NIH State-of-the-Science Conference

Preventing Alzheimer’s Disease and Cognitive Decline

Program and Abstracts

April 26–28, 2010

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Presented by
National Institute on Aging, NIH
Office of Medical Applications of Research, NIH

Cosponsors
Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH
National Center for Complementary and Alternative Medicine, NIH
National Institute of Mental Health, NIH
National Institute of Neurological Disorders and Stroke, NIH
National Institute of Nursing Research, NIH
Office of Dietary Supplements, NIH

Partners
Centers for Medicare & Medicaid Services
National Center for Chronic Disease Prevention and Health
Promotion of the Centers for Disease Control and Prevention

The Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention provided additional conference development support.
About the Program
The National Institutes of Health (NIH) Consensus Development Program has been organizing major conferences since 1977. The Program generates evidence-based consensus statements addressing controversial issues important to healthcare providers, policymakers, patients, researchers, and the general public. The NIH Consensus Development Program holds an average of three conferences a year. The Program is administered by the Office of Medical Applications of Research within the NIH Office of the Director. Typically, the conferences have one major NIH Institute or Center sponsor, with multiple cosponsoring agencies.

Topic Selection
NIH Consensus Development and State-of-the-Science Conference topics must satisfy the following criteria:

- Broad public health importance. The severity of the problem and the feasibility of interventions are key considerations.
- Controversy or unresolved issues that can be clarified, or a gap between current knowledge and practice that can be narrowed.
- An adequately defined base of scientific information from which to answer conference questions such that the outcome does not depend primarily on subjective judgments of panelists.

Conference Type
Two types of conferences fall under the purview of the NIH Consensus Development Program: State-of-the-Science Conferences and Consensus Development Conferences. Both conference types utilize the same structure and methodology; they differ only in the strength of the evidence surrounding the topic under consideration. When it appears that there is very strong evidence about a particular medical topic, but that the information is not in widespread clinical practice, a Consensus Development Conference is typically chosen to consolidate, solidify, and broadly disseminate strong evidence-based recommendations for general practice. Conversely, when the available evidence is weak or contradictory, or when a common practice is not supported by high-quality evidence, the State-of-the-Science label is chosen. This highlights what evidence about a topic is available and what directions future research should take, and alerts physicians that certain practices are not supported by good data.

Conference Process
Before the conference, a systematic evidence review on the chosen topic is performed by one of the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. This report is provided to the panel members approximately 6 weeks prior to the conference, and posted to the Consensus Development Program Web site once the conference begins, to serve as a foundation of high-quality evidence upon which the conference will build.

The conferences are held over 2-1/2 days. The first day and a half of the conference consist of plenary sessions, in which invited expert speakers present information, followed by "town hall forums," in which open discussion occurs among the speakers, panelists, and the general public in attendance. The panel then develops its draft statement on the afternoon and evening of the second day, and presents it on the morning of the third day for audience commentary. The panel considers these comments in executive session and may revise its draft accordingly. The conference ends with a press briefing, during which reporters are invited to question the panelists about their findings.

Panelists
Each conference panel comprises 12 to 16 members, who can give balanced, objective, and informed attention to the topic. Panel members:

- Must not be employees of the U.S. Department of Health and Human Services.
- Must not hold financial or career (research) interests in the conference topic.
May be knowledgeable about the general topic under consideration, but must not have published on or have a publicly stated opinion on the topic.

Represent a variety of perspectives, to include:
- Practicing and academic health professionals
- Biostatisticians and epidemiologists
- Clinical trialists and researchers
- Nonhealth professionals with expertise in fields relevant to the specific topic (ethicists, economists, attorneys, etc.)
- Individuals representing public-centered values and concerns

In addition, the panel as a whole should appropriately reflect racial and ethnic diversity. Panel members are not paid a fee or honorarium for their efforts. They are, however, reimbursed for travel expenses related to their participation in the conference.

Speakers
The conferences typically feature approximately 21 speakers: 3 present the information found in the Evidence-based Practice Center’s systematic review of the literature; the other 18 are experts in the topic at hand, have likely published on the topic, and may have strong opinions or beliefs on the topic. Where multiple viewpoints on a topic exist, every effort is made to include speakers who address all sides of the issue.

Conference Statements
The panel's draft report is released online late in the conference's third and final day. The final report is released approximately 6 weeks later. During the intervening period, the panel may edit its statement for clarity and correct any factual errors that might be discovered. No substantive changes to the panel's findings are made during this period.

Each Consensus Development or State-of-the-Science Conference Statement reflects an independent panel’s assessment of the medical knowledge available at the time the statement is written; as such, it provides a “snapshot in time” of the state of knowledge on the conference topic. It is not a policy statement of the NIH or the Federal Government.

Dissemination
Consensus Development and State-of-the-Science Conference Statements have robust dissemination:
- A press briefing is held on the last day of the conference to assist journalists in preparing news stories on the conference findings.
- The statement is published online at consensus.nih.gov.
- Print copies are mailed to a wide variety of targeted audiences and are available at no charge through a clearinghouse.
- The Conference Statement is published in a major peer-reviewed journal.

Contact Us
For conference schedules, past statements, and evidence reports, please contact us:
NIH Consensus Development Program
Information Center
P.O. Box 2577
Kensington, MD 20891
1–888–NIH–CONSENSUS (888–644–2667)
consensus.nih.gov
Upcoming Conferences

NIH Consensus Development Conference: **Inhaled Nitric Oxide Therapy for Premature Infants**
October 27–29, 2010

To receive registration notifications and updates about conferences and other program activities, please join the NIH Consensus Development Program Information Network at consensus.nih.gov/alerts.htm.

Recent Conferences

NIH Consensus Development Conference: **Vaginal Birth After Cesarean: New Insights**
March 8–10, 2010

NIH Consensus Development Conference: **Lactose Intolerance and Health**
February 22–24, 2010

NIH State-of-the-Science Conference: **Enhancing Use and Quality of Colorectal Cancer Screening**
February 2–4, 2010

NIH State-of-the-Science Conference: **Diagnosis and Management of Ductal Carcinoma In Situ (DCIS)**
September 22–24, 2009

NIH State-of-the-Science Conference: **Family History and Improving Health**
August 24–26, 2009

NIH Consensus Development Conference: **Management of Hepatitis B**
October 20–22, 2008

NIH Consensus Development Conference: **Hydroxyurea Treatment for Sickle Cell Disease**
February 25–27, 2008

NIH State-of-the-Science Conference: **Prevention of Fecal and Urinary Incontinence in Adults**
December 10–12, 2007

NIH State-of-the-Science Conference: **Tobacco Use: Prevention, Cessation, and Control**
June 12–14, 2006

NIH State-of-the-Science Conference: **Multivitamin/Mineral Supplements and Chronic Disease Prevention**
May 15–17, 2006

NIH State-of-the-Science Conference: **Cesarean Delivery on Maternal Request**
March 27–29, 2006

NIH State-of-the-Science Conference: **Manifestations and Management of Chronic Insomnia in Adults**
June 13–15, 2005

NIH State-of-the-Science Conference: **Management of Menopause-Related Symptoms**
March 21–23, 2005

To access previous conference statements, videocasts, evidence reports, and other conference materials, please visit consensus.nih.gov.
General Information

Continuing Education

The NIH Consensus Development Program aspires to offer continuing education credits to as many conference attendees as possible. If your preferred credit type is not listed, please check to see if your credentialing body will honor other credit types.

Please note that continuing education credits are not available for Webcast viewers.

Continuing Medical Education

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Centers for Disease Control and Prevention and the National Institutes of Health. The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Continuing Medical Education (ACCME®) to provide continuing medical education for physicians.

The Centers for Disease Control and Prevention designates this educational activity for a maximum of 12.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Continuing Education Designated for Non-Physicians

Non-physicians will receive a certificate of participation.

Continuing Nursing Education

The Centers for Disease Control and Prevention is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

This activity provides 12.5 contact hours.

Continuing Education Contact Hours

The Centers for Disease Control and Prevention is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the Certified Health Education Specialist to receive 12.5 Category I contact hours in health education, CDC provider number GA0082.
Financial Disclosures

The Centers for Diseases Control and Prevention, our planners, and our presenters wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, with the exception of the following:

<table>
<thead>
<tr>
<th>Planning Committee Members</th>
<th>Company</th>
<th>Financial Relationship</th>
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<tr>
<td>Sanjay Asthana, M.D., FRCP-C</td>
<td>Pfizer Pharmaceuticals</td>
<td>Clinical trial in Alzheimer’s disease during role as site principal investigator (PI)</td>
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<td>Merck Pharmaceuticals</td>
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<td>Eisai Medical Research Inc.</td>
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<td>Elan Pharmaceuticals</td>
<td>Research grant received for role as site principal PI for research study</td>
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<tr>
<td></td>
<td>Eli Lilly Pharmaceuticals</td>
<td>Research grant received for role as site PI for research study</td>
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<tr>
<td>Nancy C. Andreasen, M.D., Ph.D.</td>
<td>Johnson &amp; Johnson</td>
<td>Fee for service, research support as advisory board member</td>
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<th>Financial Relationship</th>
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<tr>
<td>Paul S. Aisen, M.D.</td>
<td>Medivation, Neurophage</td>
<td>Stock options, consulting fees received during role as consultant/advisor</td>
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<tr>
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<td>Pfizer Pharmaceuticals, Baxter</td>
<td>Research grants received during role as PI</td>
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<td>Elan Pharmaceuticals, Roche, Novartis, Eli Lilly &amp; Company, Martek, Amgen, Genentech, Abbott Laboratories, Bristol-Myers Squibb, Schering-Plough, Wyeth Pharmaceuticals, Eisai, Glaxo SmithKline, AstraZeneca, Bellus, Merck Pharmaceuticals, Astellas Pharma, Dainippon Pharmaceutical, BioMarin, Solvay, Otsuka, Daiichi Sankyo</td>
<td>Consulting fees received during role as consultant</td>
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<td>James Burke, M.D., Ph.D.</td>
<td>Toyama</td>
<td>Salary received during role as PI for clinical trial</td>
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<td>Novartis</td>
<td>Salary received during role as PI for clinical trial</td>
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<td>Bristol-Myers Squibb</td>
<td>Honorarium received during role as consultant</td>
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<tr>
<td>Carl W. Cotman, Ph.D.</td>
<td>Cortex Pharmaceuticals, Inc.</td>
<td>Consulting fees received during role as consultant</td>
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<tr>
<td>Constantine Lyketsos, M.D., M.H.S.</td>
<td>Forest Laboratories</td>
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<td>Ronald C. Petersen, Ph.D., M.D.</td>
<td>Elan Pharmaceuticals</td>
<td>Fee received during role as chair – Safety Monitoring Committee and consultant</td>
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<td>Wyeth Pharmaceuticals</td>
<td>Fee received during role as chair – Data Monitoring Committee</td>
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<td>GE Healthcare</td>
<td>Fee received during role as consultant</td>
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<th>Company</th>
<th>Financial Relationship</th>
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<tr>
<td>Frederick W. Unverzagt, Ph.D.</td>
<td>Eli Lilly and Company</td>
<td>Honorarium received for role as consultant</td>
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<td>Posit Science, Inc.</td>
<td>Research materials received for role as PI</td>
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Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of the following:

- Dr. Joseph F. Quinn’s discussion on naturally occurring investigational products. He will be describing published data on the use of naturally occurring investigational products for treatment or prevention of Alzheimer’s disease.

- Dr. John W. Williams’ discussion on potential non-Food and Drug Administration (FDA)-indicated interventions. He will be reviewing the evidence for potential interventions (e.g., fish oil, cholinesterase inhibitors) that do not have an FDA indication for preventing Alzheimer’s disease.
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Tracey Holsinger, M.D.

111 Factors That Protect Against Alzheimer's Disease and Cognitive Decline

David A. Bennett, M.D.
Background

For many older adults, cognitive health and performance remain stable over the course of their lifetime, with only a gradual and slight decline in short-term memory and reaction times. But for others, this normal, age-related decline in cognitive function progresses into a more serious state of cognitive impairment or into various forms of dementia, including Alzheimer’s disease. Such loss of cognitive function—the ability to think, learn, remember, and reason—substantially interferes with everyday function. As researchers continue to explore changes in the brain that take place possibly decades before cognitive decline and dementia symptoms appear, they also hope to discover more about the relationship between normal age-related cognitive decline and the development of cognitive impairment or Alzheimer’s disease.

Alzheimer’s disease was first described in 1906, when German psychiatrist and neuropathologist Alois Alzheimer observed the hallmarks of the disease in the brain of a female patient who had experienced memory loss, language problems, and unpredictable behavior: abnormal clumps of protein (now called beta-amyloid plaques) and tangled bundles of protein fibers (now called neurofibrillary tangles). Today, an estimated 2.5 to 4.5 million Americans are living with Alzheimer’s disease, the most common form of dementia, and those numbers are expected to grow with the aging of the baby-boomer population. Age is the strongest known risk factor for Alzheimer’s disease, with most people diagnosed with the late-onset form of the disease over age 60. An early-onset, familial form also occurs but is very rare. The time from diagnosis to death with Alzheimer’s disease ranges from as little as 3 years to 10 or more, depending on the person’s age, sex, and the presence of other health problems.

In addition to investigating the causes and potential treatments for Alzheimer’s disease and other dementias, researchers are focused on finding ways to prevent cognitive decline. Many preventive measures for cognitive decline and for preventing Alzheimer’s disease—mental stimulation, exercise, and a variety of dietary supplements—have been suggested, but their value in delaying the onset and/or reducing the severity of decline or disease is unclear. Questions also remain as to how the presence of certain conditions, such as high cholesterol, high blood pressure, and diabetes, influence an individual’s risk of cognitive decline and Alzheimer’s disease.

To examine these important questions about Alzheimer’s disease and cognitive decline in older people, the National Institute on Aging and Office of Medical Applications of Research of the National Institutes of Health will convene a State-of-the-Science Conference from April 26 to 28, 2010, to assess the available scientific evidence related to the following questions:

- What factors are associated with the reduction of risk of Alzheimer’s disease?
- What factors are associated with the reduction of risk of cognitive decline in older adults?
- 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?
- 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?
• What are the relationships between the factors that affect Alzheimer’s disease and the factors that affect cognitive decline?

• 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?
About the Artwork

The illustration on this volume’s cover and used on a variety of materials associated with the conference depicts several possible approaches to preventing Alzheimer’s disease and cognitive decline as viewed through a window. These approaches include mental stimulation, exercise, and biomedical research. The conference will examine the current evidence supporting the use of these and other preventive measures for Alzheimer’s disease and cognitive decline.

The image was conceived and created by NIH’s Division of Medical Arts and is in the public domain. No permission is required to use the image. Please credit “NIH Medical Arts.”
Agenda

Monday, April 26

8:30 a.m.  Opening Remarks
Richard Hodes, M.D.
Director
National Institute on Aging
National Institutes of Health

8:40 a.m.  Charge to the Panel
Jennifer M. Croswell, M.D., M.P.H.
Acting Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health

8:50 a.m.  Conference Overview and Panel Activities
Martha L. Daviglus, M.D., Ph.D., M.P.H.
Panel and Conference Chairperson
Professor of Preventive Medicine and Medicine
Department of Preventive Medicine
Feinberg School of Medicine
Northwestern University

General Overview

9:00 a.m.  Alzheimer’s Disease: The Nature of the Public Health Problem
Mary Ganguli, M.D., M.P.H.
Department of Psychiatry
Western Psychiatric Institute and Clinic
University of Pittsburgh Medical Center

9:20 a.m.  Alzheimer’s Disease: Early Diagnosis
Ronald C. Petersen, M.D., Ph.D.
Cora Kanow Professor of Alzheimer’s Disease Research
Director
Alzheimer’s Disease Research Center
Mayo Clinic College of Medicine

9:40 a.m.  Age-Related Cognitive Decline: The Nature of the Problem
Marilyn S. Albert, Ph.D.
Professor of Neurology
Division of Cognitive Neuroscience
Johns Hopkins University School of Medicine

10:00 a.m.  Discussion
Monday, April 26 (Continued)

General Overview (Continued)

10:30 a.m. Age-Related Cognitive Decline: Measurements of Change
Dan M. Mungas, Ph.D.
Adjunct Professor
Department of Neurology
University of California, Davis School of Medicine

10:50 a.m. Pathophysiology of Alzheimer’s Disease and Age-Related
Cognitive Decline
David A. Bennett, M.D.
Robert C. Borwell Professor of Neurological Sciences
Director
Department of Neurological Sciences
Rush University Alzheimer’s Disease Center
Rush University Medical Center

11:10 a.m. Interventions in Animal Models of Alzheimer’s Disease
Carl W. Cotman, Ph.D.
Professor
Institute for Brain Aging and Dementia
University of California, Irvine

11:30 a.m. Discussion

Noon Lunch
Panel Executive Session

I. What Factors Are Associated With the Reduction of Risk of
Alzheimer’s Disease?

II. What Factors Are Associated With the Reduction of Risk of Cognitive Decline in Older Adults?

1:00 p.m. Nutritional/Dietary Risk Reduction Factors for Alzheimer’s Disease
and Cognitive Decline in Older Adults: Foods
Martha Clare Morris, Sc.D.
Director
Sections of Nutrition and Nutritional Epidemiology
Department of Internal Medicine
Rush University Medical Center
I. What Factors Are Associated With the Reduction of Risk of Alzheimer’s Disease? (Continued)

and

II. What Factors Are Associated With the Reduction of Risk of Cognitive Decline in Older Adults? (Continued)

1:20 p.m. Nutritional/Dietary Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Complementary and Alternative Medicine
Joseph F. Quinn, M.D.
Associate Professor
Department of Neurology
Oregon Health & Science University
Portland Veterans Affairs Medical Center

1:40 p.m. Evidence-based Practice Center Presentation I: Systematic Review Methods and the Factors Associated With the Reduction of Risk of Alzheimer’s Disease and Cognitive Decline
John W. Williams, Jr., M.D., M.H.S.
Professor
Department of General Internal Medicine
Duke University

2:00 p.m. Discussion

2:30 p.m. Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Physical Activity
Arthur F. Kramer, Ph.D.
Professor of Psychology and Neuroscience
Beckman Institute
University of Illinois

2:50 p.m. Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Social Engagement and Leisure Activities
Laura Fratiglioni, M.D., Ph.D.
Professor of Geriatric Epidemiology
Director
Aging Research Center
Department of Neurobiology, Care Sciences and Society
Karolinska Institute

3:10 p.m. Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Cognitive Engagement
Yaakov Stern, Ph.D.
Professor
Departments of Neurology, Psychiatry, and Psychology
Sergievsky Center and Taub Institute
Columbia University College of Physicians and Surgeons
Monday, April 26 (Continued)

I. What Factors Are Associated With the Reduction of Risk of Alzheimer’s Disease? (Continued)

and

II. What Factors Are Associated With the Reduction of Risk of Cognitive Decline in Older Adults? (Continued)

3:30 p.m. Discussion

4:00 p.m. Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Vascular Factors  
Charles S. DeCarli, M.D.  
Professor of Neurology  
Director  
Alzheimer’s Disease Center and  
Imaging of Dementia and Aging Laboratory  
University of California, Davis

4:20 p.m. Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Depression and Related Neuropsychiatric Disturbances  
Constantine G. Lyketsos, M.D.  
The Elizabeth Plank Althouse Professor  
Johns Hopkins University  
Chairperson of Psychiatry  
Johns Hopkins Bayview Medical Center

4:40 p.m. Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Sociocultural and Demographic  
Jennifer J. Manly, Ph.D.  
Associate Professor  
Department of Neurology  
Sergievsky Center  
Columbia University College of Physicians and Surgeons

5:00 p.m. Discussion

5:30 p.m. Adjournment
III. 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?

8:30 a.m. Clinical Trials for Alzheimer’s Disease
Paul S. Aisen, M.D.
Professor
Department of Neurosciences
University of California, San Diego School of Medicine

IV. 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?

8:50 a.m. Controlled Trial of Cognitive Interventions in Community-Dwelling, Older Adults
Frederick W. Unverzagt, Ph.D.
Professor of Psychiatry
Department of Psychiatry
Indiana University School of Medicine

9:10 a.m. Evidence-based Practice Center Presentation II: Therapeutic and Adverse Effects of Interventions To Delay the Onset of Alzheimer’s Disease
James Burke, M.D., Ph.D.
Associate Professor of Medicine-Neurology
Associate Director, Bryan Alzheimer’s Disease Research Center
Director, Duke Memory Disorders Clinic
Duke University

9:30 a.m. Discussion

V. What Are the Relationships Between the Factors That Affect Alzheimer’s Disease and the Factors That Affect Cognitive Decline?

10:00 a.m. Evidence-based Practice Center Presentation III: Relationship Between the Factors That Affect Alzheimer’s Disease and Those That Affect Cognitive Decline
Tracey Holsinger, M.D.
Assistant Professor
Department of Geriatric Psychiatry
Duke University
### Tuesday, April 27 (Continued)

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<tr>
<th>Time</th>
<th>Event</th>
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<tr>
<td>10:20 a.m.</td>
<td>Factors That Protect Against Alzheimer’s Disease and Cognitive Decline</td>
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<td>David A. Bennett, M.D.</td>
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<td>Robert C. Borwell Professor of Neurological Sciences</td>
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<td>Director</td>
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<td>Department of Neurological Sciences</td>
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<td>Rush Alzheimer’s Disease Center</td>
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<td>Rush University Medical Center</td>
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<td>10:40 a.m.</td>
<td>Commentary: Evidence-based Practice Center Systematic Review</td>
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<td>Hugh C. Hendrie, D.Sc., M.B., Ch.B.</td>
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<td>11:00 a.m.</td>
<td>Discussion</td>
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### Wednesday, April 28

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<tr>
<td>9:00 a.m.</td>
<td>Presentation of the Draft State-of-the-Science Statement</td>
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<td>9:30 a.m.</td>
<td>Public Discussion</td>
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<td>Panel Meets in Executive Session</td>
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<td>2:00 p.m.</td>
<td>Press Telebriefing</td>
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Panel

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Planning Committee members provided their input at a meeting held August 19–21, 2008. The information provided here was accurate at the time of that meeting.

*Dr. Nancy Andreasen stepped down as panel chair on January 20, 2010, due to a relationship that was unforeseen to be a possible conflict of interest; we thank her for her invaluable service in this process.
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Abstracts

The abstracts are designed to inform the panel and conference participants, as well as to serve as a reference document for any other interested parties. We would like to thank the speakers for preparing and presenting their findings on this important topic.

The organizers would like to thank the planning committee, the panel, the Duke University Evidence-based Practice Center and the Agency for Healthcare Research and Quality. We also would like to thank the Centers for Medicare & Medicaid Services, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Center for Chronic Disease Prevention and Health Promotion of the Centers for Disease Control and Prevention, National Center for Complementary and Alternative Medicine, National Institute on Aging, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, National Institute of Nursing Research, and the Office of Dietary Supplements. We appreciate your continued interest in both the NIH Consensus Development Program and the area of preventing Alzheimer’s disease and cognitive decline.

Please note that where multiple authors are listed on an abstract, the underline denotes the presenting author.

The abstract for Dr. Hugh C. Hendrie’s presentation does not appear in this document, because it will be a commentary and reflection on the preceding conference presentations.
Alzheimer’s Disease: The Nature of the Public Health Problem

Mary Ganguli, M.D., M.P.H.

Alzheimer’s disease (AD) was first reported in a 51-year-old woman admitted to a mental hospital in Germany with marked changes in mood and behavior and also significant intellectual deterioration. Her clinical manifestations, together with the subsequent autopsy findings in her brain, comprised the classical picture of AD, which was published in 1907. Epidemiological population studies since the 1960s have shown that AD is not only a rare disease of middle-aged adults, but also a common disease of older adults. The symptoms of AD, as currently defined, include decline in cognitive functioning in two or more domains, including memory, and other domains such as executive, language, and visuospatial, which is sufficient to interfere with everyday functioning. Frequently, there also are behavioral disturbances including depression, psychosis, anxiety, agitation, sleep disturbance, disinhibition, and apathy. Diagnostic criteria may now be evolving toward earlier detection of disease when the symptoms are milder, may not yet be disabling, and may not yet include multiple cognitive domains. Over time, individuals with AD become progressively more symptomatic and disabled, with increasing dependency on others for everyday needs, and sometimes have disruptive behaviors. Families thus acquire increasing responsibility and suffer stress, conflict, and financial burdens.

Currently available treatments include drugs approved for the treatment of AD, among them cholinesterase inhibitors and the glutamate modulator memantine, which provide modest benefit in slowing the rate of decline but are not disease modifying. There also are effective drugs for symptom relief of many behavioral manifestations, although with some risk. Nondrug management includes psychotherapy and compensatory strategies for the patient earlier in the course of the disease, behavioral strategies later in the course of the disease, and counseling, education, and resource coordination for caregivers throughout the disease course.

Prevalence is the proportion of individuals within a defined population who are affected by the disease at a given time. Incidence is the rate at which new cases develop in a defined population at risk. Prevalence is a function of both incidence and duration of disease. Potentially, preventive or disease-modifying treatments can delay onset and/or shorten duration of disease, thus reducing prevalence.

The majority of the world’s dementia prevalence studies have been conducted in higher income, industrialized nations. In these populations, prevalence estimates range from about 5–10% of individuals age 65 and older; prevalence doubles approximately every 5 years of age and generally appears to be higher among women than among men. In all recent population studies, the majority of cases of dementia are attributed to AD, although the precise proportion varies. Autopsy studies conducted on population-based samples suggest that a very common pathological picture is a mixture of AD and cerebrovascular pathology. Studies in the low-and-middle-income (LAMIC) countries show dementia prevalence estimates of 1–3% in India and sub-Saharan Africa, and about 5% in certain Asian and Latin American countries. The lower estimates partly reflect shorter overall life expectancy, shorter survival after the onset of dementia, and lower social/functional expectations of the elderly such that mild AD may be dismissed as normal aging. Potentially, they also may reflect differences in the frequency of risk and protective factors in different populations. Given the large and rapidly aging populations of some developing countries, the numbers of expected cases of AD will exceed those in more
affluent countries where the proportion of cases is higher. Taking into account changing life expectancy, by 2040, there will be a projected 71 million cases worldwide, more than 70% of them in LAMIC countries. Incidence rates are primarily available from the more affluent countries; average annual rates of dementia incidence increase exponentially with age, from 0.3% at age 65–69 to 8.6% at age 95+, and, with some exceptions, appear to be roughly similar in men and women. The gender similarity in incidence suggests that higher prevalence in women may be due to their longer survival.

There is growing interest in detecting AD before the dementia stage, that is, at the stage when the impairment is mild and not yet disabling, yet potentially amenable to early intervention. Typically referred to as mild cognitive impairment (MCI), its diagnostic criteria are still evolving. MCI prevalence estimates have ranged from 1–23% depending on criteria. Inclusion of MCI in the definition of AD therefore will raise prevalence estimates, while a meta-analysis has shown that most people with MCI would not progress to dementia even after 10 years of follow-up.

The Alzheimer’s Association recently has estimated total costs for AD in the United States of $148 billion annually, plus $89 billion in unpaid caregiving. According to one calculation, the top 10% of Medicare beneficiaries with AD account for nearly half of total health expenditures and a third of drug expenditures. Different studies have reported a wide range of annual direct costs, but comparisons should be made cautiously because of marked variation in assumptions, methods, and healthcare financing systems.

We now can identify several knowledge gaps. Most older adults with AD will never be seen in tertiary care settings such as specialty memory disorder clinics. We need (1) to develop biomarkers with acceptable sensitivity, specificity, and predictive value, which are valid outside specialty settings; (2) to have simple, reliable, valid criteria for diagnosis, particularly early diagnosis, which can be applied at the level of the community and the primary care practitioner, and also can be used uniformly across population studies worldwide; (3) to identify predictors of future dementia among those individuals who are currently free of symptoms, and then distinguish among predictors those that are true independent risk factors and those that are early markers of the AD disease process (and could be incorporated into diagnostic criteria); (4) to understand among the true risk factors the underlying mechanisms so that potentially modifiable factors and processes can be identified; a clear understanding of the timing and underlying mechanism of action of putative risk/protective factors is needed for trials to be appropriately designed, timed, and powered; (5) to understand how the same risk factor may have different effects in different groups and regions, or at different points along the natural history of the disease; this will require replication in different regions and ethnic groups, and longitudinal cohort studies that begin no later than midlife; (6) to develop more sophisticated study designs, which are hybrids of observational and interventional studies, for when a trial of suitable length and scope is not feasible; and (7) to undertake good normative studies to allow distinctions between cognitive decline that is pathological and will progress to dementia, and that which is benign and associated with normal aging. Filling these gaps will advance public health practice with regard to AD.
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expenditures and prescription drug expenditures in Medicare beneficiaries with Alzheimer 

Alzheimer’s Disease: Early Diagnosis
Ronald C. Petersen, M.D., Ph.D.

The field of aging and dementia is moving toward prediction and prevention. Most investigators believe that the sooner we can intervene in the diagnostic process of Alzheimer’s disease (AD), the more likely we will be able to minimize the damage done to the central nervous system. Ideally, we would like to be able to identify individuals who are asymptomatic but at risk for developing AD.

Currently, however, a major task for the field involves the identification of persons at the earliest symptomatic stage who are likely to progress to AD. Toward this end, the construct of mild cognitive impairment (MCI) has been useful to describe individuals at this predementia symptomatic stage of impairment. Several longitudinal projects underway are designed to dissect the underlying evolution of pathological events that ultimately lead to dementia.¹ In Figure 1,² one hypothetical characterization of this cascade involves the initial deposition of amyloid in the brain, which can be detected on amyloid imaging studies or by cerebrospinal fluid (CSF) analyses.³

Figure 1. Hypothetical Progression of Pathological Events in Alzheimer’s Disease

Note: CSF=cerebrospinal fluid; FDG PET=18F-fluorodeoxyglucose positron emission tomography; MRI=magnetic resonance imaging; ADL=activities of daily living; eMCI=early mild cognitive impairment; Cog Perf=cognitive performance; lMCI=late mild cognitive impairment.
Subsequently, metabolic changes occur, as depicted by 18F-fluorodeoxyglucose positron emission tomography (FDG PET) scans, followed by neurodegeneration, which can be characterized on magnetic resonance imaging (MRI) scans and possibly in the CSF through tau expression. Subsequent to these events, clinical changes in memory leading to MCI and functional changes occur later, characteristic of dementia. At present, this is a theoretical scheme but worthy of investigation.

Several large longitudinal cohorts have been established to address these issues using MCI as the focal clinical condition of symptomatic subjects at risk for progressing to AD. Most notable among these projects is the Alzheimer’s Disease Neuroimaging Initiative (ADNI). The ADNI is a public-private cooperation involving the National Institute on Aging, industry, and nonprofit organizations and is designed to evaluate the role of various imaging and chemical biomarkers in predicting progression from MCI to AD. In addition, smaller groups of normal and mild AD subjects have been included to allow interpretation of the data regarding MCI. ADNI has demonstrated that, when MCI is characterized with a rather significant memory impairment, the progression rate to AD is high, in the 15–25% per year range. This rate can be enhanced by utilization of various imaging markers, such as medial temporal lobe atrophy, cortical thickness on MRI, FDG PET metabolic patterns, and by the presence of amyloid deposition on molecular imaging studies. In addition, those MCI subjects with the AD profile of CSF markers also progress more rapidly. These observations have led ADNI investigators to propose a set of milder cognitive criteria for MCI to determine if the markers will work at that stage.

The challenge now is to extend the clinical threshold for MCI to lesser degrees of memory impairment in an attempt to identify the process at an earlier stage in the development of the underlying pathology. As such, the criteria being emphasized now will enhance the sensitivity of picking up persons at an earlier stage in the process but also will likely result in a loss of specificity with respect to the predictors of the ultimate outcome. It is anticipated that, through the use of imaging and clinical biomarkers, we will be able to enhance the specificity of these outcomes.

In addition to ADNI, there are other efforts underway designed to inform us on the revision of clinical criteria for AD. The Mayo Clinic Study of Aging is a longitudinal study designed to evaluate the utility of clinical features, imaging, and chemical biomarkers in predicting MCI and predicting which subjects with MCI will progress to dementia and AD in a population-based setting. The Mayo Clinic Study of Aging is a random sample of persons age 70 to 89 years in Olmsted County, Minnesota, who are nondemented at the time of enrollment and are followed every 15 months. All receive a clinical history, neuropsychological testing, and medical exam by a physician and are classified as normal for age, MCI including its subtypes, or demented with subtypes. MCI is a strong predictor of progression to dementia, primarily AD, and the amnestic subtype is more specific than the nonamnestic subtypes with respect to prediction of AD. Therefore, efforts at characterizing persons with a clinical mild memory impairment fulfilling criteria for MCI likely will be a relevant starting point for clinical trials. This approach is not without its public health significance since the prevalence of MCI is estimated to be in the 10–20% range in relevant age groups of 70 years and older. Hence, the classification of these criteria can further elucidate predictive factors of progression.

Finally, two recent efforts are underway to address the revision of clinical criteria for AD and other disorders. The American Psychiatric Association is evaluating several proposals for redesigning criteria for neurocognitive disorders, and the construct of a “predementia” range of cognitive impairment is being considered. This approach acknowledges the movement in the field toward trying to identify persons at this earliest clinical stage of impairment.
The National Institute on Aging and the Alzheimer’s Association also are collaborating to entertain a revision of current clinical criteria for AD and are evaluating the adjustment of thresholds for dementia and/or the characterization of a predementia state of cognitive impairment. Both of these efforts reflect a trend in the field aimed at prevention of disease rather than identifying persons after the clinical symptoms are manifest.

References


Age-Related Cognitive Decline: The Nature of the Problem

Marilyn S. Albert, Ph.D.

Introduction

There is considerable evidence for age-related changes in cognitive function. Such changes are evident in a number of cognitive domains including memory, executive function, language, and spatial skill. The age at which these changes occur appears to vary with the cognitive domain in question. Some aspects of cognition, however, appear relatively stable with advancing age, such as sustained attention and general knowledge. These conclusions stem largely from studies of both humans and animal models in which optimally healthy subjects have been examined.

There are a number of reasons why it is important to focus on optimally healthy subjects when discussing age-related changes in cognition. First, when studying humans, it is important to exclude subjects in the early stages of Alzheimer’s disease (AD), since it is now known that individuals in the symptomatic predementia phase of AD have significantly lower scores in some cognitive domains, particularly memory. The inclusion of such individuals would therefore confound disease-related change with age-related change. Second, medical diseases are common in the elderly (e.g., severe hypertension; respiratory, cardiac, or kidney disease; vitamin deficiencies), all of which may impair intellectual function. Ideally, subjects with these disorders (whether human or animal models) should be excluded from studies of age-related change as well. It is recognized that subjects selected without evidence of clinical disease will differ greatly from subjects chosen to represent the average for their age, because the latter will include many individuals with serious medical diseases. Thus, although nonrepresentative, the former group can be of substantial heuristic value. It will permit one to differentiate changes related to disease from those related to age and demonstrate whether age-related cognitive decline does, in fact, exist.

It should be noted that most studies of age-related cognitive decline are cross-sectional in nature, with investigators comparing groups of subjects of different ages (equated, as much as possible, on other factors). Longitudinal studies, which are less common, also have demonstrated age-related cognitive declines, although the age at which the declines are found may differ slightly from cross-sectional studies.¹

Evidence for Age-Related Cognitive Decline

The most extensive evidence for age-related changes in cognition concerns the domains of memory and executive function. This is because comparable studies have been conducted in both humans and animal models. This also makes it possible to determine the degree to which age-related changes in cognition found in one species are corroborated in another. When such parallels are found, it strengthens the likelihood that the cognitive change is related to age and not to early signs of a neurodegenerative disorder such as AD.

Workers in the field of memory have concluded that memory is not a unitary phenomenon, and most models of memory function hypothesize that memory consists of a series of specific yet interactive components. The aspect of memory that changes the most with age is generally referred to as episodic memory, that is, the ability to learn consciously and retain new
information. In humans, this ability can be evaluated in many ways; the most common method is to ask someone to try to learn the elements of a new story or a list of words. The specific procedures differ, of course, in animal models (such as monkeys or rodents), but the components of the process are similar in that the goal is to see if the animal has learned something that it did not know previously (for example, which of two objects is the new one).

The studies in humans and in animal models are consistent in finding that there are age-related declines in episodic memory. Moreover, the age at which these declines occur also appears to be consistent, in that significant declines are typically seen in middle age. There also is cross-species consistency among studies showing age-related declines in executive function. The complex set of abilities known as “executive function” includes cognitive flexibility or set shifting, problem solving, and self-monitoring. As with the area of memory, this constellation of abilities can be assessed quite differently in humans versus animal models, but the underlying nature of the task is comparable. Again, studies across species, particularly those involving humans and nonhuman primates, show an age-related decline. There is, however, less consistency across species regarding the age at which these changes occur; the decline in humans is most consistently seen among individuals over 65, whereas monkeys can show such changes by middle age.

Another finding that is consistent across species is the increased variability that is seen in cognitive performance as subjects get older. Many subjects perform more poorly than younger individuals, while others appear relatively unimpaired. The importance of this finding cannot be overemphasized, since it suggests that declines in cognitive performance with age are not inevitable in all individuals.

Importantly, neurobiological studies in both humans and animal models have identified a number of age-related changes in brain function and structure that appear to underlie the age-related cognitive changes described above, as well as intersubject variability. For example, in most subfields of the hippocampus, although neuronal loss is minimal, there is evidence of alterations in long-term potentiation and selective declines in synaptic number. Neuronal loss is observed in several subcortical nuclei that project broadly to cortex and influence neurotransmitter levels; alterations in myelin also are seen in a number of cortical regions.

**Future Directions**

There are a number of important issues that remain to be resolved concerning age-related cognitive decline. First, more needs to be learned about the neurobiological underpinnings of age-related cognitive decline, and particularly interindividual variability. Recent findings suggest that preserved performance may result from adaptive mechanisms, as well as the absence of the mechanisms responsible for age-related decline. If, indeed, adaptive mechanisms are present, it may be possible to promote these mechanisms among individuals who do not normally express them. Second, the overlap between the earliest stages of neurodegenerative disorders such as AD and age-related declines in cognition remains to be resolved. In particular, it has become clear in recent years that a subset of older individuals who are cognitively normal have evidence of AD pathology in their brain. Some reports suggest that lower episodic memory performance among such individuals is associated with increased likelihood of progression to a diagnosis of mild cognitive impairment. Thus, the inclusion of such individuals among groups of persons who do not have AD pathology may confound the ability to determine the nature and severity of age-related declines in cognition. Third, it is unclear whether these age-related declines in cognition are modifiable in the majority of individuals and, if so, if there are optimal ages for intervention. For example, a number of lifestyle factors have been identified that...
influence likelihood of maintenance of cognition with advancing age. The speakers at this meeting are discussing those that have been replicated by multiple observational studies; however, much needs to be learned about the intensity of intervention that is needed, the optimal age for such intervention, and the degree to which cognition can be modified, even given the ideal intervention. Fourth, it is unclear whether early-life events, such as nutrition or infections, influence declines in cognition later in life. The fact that these topics are the focus of this meeting, and other comparable endeavors, is an indication that efforts are already underway to address these issues and that answers to these important questions may be available in the not too distant future.

References


Age-Related Cognitive Decline: Measurements of Change

Dan M. Mungas, Ph.D.

Cognitive decline in older populations is a major cause of disability that has profound impacts on older persons, their families, and society in general. Alzheimer’s disease (AD) is one of the major causes of age-related cognitive decline. It is characterized by an insidious onset and slow progression, and AD-related brain changes may precede the onset of the first clinical symptoms by many years. Sensitive measurement of the earliest changes associated with AD has readily apparent relevance for prevention of cognitive decline. Initiation of prevention strategies and treatments prior to or early in the course of irreversible brain injury is likely to have the greatest impact on maintaining cognitive health and reducing the negative impact of AD and other age-related diseases that cause cognitive decline.

Cognitive decline is the cardinal feature of AD and related diseases; consequently, sensitive measurement of cognitive change is essential for research and will be increasingly important for clinical care as more effective prevention and treatment interventions become available. There are critical challenges associated with measuring cognitive change. Measurement must be able to track change from fully normal function to dementia, but this is complicated by the fact that normal cognition extends across a nearly four standard-deviation range. Another issue is that trajectories of change may differ across cognitive domains, but equivalent psychometric characteristics of measures from different domains are needed to separate true differences from measurement artifact.

Many of the measures of global and specific cognitive abilities that are widely used in research and clinical care have important limitations for measuring cognitive change, especially in the very early stages. Ceiling effects and nonlinear measurement are particular concerns, and psychometric matching of measures of different domains most often has not been a consideration. Consequently, these measures have limited value for characterizing the natural course of cognitive decline, monitoring response to interventions, and identifying differential patterns of change that are relevant to understanding disease progression and differences across diseases.

Modern psychometric methods based on item response theory can be used to characterize measurement properties of existing measures, create composites of existing measures that have desired psychometric properties, and develop new tests with desired measurement characteristics. These methods can be used to construct scales that (1) are sensitive across the entire ability range relevant to cognitive change, progressing from fully normal function to dementia in persons with wide heterogeneity in premorbid function; (2) do not have floor and ceiling effects that limit measurement sensitivity; and (3) provide linear measurement across the broad ability range of interest. Psychometric matching of measures of different domains also can be achieved, enabling identification of differential cognitive deficits.

These issues will be illustrated by results from two different projects examining age-related cognitive decline. Existing cognitive tests were used to create matched measures of episodic memory and executive function in one project, while new tests of episodic memory and executive function were developed for use with demographically diverse older persons in the second. These measures were used to show how trajectories of cognitive change were differentially related to magnetic resonance imaging measures of change in brain structure.
and to examine the utility of clinical diagnosis for explaining heterogeneity in cognitive change in a cognitively and demographically diverse sample.\(^5\)

Accurate measurement of cognition is a prerequisite for studies of the natural history of and risk factors for cognitive decline, for clinical trials to develop pharmacological and nonpharmacological interventions, and ultimately for monitoring the effects of these interventions when they are applied in clinical settings. Modern psychometric methods that are widely used in other fields have important applications for addressing measurement issues in cognitive aging.

References


Pathophysiology of Alzheimer’s Disease and Age-Related Cognitive Decline

David A. Bennett, M.D.

Pathophysiologic Hallmarks of Alzheimer’s Disease (AD)

Pathology of AD

The neuropathologic hallmarks of AD are the accumulation of neuritic plaques and neurofibrillary tangles, composed of extracellular deposits of amyloid-beta peptide and the intracellular accumulation of hyperphosphorylated tau proteins. They are most commonly visualized by silver stain but also can be visualized with antibodies specific to amyloid-beta and tau. AD pathology is not uniformly distributed across the brain. Rather, specific anatomic regions are selectively vulnerable to AD pathology. These regions include the hippocampus and entorhinal cortex, which are critical for laying down new memories; neocortical association areas, which are important for storage of domain-specific knowledge; and the basal forebrain, which is the source of cholinergic innervation of the neocortex. As AD is defined as a clinical dementia syndrome, there is no accepted “pathologic diagnosis.” Rather, pathologic criteria for AD make probabilistic statements regarding the likelihood of clinical AD from “not present” to “high likelihood” of AD. Up to 90% of persons meeting clinical criteria for AD have significant AD pathology at autopsy.

Amyloid Metabolism

Amyloid-beta are fibrillar aggregates of 40 to 42 amino acid peptides that result from endoproteolysis of a large transmembrane protein called the amyloid precursor protein (APP). APP is cleaved by three enzymes: alpha-, beta-, and gamma-secretase. The initial cleavage is beta-secretase, which is beta-site, APP-cleaving enzyme 1. Subsequent cleavage by alpha-secretase, which acts in the middle of the amyloid-beta sequence, results in an innocuous fragment. By contrast, cleavage by gamma-secretase, an enzyme complex that includes the protein presenilin, results in amyloid-beta. Deposited amyloid visible under the microscope is thought to be preceded by the accumulation of soluble amyloid species. Altered amyloid metabolism is considered an essential pathway in the development of AD, as genetic mutations in the three genes causative for AD and the APOE polymorphism associated with AD risk all alter amyloid metabolism. However, tangles are a much stronger correlate of cognitive status among persons with AD compared to amyloid.

Tau Metabolism

Tau is a binding protein involved in the formation and stabilization of microtubules. Tau function is regulated by phosphorylation catalyzed by protein kinases. In AD brain, tau hyperphosphorylation results in aggregation and the formation of filaments which can be visualized under a microscope as neurofibrillary tangles and the neuritic component of plaques. In contrast to amyloid deposition, which is specific for AD, tau-positive tangles are seen in a variety of neurodegenerative diseases and mutations in the tau gene cause neurodegenerative diseases other than AD.
Neurodegeneration in AD

Loss of memory and other cognitive abilities in AD result from dysfunction or death of neural elements that subserve cognition. AD pathology is accompanied by shrinkage and loss of neurons and synapses, particularly in the hippocampal formation and basal forebrain.12–14

Comorbidities

Recent data suggest that the most common cause of dementia in older persons is AD pathology in addition to other common age-related neuropathologies, especially cerebral infarctions and Lewy bodies.15–17 Similarly, mixed disease also appears to be the most common cause of clinically diagnosed probable AD.18

Pathophysiologic Hallmarks of AD in Persons Without Dementia

It has long been known that persons without dementia can exhibit AD pathology.19–21 Over the past several years, prospective cohort studies have elucidated the extent to which AD pathology is related to mild cognitive impairment (MCI) and cognition in persons without dementia or MCI. In general, these studies find that persons with MCI have intermediate amounts of AD pathology compared to those with clinical AD or those without dementia or MCI.17,18,22–25 In addition, AD pathology is only slightly more common among persons with amnestic MCI compared to those with nonamnestic MCI; comorbidities also are common among persons with amnestic or nonamnestic MCI.18 Furthermore, data suggest that neuronal loss already has occurred by the time persons are symptomatic with MCI.13 Finally, studies also report that AD pathology is related to cognition in persons without dementia or MCI.23,26

Summary

Overall, the available data suggest that the same pathologic processes that cause AD also result, to a large degree, in MCI and “cognitive aging.” In other words, cognitive aging, MCI, and clinical AD appear to be pathologically and clinically on a continuum rather than being qualitatively different from one another. This is consistent with an emerging consensus that the pathology of AD begins long before older persons are clinically symptomatic.27,28 In fact, essentially all common chronic conditions of aging have long asymptomatic and preclinical phases (e.g., osteoporosis, chronic obstructive pulmonary disease, atherosclerotic heart disease).

However, it also is clear that other pathologic processes contribute to cognitive aging, MCI, and clinical AD, especially cerebrovascular disease and Lewy bodies. Because these comorbid conditions, especially cerebrovascular disease, increase the likelihood that AD pathology is expressed clinically as MCI and dementia, strategies to prevent cerebrovascular disease will likely reduce the occurrence of cognitive impairment. There also are a number of other important but as yet unidentified processes that contribute to cognitive impairment. For example, a recent study found that the relation of AD pathology to dementia is weaker in the old compared to the young old.29 In addition, several risk factors have been identified that are related to cognitive decline and the development of MCI and clinical AD that are not related to the accumulation of AD pathology, cerebral infarctions, or Lewy bodies.30,31
Gaps in Knowledge and Implications for Further Research

The prevention of cognitive decline, MCI, and AD likely will require interventions prior to the onset of clinical symptoms. Therefore, it is important to consider adopting a pathophysiologic definition of AD that includes preclinical and asymptomatic stages of disease, in contrast to the syndromic definitions of AD and MCI in current use which are conditional based on the presence of overt clinical symptoms. The identification of relatively inexpensive and safe disease biomarkers will be needed to guide future interventions. However, this will need to be accompanied by novel clinical trial designs that do not make too many assumptions regarding how biomarkers will inform the results of intervention trials. Finally, many other processes in addition to AD pathology are involved in cognitive decline and efforts to identify these biologic pathways may result in novel therapeutic targets for the prevention of cognitive impairment.

References


Interventions in Animal Models of Alzheimer’s Disease

Carl W. Cotman, Ph.D.

Animal models have proven invaluable for pioneering interventions and intervention strategies to prevent and treat age-related cognitive decline and Alzheimer’s disease (AD). Most studies have utilized rodent models and, in particular, a variety of transgenic mouse models of AD (e.g., Tg2576, 3XTg AD) that express mutations in the amyloid precursor protein (APP) and other AD risk-factor genes. These models simulate one or more aspects of AD pathology and show varying degrees of cognitive impairment. Other studies have used higher animal models (e.g., nonhuman primates and aged canines), which share many of the features of human brain aging including cognitive decline and the accumulation of brain pathology.

Pharmacological-Based Interventions in Rodent Models

Rodent animal models have been used extensively to discover and evaluate various pharmacological interventions that have gone on to be evaluated in clinical trials. Several leads developed in animal models have produced successful trials (Table 1). However, other leads developed in animals have been unsuccessful or inconclusive. Thus, the accuracy of mouse-based pharmacological interventions to predict successful outcomes in clinical trials is at best imperfect. Inconsistencies in the results from mouse and human studies could arise from several factors, including the following: (1) APP overexpression and other gene mutations in mice do not model sporadic AD; (2) APP transgenic mice might reflect an earlier phase of cognitive aging than the majority of participants in clinical trials; (3) outcome measures in mice, including behavioral measures, are inadequate surrogates to predict efficacy in AD patients; and (3) most animal studies consist of small group sizes.

Behavior-Based Intervention Strategies in Rodent Models

In recent years, studies in animal models suggest that behavioral-based intervention strategies may be a successful intervention approach to delay cognitive decline and improve cognitive function, even after cognitive decline has progressed. In wild-type rodents and transgenic models of AD, much evidence is converging on the concept that lifestyle factors such as exercise participation can improve learning and memory, delay age-related cognitive decline, and reduce the risk of neurodegeneration. Rodent studies demonstrate that exercise can facilitate both acquisition and retention in young and aged animals in various hippocampus-dependent tasks including the Morris water maze, radial arm maze, passive avoidance, and object recognition. Along with improved behavioral performance, exercise facilitates synaptic plasticity in the hippocampus, where exercise enhances both short-term potentiation and long-term potentiation (LTP), synaptic analogs of learning. Exercise-facilitated LTP in the dentate gyrus is paralleled by altered cytoarchitecture including increased dendritic length, dendritic complexity, spine density, and neural progenitor proliferation and survival of newly generated neurons. Overall, rodent studies demonstrate that exercise increases growth factors in the brain such as brain-derived neurotrophic factor (BDNF), enhances synaptic machinery and plasticity, stimulates neurogenesis, and increases vascularization, particularly in brain regions critical for higher cognitive function. In addition, recent studies in humans reveal that exercise prevents age-related declines in cerebral perfusion and increases hippocampal blood volume, a mechanism that appears to be related to neurogenesis. In transgenic mouse models of AD, exercise and environmental enrichment (where exercise is a key component of the enrichment
Table 1. Interventions From Animal Models and Outcomes in Clinical Trials

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Proposed Mechanism of Action</th>
<th>Outcomes in Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Promote Abeta degradation</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Anti-inflammation</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Anti-inflammation</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Anti-inflammation</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>Reduction of Abeta levels</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Secretase inhibitors</td>
<td>Block conversion of APP to Abeta</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Alpha-7 nicotinic receptor partial agonist</td>
<td>Increase acetylcholine, neuroprotection</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Decrease oxidative stress</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Tramiprosate</td>
<td>Prevent amyloid formation and deposition</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Cucumin</td>
<td>Decrease oxidative stress</td>
<td>Unclear</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Antioxidant, decrease Abeta levels</td>
<td>Unclear</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Reduction of Abeta plaque</td>
<td>Unclear</td>
</tr>
<tr>
<td>PPAR-gamma agonist</td>
<td>Reduction of Abeta plaque formation and Abeta levels in vivo</td>
<td>Marginal</td>
</tr>
<tr>
<td>Dimebon</td>
<td>Cholinesterase inhibitor, NMDA receptor antagonist</td>
<td>Significant</td>
</tr>
<tr>
<td>Huperzine A</td>
<td>Cholinesterase inhibitor</td>
<td>Significant</td>
</tr>
<tr>
<td>SB-742457</td>
<td>5HT6 receptor antagonist</td>
<td>Significant</td>
</tr>
<tr>
<td>Memantine</td>
<td>NMDA blockers</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Note: HMG-CoA=3-hydroxy-3-methylglutaryl-CoA; APP=Abeta=amyloid beta; PPAR=peroxisome poliferator-activated receptor; APP=amyloid precursor protein; NMDA=N-methyl-D-aspartic acid.

paradigm) can improve learning and memory and reduce amyloid-beta (Abeta) pathology, particularly the levels of oligomers. However, some studies suggest that cognitive improvements with exercise or environmental enrichment can occur even when Abeta levels are not reduced and may, in fact, be increased. Thus, exercise and environmental enrichment may build cognitive reserve so the brain can function despite additional pathology, a concept also seen in humans.
A Higher Animal—the Aged Canine—as a Model To Identify Behavior-Based Interventions

Because findings from rodents do not always translate to humans, it is important to extend studies on potential intervention strategies to higher animal models that more closely reflect human brain aging and age-related cognitive decline. The aged canine (dog) is in many ways an ideal higher animal model, as dogs—like humans—can be categorized into tiers of cognitive capacity as they age, modeling the cognitive profiles of successful brain aging, mild cognitive impairment (MCI), and early AD. Dogs have a median lifespan of 12–14 years, making it feasible to carry out longitudinal studies across the entire dog lifespan. Over the past several years, we have developed cognitive tasks that detect cognitive deterioration with age in the canine, leading to the discovery that aged dogs show deficits in a number of complex learning tasks, including size concept learning, delayed nonmatch to position, oddity discrimination learning, size discrimination learning, reversal learning, and spatial learning (reviewed in Cotman and Head, 2008). Declines in cognitive performance on these complex learning tasks are progressive in the canine and begin early in the aging process, between 6–7 years of age. In contrast, on simple learning tasks and procedural learning measures, aged dogs perform as well as younger animals, suggesting that a subset of cognitive functions remains intact with age. We have identified three groups of old dogs based on cognitive capacity with aging: successful agers, mildly impaired dogs, and severely impaired dogs (who failed to learn the task). Thus, in terms of the pattern and severity of cognitive decline, the aged canine shows similar features to normal aging, MCI, and early/mild AD in humans. If multiple cognitive domains are affected, and functional decline also is observed (e.g., abnormal behavioral activity), these animals might be considered to be similar to an individual with early/mild AD. In addition to paralleling the cognitive decline apparent in human aging, the aged canine brain closely models many of the cellular and molecular features of the aging human brain that contribute to poorer brain health and likely underlie age-related cognitive decline. In particular, like the human brain, the canine brain atrophies with age, undergoing selective neuron loss and decreased hippocampal neurogenesis. In parallel, mitochondrial reactive oxygen species generation increases with age and the brain accumulates oxidative damage, similar to reports of oxidative damage in human brain aging, MCI, and more extensive damage in AD. Moreover, the accumulation of Abeta progresses in a similar fashion to that occurring in the human brain.

Multiple Mechanisms May Need To Be Targeted for Optimal Cognitive Benefits

We have recently evaluated the effect of behavioral enrichment (ENR) (consisting of social and cognitive enrichment and exercise), an antioxidant diet targeting mitochondrial function (AOX), and the combination of the ENR and AOX interventions in the aged canine. Interestingly, the combined AOX/ENR treatment appears to have additive or synergistic effects on preserving cognitive function, as well as on several neurobiological endpoints, which are likely mechanisms underlying the cognitive benefits. In parallel with improved cognitive performance, the AOX/ENR intervention counteracted oxidative stress, improved mitochondrial function, preserved neuron number, and increased availability of growth factors such as BDNF. Unexpectedly, the interventions had little, if any, effect on Abeta levels.

We hypothesize that improved mitochondrial function, achieved by the AOX diet, is a key factor in the synergistic/additive effect of the combined intervention on cognitive function. Specifically, improved mitochondrial function positions the aged brain to better respond to behavioral interventions, relative to the brain’s capacity to respond when mitochondria are partially dysfunctional. Thus, neurons with healthy mitochondria are more able to benefit from ENR, a novel concept in the field. Taken together, our findings suggest that the AOX and ENR
interventions likely engage molecular mechanisms that enhance “cognitive reserve,” allowing the canine to maintain intact cognitive abilities despite the continued presence of Abeta in the brain. These data suggest that strategies to improve overall neuron health, in particular by improving mitochondrial function, may be critical for the effectiveness of behavioral-based interventions, as well as the effectiveness of some pharmacological-based strategies.

References


Nutritional/Dietary Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Foods

Martha Clare Morris, Sc.D.

The study of dietary risk factors in the prevention of cognitive decline and Alzheimer’s disease is arguably one of the most important areas in the field. Nutrients are essential for brain function, and because all human beings must eat, we are all exposed. Dietary prescriptions also are economically advantageous over medical interventions and without adverse side effects. The dietary components with the strongest evidence to date for dementia prevention include antioxidant nutrients, fat composition, and B vitamins. Studies of foods and dietary patterns tend to support the findings for these dietary components. What is becoming clear as the field develops is that attention to the level of nutrient exposure is critical for interpreting the literature.

Antioxidant Nutrients

The brain is particularly vulnerable to oxidative damage due to its high metabolic activity and the presence of relatively few antioxidant enzymes. Alzheimer’s disease involves oxidative processes, and antioxidant nutrients (vitamin E, vitamin C, carotenoids, flavonoids) are a natural defense mechanism against these processes. Of the antioxidant nutrients, the evidence for brain protection is strongest for vitamin E; that for carotenoids, vitamin C, and flavonoids is limited and inconsistent but promising. Animal and laboratory data indicate that vitamin E protects the brain from oxidative damage and age-related neuropathology. Paradoxically, both epidemiologic studies and clinical trials of vitamin E supplements generally do not show disease protection, even while animal models and epidemiologic studies of vitamin E food intake do. Dose level may explain the apparent discrepancy. Of eight prospective studies that measured dietary intake of vitamin E, six reported statistically significant reductions in the development of dementia, Alzheimer’s disease, and cognitive decline. Two prospective studies did not find an association of food intake of vitamin E. Intake levels were not reported for one of these studies; however, that reported in the other negative study suggests that the food intake levels of vitamin E (top tertile median of 7 IU/day) may have been too low for neuroprotective benefit. This contention is supported by findings of at least two other studies. In one study, vitamin E supplement use was not significantly associated with a slower rate of cognitive decline over 6 years except among persons with low food intake. In subgroup analyses of the Women’s Health Study, a randomized trial of 600 IU alpha-tocopherol treatment over 9.6 years, a positive effect on cognitive decline was observed among women who had low baseline dietary intake levels of 9.15 IU/day but not in women whose intakes were above this level. In another randomized trial of vitamin E supplement effects on cognitive decline, subgroup analyses by baseline dietary vitamin E levels below 22 IU/day revealed no protective benefit. Based on these previous studies, this cutpoint may have been too high to observe a supplement effect.

Fat Composition

The primary genetic risk factor for late-onset Alzheimer’s disease encodes apolipoprotein E (APOE), which plays a central role in cholesterol uptake and transport in the brain. Elevated cholesterol increases Abeta in cellular and animal models of Alzheimer’s disease. Some epidemiologic studies have reported that hypercholesterolemia in midlife increases the risk of late-life dementia, and that use of cholesterol-lowering medications reduces the risk. In humans, a diet that is high in saturated and trans fats, and low in polyunsaturated and monounsaturated
fats is a primary cause of hypercholesterolemia. Of five prospective epidemiologic studies that examined the effect of dietary fat intake on the development of Alzheimer’s disease, four observed associations with fat composition. The studies of cognitive decline support these findings. Total, saturated, or trans fats are associated with increased risk, and monounsaturated fats and a high ratio of polyunsaturated to saturated fats with decreased risk. Thus, these several lines of evidence provide support for the hypothesis that dietary fat composition is related to cognitive decline and Alzheimer’s disease.

Docosahexaenoic acid (DHA), a type of n-3 fatty acid consumed through marine sources, is the primary lipid in the most metabolically active areas of the brain. In aging animal models, dietary DHA improves memory function and protects against oxidative damage, inflammation, and synaptic loss. Epidemiologic studies have largely shown protective associations against AD and cognitive decline with just one fish meal per week versus less often. Studies with higher comparisons of two or more fish meals per week versus less often report associations that are in the protective direction but not statistically significant. The inclusion of weekly fish consumers in the comparison category may have diluted the observed estimates of effect. Studies that examine different types of n-3 fatty acids are equivocal for findings of protection against dementia outcomes, and randomized clinical trials of DHA supplementation have been null. Thus, it is possible that some dietary component other than n-3 fatty acids is responsible for the protective association with fish consumption. However, another plausible explanation is that participants in the placebo group already are consuming the level of protective benefit of DHA through weekly fish consumption, thus obscuring an effect of the supplement.

**B Vitamins**

Vitamin B12 and folate are cofactor nutrients that are widely believed to be protective risk factors of cognitive decline and Alzheimer’s disease. Vitamin B12 deficiency results in a neurologic syndrome that involves impaired cognition. Recent interest in folate deficiency as a risk factor for dementia is primarily due to its effect on raising homocysteine concentration, which has been related to the risk of developing Alzheimer’s disease in some studies, although the mechanism for this association is unclear. The findings from prospective studies and randomized trials of the B vitamins and their metabolites on dementia and cognitive decline have not been consistent. Some of the inconsistencies may be due to the range of nutrient status in the study population. This consideration is particularly important for folate because the U.S. grain supply is fortified with folic acid, so dietary insufficiency is rare. It appears likely from the available evidence that both low vitamin B12 and low folate status are associated with cognitive decline, and that high folate exposure in persons with low vitamin B12 also may be associated with cognitive decline. There is limited evidence that the B vitamins are associated with risk of developing AD.

**Recommendations for Future Studies**

Randomized trials of antioxidant nutrients, DHA, and vitamin B12 and folate need to be conducted among persons who have insufficient nutrient status (vitamin B12, folate) or low dietary intake (e.g., beta-carotene, vitamin E, DHA) based on levels reported in epidemiologic studies. To this end, the range of nutrient intake and/or level of protective benefit should be carefully considered and reported in future studies. The field would benefit greatly by additional studies on the cognitive effects of different carotenoids and flavonoids, dietary patterns, and interaction effects of nutrients with APOE and with other dietary components.
References


Nutritional/Dietary Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Complementary and Alternative Medicine

Joseph F. Quinn, M.D.

Although the use of omega-3 fatty acids, antioxidants, vitamin D, and B vitamins to slow cognitive decline might qualify as “complementary and alternative” in some circles, those topics are nicely covered in the preceding lecture. We will consequently limit the present discussion to other complementary and alternative strategies that are plausible for the prevention of Alzheimer’s disease (AD) or cognitive decline based on animal models or clinical trials. Interventions with only a theoretical rationale or only in vitro data will not be discussed. With these criteria in mind, the discussion will cover nonvitamin antioxidants, herbal/botanical therapies, and metal chelation therapy. Representative examples from each category are cited here, and additional examples will be discussed as time permits.

Nonvitamin Antioxidants

Lipoic acid is a naturally occurring antioxidant, which has shown antiaging effects in animal studies in association with free radical scavenging, metal chelating, and glucose-modulating effects. Lipic acid has been tested as an anti-amyloid therapy in the Tg2576 strain of amyloid precursor protein (APP) mice in two independent laboratories, with improved spatial memory in one report but no evidence of amyloid-lowering effects in either study. Concerns about brain bioavailability of lipoic acid also have been raised. Nevertheless, an open-label trial of lipoic acid in mild to moderate AD described “stabilization” of cognitive decline, and lipoic acid has been combined with other agents in two small double-blind randomized trials with encouraging results.

Coenzyme Q (CoQ), a component of the mitochondrial electron transport chain, has attracted some interest as a treatment for AD based in part on the “mitochondrial hypothesis” of AD, with interest heightened by reports of a possible disease-modifying effect of CoQ in Parkinson’s disease. Orally administered CoQ attenuates brain protein oxidation in wild-type mice and reduces beta-amyloid pathology and brain atrophy in transgenic mice with APP and presenilin mutations. However, there have been no reported trials of CoQ therapy for prevention or treatment of AD, perhaps because of a negative outcome in a clinical trial of idebenone, a CoQ analog.

N-acetylcysteine (NAC) is a glutathione-restoring antioxidant, which the Food and Drug Administration (FDA) approved for the treatment of acetaminophen overdose and is commonly used for the prevention of contrast-induced nephropathy. NAC reduces oxidative damage in the brains of apolipoprotein E (APOE)-deficient mice and reduces cerebral beta-amyloid in an APP transgenic mouse. A small placebo-controlled trial of NAC in AD showed trends to clinical efficacy, but statistical significance was limited to a modest number of outcome measures. NAC also is a component of a “medical food,” which is currently marketed for patients with cognitive impairment and AD. Due to the unique regulatory requirements for medical foods, this combination supplement has been FDA-approved in the absence of evidence of disease-specific efficacy.
Herbal/Botanical Therapies

Several herbal/botanical therapies have been examined for their potential to slow cognitive decline or dementia (reviewed in Anekonda and Reddy, 2005\textsuperscript{15}). Ginkgo biloba extract is the most extensively studied of these agents, with evidence for antioxidant, anti-amyloid, and other effects \textit{in vitro}. In an APP mouse model, ginkgo biloba improved spatial memory but had no effect on cerebral beta-amyloid, and paradoxically increased brain protein oxidation.\textsuperscript{16} Although one controlled trial suggested that ginkgo biloba has potential for slowing the rate of progression to mild cognitive impairment in healthy elderly persons,\textsuperscript{17} a large randomized controlled trial found that ginkgo biloba did not affect progression to dementia\textsuperscript{18} or modify the rate of change on a spectrum of psychometric measures in healthy elderly persons or those with mild cognitive impairment.\textsuperscript{19}

Curcumin, a component of the Indian spice turmeric, also has been studied in both animal models and early clinical trials, based on epidemiologic evidence indicating that eating curry is associated with a lower prevalence of dementia. \textit{In vitro} studies showed that curcumin interferes with beta-amyloid fibril formation and has antioxidant and anti-inflammatory effects. In an APP mouse model, orally administered curcumin diminished cerebral beta-amyloid and oxidative damage.\textsuperscript{20} However, a pilot study of curcumin therapy in AD patients, designed with cerebrospinal fluid biomarkers as the primary outcome measure, failed to show evidence of a benefit of curcumin therapy.

Another botanical therapy moving toward clinical trials in AD is resveratrol, a component of the seeds of the red grape, with antioxidant effects and, more uniquely, sirtuin-activating effects. Sirtuin activation has been associated with antiaging effects in several model systems, and sirtuin activation has been proposed as a strategy for the prevention and treatment of AD,\textsuperscript{21} with resveratrol as perhaps the best candidate for this approach. A clinical trial of resveratrol sponsored by the Alzheimer’s Disease Cooperative Study has been delayed by concerns about blood-brain barrier penetration of sirtuin, but this issue is being clarified and a resveratrol trial is expected in 2010.

Metal Chelation

Although the idea of metal chelation therapy may conjure images of either outright quackery or modern-day blood-letting, this approach has gained credibility for AD with the publication of several persuasive reports implicating copper in the pathogenesis of AD. These studies demonstrate that beta-amyloid aggregation and neurotoxicity are dependent on the presence of copper (reviewed in Quinn et al., 2009\textsuperscript{22}). In an APP mouse model, the copper-binding agent clioquinol robustly lowered cerebral beta-amyloid levels,\textsuperscript{23} while a high-copper diet exacerbated AD pathology in another murine model.\textsuperscript{24} Clioquinol was well tolerated in a small clinical trial with encouraging results,\textsuperscript{25} but concerns about possible spinal cord toxicity have prevented further clinical development of clioquinol \textit{per se}. A clioquinol analog, PBT2, has shown promising results in a preliminary clinical trial.\textsuperscript{26} It may be important to emphasize, however, that these copper-binding agents appear to interfere with copper-amyloid binding without actually depleting systemic copper levels. Since systemic copper depletion is associated with both hematologic and neurologic complications, the clioquinol/PBT2 mechanism may be safer than alternatives. There are, however, other copper-modulating agents in the complementary and alternative medicine armamentarium that may prove effective in the future.
Summary

A number of agents from complementary and alternative medicine have the potential for preventing late-life cognitive decline and AD, but clinical trials have either been negative or inconclusive. Clinical evaluation of these agents is most meaningful when the target mechanism is carefully defined, and when efficacy at the level of the target mechanism is established with certainty.

References


Evidence-based Practice Center Presentation I: Systematic Review Methods and the Factors Associated With the Reduction of Risk of Alzheimer’s Disease and Cognitive Decline

John W. Williams, Jr., M.D., M.H.S.; Brenda L. Plassman, Ph.D.; James Burke, M.D., Ph.D.; Tracey Holsinger, M.D.; Sophiya Benjamin, M.D.

Introduction

To determine if there is sufficient evidence to warrant specific recommendations for preventing Alzheimer’s disease (AD) or cognitive decline (CD), it is necessary to review systematically the evidence on the association with behavioral, lifestyle, and pharmaceutical interventions/modifications.

Objectives

We conducted a systematic review to synthesize the published data on purported risk or protective factors for AD and CD. In this discussion, we focus on the methods of the review and the association between AD/CD and medical conditions, social/economic/behavioral factors, toxic environmental exposures, and genetic factors.

Review Methods

The list of factors to be evaluated were developed by a formal conference planning committee, which included experts in the field from both within the Federal Government and academic medical centers; additional guidance was provided by a Technical Expert Panel. We grouped the factors into the following categories: nutritional factors, medical conditions and prescription and nonprescription medications, social/economic/behavioral factors, toxic environmental exposures, and genetics. We searched MEDLINE® and the Cochrane Database of Systematic Reviews for relevant publications in English from 1984 through November 2009. For genes identified as being of particular interest, we searched the ALZGene databases to identify relevant systematic reviews. Additional studies were identified from reference lists and technical experts. Using duplicate review, we identified relevant articles by reviewing the titles, then abstracts, and finally full-text articles. When a good-quality systematic review was identified, we summarized and updated this review. For primary literature, both observational and intervention studies that compared subjects with an exposure of interest to those unexposed and reported an association with incident AD or CD were evaluated. We limited our review to studies that enrolled adults age 50 or older drawn from general populations in economically developed countries. Studies were evaluated for eligibility and quality, and data were abstracted in duplicate on study design, demographics, intervention or predictor factor, and cognitive outcomes. When substantial new evidence was available and appropriate for quantitative synthesis, we performed a meta-analysis. We rated the strength of evidence using principles from the Grading of Recommendations Assessment, Development and Evaluation working group including risk of bias, consistency, precision, strength of association, publication bias, and dose response relationship.
Results

Evidence considered was limited to cohort studies except for traumatic brain injury, pesticides, and pollutants, where case-control studies were considered. There was substantial heterogeneity in the assessment of exposure variables including timing of the exposure (e.g., midlife vs. late life), cross-sectional versus longitudinal assessments, and validity of the exposure measure. For studies examining CD, outcomes were assessed using a wide range of cognitive measures with little consistency across studies. Analyses typically controlled for age, sex, and education, and many controlled for additional potential confounding variables. The variability in study design often precluded quantitative synthesis.

Alzheimer’s Disease

A total of 15 systematic reviews and 36 primary research studies were included, which evaluated the association with AD and factors considered in this presentation. Among the factors considered, only a few showed a consistent association with AD across multiple studies. In systematic reviews, factors associated with increased risk of AD were diabetes mellitus (relative risk [RR] 1.39, 95% confidence interval [CI] 1.17–1.66), epsilon 4 allele (e4) of the apolipoprotein E gene (APOE e4, odds ratio [OR] 3.68, 95% CI 3.31–4.11) compared to the epsilon 3 allele, current smoking (RR 1.79, 95% CI 1.43–2.23), and depression (OR 1.90, 95% CI 1.55–2.23). In a systematic review of case-control studies, traumatic brain injury was associated with increased risk in men (OR 2.29, 95% CI 1.47–3.58). A meta-analysis found an association between obesity and AD (RR 1.80, 95% CI 1.00–3.29), but a subsequent cohort study in late-life adults found decreased risk. Limited evidence suggests an increased risk of AD for midlife but not late-life adults with elevated cholesterol and for individuals exposed to pesticides. Factors showing a consistent association with decreased risk of AD were more years of education (no summary estimate) and light to moderate alcohol use (RR 0.72, 95% CI 0.61–0.86). The magnitude of the risks was small to moderate except for a strong association with APOE e4. The overall strength of evidence was rated as low for all factors except for APOE e4, which was rated as moderate due to the consistency of results and magnitude of the association. There was no consistent association for hypertension, homocysteine, early childhood factors, occupation, solvents, lead, or aluminum, but for some of these exposures the evidence was quite limited. We did not identify eligible studies for anxiety disorders, resiliency, or sleep apnea.

Cognitive Decline

A total of 5 systematic reviews and 67 primary research studies were included. Among the factors considered, only a few showed a consistent association with CD across multiple studies. Factors associated with increased risk of CD were low education, depression, and current smoking. APOE e4 was associated with CD on some measures, but effects were not consistent across studies. No factors were consistently associated with decreased risk for CD. Early childhood factors, occupation, social engagement, hyperlipidemia, elevated homocysteine, and obesity were not consistently associated with CD, and in some instances the evidence was sparse. The strength of evidence was rated as low for all factors. We did not identify eligible studies for resiliency, traumatic brain injury, sleep apnea, pesticides, or pollutants.
Conclusions

Because of heterogeneity in study designs, particularly related to exposure measurement and cognitive outcomes, quantitative synthesis is not often possible. The current research on the list of putative risk or protective factors is largely inadequate to assess confidently their association with AD or CD. Further research that addresses the limitations of the previous studies is needed prior to being able to make recommendations on interventions.

References


Physical activity and exercise have been found, over the past several decades, to reduce the risk of a multitude of diseases including cardiovascular disease, breast and colon cancer, obesity, and type II diabetes. Many of these diseases have been associated with diminished cognitive and brain health and serve as risk factors for age-associated neurodegenerative disorders such as Alzheimer’s disease. Therefore, physical activity appears to enhance cognition and brain health through disease reduction and prevention. However, increased physical activity also has been found to have more direct effects on both brain health and cognition. Research with animal models, primarily rodents, has discovered a number of molecular and cellular changes in the brain that are attributable to increased physical activity. These exercise-induced changes include increased neurotrophin (e.g., brain-derived neurotrophic factor, insulin-like growth factor 1 [IGF-1], and vascular endothelial growth factor) levels in several regions of the brain that engender a variety of structural and functional modifications such as neurogenesis in the dentate gyrus of the hippocampus, synaptogenesis, and the development of new vascular structure. These brain modifications have, in turn, been associated with enhanced learning and memory.

In the present brief review, we address a number of important issues concerning the influence of physical activity and exercise on the risk for dementia and the maintenance and enhancement of cognition and brain health in humans. Each of the questions that will be addressed is stated below, followed by a brief discussion of the relevant literature.

**In Epidemiological Studies, Has Physical Activity Been Shown To Be Associated With Reducing the Risk of Developing Alzheimer’s Disease or Age-Related Cognitive Decline?**

Epidemiological studies generally assess physical activity and exercise with self-report questionnaires and then follow up, often 2 to 10 years later, with an examination of cognitive function or an assessment of Alzheimer’s disease or other forms of dementia. Given that the decision to partake in physical activity often is related to other lifestyle choices and medical conditions such as obesity, socioeconomic status, smoking, and drinking, these observational studies also assess such lifestyle and demographic factors, which are then used as covariates in the examination of the effects of physical activity on cognition.

In recent years, an increasing number of studies have found a link between physical activity and the maintenance of cognition or reduced risk of neurodegenerative diseases. For example, Larson et al. assessed 1,740 adults over the age of 65 on the frequency of participation in a variety of physical activities (e.g., walking, hiking, bicycling, swimming). After a mean follow-up of 6.2 years, 158 of the original participants had developed dementia. After adjusting for age, sex, and medical conditions, individuals who exercised more than three times per week during initial assessment were found to be 34% less likely to be diagnosed with dementia than those who exercised fewer than three times per week. A number of prospective observational studies also have found that physical activity is related to maintenance of cognition, often on global measures of cognitive function, for older individuals who stay physically active.
Although many of the epidemiological studies have found a positive relationship between physical activity and cognition or risk of dementia, it is important to note that some studies have failed to find such a relationship.\textsuperscript{11,12} It is difficult to know which factors are most important in moderating the influence of physical activity on later life cognition and dementia. However, some possibilities that merit further study include the following: the distinction between aerobic and nonaerobic physical activities; the utility of self-report versus more objectively measured physical activities and fitness; the relative contribution of social, intellectual, and physical factors to different everyday activities; the role of physical activity duration, intensity, and frequency; the nature of the components of cognition that serve as the criterion variables, the age of participants at initial and final assessment; and genetic factors.

**From These Studies, Is It Clear Which Kinds of Physical Activities Are Most Effective?**

The epidemiological studies have obtained self-reports from participants on a variety of different physical activities including sporting activities, household activities such as gardening and cleaning, leisure time activities, and walking. Some studies have had participants rate how strenuous the activities were, but many studies did not collect this information. Most studies obtained information on the frequency and duration of physical activities on a weekly or monthly basis.

Given that many of the studies derive a single metric of physical activity across different activities, often in terms of energy expenditure over a specified time period, it is difficult to discern the relative contribution of different physical activities to reduced risk for dementia or maintenance of cognition.\textsuperscript{6,13} However, one activity that is frequently examined in the epidemiological studies is walking; the frequency of walks and distance covered has been related in a dose response manner to reduced risk for dementia and maintenance of cognition in relatively healthy older adult samples.\textsuperscript{8–10}

**In Clinical Studies or Trials With an Exercise Intervention, What Are the Effects of Physical Activity on Brain and Cognitive Measures?**

As is the case with epidemiological studies, some intervention studies have found that sedentary older adults who participate in exercise studies show improvements in cognition and brain function, while other studies do not find such effects (likely as a result of small sample sizes and other factors such as those discussed above). Therefore, we believe that it is instructive to examine the results of meta-analyses that have examined the relationship between fitness and cognition over a number of different studies.\textsuperscript{14–16} Several interesting results were obtained from these meta-analyses. First, significant small-to-moderate effect sizes were obtained for the relationship between exercise and cognition. Second, some cognitive processes, most notably executive control processes, showed larger benefits than other cognitive processes. Third, exercise benefits were observed for both normal elderly persons and those with early dementia. Fourth, no significant relationship was observed between amount of fitness improvement and degree of cognitive improvement. Although initially surprising, the fact that fitness is measured peripherally rather than in the central nervous system in these studies provides a potential explanation for this result. Indeed, a dose response function between cognitive improvement and brain blood flow has been reported recently.\textsuperscript{17}

Given the small number of clinical trials that have examined the relationship between fitness training and brain function, it is not possible to conduct a meta-analysis on these data. However, several studies have found improvements in the efficiency of functional brain networks,
increased regionally specific brain volume, and increased blood flow in the hippocampus with fitness training in middle-aged and older adults.\textsuperscript{17–19}

**Is It Known What Kinds of Physical Activity and What Durations and Frequencies of Such Activities Produce the Greatest Changes in Brain and Cognition?**

At present, there has been little examination of duration or frequency effects within single intervention trials. However, one meta-analysis did examine a variety of moderators of the relationship between fitness training and cognition.\textsuperscript{14} Training sessions longer than 30 minutes led to a larger effect size than shorter training sessions. Effect sizes also were larger when cardiovascular training was combined with strength training than when focusing on cardiovascular training alone. It is interesting to note that the great majority of human intervention studies have focused on aerobic activities such as walking, bicycling, and swimming, likely as a result of the large rodent database obtained from wheel-running studies.\textsuperscript{4} However, a number of recent studies have begun to explore the cognitive implications of strength training and have found improvements in a number of aspects of cognition including executive control,\textsuperscript{20} immediate and delayed memory,\textsuperscript{21} and increases in serum IGF-1.\textsuperscript{22}

**What Studies Need To Be Done To Advance Research in This Area?**

The research described above has begun to address a number of questions concerning the relationship between exercise and physical activity, and cognition and brain function in humans. However, there are a number of important unanswered questions. For example, we currently know little about dose response (in terms of intensity, frequency, and duration) effects of physical activity and exercise on cognition and the brain of humans, particularly with regard to clinical trials. Retention effects of exercise on cognition and brain function also are relatively unknown. Second, whether physical activity and exercise effects differ as a function of age and disease state is largely unexplored. Another important question concerns potential interactions between exercise and physical activity on one hand and social interaction, intellectual engagement, diet, and stressors on the other. Several studies have examined whether exercise effects on cognition are moderated by genotype, but thus far studies have focused on only the apolipoprotein E (APOE) gene. Clearly, other genes that influence neurotransmitter and neurotrophin function should be examined. Finally, although laboratory-based cognitive outcome measures have shown benefits of exercise and physical activity, there is little knowledge of exercise effects on cognition outside the laboratory.

**References**


Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Social Engagement and Leisure Activities

Laura Fratiglioni, M.D., Ph.D.

Brain aging is characterized by the progressive and gradual accumulation, across the life course, of detrimental changes in structure and function, which leads to an increased risk of age-related brain disorders such as dementia. Dementia, together with hypertension, is the most common chronic disorder in persons age 75+, and 70% of dementia patients in the general population are older than age 75. Therefore, we may presume that the majority of the dementia cases are due to the combined effect of different pathological lesions including Alzheimer’s disease (AD)-like pathology and vascular damage. Following this perspective, in this review we will focus on the dementia syndrome rather than on specific dementing disorders. Evidence has been accumulating that psychosocial factors that lead to an active lifestyle over the lifespan may postpone dementia onset, possibly by enhancing brain reserve. These factors include, among others, a rich social network and social engagement, mentally stimulating activity, and regular physical exercise.

Social Network

Longitudinal studies have detected an association between a poor social network and decline in social engagement from middle age to late life, with an elevated risk of AD and dementia. A rich social network may provide better social support and consequently better access to resources and material goods. Large social networks also may enhance brain reserve by providing intellectual stimulation. A recent report concerning increased AD risk in subjects widowed from midlife has been interpreted in this line, by concluding that partnership may provide a protective effect due to daily cognitive and social challenges. In addition, neuropathological data have shown that subjects with a similar amount of neuropathological lesions had higher cognitive performances if they also had larger social networks.

Leisure Activities

A substantial number of longitudinal studies with a follow-up time ranging from 2 to 16 years have explored the association between leisure activities and risk of dementia/AD. Some studies grouped the activities according to the predominant component (physical, mental, and social activities), others focused on specific individual activities, and others used component scores. In spite of differences in study design and activities studied, most of the reports have suggested a protective effect of leisure activities, especially mentally stimulating activities, against dementia. These activities, which include reading, playing board games and musical instruments, knitting, gardening, and dancing, often have been associated with a reduced risk of dementia. Furthermore, a recent review of prospective studies also has concluded that physical activity may reduce the risk of AD by approximately 45%. However, most physical activities also include social and mental components in addition to the physical component. Indeed, complex leisure activities composed of all three components of physical, mental, and social activities seem to have the most beneficial effect.
Summary and Future Perspectives

At the moment, we may conclude that moderately strong evidence from observational studies supports the hypothesis that psychosocial factors are involved in the development and clinical manifestation of dementia, suggesting that the maintenance of socially integrated lifestyles and mentally stimulating activities may help delay the development and progression of the dementia syndrome. However, to implement efficacious preventive strategies, further research is necessary to better clarify the following specific issues: (1) All the different components of leisure activities need to be assessed to better identify which qualitative and quantitative characteristics are the most efficacious in preventing/delaying dementia onset. (2) The protective effect of a social network and leisure activities in late life may be a result of a cumulative protective effect across the life course. Indeed, two studies have shown that a greater mental complexity at work could reduce the risk of AD\textsuperscript{13,14} and a reduced rate of hippocampal atrophy has been reported in subjects who engaged in complex mental activity across the lifespan.\textsuperscript{15} (3) Different biological mechanisms may alternatively explain, or in a synergistic way contribute to, this positive effect. At the moment, most of the focus has been devoted to vascular and brain reserve hypotheses. Other mechanisms such as premorbid cognitive ability\textsuperscript{16} and psychological stress\textsuperscript{17} need to be further explored.

References


Normal aging is associated with cognitive decline, as measured by cognitive tasks. The causes of this decline remain a topic of investigation. A set of measurable brain changes occurs with aging, all of which correlate with cognitive decline to some degree. Normal aging is associated with brain atrophy, cortical thinning, and loss of white matter integrity. Other measurable brain changes common with aging that correlate with cognitive decline, including increases in white matter hyperintensities and small strokes, may be associated with vascular risk factors. Finally, certain brain changes occur with aging that are not considered to be part of a typical aging process but rather as pathological changes associated with disease. The most common of these are the brain changes associated with Alzheimer’s disease (AD), including neurofibrillary plaques, tangles, and synapse loss.

Although all of these brain changes have been associated with cognitive loss, it has been observed repeatedly that the associations between the extent of these changes and their cognitive/clinical consequences are weak. The idea of reserve stems from these observations and is an attempt to account for individual differences in the clinical manifestation of the brain changes.

Two forms of reserve have been proposed. Brain reserve suggests that there are individual differences in physical features of the brain itself such as size or neuronal count. These differences allow some individuals to cope with more brain damage than others. On the other hand, the concept of cognitive reserve (CR) suggests that the brain actively attempts to cope with brain changes by using preexisting cognitive processing approaches or by enlisting compensatory approaches. Thus, individuals with more CR would be more successful at coping with the same amount of brain damage.

Support for the concept of CR in aging and AD comes from both epidemiologic and imaging studies. Epidemiologic data suggest that high education level, occupational attainment, or more active engagement in intellectual, social, and physical activities are associated with decreased risk for incident dementia. A review paper found 22 papers published up to 2004 reporting cohort studies of the effects of education, occupation, premorbid IQ, and mental activities in incident dementia. Integrating these studies, the authors reported that higher reserve was associated with a 46% decrease in risk for incident dementia (odds ratio [OR]=0.54; 95% confidence interval, 0.49–0.59). The CR hypothesis would suggest that these life experiences all impart CR, allowing individuals with greater CR to cope with AD pathology for a longer period of time.

Similar epidemiologic data suggest that increased CR also can reduce the risk of the cognitive changes that occur in normal aging. Education was related to maintenance of intellectual performance in a sample of World War II veterans tested twice over a 40-year period. Low education has been associated with poor health and function in older adults as well as with a faster rate of cognitive decline.

Supporting the concept of CR, positron emission tomography studies in AD subjects matched for clinical severity have reported negative correlations between resting cerebral blood flow (CBF; taken as a surrogate for AD pathology) and education, IQ, occupation, and leisure. The negative correlations are consistent with the prediction that at any given level of behavioral
symptomatology, a subject with a higher level of CR should have greater AD pathology (i.e., lower CBF). Subsequent clinicopathologic studies have confirmed that at any level of clinical severity, AD patients with higher CR have more AD pathology. More recently, studies have documented that proxies for CR are associated with more intact cognitive function in the face of measured brain atrophy, cortical thinning, white matter hyperintensities, and amyloid burden. These findings suggest that sets of lifetime exposures can help provide reserve against clinical expression of age- or AD-related brain changes. The literature suggests that reserve can be imparted at late age. For example, controlling for educational and occupational experiences, increased leisure activity does provide reserve against developing dementia. A reasonable next step would be to begin to determine whether interventions that supply these experiences at a later age might provide similar reserve. The ultimate test of such interventions would be whether they could reduce or slow the rate of cognitive change in healthy elders, or reduce the relative risk of developing dementia.

References


Health statistics compiled over the last 10 years reveal only slight increases in prevalent cardio- and cerebrovascular disease (CVD) but steady declines in mortality (Figure 1). Recognizing that prevalent disease increases with advancing age, it is not surprising that many individuals at the age of risk for dementia also suffer with coincident vascular disease. In fact, recent evidence suggests that beginning at age 55, the risk for incident stroke and Alzheimer’s disease (AD) are nearly identical (Figure 2). Clinical stroke, however, underestimates the true prevalence of cerebrovascular brain injury. For example, application of magnetic resonance imaging (MRI) to epidemiological studies suggests that the prevalence of MRI-detected cerebral infarction averages nearly 25% for individuals over age 65. Pathological studies confirm the coincidence of CVD and AD pathologies in the majority of older individuals with dementia and suggest that the presence of concurrent cerebrovascular pathology increases the likelihood of clinical dementia during life by a factor of twofold. Although AD and CVD pathologies are believed to affect the likelihood of dementia in an additive fashion, MRI studies suggest that these two pathologies may affect cognition through injury to overlapping cognitive systems, particularly through injury to parietal systems.

Figure 1. Prevalent Disease and Mortality

Source: National Center for Health Statistics/Centers for Disease Control and Prevention, 2009.
Note: HTN=hypertension
       CAD=coronary artery disease
       CVA=cerebrovascular accident
Modification of cerebrovascular risk factors, therefore, seems a prudent approach to the prevention of late-life dementia. Questions remain, however, as to which vascular factors have the greatest influence and how and when these factors need to be addressed for maximal protective effect. Table 1 briefly reviews known vascular risk factors associated with later life dementia. A series of recent studies \cite{14-20} have identified significant increased risk associated with each of these of vascular diseases, although the impact of cholesterol and cholesterol-lowering medications remains less clear.\textsuperscript{21}

**Table 1.** Recognized Vascular Risk Factors

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<td>1.</td>
<td>Hypertension</td>
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<td>2.</td>
<td>Hypercholesterolemia</td>
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<td>3.</td>
<td>Diabetes</td>
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<td>4.</td>
<td>Metabolic Syndrome</td>
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<td>5.</td>
<td>Smoking</td>
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<tr>
<td>6.</td>
<td>Hyperhomocystemia</td>
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Although evidence suggests that CVD causes cognitive impairment directly through vascular brain injury,\textsuperscript{10} it also is possible that brain injury associated with vascular risk factors may be mediated through secondary processes such as inflammation, oxidative stress,\textsuperscript{22} or even adipose-associated peptides.\textsuperscript{23} Recent MRI studies support this possibility.\textsuperscript{24-26} Furthermore, vascular diseases are systemic and vascular injury to other organs may enhance brain injury.\textsuperscript{27}
Importantly, however, many studies that find strong associations between vascular risk factors and late-life dementia measured these risk factors during midlife as opposed to other negative studies where these factors were measured more proximal to the diagnosis of dementia. In fact, the impact of vascular disease on cognition may be greatest when individuals have no obvious cognitive impairment, leading to the speculation that the impact of asymptomatic CVD on cognition may evolve over many years. Consistent with a proposed long duration of effect for vascular risk factors, recent reviews of therapeutic trials do not always strongly support treatment of vascular risk factors in the setting of clinical dementia, and overzealous treatment of some diseases such as diabetes may even be detrimental. In addition, additional biological markers may be necessary to identify individuals at greatest risk for cognitive decline associated with CVD and who might best respond to aggressive treatment.

In summary, the advancing average age of the general population and greater survival after vascular events has increased the likelihood that older individuals, at greatest risk for late-life dementia, also frequently have concomitant cerebrovascular brain injury. CVD and AD pathologies combine to increase the likelihood of late-life dementia. Vascular risk factors likely contribute directly to increased dementia risk through vascular brain injury mechanisms such as stroke, asymptomatic brain infarction, and even possibly white matter injury, but also may affect brain function through systemic vascular organ injury or secondary mediation such as increased oxidation or inflammation. Treatment of vascular risk factors at the time of diagnosed dementia has met with modest success, but treatment of high-risk cognitively normal individuals with asymptomatic CVD may be met with even greater success. Moreover, aggressive treatment of vascular risk factors during midlife also may prevent late-life dementia, as might the treatment of secondary effects of vascular risk factors such as inflammation. Although definite recommendations remain currently elusive, further research in this area appears promising and likely will lead to improved public health and lowered risk for dementia.

References


Introduction

The association between depression and cognitive decline has been the subject of considerable investigation and discussion. Recent findings indicating that depression is a risk factor for Alzheimer’s disease (AD) dementia have raised the possibility that depression treatment may lead to prevention of cognitive decline and dementia. This presentation will summarize the available evidence regarding the association between depression and AD dementia. It will address the question of whether treating depression may succeed in reducing AD risk. Specific recommendations also are made regarding studies needed to advance research in this area.

What Is the Relationship of Depression in Older People With Risk of Developing AD Disease or Age-Related Cognitive Decline?

Depressive symptoms affect about 15% of people over 65, with major depression affecting about 4%. A 2006 meta-analysis involving data from 20 studies and 102,172 individuals estimated that depression approximately doubles the risk for AD dementia.¹ Since the publication of that study, two cohort studies from the United States²–³ and studies from Spain,⁴ Canada,⁵ and The Netherlands⁶ have confirmed this association, with one study failing to confirm.⁷Uncertainty remains regarding the characteristics of depression that most strongly predict AD risk. In general, the association is strongest for moderate or more severe depression, especially major depression. The data are contradictory regarding the role of age of onset of depression, although most studies suggest that late-onset depression is most closely associated with dementia. One Dutch study, in which age of onset was retrospectively assessed, suggests that early-onset depression confers greater risk.⁶ Data from the Baltimore Epidemiologic Catchment Area Study, where depression age of onset was ascertained prospectively early in life, do not support early-onset depression as a risk factor for cognitive decline or dementia 20 years later. Some studies suggest that the depression-dementia association is stronger in men, while others suggest it is stronger in women. The Honolulu-Asia Aging Study reported that the depression-dementia association may be limited to ApoE4 carriers. In the Cache County Study, we find late-onset depression, especially major depression, but not early-onset depression to be a risk factor for AD, independent of other variables and apolipoprotein E (APOE) genotype.

Depression and other neuropsychiatric symptoms (NPS) such as apathy, irritability, anxiety, and agitation affect as many as 50% of individuals with mild cognitive impairment (MCI),⁸,⁹ and are comparably prevalent in amnestic and nonamnestic MCI.¹⁰ Several studies on MCI have reported an association between NPS and transition to dementia,¹¹,¹² although a recent study reported an inverse association between NPS and dementia incidence.¹³ In one study, major
depression in MCI conferred a 2.6-fold increased risk for AD. Late-life onset “mild behavioral impairment” is a strong risk factor for dementia, both in the presence and absence of MCI. An examination is underway of the predictive value of NPS in MCI using the large MCI cohort of the National Alzheimer’s Coordinating Center (n>4,000), allowing for nuanced study.

Is It “Normal” That People Who Are Diagnosed With AD Become Depressed?

If we attempt to explain depression meaningfully, then it makes sense that people diagnosed with AD become depressed. This implies that everyone develops clinical depression upon being diagnosed with AD, which is not supported by the data. Furthermore, since most people with AD do not have insight into their impairment, it is predicted that patients with better insight are more likely to be depressed; this is not supported by the available data. Suicidal ideation and suicide are rare in AD, and are no more common than in the general population, which does not support the view that it is “normal” to become depressed after a diagnosis of AD. This is further borne out in studies of individuals who are told of a terminal diagnosis such as cancer or AIDS.

Is Depression an Independent Risk Factor for AD, or Is It Associated With the Disease Process?

Since depression is a heterogeneous constellation of signs and symptoms with multiple etiologies, it is unlikely that these signs and symptoms are risk factors for AD. Rather, the question is whether the brain pathology underlying depression is the same pathology underlying AD dementia or whether it causes AD pathology. Both are likely to be the case.

Late-life depression is associated with cerebrovascular conditions including stroke, white matter change, and vascular risk factors. This has led to the concept of “vascular depression,” thought to be more prevalent in later life. For example, there is now evidence that depression after coronary artery bypass graft surgery is associated with preoperative internal carotid stenosis, assessed using intracranial Doppler. Depression is associated with insulin resistance (diabetes), itself a risk factor for AD, and other neurodegenerative diseases, notably Parkinson’s and Lewy body disease. Depression, especially chronic depression, is associated with activation of the hypothalamic-pituitary-adrenal axis, which may be toxic to the brain, especially the hippocampus. Depression in earlier life has been consistently associated with smaller hippocampal size. Although depression is heritable, it is not associated with known genetic risk factors for AD, including the ApoE4 genotype. Thus, the occurrence of depression in later life, especially of new onset, likely reflects brain pathology that is a risk factor for AD, or may lower the threshold for the occurrence of the syndrome of dementia. Brain vascular disease appears to be a determinant of cognitive impairment in older people with depression. However, the depression-dementia association cannot be fully explained by vascular disease.

The relationship between depression and AD pathology (i.e., amyloid plaques, tangles, microglial activation) has been poorly studied. Postmortem studies of depression in AD dementia associated depression with loss of monoaminergic nuclei in dorsal raphe and locus ceruleus. One small study suggested that a peripheral biomarker of microglial activation is associated with more severe NPS in AD. Brain imaging studies of older depressed people with cognitive symptomatology have found amyloid levels comparable to MCI or a correlation with depressive symptoms. Postmortem studies of depressed individuals who develop dementia report significant AD pathology. In contrast, a study of people dying with full-blown AD pathology without cognitive symptoms found lower rates of depression and proposed that depression was a risk factor for dementia in the presence of AD pathology but not for the...
pathology itself. Interestingly, in one study, older patients with depression and elevated blood amyloid biomarkers were more likely to have impaired memory, visuospatial ability, and executive dysfunction.

**Can Treating Depression Reduce the Risk of Developing AD or Age-Related Cognitive Decline?**

Clinical experience, and the limited available research, suggests that treatment of depression in older persons using currently available antidepressants often will lead to improvement but not complete remission of cognitive symptomatology. Among treated people with late-life depression, even if cognitive symptoms remit, the risk of progressive dementia in the ensuing years may be as high as 60%. Antidepressant trials in AD dementia do not show improvement of cognitive symptoms and are producing disappointing results about antidepressant efficacy in general. A reanalysis of a clinical trial targeting MCI with donepezil reported that moderate to severe depression was a risk factor for incidence of AD and that, in the subgroup of depressed participants, donepezil attenuated transition to a dementia. In contrast, a recently completed trial of donepezil augmentation of an antidepressant found modest cognitive benefits in older adults with recent major depression but a substantial risk of recurrence of depression. Hence, the very limited treatment literature suggests that antidepressant therapies are not good treatments for cognitive symptoms, but that the Food and Drug Administration-approved treatments for AD might prevent dementia incidence in depressed individuals with MCI. This is no surprise since currently available antidepressants were designed to be symptomatic treatments for depression, although there is some evidence that at least one (paroxetine) might attenuate amyloid pathology and its effects in a transgenic model of AD.

**What Studies Need To Be Done To Advance Research in This Area?**

Three types of studies are needed:

- Studies of late-life depression examining the etiology of cognitive impairment and dementia risk in this high-risk population. These studies would use brain imaging and other methods to quantify the contribution of different etiologies to cognitive impairment in late-life depression. How much cognitive impairment can be accounted for by brain vascular disease, diabetes (insulin resistance), or AD pathology? What is the relationship between amyloid pathology and late-life depression as determined by amyloid biomarkers? How do the several pathologies underlying late-life depression explain treatment resistance defined as failure to induce depression remission or to alleviate cognitive symptoms? These studies would lay the foundation for treatment studies to alleviate cognitive impairment and dementia risk.

- Studies of individuals with MCI who also have depression or other NPS. What factors explain the association between NPS and dementia conversion? Is this related to amyloid pathology, microglial activation, or other variables? This would lay the foundation for targeting treatments to MCI patients at risk for dementia conversion by virtue of depression or NPS.

- Treatment studies targeting depression in mild AD dementia. Recent failures of selective serotonin reuptake inhibitor (SSRI) antidepressants to ameliorate depression leave open the question about treating depression in AD dementia. Better understanding of pathophysiology should be pursued, and trials of available non-SSRI or novel antidepressants should be conducted.
References


Risk Reduction Factors for Alzheimer’s Disease and Cognitive Decline in Older Adults: Sociocultural and Demographic

Jennifer J. Manly, Ph.D.

Several large longitudinal community studies have found higher rates of cognitive impairment, dementia, and Alzheimer’s disease (AD) among African Americans and Hispanics than among whites, although this is not entirely consistent. The prevalence of dementia among older Japanese Americans was higher than among Japanese men living in Japan. Researchers have focused on possible causes of differences in rates of cognitive impairment and AD across diverse ethnic and sociocultural groups, because they may shed light on risks for cognitive decline in aging and potential interventions to reduce risk of decline.

Consideration of variables that underlie ethnic and racial differences in rates of cognitive impairment highlight the importance of a model that considers early-life conditions as relevant to cognitive function, the development and maintenance of cognitive skills, cognitive aging, and the onset and expression of neurodegenerative diseases. Understanding the key pathways and the most important time periods of exposure would be invaluable in designing and prioritizing efforts to reduce racial disparities in cognitive impairments. Figure 1 illustrates possible primary mediators in this process, moving from very broad social patterns such as migration and concluding with individual-level mediators, including physical health (e.g., cardiovascular disease) and health behaviors (e.g., exercise).

Figure 1. Pathways Linking Race/Ethnicity and Cognitive Function

This research approach recognizes that race/ethnicity serves as a proxy for more meaningful variables, and explicit measurement of these constructs will improve research on cognitive function within majority and minority ethnic groups. Possible explanations for findings of ethnic/racial differences in rates of cognitive impairment and AD include limitations in measurement of sociodemographic factors, bias in cognitive tests, differential genetic factors, differences in prevalence of nongenetic medical risk factors, differences in the social meaning and reaction to cognitive decline, and differential exposure to environmental risk factors.
Racial/ethnic differences in rates of cognitive decline and AD may be primarily driven by regional differences in the quality and quantity of schooling. Systematic differences between African Americans and whites in quality of school result in persistence of racial differences in cognitive test performance despite matching groups on years of education. When quality of education is determined along with quantity of schooling, racial/ethnic differences in cognitive test performance and incidence of AD (Table 1) are accounted for.

**Table 1.** Adjusted Cox Model Showing Relative Risk for Incident Dementia Among 1,192 African American and White Older Adults

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<tr>
<th>Variables in the Model</th>
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<td>Relative Risk (95% CI*)</td>
<td><em>P</em> Value</td>
<td>Relative Risk (95% CI*)</td>
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<td>Relative Risk (95% CI*)</td>
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<tr>
<td>Sex</td>
<td>1.0 (0.7–1.7)</td>
<td>0.770</td>
<td>1.0 (0.6–1.5)</td>
<td>0.835</td>
<td>1.0 (0.6–1.1)</td>
<td>0.941</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.2 (1.1–1.8)</td>
<td>0.000</td>
<td>1.2 (1.1–1.2)</td>
<td>0.000</td>
<td>1.2 (1.1–1.2)</td>
<td>0.000</td>
<td></td>
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</tr>
<tr>
<td>White vs. nonwhite</td>
<td>2.3 (1.5–3.7)</td>
<td>0.000</td>
<td>2.0 (1.3–3.3)</td>
<td>0.003</td>
<td>1.4 (0.9–2.3)</td>
<td>0.177</td>
<td></td>
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</tr>
<tr>
<td>&lt;12 Years of education</td>
<td>2.5 (1.4–4.5)</td>
<td>0.002</td>
<td>2.0 (1.1–3.7)</td>
<td>0.017</td>
<td></td>
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</tr>
<tr>
<td>Low Reading level</td>
<td></td>
<td></td>
<td>3.0 (1.5–6.0)</td>
<td>0.002</td>
<td></td>
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*CI: Confidence interval.

There are other within- and between-group cultural factors that must be considered in studies of ethnic/racial differences in risk of cognitive decline and AD. Rural residence has been reported to have a modest effect on risk for developing AD in studies outside and inside the United States. There is increasing evidence that the cognitive demands of functioning in a second language may affect cognitive function. Bilingualism previously has been linked to improved cognitive outcomes among older adults. Racial socialization, such as stereotype threat, has been shown to compromise, for example, academic test performance among blacks.

In conclusion, life histories of older ethnic minorities are relevant for interpreting cognitive measures and for research on causes of racial/ethnic differences in rates of AD. This topic also is important to understanding and anticipating the population burden of cognitive dysfunction. Increased investments in education and improved conditions for U.S.-born African Americans may reduce the incidence of dementia and cognitive impairment, offsetting increased burden expected as a consequence of population aging.

**References**


Clinical Trials for Alzheimer’s Disease

Paul S. Aisen, M.D.

Just over a century ago, Alois Alzheimer described a case of dementia in a middle-aged woman who, at autopsy, had plaques and tangles. For the next 70 years, Alzheimer’s disease (AD) was considered to be a rare and untreatable disease of middle age, a “presenile” dementia. But in the mid-1970s, through the ground-breaking work of Robert Katzman and others, AD was recognized as the major cause of dementia in aging individuals worldwide. In response to this newly appreciated public health need, research funded by the National Institutes of Health and other agencies identified therapeutic targets and established the methodology necessary to develop treatments for AD.

The cholinergic hypothesis of AD suggested that memory impairment might be treatable and led to the first successful trial of a cholinesterase inhibitor in 1985; the approval of four drugs in this class (tacrine, donepezil, galantamine, rivastigmine) followed. In 2003, with the approval of memantine, a new class of drugs targeting the glutamatergic system was established for the management of moderate to severe AD. All current treatments thus modulate synaptic function but do not change the underlying pathophysiological processes. They provide modest but meaningful amelioration of symptoms without altering the disease trajectory.

The main focus of therapeutic research today is the development of disease-modifying therapies that aim to influence amyloid dysregulation and toxicity, tangle formation, or other aspects of the neurodegenerative cascade. Clear targets have been identified. Two enzymes, beta-secretase and the gamma-secretase complex, appear to be essential for cleavage of the amyloidogenic Abeta fragment from its transmembrane amyloid precursor protein (APP); inhibition of one or both is expected to reduce amyloid accumulation. Genetic evidence provides strong support for these approaches: all known genetic causes of AD either increase the expression of APP or increase the generation of amyloidogenic fragments. There also is hope that inhibiting receptors that mediate Abeta trafficking and/or toxicity may modify AD neurodegeneration. Tangle-related targets, including kinase inhibitors aiming to reduce the hyperphosphorylation that characterizes the abnormal tau protein in tangles, have seen more limited efforts. Neurotrophic programs include direct neurosurgical delivery of nerve growth factor to the nucleus basalis using a viral vector.

In spite of the proliferation of clinical development programs, early results have been disappointing. The first two anti-amyloid drugs to reach the pivotal stage of development, tramiprosate and tarenflurbil, failed in phase III. Although most of the early disease-modifying studies have had disappointing results, at least one new drug may be close to approval and many others are advancing through the late phases of testing. A major challenge today is moving beyond the trial methodology that successfully launched current symptomatic treatments toward new study designs that will facilitate the development of disease-modifying treatments.

In AD, pathology likely precedes dementia onset by a decade or longer, with dementia representing a late stage along the neurobiological pathway. It is plausible that effective disease-modifying interventions for AD might be only minimally effective or even futile at the dementia stage; neuroprotection or favorable effects on amyloid or tau pathways might be overwhelmed by extensive neuronal/synaptic degeneration and plaque pathology. For this
reason, to optimize the impact of disease-modifying treatments, they must be initiated at the earliest possible stage of disease. The ideal population for treatment may be individuals at the asymptomatic stage of AD neurobiology.

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) as well as other longitudinal studies have enormously advanced our understanding of biomarkers of AD neurobiology, facilitating earlier treatment interventions (Figure 1). The community of AD clinical investigators is strongly weighing alteration of the diagnostic criteria for AD to include individuals with amnestic mild cognitive impairment (i.e., predementia impairment) plus biomarker evidence of AD neuropathology. ADNI has demonstrated that subjects with “early AD” defined in this way have accelerated decline on continuous measures of cognition and clinical status. Thus it may now be feasible to test disease-modifying interventions in early AD using standard outcome measures; trial power can be increased by using biomarker covariates, and disease modification can be supported by neuroimaging outcomes such as volumetric magnetic resonance imaging.

This trial design evolution, essential to advancing many promising therapeutic programs, will involve much earlier diagnosis of AD and incorporation of biological markers to facilitate efficacy studies. Such methodological advances, along with the rich pipeline of anti-amyloid, anti-tangle, and neuroprotective therapies, make the outlook for major therapeutic advances in the coming decade very bright indeed.

**Figure 1.** Hypothetical Graph Developed by Alzheimer’s Disease Neuroimaging Initiative (ADNI) Investigators Showing the Relationship Among Various Biomarkers of Alzheimer’s Disease Neurobiology and Clinical Disease Progression

![Graph showing the relationship among various biomarkers of Alzheimer’s Disease Neurobiology and clinical disease progression.](image)

Note: CSF=cerebrospinal fluid; FDG PET=18F-fluorodeoxyglucose positron emission tomography; MRI=magnetic resonance imaging; ADL=activities of daily living; eMCI=early mild cognitive impairment; Cog Perf=cognitive performance; lMCI=late mild cognition impairment.
References


More than 50% of community-dwelling older adults report cognitive decline. Age-related cognitive decline also has been documented on objective psychometric assessment where performance losses may exceed 50% compared to younger adults. Longitudinal studies indicate that decline in cognitive function leads to incident functional loss (i.e., decline in activities in daily living) in older adults and increased risk for institutionalization and mortality.

Epidemiological research suggests that stimulation broadly considered, including cognitive stimulation in the form of reading, interpersonal interaction, and avocational activities, is associated with reduced risk of cognitive decline and dementia. Although suggestive of an active role for mental activity in reversing or otherwise delaying the functional deficits associated with aging, the observational nature of these studies leaves open the possibility of reverse causation.

A number of specific cognitive and perceptual interventions have shown promise in enhancing function in older adults. Randomized controlled clinical trials offer an opportunity to establish a direct causative role for these interventions in improving or maintaining mental function in older adults, and thus preserving functional status and quality of life for this segment of the population.

What Kinds of Clinical Trials or Studies Have Been Done To Assess the Effects of Cognitive Training on Cognitive Aging?

A recent small-scale study demonstrated that older adults (n=54), compared to younger adults (n=72), have less spontaneous use of strategies when memorizing word pairs. After instruction in use of an associative strategy (i.e., creating a sentence that included the two words in the pair at encoding and also using the created sentences in guiding their responses during a retrieval phase), the performance of the older adults matched that of the younger adults. This study did not have a long-term follow-up, so the durability of the training-related gain is not known. Also, this study did not look at far transfer or generalization of the training to other cognitive or functional outcomes.

Another recent small-scale trial looked at the role of self-generated versus tutored memory strategies on later recall efficiency. Eighty-one older adults were divided into an instruction group, a self-generated strategy group, and a control group and were assessed on the accuracy of recall of multiple four-digit series. The instruction group was trained in the use of a number-consonant mnemonic in which digits were transformed into letters according to a key. Words were subsequently generated by adding vowels to make a meaningful encoding word-phrase (e.g., 3,481 is transformed to MRFD, which becomes MoRe FooD with the addition of vowels). The self-generating group was not given a strategy to learn; rather, participants in this group were encouraged to make their own strategy and to refine and systematize it to greatest effect. Some subjects in this condition grouped the numbers into meaningful units like a year or day of month or jersey number of a sports player. Eight months after training, both strategy groups performed better than the control group in recalling newly presented four-digit series with a slight advantage for the self-generated strategy group in conditions when approach to the recall
task was less structured. This study did not look at far transfer or generalization of the training to other cognitive or functional outcomes.

One study examined the effects of single and combined (or multifactorial) interventions (memory, problem solving, and psychomotor ability) and found the largest treatment effect for the combined intervention over a 5-year follow-up.12

Very recently, the Improvement in Memory With Plasticity-Based Adaptive Cognitive Training (IMPACT) study, a large-scale, multisite, randomized controlled trial of a cognitive intervention was completed.13 This project randomly assigned 487 basically healthy older adults to training to improve the speed and accuracy of auditory processing (e.g., syllable discrimination, recognition of syllable sequences, detail identification in verbally presented stories) versus an active control consisting of exposure to and recall of factual information from educational DVDs. Results demonstrated a clear advantage for the auditory processing intervention on speed and accuracy of auditory discriminations (the trained ability), a broader psychometric index of verbal memory and attention (transfer to a nontrained cognitive function), and patient-reported cognitive ability.

A total of 56% of the trained group exhibited a reliable improvement on the primary outcome of verbal memory compared to 43% of the control sample. This well-designed study was among the first to suggest a transfer of training beyond the ability targeted by the intervention; however, it did not examine the long-term durability of the training effect.

The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial,14-16 a response to a National Institutes of Health Request for Applications (RFA AG-96-001), has provided the largest multicenter, randomized controlled trial of the effectiveness of cognitive interventions ever conducted in older adults.

Participants in ACTIVE were randomly assigned to one of three treatment arms (memory, reasoning, or speed of processing training) or a no-contact control group. Outcome assessments were conducted at baseline, immediately following the intervention (post-test), and annually at 1, 2, 3, and 5 years after the intervention. A final annual assessment is underway 10 years after intervention.

The critical hypothesis in ACTIVE is that systematic training of different cognitive abilities will result in specific improvement in mental abilities and that these improvements in mental abilities transfer in a general way to improved functional status (i.e., daily living skill; see Figure 1).

The ACTIVE sample was recruited from community volunteers in six metropolitan areas (Baltimore, Maryland; Birmingham, Alabama; Boston, Massachusetts; Detroit, Michigan; State College, Pennsylvania; and Indianapolis, Indiana) with a final sample consisting of 2,802 persons. The sample was predominantly white (although approximately 25% was African American) and female (76%) with an average age of 74, average education of 13 years, and normal-range general cognitive function (Mini-Mental State Examination [MMSE], mean=27.3, standard deviation 2.0).15

The three areas of cognitive intervention in ACTIVE were chosen because earlier research had shown that age-related declines in these skills were associated with performance of activities of daily living.15 All treatment modules were standardized to consist of 10 sessions lasting 60–75
In the short term, each ACTIVE intervention produced an immediate improvement in the cognitive ability trained. The training effects were ability specific, which means, for example, that subjects who received reasoning training improved reasoning skill but not their memory or speed of processing performances. This was true for each type of cognitive intervention. The biggest improvements were observed for the speed of processing intervention, followed by the reasoning and memory interventions. Each type of training produced its largest effect immediately after the intervention (at post-test). The treatment gains (relative to the control group) dissipated over time to a degree but remained statistically and practically significant at the 5-year follow-up. There was an indication that more intensive training resulted in better
long-term maintenance of cognitive improvement for the reasoning and speed of processing interventions.\textsuperscript{17}

More notably, ACTIVE cognitive training did show far transfer to the primary outcome of daily function over the long term.\textsuperscript{16} Although each of the ACTIVE training programs produced roughly comparable positive effects on self-reported difficulty in performing instrumental activities of daily living by year 5, only the reasoning training arm was significant beyond \(p<0.001\). These data support the hypothesis that cognitive training improvements could transfer to daily function in a general way over time.

Preliminary analyses of the ACTIVE cohort suggest that most demographic factors do not have strong interactions with training. In addition, there is no indication that general cognitive status, as measured by the MMSE, differentially affected training outcomes across groups. On the other hand, one subgroup analysis looking at the role of baseline memory impairment did show differential training effects.\textsuperscript{18} An algorithm-based definition of mild cognitive impairment (MCI) was developed, resulting in a total of 193 ACTIVE subjects defined as MCI with the rest \((n=2,580)\) designated as memory-normal. MCI participants failed to benefit from memory training but did show normal training gains after reasoning and speed of processing training. Thus, MCI status appeared to mediate response to ACTIVE interventions.

**What Kinds of Interventions Need To Be Developed and Tested To Provide Evidence for Effectiveness in Reducing the Risk of Cognitive Decline in Older Adults?**

The results from IMPACT and ACTIVE indicate that further research on nonpharmacologic interventions in older adults is needed. Randomized controlled trials are key to establishing the effectiveness of cognitive interventions in reducing cognitive decline in older adults. The use of an active control group, as used in the IMPACT and ACTIVE trials, helps to establish the specific nature of the benefit attributable to the interventions. In addition, outcome assessors need to be blind to treatment assignment. Other key design features for studies in this area include outcome assessment focused on generalization and transfer first to related mental abilities (as in IMPACT) but also to real-world outcomes such as activities of daily living (as in ACTIVE), quality of life (e.g., subject satisfaction or quality-adjusted life years), health service utilization (e.g., delayed time to nursing home placement), and mortality. The last four outcomes require very long-term follow-up with all the attendant challenges including cost and attrition.

At the level of interventions themselves, future research should focus on dose response effects of training. Is there an asymptote in training response as a function of intensity of training in terms of session length, frequency, or duration of training? In addition, more refined prospective approaches to subgroups and head-to-head comparisons of effectiveness of specific training modules would help to tailor training modules to specific participants. Multisite studies will likely be required to provide the large samples needed for the stratified randomization and specialized analytic approaches and statistical power needs inherent in these approaches.

Future research also should focus on ways to increase the potency of cognitive interventions. It is possible that training in executive cognitive function could enhance control and contention-scheduling modules that underlie a wide range of daily life skills and challenges, and thus hold the potential to improve transfer and generalization to real-life outcomes.

Another unexplored area relates to the effectiveness of combinatorial interventions. It is possible that multimodal cognitive interventions, ones that combine training in more than one mental ability, produce training gains that are stronger and more durable over time and more likely to
show far transfer to functional outcomes. Combinatorial approaches could occur at other levels as well, for example, mental training in conjunction with physical training or changes in diet. The varied physiological pathways inherent in these diverse combinatorial approaches might hold the possibility of synergistic effects and enhanced treatment outcomes. Alternatively, direct training on instrumental activities of daily living may offer a more direct and sustainable path to preserving functional independence in older adults.

This is an exciting time in behavioral research. Randomized clinical trials provide a scientific basis for identifying targeted interventions that improve cognition and preserve functional status and quality of life for older adults.

References


Evidence-based Practice Center Presentation II: Therapeutic and Adverse Effects of Interventions To Delay the Onset of Alzheimer’s Disease

John W. Williams, Jr., M.D., M.H.S.; Brenda L. Plassman, Ph.D.; James Burke, M.D., Ph.D.; Tracey Holsinger, M.D.; Sophiya Benjamin, M.D.

Introduction

Alzheimer’s disease (AD) is the most common form of dementia. Numerous lifestyle factors, medications, and medical conditions have been proposed to alter the risk of developing AD. To determine whether adequate evidence currently exists to warrant recommendations for reducing the risk of developing or delaying the onset of AD, we conducted a systematic review of the current scientific literature.

Objective

The objective is to synthesize the published data on purported risk or protective factors for AD. In this presentation, we focus on data from studies of nutrition, vitamins, cognitive and physical activity, and medications (antihypertensives, statins, gonadal steroids, non-steroidal anti-inflammatory drugs [NSAIDs], and approved Alzheimer’s disease medications).

Review Methods

We searched MEDLINE® and the Cochrane Database of Systematic Reviews for relevant publications in English from 1984 to November 2009. Additional studies were identified from reference lists and technical experts. Using duplicate review, we identified relevant articles by reviewing the titles, then abstracts, and finally full-text articles. Both observational and intervention studies that compared subjects with an exposure of interest to those unexposed and reported an association with incident AD 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

The role of dietary factors and vitamins in development of AD has been a subject of intense interest. Systematic reviews have summarized data from observational and randomized controlled trials (RCTs) of omega-3 fatty acids, B vitamins, and vitamin E. A 2009 systematic review of seven prospective cohort studies of omega-3 fatty acid consumption with follow-up ranging from 3.9 to 7 years found no consistent association with incident AD.1 There were, however, significant differences in how omega-3 exposure was assessed, with most studies focusing only on fish consumption. Studies that examined the effect of B vitamins on development of AD had variable results. Studies that measured serum folate levels (n=3) found that low baseline serum folate was consistently associated with increased risk of AD and dementia. In contrast, vitamin B6 and B12 levels were not typically associated with development
of AD. The preponderance of evidence suggests that there is no association between vitamins E or C, folate, or beta carotene supplements and risk of AD. However, for vitamin C, vitamin E, or a combination of vitamins, there was substantial variability for the observed associations. A 3-year RCT of vitamin E in subjects with mild cognitive impairment showed no difference in progression to AD when compared with the placebo group. We identified one eligible cohort study examining the risk of AD and the Mediterranean diet, which found that greater compliance with this type of diet was associated with a significantly lower risk of AD. Increased consumption of saturated and trans fats also has been linked to risk of AD in a single eligible observational trial. These results are intriguing, but confirmation of the findings is necessary. An RCT of gingko biloba versus placebo in individuals with normal cognition or mild cognitive impairment showed little evidence that gingko delays the onset of AD.

We separated leisure activities into three categories: cognitively engaging activities (games, reading, etc.); physical activities; and other leisure activities that do not fall into the other categories (e.g., organization membership). Cognitive engagement was studied in three eligible cohort studies with follow-up from 3 to 5 years, and all reported a decreased risk of AD. The effect of physical activity on risk of AD was examined in eight eligible cohort studies. A meta-analysis of physical activity demonstrated a hazard ratio (HR) of 0.56 (95% confidence interval [CI] 0.37–0.86), suggesting that regular physical activity protects against development of AD. A single cohort study examining other leisure activities was eligible for inclusion in our review. The authors found that participation in more leisure activities was associated with a decreased risk of AD. A caveat about studies examining leisure activities is that individuals involved in one of the above-described categories of activity may be more likely to be involved in all three, potentially confounding results.

Medications for a wide range of indications have been studied for a potential effect on developing AD. Six eligible observational studies (including a secondary analysis of data from an RCT) involving almost 20,000 subjects followed for 3 to 17 years showed a consistent reduction in risk of AD with statin use. We used a random-effects model to compute a summary estimate of effect, which showed a significant association between statin use and decreased incidence of AD (HR 0.73, 95% CI 0.57–0.944). The forest plot, chi-square test (Q=5.132, df=5, p=0.40), and I²=2.58 did not suggest significant statistical heterogeneity. The effect of antihypertensives on incident AD was more complicated. Three of eight eligible studies showed a significant effect of antihypertensives. Age of cohort group studied, length of time followed, and prevalence of hypertension do not consistently explain the variability in outcomes across studies. A combination of three large, multisite RCTs also did not suggest a protective effect of antihypertensives on incident dementia.

A meta-analysis evaluating NSAID use and risk of AD (15,990 subjects with 672 incident cases of AD) showed a relative risk of 0.74 (95% CI 0.62–0.89). Three additional studies have been published since the meta-analysis, and only one found that NSAIDs reduced the risk of AD. However, two RCTs suggest that NSAIDs increase the risk of incident AD, but early trial termination, short duration of therapy, and low number of conversion events may complicate interpretation. There have been a number of trials of gonadal steroids. RCTs of conjugated equine estrogen (CEE) did not demonstrate a reduction in the incidence of AD, and a combination of CEE plus medroxyprogesterone acetate was shown to increase risk (HR 2.05, 95% CI 1.21–3.48). Evidence for the selective estrogen receptor modulators on AD is limited. A number of RCTs examining the effect of cholinesterase inhibitors to prevent progression to AD have been performed. Study heterogeneity precluded a valid summary estimate of effect, but conversion rates were similar in intervention and control subjects. No eligible studies of memantine on development of AD have been reported.
Conclusions

The current research on the list of putative risk or protective factors is largely inadequate to confidently assess their association with AD. Only a few of the factors reviewed here showed a consistent association with AD across multiple studies. Factors showing a consistent association with decreased risk of AD were high folate level, statin use, cognitive engagement, and physical activities. No consistent benefit in reducing the risk of developing AD was found for omega-3 fatty acids, vitamins, gingko biloba, antihypertensives, gonadal steroids, NSAIDs, or cholinesterase inhibitors. A consistent association does not imply that findings were robust, as data often were limited. In addition, the risk modification effect of reported associations was typically small to moderate for AD. Some of the factors that have not shown an association with AD or cognitive decline may still play an influential role in late-life cognition, but there was not sufficient evidence to draw this conclusion. Timing of exposure to various factors also may be critical. For example, controlling hypertension in midlife may be important, even if it is not proven to reduce AD when instituted in late life. Reliably assessing compliance with factors of interest over decades is also a problem. Many of these factors evaluated are not amenable to randomization, so rigorous observational studies are required to assess their effect on AD.

References


Evidence-based Practice Center Presentation III: Relationship Between the Factors That Affect Alzheimer's Disease and Those That Affect Cognitive Decline

John W. Williams, Jr., M.D., M.H.S.; Brenda L. Plassman, Ph.D.; James Burke, M.D., Ph.D.; Tracey Holsinger, M.D.; Sophiya Benjamin, M.D.

Introduction

Concordance between factors affecting cognitive decline (CD) and those affecting Alzheimer's disease (AD) has a number of potential implications. A consistent body of evidence would increase our confidence in any observed association. It also would be consistent with a paradigm that postulates that the symptoms of AD begin with insidious CD, which then progresses to more marked cognitive and functional impairment. Finding consistent evidence for factors associated with CD and AD would reinforce the potential effectiveness of early interventions for reducing the risk of both. Discordant findings weaken our confidence in the association but may simply reflect the heterogeneity of the etiology of CD; that is, CD may be due to normal aging mechanisms or may represent the prodromal stage of other types of dementing disorders such as vascular or frontal lobe dementia.

Objectives

The objectives are to describe the relationship between factors affecting AD and those affecting CD, and to identify priorities for future research.

Review Methods

To address the question of the relationship between factors affecting AD and those affecting CD, we used the results of the evidence review to establish consistency or lack of consistency of findings. Consistency of evidence in AD was compared with consistency of evidence in CD for each family of factors: nutritional, medical conditions and prescription and nonprescription medications, social/economic/behavioral, toxic environmental exposures, and genetics. We classified findings as “concordant” when the direction and magnitude of associations from observational and trial data (when available) were similar for AD and CD. When results were “discordant,” we evaluated differences in exposure classification, study duration, and study populations as potential sources of discrepant findings. When studies were available for only one of the two conditions (AD or CD), we could not determine concordance.

Based on the evaluation of consistency, along with an overall assessment of study quality and gaps in evidence, we identified priorities for future research.
Results

*We found concordant but low-quality evidence for risk of AD and CD and exposure to the following factors*: 

- **Increased risk:** Higher fat intake (limited evidence), diabetes, depression, current tobacco use, and the epsilon 4 allele of the apolipoprotein E gene (APOE e4).

- **Decreased risk:** Physical activity, cognitive engagement, leisure activities (limited data), and higher levels of education.

- **No consistent association:** Gingko biloba (limited evidence); beta carotene; flavinoids; multivitamins; vitamins B12, C, and E; hypertension; cholinesterase inhibitors; estrogens; and occupation. For estrogens, observational studies suggested a decreased risk of AD and CD in postmenopausal women, but randomized controlled trials (RCTs) did not show a decreased risk.

Only a few of these factors have been evaluated in RCTs, and with the exception of APOE e4, the quality of evidence was considered low.

*We found discordant evidence for risk of AD and CD for exposure to the following factors:*

- **Nutritional factors:**
  - Omega-3 fatty acids: No association with higher exposure for AD; decreased risk of CD.
  - Folic acid: Decreased risk of AD with higher exposure levels; inconsistent results for CD, but lowered risk of CD observed with higher blood levels of folic acid, whereas the results were inconsistent when self-reported dietary history was used as the exposure measure.

- **Medical and psychological factors:**
  - Homocysteine: Likely higher risk of AD at higher levels; inconsistent effect on CD.
  - Metabolic syndrome: No association with AD; association with CD for individuals <85 years old.

- **Medications:**
  - Statins: Decreased risk of AD in observational studies; inconsistent CD risk in observational studies but no association in secondary analysis of two RCTs.
  - Non-steroidal anti-inflammatory drugs (NSAIDs): Decreased risk of AD in cohorts; inconsistent CD risk in cohorts; RCTs higher but inconsistent risk for AD (some NSAIDs higher risk, some no change), and no consistent association for CD.
  - Antihypertensives: Decreased risk of AD in cohorts but no association with CD. RCTs have not shown a consistent reduction in risk of dementia or CD but have multiple limitations.

*We were unable to determine concordance for the following factors:*

- **Nutritional factors:** Diet composition, Mediterranean diet, trace metals, vitamins B3 and B6, and fruits and vegetables.

- **Medical and psychological factors:** Anxiety symptoms, obesity, traumatic brain injury, sleep apnea, and psychological resiliency.
• Medications: Raloxifene and dehydroepiandrosterone (insufficient data).

• Social and behavioral factors: Social engagement, midlife physical activity.

Future Research Needs

Considering our results on concordance, the quality of evidence, and gaps in evidence more broadly, currently available evidence does not support recommendations for interventions to delay or prevent CD or AD. In any case, only a subset of the factors examined are amenable to interventions. Possible interventions include pharmacologic agents (such as statins, antihypertensives, and cholinesterase inhibitors); dietary interventions and supplements; cognitive stimulation; and physical exercise. However, only cognitive engagement and physical exercise have concordant evidence to suggest a lower risk for AD and CD. Although promising, none of these factors has been studied for AD in an RCT and the overall quality of evidence is low. Other risk factors and protective factors may be amenable to effective intervention at the public health level (e.g., leisure activities) or by intervening to treat the condition associated with elevated risk (e.g., diabetes); these are potential areas for future investigation.

Our review also identified important methodological challenges when conducting future research. Some of the most important challenges are related to the early onset of initial pathological changes, measuring the exposure, and the wide array of measures for cognition. Assessing the effect of exposures on the development of AD is particularly challenging, as neuropathological evidence suggests that the changes associated with AD begin as early as the fourth decade of life, while clinical symptoms do not typically begin until decades later. The majority of papers in this review used subjects well beyond the likely onset of pathological changes in the brain, possibly missing the critical time period when protective factors or risk factors may have the most impact. To address this gap, observational studies would need to follow subjects for decades. Clearly, this would be very expensive and would risk loss of subjects over time. Some exposures could possibly be studied using registries or the databases of large healthcare organizations such as the Veterans Administration.

Also problematic in studying the effect of exposures on AD is the variably long prodromal phase. Early effects of AD during this prodrome could be mistaken for a risk factor (e.g., depression). With a prodrome extending for a long period, RCTs would need to be of sufficient length to capture an effect. Interventions carried on for long periods of time would need to be low risk. Furthermore, as long-term studies progress, subjects most at risk of CD and those with early symptoms may be more likely to leave the study early.

Problems in measuring exposures create further difficulties in interpreting existing evidence. Often studies are dependent on self-report of exposures. Instruments to collect information are often not validated. An exposure can change in an individual over years so that even a cognitively intact subject may be unable to answer questions about dietary intake or physical exercise if such factors have varied widely over time. Studies attempting to measure a single exposure (such as a dietary factor or supplement) may be complicated by interrelations with other exposures (e.g., healthy behaviors tend to track together). Prospective steps could be taken to strengthen data from future studies. Exposures could be established using standardized measures. Validated batteries of neurocognitive testing would allow more meaningful comparisons across studies. As information regarding risk factors increases, consensus about factors needed for adjustment will be possible.
References


Factors That Protect Against Alzheimer’s Disease and Cognitive Decline

David A. Bennett, M.D.

Factors Conclusively Shown To Protect Against Alzheimer’s Disease (AD) or Age-Related Cognitive Decline

None.

Life-Course Approach to AD Risk and Cognitive Decline

It has long been recognized that the intrauterine and early-life and midlife external environments are related to the development of late-life chronic diseases. This idea has been integrated into a life-course approach to chronic disease epidemiology, which seeks to understand the importance of time and timing in associations between exposures and outcomes. A life-course approach to AD risk recently has gained considerable support. Although the clinical hallmark of AD is cognitive decline in later life, a life-course disease model includes early-life and midlife factors associated with both cognitive decline and the development of cognitive capital, that is, peak cognitive performance. A number of early- and midlife factors appear to be related to late-life cognition and cognitive decline.

Table 1 lists a number of factors across the life course and their association with relevant cognitive outcomes. The list is intended to illustrate the range of factors associated with AD risk across the life course. Furthermore, it highlights the fact that, in some cases, the direction of the association differs depending on the timing of the exposure. For example, high body mass index (BMI) in midlife obesity is associated with an increased risk of AD, whereas low BMI in old age is associated with an increased risk of AD. The list is not exhaustive, and some findings are controversial.

Risk Factors for Age-Related Cognitive Decline, Mild Cognitive Impairment (MCI), and Clinical AD

Age-related loss of cognitive abilities, MCI, and clinical AD result from a complex relationship between genetic and environmental risk factors that lead to disease pathology and neurodegeneration. There is little evidence from humans to suggest that risk factors for AD differ from those for MCI or cognitive aging. Such data would ideally come from studies that collect repeated measures of cognition over time, and also document the occurrence of incident MCI and incident AD. Unfortunately, few such studies of sufficient size and length of follow-up exist.

Table 2 lists several factors associated with incident AD and MCI, and cognitive decline among those without dementia, in the same cohort. In some cases, data also are available on cognitive decline among those without dementia or MCI. The findings are substantially the same across the different outcomes. This does not mean that amyloid deposition and tangle formation, the pathologic hallmarks of AD, account for all of cognitive aging and MCI. In fact, some risk factors for cognitive decline, MCI, and clinical AD are not related to AD pathology or other common comorbidities such as cerebrovascular disease or Lewy bodies. Rather, the data suggest that the same set of processes result in the entire continuum of cognitive outcomes.
Table 1. Factors Across Different Life Epochs Associated With Relevant Cognitive Outcomes

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>Epoch</th>
<th>Risk Factor</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Intrauterine</td>
<td>Birth Weight</td>
<td>Young adult cognition</td>
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<tr>
<td>12</td>
<td>Early life</td>
<td>Mental ability</td>
<td>Incident dementia</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Early life</td>
<td>Household SES</td>
<td>Late-life cognition</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Early life</td>
<td>County SES</td>
<td>Late-life cognition</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Early life</td>
<td>Residence at birth</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Early life</td>
<td>Cognitive activity</td>
<td>Incident AD, cog decline</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Early life</td>
<td>Education</td>
<td>Incident AD</td>
<td>Findings controversial</td>
</tr>
<tr>
<td>16</td>
<td>Early life</td>
<td>Head circumference</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Early life</td>
<td>Knee height</td>
<td>Incident AD</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Midlife</td>
<td>Occupation</td>
<td>Incident AD</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Midlife</td>
<td>Cognitive activity</td>
<td>Incident AD, cog decline</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Midlife</td>
<td>Physical activity</td>
<td>Incident AD</td>
<td>Findings controversial</td>
</tr>
<tr>
<td>19</td>
<td>Midlife</td>
<td>Body mass index</td>
<td>Incident dementia</td>
<td>High body mass index high risk</td>
</tr>
<tr>
<td>20</td>
<td>Midlife</td>
<td>Serum cholesterol</td>
<td>Incident cog impairment</td>
<td>High cholesterol high risk</td>
</tr>
<tr>
<td>21</td>
<td>Midlife</td>
<td>Systolic blood pressure</td>
<td>Incident AD</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Midlife</td>
<td>Neuroticism</td>
<td>AD age of onset</td>
<td></td>
</tr>
</tbody>
</table>

Note: SES = socioeconomic status; cog = cognitive.
Table 1. Factors Across Different Life Epochs Associated With Relevant Cognitive Outcomes (continued)

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>Epoch</th>
<th>Risk Factor</th>
<th>Outcome</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>23</td>
<td>Midlife</td>
<td>Head injury</td>
<td>Incident AD</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Late life</td>
<td>Cognitive activity</td>
<td>Incident AD, cog decline</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Late life</td>
<td>Social activity</td>
<td>Incident dementia</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Late life</td>
<td>Physical activity</td>
<td>Incident AD</td>
<td>Interaction with APOE</td>
</tr>
<tr>
<td>26</td>
<td>Late life</td>
<td>Leisure activity</td>
<td>Incident AD</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Late life</td>
<td>Social network</td>
<td>Incident AD</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Late life</td>
<td>Body mass index</td>
<td>Incident dementia</td>
<td>Low body mass index increases risk</td>
</tr>
<tr>
<td>28</td>
<td>Late life</td>
<td>Diabetes</td>
<td>Incident AD, cog decline</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Late life</td>
<td>Serum cholesterol</td>
<td>Incident cog impairment</td>
<td>Lower cholesterol high risk</td>
</tr>
<tr>
<td>29</td>
<td>Late life</td>
<td>Blood pressure</td>
<td>Incident AD, cog decline</td>
<td>Findings controversial</td>
</tr>
<tr>
<td>9</td>
<td>Late life</td>
<td>Psychological distress</td>
<td>Incident AD, cog decline</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Late life</td>
<td>Depression</td>
<td>Incident AD</td>
<td>Findings controversial</td>
</tr>
<tr>
<td>10</td>
<td>Late life</td>
<td>Conscientiousness</td>
<td>Incident AD, cog decline</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Late life</td>
<td>Loneliness</td>
<td>Incident AD, cog decline</td>
<td></td>
</tr>
</tbody>
</table>

Note: SES=socioeconomic status; cog=cognitive; APOE=apolipoprotein E.
Table 2. Factors Related to Incident Alzheimer's Disease and Mild Cognitive Impairment, and Cognitive Decline From the Same Cohort

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>Risk Factor</th>
<th>Incident AD</th>
<th>Cog Dec*</th>
<th>Incident MCI</th>
<th>Cog Dec**</th>
</tr>
</thead>
<tbody>
<tr>
<td>32, 33</td>
<td>Hypertension</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>34</td>
<td>Insulin</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>35, 36</td>
<td>Mediterranean diet</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>37, 38</td>
<td>Leisure activity</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>39, 40</td>
<td>Apolipoprotein E</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>10</td>
<td>Conscientousness</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>41, 42</td>
<td>Physical frailty</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>43</td>
<td>Strength</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>44</td>
<td>Purpose</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>8</td>
<td>Cognitive activity</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>45, 46</td>
<td>Odor identification</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>9, 47, 48</td>
<td>Psychological distress</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Cognitive decline among persons without dementia at baseline.  
**Cognitive decline among persons without dementia or MCI at baseline.

Implications for Randomized Controlled Trials

Translating findings from epidemiologic studies into interventions that improve public health can be a difficult and frustrating process. Experience with estrogen and non-steroidal anti-inflammatory drug use highlights the potential hazards, as randomized controlled trials failed to confirm the beneficial effects reported in observational studies and even found associations in the opposite direction. Likewise, despite findings from observational studies reporting a link between hypertension and AD risk, the results of many ongoing hypertension trials that include cognitive assessments have failed to find a reduction of cognitive impairment.

Randomized controlled clinical trials are generally considered to be the gold standard. However, it is essential that epidemiologic data be evaluated carefully to determine the timing, dose, duration of exposure, and likely effect size that can be expected in a trial. Many observational cohort studies are large and collect outcomes over years or decades, much longer than a trial can be practically or financially implemented. Thus, some interventions may not be readily amenable to controlled trials. For example, among the greatest public health successes of the last century was the marked reduction of smoking with the prevention of disability and death due
to many types of cancer, chronic obstructive pulmonary disease, and heart disease. The link between smoking and these chronic diseases was based on epidemiologic data, supported by animal models demonstrating biologic plausibility. The intervention was public policy and outcomes measured by disease surveillance.

Gaps in Knowledge and Implications for Further Research

Some interventions with the potential to prevent AD have wide applicability and minimal side effects, such as engagement in cognitive, physical, social, and leisure activities. The timing of these interventions may be across the life course, the dose small, the duration of exposure years or decades, and the effect size small and cumulative. The situation may be similar to smoking risk, which is measured in pack years. For such interventions, it may not be feasible or advisable to conduct the kinds of randomized clinical trials that would be needed to prove that the intervention is effective. Rather, the monies may be better spent on public policy strategies to encourage the adoption of “brain healthy” lifestyles combined with national surveillance. For example, one recent study, using changes in state compulsory schooling laws as a natural experiment, found that greater years of education related to changes in schooling laws was associated with better late-life cognition, providing evidence of a causal effect.

By contrast, clinical trials will be needed for some interventions with more adverse risk-to-benefit profiles. The conduct of such trials will require a serious re-evaluation of the proper study design. It will not be possible to use trial designs currently in vogue for the secondary or tertiary prevention of AD. Rather, they likely will need to enroll subjects across a range of life epochs and require tens of thousands of individuals followed over many years. As is done in many cardiovascular disease or cancer trials, they will require minimal inclusion and exclusion criteria, and a relatively simple and brief assessment of outcomes. Because cognitive decline is likely the result of the same processes that eventually lead to MCI and AD, one approach might be to test cognitive function over time, probably by telephone or the Internet, and use change in cognitive function as the primary study outcome.

References


44. Boyle PA, Buchman AS, Barnes LL, Bennett DA. Purpose in life is associated with a reduced risk of incident Alzheimer’s disease among community-dwelling older persons. *Arch Gen Psychiatry*. 2010; in press.


