Evidence Report/Technology Assessment
Number 193

Preventing Alzheimer's Disease and Cognitive Decline

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA 290-2007-10066-I

Prepared by:
Duke Evidence-based Practice Center
Durham, North Carolina

Authors:
John W. Williams, M.D., M.P.H.
Brenda L. Plassman, Ph.D.
James Burke, M.D, Ph.D.
Tracey Holsinger, M.D.
Sophiya Benjamin, M.D.

AHRQ Publication No. 10-E005
April 2010

This report is based on research conducted by the Duke Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2007-10066-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

Suggested Citation:
Williams JW, Plassman BL, Burke J, Holsinger T, Benjamin S. Preventing Alzheimer's Disease and Cognitive Decline. Evidence Report/Technology Assessment No. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.

No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in this report.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) requested and provided funding for this report. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Jennifer Crossman, M.D.
Acting Director
National Institutes of Health (NIH)
Office of Medical Applications of Research
(OMAR)

Beth A. Collins Sharp, Ph.D., R.N.
Director, EPC Program
Agency for Healthcare Research and Quality

Steven Fox, M.D, S.M., M.P.H
EPC Program Task Order Officer
Agency for Healthcare Research and Quality

Acknowledgments

The authors thank the following individuals: for help with literature search and retrieval, Connie Schardt; for statistical support, Victor Hasselblad, Ph.D.; for assistance in the preparation of evidence tables, Remy Coeytaux, M.D., Ph.D.; Jennifer McDuffie, Ph.D.; Ravi Dhurjati, D.Phil.; Carolina Aponte Urdaneta, M.D.; and Katie Dore, P.A-C.; for project management, Julian Irvine, M.C.M.; for editorial assistance, Rebecca Gray, D.Phil.; and for research assistance, Alice Thacher and Vincent Miller.

Structured Abstract

Objectives: To assess whether previous research on purported risk or protective factors for Alzheimer's disease (AD) and cognitive decline is of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints.

Data Sources: MEDLINE® and the Cochrane Database of Systematic Reviews. Additional studies were identified from reference lists and technical experts.

Review Methods: A group of experts in the field developed the list of factors to be evaluated in preparation for an upcoming National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) State-of-the-Science Conference addressing the prevention of AD and cognitive decline. We grouped the factors into the following categories: nutritional factors, medical conditions and prescription and non-prescription medications, social/economic/behavioral factors, toxic environmental factors, and genetics. Outcomes of interest were the development of AD or cognitive decline. Both observational and intervention studies were evaluated. Studies were evaluated for eligibility and quality, and data were abstracted on study design, demographics, intervention or predictor factor, and cognitive outcomes.

Results: A total of 25 systematic reviews and 250 primary research studies were included. Only a few factors showed a consistent association with AD or cognitive decline across multiple studies, including both observational studies and randomized controlled trials (when available). Such factors associated with increased risk of AD and cognitive decline were: diabetes, epsilon 4 allele of the apolipoprotein E gene (APOE e4), smoking, and depression. Factors showing a fairly consistent association with decreased risk of AD and cognitive decline were: cognitive engagement and physical activities. A consistent association does not imply that findings were robust, as the data were often limited, and the quality of evidence was typically low. In addition, the modification of risk for reported associations was typically small to moderate for AD, and small for cognitive decline. Some of the factors that did not show an association with AD or cognitive decline in this review may still play an influential role in late-life cognition, but there was not sufficient evidence to draw this conclusion. Many of the factors evaluated are not amenable to randomization, so rigorous observational studies are required to assess their effect on AD and cognitive decline.

Conclusions: The current research on the list of putative risk or protective factors is largely inadequate to confidently assess their association with AD or cognitive decline. Further research that addresses the limitations of existing studies is needed prior to be able to make recommendations on interventions.

Contents

Figures

Tables

Appendixes

Appendixes (including evidence tables) for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/alzheimers/alzcog.pdf.

Executive Summary

Introduction

Dementia is a loss of cognitive abilities in multiple domains that results in impairment in normal activities of daily living and loss of independence. Alzheimer's disease (AD) is the most common cause of dementia, responsible for 60 to 80 percent of all dementia. AD causes severe suffering for patients, including progressive functional impairment, loss of independence, emotional distress, and behavioral symptoms. Families and caregivers often experience emotional and financial stress.

The major risk factor for AD is age, with the prevalence doubling every 5 years after the age of 65. Most estimates of the prevalence of AD in the United States are about 2.3 million for individuals over age 70, but some estimates are as high as 5.3 million individuals over the age of 65. The number of individuals with mild cognitive impairment exceeds the number with AD. These individuals have mild impairment in cognition or daily functions that does not meet the threshold for a diagnosis of dementia, but they are at increased risk for development of AD, which makes them a prime target for intervention protocols.

Studies of selected risk or protective factors for cognitive decline and AD have been published, but it is not clear whether the results of these previous studies are of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints.

As background for an upcoming State-of-the-Science Conference in April 2010, the National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) commissioned this evidence report on "Preventing Alzheimer's Disease and Cognitive Decline" through the Agency for Healthcare Research and Quality (AHRQ). The aim is to summarize the available literature, frame the discussion regarding potential risk factors, and highlight the limitations of the evidence base.

We synthesized the existing literature on the following key questions:

Key Question 1: What factors are associated with the reduction of risk of Alzheimer's disease?

Key Question 2: What factors are associated with the reduction of risk of cognitive decline in older adults?

Key Question 3: What are the therapeutic and adverse effects of interventions to delay the onset of Alzheimer's disease? Are there differences in outcomes among identifiable subgroups?

Key Question 4: What are the therapeutic and adverse effects of interventions to improve or maintain cognitive ability or function? Are there differences in outcomes among identifiable subgroups?

Key Question 5: What are the relationships between the factors that affect Alzheimer's disease and the factors that affect cognitive decline?

Key Question 6: If recommendations for interventions cannot be made currently, what studies need to be done that could provide the quality and strength of evidence necessary to make such recommendations to individuals?

Methods

We searched MEDLINE® using Medical Subject Heading (MeSH) search terms, supplemented by keyword searches. In addition to MEDLINE®, we manually searched reference lists and searched the Cochrane Database of Systematic Reviews to identify relevant systematic reviews. For topics with a recent good-quality systematic review, we updated the search by identifying relevant primary literature published from 1 year prior to the search date of the review through October 27, 2009. When we did not identify a relevant good-quality review, we searched the primary literature for studies from 1984 through October 27, 2009. Because of the large volume of literature and the availability of specialized registries for genetic studies, we developed a separate search strategy for this topic and limited our review to select genes of special interest.

We restricted our review to human studies conducted in economically developed countries and published in English. We considered studies with participants ≥ 50 years old, of both sexes, all racial and ethnic populations, and drawn from general populations. We limited the sample size to ≥ 50 for randomized controlled trials (RCTs) and ≥ 300 for observational studies. We required at least 1 year between exposure and outcomes assessment for studies of cognitive decline, and 2 years for studies of AD. For Key Questions 1 and 2, we evaluated studies using observational designs; for Key Questions 3 and 4, we evaluated RCTs. Two reviewers independently assessed study eligibility and study quality and abstracted data. For Key Questions 1 through 5, we considered factors identified by the OMAR planning committee in five major categories: (1) nutritional factors; (2) medical factors (including medical conditions and prescription and non-prescription medications); (3) social/economic/behavioral factors; (4) toxic and environmental factors; and (5) genetics. Data were synthesized qualitatively and, when appropriate, using quantitative methods. We rated the overall level of evidence for each factor as high, moderate, or low using principles developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. The level of evidence is considered "high" when further research is very unlikely to change our confidence in the estimate of effect, and "low" when further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Results

A total of 25 systematic reviews and 250 primary studies met our inclusion criteria. The number of included studies differed markedly across the factors considered. Results are summarized immediately below by key question. We focus in this summary on the factors that showed an association with AD or cognitive decline. Those factors that did not show a consistent association with cognitive outcomes are described in more detail in the full report; this highlights

the point that among the many factors investigated, only a few have sufficient evidence to indicate a potential association with late-life cognitive outcomes.

Finally, at the conclusion of this section, we present two summary tables that show the direction of association (if any) and the level of evidence for all factors considered in the report.

Key Question 1 – Factors Associated with Risk of Developing AD

The results reported here are based on observational studies of AD, but to fully understand the associations between factors and cognitive outcomes, it is important to consider the results from both observational studies and RCTs when the latter are available.

In the nutrition category, both higher levels of folic acid and higher adherence to a Mediterranean diet were associated with a small to moderate decrease in risk of AD. The level of evidence was low for both of these factors.

For medical conditions, diabetes (summary odds ratio [OR] 1.39; 95 percent confidence interval [CI] 1.17 to 1.66), hyperlipidemia in mid-life, depression (summary OR 1.90; 1.55 to 2.33), and traumatic brain injury in males (summary OR 2.29; 1.47 to 3.58) were all associated with increased risk of AD. The level of evidence was low for each of these factors. No other factors showed a consistent relation to AD.

In the medication category, use of statins (summary hazard ratio [HR] 0.73; 95 percent CI 0.57 to 0.94) showed an association with decreased risk of AD. The observational studies for estrogen (summary relative risk [RR] 0.50; 95 percent CI 0.30 to 0.80) and antihypertensives showed a likely protective association with AD. The level of the evidence was low for these factors.

In the social, economic, and behavioral category, current smoking (summary RR 1.79; 95 percent CI 1.43 to 2.23) was associated with increased risk of AD. Moderate use of alcohol (summary RR 0.72; 0.61 to 0.86), more years of education, and higher levels of cognitive engagement showed an association with a moderately decreased risk of AD. Participation in physical leisure activity (summary HR 0.72; 95 percent CI 0.53 to 0.98) was generally associated with decreased risk of AD. Limited data on marriage and social support suggest that never being married and having less social support are associated with a moderately increased risk of AD. The level of evidence for all of these factors was low.

For the environmental exposure category, case-control studies were included for the subtopics reviewed (solvents, pesticides, lead, and aluminum) because there were few cohort studies that met inclusion criteria. Only pesticides showed a consistent and large association with higher risk of AD, but the level of the evidence was low.

For the review of genes, we identified 10 genes with the strongest and best quality evidence of an association with AD based on a systematic review and quality ratings conducted by ALZGene, an online database of genetic association studies performed on AD phenotypes. Based on the selection criteria, it is not surprising that all genes showed a significant association with AD. It is noteworthy that the epsilon 4 allele of the apolipoprotein E gene (APOE e4) allele showed the highest and most consistent risk for AD (summary OR 3.68; 95 percent CI 3.3 to 4.1). The level of evidence was moderate for the APOE e4 allele.

Key Question 2 – Factors Associated with Risk of Cognitive Decline

The results reported for this question are based on observational studies for cognitive decline.

Effect sizes in all cases were small to moderate. In the nutrition category, low plasma selenium showed an association with higher risk of cognitive decline. Higher amounts of vegetable intake, adherence to a Mediterranean diet, and higher levels of omega-3 fatty acids showed a likely association with decreased risk of cognitive decline, but evidence was limited for some of these factors. The level of evidence was low for all of these factors.

For the medical category, diabetes, metabolic syndrome, and depression showed fairly consistent associations with a small increased risk of cognitive decline. There were no studies that met inclusion criteria on cognitive decline and traumatic brain injury, sleep apnea, resiliency, or anxiety.

For the medication category, two types of medication (non-steroidal anti-inflammatory drugs [NSAIDs] and estrogen) showed possibly decreased risk for cognitive decline in select subgroups, but the other medications evaluated (statins, antihypertensives, and cholinesterase inhibitors) showed no association or no consistent association with cognitive decline.

Among the social, economic, and behavioral factors, smoking showed an increased risk of cognitive decline. Participation in non-physical/non-cognitive leisure activities, cognitive engagement, and physical activity all showed a fairly consistent protective association against cognitive decline. For observational studies, the level of evidence was low for these factors.

There were no eligible studies identified for the environmental exposure category.

In the genetic category, only APOE has been assessed in relation to cognitive decline. The studies fairly consistently report that APOE e4 is associated with greater cognitive decline on selected cognitive measures that were not consistent across studies. The level of evidence was rated as low for this factor.

Key Question 3 – Interventions to Delay the Onset of AD

There were relatively few RCTs assessing the association between the factors examined and AD. This is at least partially attributable to the fact that many of the factors are not amenable to testing in an RCT. There were also sparse, if any, data on differences in outcomes among subgroups because the few RCTs conducted have generally not been designed to assess such differences.

For the nutrition category, there was one RCT on vitamin E and one on gingko biloba that showed no association with AD. There were no other RCTs for nutritional factors, including folic acid and Mediterranean diet, factors suggested to decrease risk by observational studies.

The factors in the medical conditions category are not appropriate for randomization.

For the medications category, the three RCTs using antihypertensive medication showed no association with AD, but findings were limited by low power to detect a clinically important effect and assessment for all-cause dementia rather than AD. The eight RCTs using cholinesterase inhibitors showed no association with AD (moderate level of evidence). The two RCTs assessing NSAIDs showed increased risk of AD with rofecoxib, a medication that was subsequently withdrawn from the market for safety reasons, and increased risk for non-specific dementia with naproxen (HR 3.57; 95 percent CI 1.09 to 11.7) but the study was stopped early and findings were based on few cases. In intervention trials, estrogen alone showed no association, but estrogen combined with progesterone showed an increased risk of AD (HR 2.05;

95 percent CI 1.21 to 3.48). The level of evidence was rated as moderate for estrogen combined with progesterone and low for NSAIDs.

For the social, economic, and behavioral factors, there were no intervention trials for any factors, including physical activity and cognitive engagement, interventions suggested to be beneficial by observational studies.

Key Question 4 – Interventions to Improve or Maintain Cognitive Ability or Function

There were few RCTs assessing the effect of the various factors on cognitive decline. Additionally there was no information on differential outcomes by subgroups.

For the nutrition category, intervention trials of vitamin B6 and B12, vitamin E, and folic acid showed either no effect on cognitive decline or no consistent effect across trials. The level of evidence was judged to be high for vitamin E and moderate for the other supplements. We did not identify any trials that evaluated the Mediterranean diet or diets high in vegetables, practices that have been associated with lower risk of cognitive decline in observational studies.

The medical conditions were not appropriate for RCTs.

For the medication category, there was no effect of statins (level of evidence = high), antihypertensive medications (low), cholinesterase inhibitors (moderate), or estrogen (high). Some of the types of NSAIDs showed no effect, but one (naproxen) showed increased risk of cognitive decline. The level of evidence for NSAIDs was rated as low. Observational studies had suggested lower risk for both NSAIDs and estrogen.

For the social, economic, and behavioral categories, physical activity and cognitive training interventions showed a small protective association against cognitive decline. The level of the evidence for cognitive training was rated high, but that for physical activity was rated low.

Key Question 5 – Relationships Between Factors Affecting AD and Cognitive Decline

To address this question, we used the results from Key Questions 1 through 4 to compare the evidence for the effects of each exposure on risk of AD and cognitive decline. For factors with both RCT and observational evidence, we first compared the consistency of findings across study designs for each outcome. RCTs were preferred when of high quality. When studies showed a consistent effect on risk that was in the same direction for both AD and cognitive decline, we judged the results concordant. For many factors, the available data are quite limited, and concordant evidence across outcomes should not necessarily be interpreted as a robust finding. For other factors, not only were data limited but there was also marked heterogeneity in exposure or outcome measures across studies, so it was not possible to draw a conclusion about concordance. It is important to note that risk modification was generally small to moderate when factors were associated with AD (i.e., odds ratios and relative risk ratios were often substantially < 2.0). For cognitive decline, it is more difficult to determine the threshold for a meaningful change due to the numerous cognitive measures used to assess cognitive decline. But generally the differences in annual rate of decline between the exposed and unexposed groups were quite small.

To summarize results for Key Question 5, **factors showing an association for <u>both</u> AD and cognitive decline were:**

Increased risk:	Diabetes
	APOE e4
	Smoking
	Depression
Decreased risk:	Mediterranean diet (limited data)
	Cognitive engagement
	Physical activities

Key Question 6 – Future Research Needs

The current evidence is insufficient to recommend interventions. Weaknesses in the research methodology used in many of the studies reviewed have led to gaps in our knowledge. Critical improvements that are needed are: more precise, better validated, and more standard exposure measures; more standardized cognitive assessment measures across studies that are appropriate for the functional level of the sample (e.g. cognitively normal, mild cognitive impairment [MCI]); studies of longer duration; and better documentation and reporting of methods and results. Studies should also take into account the intensity, duration, and timing of the exposure, as exposures may be more influential and interventions more effective during critical or sensitive windows of time throughout life. Given the long sub-clinical, prodromal period of AD, RCTs need to continue for extended periods of time, and/or better methods need to be devised to evaluate potential interventions more rigorously in long-term observational studies. Although long-term RCTs are the ideal approach, in many cases the barriers to implementing such studies may make them unrealistic. For this reason, RCTs might aim to identify individuals at high risk of cognitive decline to make trials more efficient and economical. In addition, alternative research designs and analytical approaches should be considered. The development of research consortia might be considered to address the problems of inconsistent measurement of exposures and small sample sizes commonly found in previous research. Factors that may now be ready to be assessed further in RCTs are physical exercise and cognitive engagement. Although a few intervention trials have been done on some aspects of these factors, there is a need for trials that consider multiple components of the same general factor and multiple factors simultaneously.

Summary Tables

Tables ES1 and ES2 provide an overall summary of the direction of association (if any) and the level of evidence for all factors considered in the report for AD and cognitive decline, respectively.

Table ES1. Summary of findings on potential risk factors and interventions for AD

Direction of association	Factors	Level of evidence‡
Increased risk	• APOE e4 genotype • Conjugated equine estrogen with methyl progesterone*	Moderate
	• Some non-steroidal anti-inflammatory drugs* • Depressive disorder • Diabetes mellitus • Hyperlipidemia in mid-life • Traumatic brain injury in males • Pesticide exposure • Never married, less social support • Current tobacco use	Low
Decreased risk	• Mediterranean diet • Folic acid • HMG-CoA reductase inhibitors (statins) • Higher levels of education • Light to moderate alcohol intake • Cognitively engaging activities • Physical activity, particularly high levels	Low
No association	• Ginkgo biloba*	High
	• Vitamin E* • Cholinesterase inhibitors*	Moderate
	• Anti-hypertensive medication* • Conjugated equine estrogen • Omega-3 fatty acids* • Vitamins B12, C, beta-carotene • Homocysteine • Hypertension • Obesity • Metabolic syndrome • Early childhood factors • Occupational level • Lead	Low
Inadequate evidence to assess association	• Saturated fat intake • Fruit and vegetable intake • Trace metals • High caloric intake • Memantine • Sleep apnea • Anxiety disorders • Resiliency • Non-cognitive, non-physical leisure activities • Agent Orange, Gulf War Syndrome • Solvents, aluminum • Genetic factors other than APOE	(Not applicable)

* Data from observational studies and RCTs.
Abbreviations: APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; RCTs = randomized controlled trials
‡GRADE criteria (see Methods section)

Table ES2. Summary of findings on potential risk factors and interventions for cognitive decline

Direction of association	Factors	Level of evidence‡
Increased risk	• APOE e4 genotype • Low plasma selenium • Depressive disorder • Diabetes mellitus • Metabolic syndrome • Current tobacco use	Low
Decreased risk	• Cognitive training*	High
	• Vegetable intake • Mediterranean diet • Omega-3 fatty acids* • Physical activity* • Non-cognitive, non-physical leisure activities	Low
No association	• Vitamin C, Vitamin E, beta-carotene supplements* • Conjugated equine estrogen* • HMG-CoA reductase inhibitors (statins)*	High
	• Aspirin* • Dehydroepiandosterone* • Cholinesterase inhibitors* • Multivitamin supplement* • Vitamins B6, B12 and folic acid supplements*	Moderate
	• Alcohol intake • Non-steroidal anti-inflammatory drugs*† • Anti-hypertensive medication* • Homocysteine • Hyperlipidemia • Anxiety disorders • Hypertension • Obesity • Early childhood factors • Higher levels of education • Social network, social supports	Low
Inadequate evidence to assess association	• Trace metals • Fat intake • High caloric intake • Gingko biloba* • Memantine • Sleep apnea • Resiliency • Occupational level • Traumatic brain injury • Toxic environmental exposures • Agent Orange, Gulf War Syndrome • Genetic factors other than APOE	(Not applicable)

*Data from observational studies and RCTs.
† Not associated with decreased risk but may be associated with increased risk.
Abbreviations: APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; RCTs = randomized controlled trials
‡GRADE criteria (see Methods section)

Discussion and Conclusions

Many putative risk or protective factors for AD and cognitive decline have been proposed, but for few of them can any firm conclusions be drawn about their association with cognition in late life. It is important to note that some factors considered in this report that lack even moderate supporting evidence may, in fact, be associated with cognitive decline and AD; there simply was not sufficient evidence to draw such a conclusion. The main issues that preclude drawing conclusions are: few studies and thus limited evidence on any given factor; heterogeneity and imprecision in exposure and outcome measures, prohibiting thorough synthesis of the literature; inconsistent results among observational studies and between observational studies and RCTs; inconsistent results across the two outcomes of AD and cognitive decline; and when associations were found, the effect sizes were generally modest. Rigorous research methods addressing these issues will need to be developed to identify risk or protective factors with confidence, particularly with regard to the value of potential interventions.

A few of the factors on the list are ready for further investigation using RCTs. But although RCTs are the preferred source for investigating the effect of exposures, many of the factors on the list are not appropriate for intervention trials. This means that obtaining evidence on these factors is dependent on conducting well-designed observational studies. Adding further complexity to the issue, many of the exposures reviewed in this report likely do not work in isolation in their effect on risk of AD or cognitive decline; instead, they probably work in combination with other factors. Thus, for future research the ideal interventions should be multi-dimensional, combining interventions for multiple risk factors and controlling for many other factors.