cognitive decline or AD. Several members of the panel and authors of a related evidence-based review[3] were invited to write this article to address the many concerns generated by this panel's report among researchers, clinicians, and the general public. We describe the NIH Consensus Development Program and present key findings on risk factors and preventive measures for AD—specifically focusing on nutritional supple-

ments, dietary factors, lifestyle behaviors, and chronic disease risk factors—that led the panel to their conclusion. The panel's conclusions on cognitive decline are not addressed in this article.

METHODS

A State-of-the-Science Conference was convened from April 26 through 28, 2010, by the National Institute on Aging and the NIH Office of Medical Applications of Research to evaluate current scientific evidence on risk factors for and preventive measures against development of cognitive decline and AD. A multidisciplinary independent panel with no financial or intellectual conflicts with regard to the conference topic was convened to judge the scientific evidence, including a formal evidence report prepared by Duke University researchers.

EVIDENCE REPORT

A standard protocol for all steps of the review was developed based on procedures used in previous Agency for Healthcare Research and Quality systematic reviews.[3] The evidence review and State-of-the-Science Conference addressed 6 key research questions developed by an NIH Office of Medical Applications of Research State-of-the Science Conference planning committee, which also identified the specific factors to be reviewed. This article discusses the methodological issues, strength of the evidence, results, and conclusions regarding the association of selected modifiable factors with risk of AD.

English-language publications in MEDLINE and the Cochrane Database of Systematic Reviews from 1984 through October 27, 2009, were searched. Study inclusion criteria were as follows: (1) samples of adults aged 50 years and older drawn from general populations in developed countries; (2) sample sizes of at least 300 for cohort studies and 50 for randomized controlled trials (RCTs); (3) determination of AD based on well-accepted diagnostic criteria; and (4) at least 2 years between exposure and diagnosis of dementia. Studies lacking baseline cognitive assessment were required to demonstrate some evidence of minimal likelihood of dementia at baseline. No animal studies were considered.

Study information on applicability, quality, intervention or exposure, and outcomes was extracted. Standard criteria for assessing methodological quality were used for systematic reviews and RCTs.[3] For observational studies, quality criteria used in previous Agency for Healthcare Research and Quality reports were adapted; these assessed cohort selection methods, adequacy of sample size, exposure and outcomes ascertainment methods, adequacy and completeness of follow-up, and appropriateness of analytic methods.[3]

Principles from the Grading of Recommendations Assessment, Development, and Evaluation working group (http://www.gradeworkinggroup.org) were used to summarize the level of evidence overall for each factor (low, moderate, or high) reflecting the confidence in the estimate of effect. This approach evaluates the body of evidence for each outcome, assigning an initial rating of low to observational studies and high to RCTs. Ratings were modified by the following factors: detailed study design, consistency of results, strength of association, dose-response effect, directness, precision, and whether all plausible confounders would reduce a demonstrated effect. Of note, *low-quality evidence* indicates that additional research may affect the direction or magnitude of the observed association and is not a judgment of an individual study.

DATA SYNTHESIS AND ANALYSIS

The evidence was generally summarized in narrative form. Primary meta-analyses were done only when studies were of high quality, were conceptually and methodologically homogeneous, and had the necessary data for the summary estimate. The complete evidence report is available at http://www.ahrq.gov/clinic/tp/alzcogtp.htm.

CONFERENCE PROCEEDINGS AND FINAL REPORT

At the conference, presentations by experts were followed by public discussions with questions and statements from attendees. After weighing the evidence, the panel prepared and presented a statement addressing the conference questions. The panel's charge was limited to assessing existing evidence on specific factors related to prevention of AD and cognitive decline. The full report is available at http://consensus.nih.gov/2010/alzstatement.htm; an abridged report was also published.[2]

RESULTS

Existing studies were compromised by methodological limitations in the assessment of both exposures and outcome, ie, AD. A number of the cohort studies were designed to investigate other outcomes (eg, cardiovascular disease, cancer), with AD examined as a secondary and/or post hoc interest. Furthermore, dementia is associated with cardiovascular diseases, which in turn may coexist with AD pathology, potentially confounding attempts to identify true associations.

We summarize here the evidence on selected potential modifiable factors for prevention of AD. The methods and findings of the studies reviewed are detailed in supplementary tables available at http://depot.northwestern.edu/mld710/ADSupplementalTables.

NUTRITIONAL SUPPLEMENTS AND DIETARY FACTORS

Five eligible cohort studies examining effects of B vitamins or folate on prevention of AD were identified. Low baseline serum folate levels were associated with increased risk of AD.[4,5] Studies that estimated dietary intake of folate and B vitamins from self-reported information yielded conflicting results on association of folate intake with risk of AD.[6,7] Vitamins B_6 and B_{12} were not associated with risk of AD. Only one study examined niacin (vitamin B_3) intake, reporting a lower risk for AD associated with higher intakes (for highest vs lowest quintile of total niacin intake: relative risk [RR] = 0.2; 95% confidence interval [CI], 0.01-0.7; *P* for trend = .04).[8]

In an RCT on supplemental vitamin E intake and progression of amnestic mild cognitive impairment to AD, rate of progression from amnestic mild cognitive impairment to AD did not differ between the treatment and placebo groups (hazard ratio [HR] = 1.02; 95% CI, 0.74-1.41).[9] Cohort studies that have examined antioxidant and multivitamin use and risk of AD have yielded inconclusive findings. However, the bulk of the evidence suggests that there is no association between intakes of vitamins E or C, flavonoids, and beta carotene and risk of AD.

Eligible cohort studies on the association of ω-3 fatty acid intake and incident AD mostly focused on fish consumption to estimate ω-3 fatty acid intake without considering other dietary sources or supplements. There was considerable heterogeneity in the assessment of ω-3 consumption including types of fish, dosage, and duration of use. No consistent association was found.[10-16]

Two eligible cohort studies that examined association of fat intake with risk of AD were identified.[17,18] Dietary fat intake (total, polyunsaturated, or monounsaturated), determined based on a self-reported 20-question multiple-choice questionnaire in midlife, was not associated with risk of AD.[17] Higher intakes of saturated fats and transunsaturated fats later in life—assessed by the Food Frequency Questionnaire—were associated with increased risk of AD (for highest vs lowest quintile of saturated fat intake: RR=2.2; 95% CI, 1.1-4.7; for transunsaturated fat intake, only quintiles 2 and 3 compared with quintile 1 were significantly associated with higher AD risk), while higher intake of ω-6 fatty acids was associated with decreased risk (for quintile 5 vs 1: RR=0.3; 95% CI, 0.1-0.8).[18]

Two eligible cohort studies examining the association of intake of fruits and vegetables[19] or of fruit and vegetable juices with risk of AD were identified.[20] Medium or high fruit and vegetable intake compared with no or little consumption in midlife determined based on response to 1 question on fruit and vegetable consumption was associated with lower risk of AD in late life among women (odds ratio [OR]=0.47; 95% CI, 0.31-0.73) but not men.[19] Intake of fruit and vegetable juices at least 3 times per week vs less than once per week in later life was associated with reduced risk of incident AD (HR=0.24; 95% CI, 0.09-0.61). While self-reported semiquantitative Food Frequency Questionnaires were used, only low to moderate correlations were seen between food records and Food Frequency Questionnaire responses for major nutrient groups.[20]

Multiple studies on one US cohort reported lower risk of AD with adherence to a Mediterranean diet (eg, for highest [6-9] vs lowest [0-3] Mediterranean diet score range: HR=0.60; 95% CI, 0.42-0.87).[21-23] While a study on a separate sample also reported lower risk of AD with high adherence to a Mediterranean diet, findings were not significant (for high [6-9] vs low [0-3] Mediterranean diet score range: HR=0.86; 95% CI, 0.39-1.88).[24]

The effectiveness of *Ginkgo biloba* vs placebo in reducing incident AD was examined by one RCT among 3069 individuals aged 75 years and older with normal cognition or mild cognitive impairment (n=482).[25] The HR for AD among the entire sample for the treatment vs placebo group was 1.16 (95% CI, 0.97-1.39). *Ginkgo biloba* had no effect on the rate of progression from mild cognitive impairment to AD (HR=1.10; 95% CI, 0.83-1.47).

PHYSICAL ACTIVITY

Twelve eligible cohort studies examining the association between physical activity and incident AD were identified.[22,26-35] All studies assessed self-reported physical activity, most assessed current physical activity, and one asked about activities during the past 25 years (from ages 25-50 years).[29] In general, the accuracy of self-reported physical activity measures was not objectively validated. Eight studies reported a protective effect of moderate to high levels of physical activity on risk of AD; however, associations were not always significant after adjusting for confounding factors or across both moderate and high activity levels. A random-effects meta-analysis combining 9 cohort studies found that higher physical activity was associated with lower risk of incident AD (HR=0.72; 95% CI, 0.53-0.98). However, there was substantial heterogeneity among the studies. Associations were not always statistically significant, and in some studies the risk estimates were in the direction indicating increased risk of AD.

DIABETES MELLITUS

Several cohort studies and systematic reviews reported associations between diabetes mellitus and incident AD,[36-41] but results of individual studies varied. Biessels et al[36] conducted a systematic review of 11 cohort studies with fair to good cohort design quality. Nine of 10 studies reported an increased risk of incident AD among diabetic individuals (risk estimates range, 1.2-2.4; 95% CI>1.0 in 5 studies). Of the 5 studies that adjusted for vascular risk factors, 4 reported risk estimates greater than 1 (range, 0.8-2.0), but for only 2 studies the adjusted HR excluded no effect. Midlife diabetes status was inconsistently associated with risk of incident AD. Longitudinal studies assessing dementia and diabetes later in life reported fairly consistent results, with 7 of 11 studies reporting a 50% to 100% increase in AD incidence. Biessels and colleagues concluded that diabetes is associated with an increased risk of AD. A subsequent review by Lu et al[37] identified 2 additional cohort studies; both reported nonsignificantly higher risks of AD among diabetic individuals compared with nondiabetic individuals. In their meta-analysis, using data from 8 prospective cohort studies, Lu and colleagues found a 39% higher combined RR for incident AD among diabetic individuals compared with nondiabetic individuals (95% CI, 1.16-1.66). Limitations of the studies we have described included variable diagnostic criteria for diabetes and failure to consider duration of diabetes and degree of glycemic control. Two subsequent studies variously reported an increased risk of AD among individuals with diabetes[40] and an increased risk of AD among individuals with borderline diabetes or undiagnosed diabetes but not among individuals diagnosed as having diabetes.[41]

HYPERCHOLESTEROLEMIA

One good-quality systematic review examined total cholesterol levels as a risk factor for AD[42]; however, the 8 studies included were too heterogeneous to combine in a single analysis. Two studies reported that a midlife high cholesterol level was associated with increased risk of AD (for incident AD for total cholesterol ≥251 vs <251 mg/dL [to convert to millimoles per liter, multiply by 0.0259]: OR=2.8; 95% CI, 1.2-6.7 in one study; OR=3.1; 95% CI, 1.2-8.5 in the other study). In the Framingham cohort,

cholesterol measures averaged across the study period were not associated with incident AD, while in another study, decreasing cholesterol level from mid to late life was associated with increased risk of AD. Fixed-effects meta-analysis on 3 studies examining cholesterol levels in late life found no association between total cholesterol level and incident AD (for the highest vs lowest quartile: pooled RR=0.85; 95% CI, 0.65-1.12).

HYPERTENSION

Among the 10 eligible cohort studies examining the association between hypertension and incident AD, definitions of hypertension varied. Two studies assessed self-reported hypertension only and found no association with incident AD.[43,44] When hypertension was defined as systolic blood pressure higher than 140 mm Hg,[45-48] there was no consistent association with increased risk. When hypertension was defined as systolic blood pressure higher than 160 mm Hg,[48-51] only 1 of 4 studies (an analysis of the FINMONICA cohort[51]) showed a statistically significant increased risk of AD (for systolic blood pressure >160 vs <140 mm Hg: OR=2.8; 95% CI, 1.1-7.2). Of 6 studies examining high diastolic blood pressure as a risk factor,[46,48-53] only 1 reported significant results: among middle-aged men who had never been treated with antihypertensive medications, diastolic hypertension (≥95 mm Hg) was significantly associated with incident AD in the Honolulu-Asia Aging Study cohort (for high diastolic blood pressure vs diastolic blood pressure 80-89 mm Hg: OR=4.47; 95% CI, 1.53-13.09).[49]

CIGARETTE SMOKING

Studies examining cigarette smoking consistently showed an increased risk of AD among current smokers compared with never or former smokers, although findings were not always significant. A systematic review examining the association between tobacco use and the development of AD[54] found that current smokers were at greater risk for AD compared with never smokers or former smokers (for current vs never smokers: pooled RR=1.79; 95% CI, 1.43-2.23; and for current vs former smokers: pooled RR=1.70; 95% CI, 1.25-2.31). However, former smokers included a broad range of exposure periods, with too few studies with data on the number of pack-years to use this as the exposure variable. Two additional cohort studies showed an increased risk of AD among current smokers compared with never smokers.[55,56]

ALCOHOL USE

In the single good-quality systematic review on the association of alcohol use and development of AD,[57] both all drinkers combined and light to moderate drinkers had a lower risk of AD compared with nondrinkers; however, heavy drinkers showed no difference in risk compared with nondrinkers (for all drinkers vs nondrinkers: pooled RR=0.66; 95% CI, 0.47-0.94; for light to moderate drinkers vs nondrinkers: pooled RR=0.72; 95% CI, 0.61-0.86; and for heavy drinkers vs nondrinkers: pooled RR=0.92; 95% CI, 0.59-1.45). Limitations included variations in type of beverage consumed and criteria for measuring and categorizing quantity. In addition, these meta-analyses and many of the studies were limited to current alcohol use, but alcohol patterns may change over a lifetime and former drinkers may differ from lifetime abstainers. Of the 5 studies in the review that collected data on former drinkers and lifetime abstainers, 3 showed no differences in the associations between the 2 groups, while the other 2 suggested that former drinkers may account for much of the cognitive impairment seen among nondrinkers. This implies that former drinkers may have stopped drinking for reasons such as health issues that also predispose to cognitive impairment. Thus, it remains unclear whether any association seen is due to confounding factors.

COGNITIVE ENGAGEMENT

Four eligible cohort studies on the association between cognitive engagement and development of AD were identified.[27,28,58,59] In all 4 studies, participants had normal cognition at baseline, and self-reported frequency of involvement in specific activities was assessed; 3 of the studies assessed current involvement in cognitive activities,[27,28,58] while the fourth inquired about activities across the life span. There was no objective validation of this method, although 1 study did seek confirmation of activities by an informant.[27] Only 1 study used sample selection methods that fully minimize selection bias.[28] All 4 studies showed a somewhat decreased risk of AD associated with greater involvement in cognitive activities. However, in 1 study, although frequent past cognitive activity was associated with decreased risk of AD when current and past activity were assessed in the same model, the effect of past activity was eliminated and that of current activity persisted.[59] This suggested that the latter explained the protective association (for more frequent current cognitive activity level: adjusted HR=0.58; 95% CI, 0.44-0.77).

COMMENT

Diabetes mellitus, hyperlipidemia during midlife, and current tobacco use have been associated with increased risk of AD, and Mediterranean diet, folic acid intake, light to moderate alcohol intake, cognitive activities, and physical activity (particularly high levels) have been associated with decreased risk of AD. However, the level of evidence based on Grading of Recommendations Assessment, Development, and Evaluation criteria is low. Further studies using validated exposure measures are needed to confirm these findings. *Ginkgo biloba* and vitamin E intakes had no association with risk of AD based on evidence of high and moderate quality, respectively. Hypertension and intakes of ω-3 fatty acids, vitamin B_{12}, and beta carotene were not associated with risk of AD, although the level of evidence was low. Finally, there was inadequate evidence to assess the association of dietary factors such as saturated fat intake and fruit and vegetable intake with risk of AD.

Although numerous studies have investigated risk factors and potential therapies for AD, significant gaps in

scientific knowledge exist. Currently, firm conclusions simply cannot be drawn about the association of any modifiable risk factor with AD, and there is insufficient evidence to support the use of any lifestyle interventions or dietary supplements to prevent AD. Existing studies have been hampered by methodological issues, including reliance on self-reported information, limited knowledge of the natural history of AD, and inconsistent use of consensus-based diagnostic criteria for AD. Large-scale, long-term, population-based studies and clinical trials are urgently needed to identify risk factors for AD and measures that may slow the progression of established AD, using consensus-based diagnostic criteria to characterize the natural history of AD similar to those studies conducted fruitfully for other major chronic diseases. Future studies should include women and men from diverse socioeconomic and ethnic groups to identify specific population subgroups that may be at higher risk for developing AD based on nonmodifiable factors such as age, ethnicity, or gene variation.

It is important to note that the panel was charged with the task of compiling and assessing quality of existing evidence on specific risk factors and preventive measures for AD and determining whether any recommendations could be made based on their findings. The panel's findings did not shed new light on risk factors for AD; rather, they clarified the state of existing knowledge and helped to establish priorities for future research. The NIH Consensus Development Program functions as a "science court" model, with an independent multidisciplinary panel (free from intellectual or financial conflicts with regard to the conference topic) assembled to serve as an impartial jury judging the evidence.

It cannot be emphasized enough that while risk factors and preventive measures studied so far have at best been only loosely associated with AD, carefully designed future studies may yet establish significant associations between these same factors with prevention of AD. It is hoped that the panel's report will instigate rigorous high-quality research that can provide conclusive evidence on this issue. Many of the putative risk factors for AD are those that have been targeted for prevention of other late-life chronic diseases. Thus, until more conclusive results are available, individuals should continue to aim for a physically and mentally active and healthy lifestyle and prevention of the well-known major risk factors for chronic diseases.

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