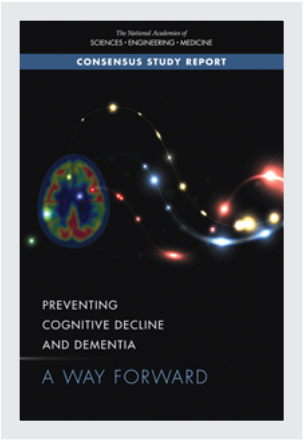

Preventing Cognitive Decline and Dementia: A Way Forward

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PREVENTING COGNITIVE DECLINE AND DEMENTIA
A WAY FORWARD

Committee on Preventing Dementia and Cognitive Impairment

Alan I. Leshner, Story Landis, Clare Stroud, and Autumn Downey,
Editors

Board on Health Sciences Policy

Health and Medicine Division

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **Enriqueta C. Bond,** Burroughs Wellcome Fund, and **Huda Akil,** University of Michigan. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

PREFACE

The prospect of potential cognitive decline and the development of dementia is a significant source of anxiety for many people as they age, raising deep concerns about their future independence and quality of life. Yet for those interested in taking active steps to maintain, to the extent possible, their brain health, it is difficult to know how best to invest their time and resources. A bewildering number of products and behaviors have been touted as potential preventive measures, but very few have been subjected to rigorous testing for effectiveness. Recognizing that many people turn to the National Institute on Aging (NIA) of the National Institutes of Health for up-do-date information on both normal cognitive decline and neuropathological processes that can occur with aging, NIA asked the National Academies of Sciences, Engineering, and Medicine to convene a committee to examine and comment on the state of knowledge about what works in preventing or slowing cognitive decline and dementia.

This report examines the current state of the evidence on interventions for preventing cognitive decline and dementia and is intended to inform future efforts to develop public health strategies and messages, as well as to suggest future research priorities for improving the quality of the relevant knowledge base. Although the evidence has not yet matured to the level that would support an assertive public health campaign aimed at widespread adoption of any such intervention, the report does identify those interventions, supported by some evidence of benefit, that the committee believes should be discussed with members of the public who are actively seeking advice on steps they can take to maintain brain health as they age. Two key points add important context to the committee's recommendations.

First, the committee was asked to make its recommendations based largely on the most stringent form of evidence—randomized controlled trials (RCTs). RCTs are the gold standard in evidence generation but require large investments of money and time. Moreover, while they are particularly effective for testing single-intervention solutions, the apparent complexity of the pathophysiology underlying cognitive decline and dementia suggests that a multifaceted approach may be most effective. Such an approach is challenging to evaluate through an RCT. To lend confidence to the suggestions emerging from RCTs, then, the committee considered other salient sources of evidence that, when combined with RCT-based evidence, offer a fuller picture.

Second, it should be emphasized that the committee's analysis is of necessity based on the current state of knowledge, and addresses a rapidly evolving scientific field. Fundamental understanding of the processes of cognitive decline and dementia is advancing at an impressive pace. Moreover, additional intervention studies were being conducted even as this report was being written, and they are expected to yield important insights. The committee's suggestions for prioritizing future research, including methodological recommendations, are intended to help shape future research efforts in this domain and generate a more comprehensive and stronger evidence base.

We wish to offer our deep gratitude to the members of this National Academies of Sciences, Engineering, and Medicine committee. Leading such an expert and committed group of scholars, all of whom gave generously of their time, has been an incredibly rewarding experience. This work also benefited greatly from the exceptional competence and dedication of the National Academies staff and many others cited in the acknowledgments that follow.

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Committee on Preventing Dementia and Cognitive Impairment

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The committee first would like to recognize and honor the contributions of Robert Lewis Kane to this project. Dr. Kane led the work of the Minnesota Evidence-based Practice Center to develop the Agency for Healthcare Research and Quality (AHRQ) systematic review that formed the primary evidence base used by the committee. His leadership and deep knowledge in this area were critical to the development of this extensive, thorough, and thoughtful analysis of interventions for cognitive decline and dementia. Sadly, Dr. Kane died unexpectedly while the committee was writing this report. Dr. Kane was the Minnesota Chair of Aging and Long-Term Care at the University of Minnesota's School of Public Health, where he had a long and productive career. He was known for his scholarship, his deeply felt advocacy to help individuals age with grace and dignity, his generosity to colleagues and students, and his sense of humor. Among many other important contributions, his work with the Office of Technology Assessment's Advisory Committee on Alzheimer's Disease and Related Disorders helped put Alzheimer's disease "on the map" from the perspective of research, clinical care, and policy. He was a true force in the field and will be greatly missed.

The committee also acknowledges and thanks the study sponsor—the National Institute on Aging—and particularly Richard Hodes, Marie A. Bernard, and Melinda Kelley for their leadership and vision in the development of this project. We are grateful to David Niebuhr, Kim Wittenberg, and colleagues at AHRQ for overseeing the systematic review that formed the primary evidence base used for the study. We also wish to recognize and thank Mary Butler, Howard Fink, and the many others at the Minnesota

Evidence-based Practice Center who worked with Dr. Kane on the preparation of the AHRQ systematic review.

We wish to express our gratitude to the many individuals who gave presentations to and participated in discussions with the committee. We especially thank Walter Koroshetz (National Institute of Neurological Disorders and Stroke) and William Thies (Alzheimer's Association) for sharing their insights with the committee during the initial phase of the project, as well as the following workshop presenters: James Appleby (Gerontological Society of America), Matthew Baumgart (Alzheimer's Association), Michael Ellenbogen (Alzheimer's disease/dementia advocate), Mary Ann Forciea (University of Pennsylvania and American College of Physicians), Rebecca Gottesman (Johns Hopkins University), Stacy Pagos Haller (BrightFocus Foundation), Julene Johnson (University of California, San Francisco), Brian LeBlanc (Alzheimer's disease advocate), Sarah Lenz Lock (AARP), Susan McCurry (University of Washington), Regina Davis Moss (American Public Health Association), Edo Richard (Radboud University), Walter Rocca (Mayo Clinic), Mary Sano (Mount Sinai School of Medicine), Lisa Shulman (University of Maryland and American Academy of Neurology), Brian Southwell (RTI International), Joe Verghese (Albert Einstein College of Medicine), Jeff Williamson (Wake Forest Baptist Health), and Sherry Willis (University of Washington).

Finally, the committee would like to express its gratitude to and admiration for the National Academies of Sciences, Engineering, and Medicine staff who worked so hard and so well on the study: Clare Stroud, Autumn Downey, Sheena Posey Norris, Benjamin Kahn, Olivia Yost, and Daniel Flynn. We also are grateful for the contributions of James Burke, Gilbert S. Omenn Fellow at the National Academy of Medicine; Rona Briere, for her careful editing of the report; and Rebecca Morgan of the National Academies Research Center, for her assistance with fact-checking.

CONTENTS

ACRONYMS AND ABBREVIATIONS

ACCORD-MIND	Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes trial
ACE	angiotensin converting enzyme
AChEI	acetylcholinesterase inhibitor
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly trial
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADRD	Alzheimer's disease-related dementias
ADVANCE	Action in Diabetes and Vascular Disease: PreterAx and DiamicroN-MR Controlled Evaluation trial
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blockers
ARCD	age-related cognitive decline
BDNF	brain-derived neurotrophic factor
CATD	clinical Alzheimer's-type dementia
CBTI	cognitive-behavioral therapy for insomnia
CFAS	Cognitive Function and Ageing Study
CI	confidence interval
COX-2	cyclooxygenase-2
DASH	Dietary Approaches to Stop Hypertension

EPC	evidence-based practice center
EXERT	Exercise in Adults with Mild Memory Problems trial
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GRADE	Glycemic Reduction Approaches in Diabetes trial
HOPE-3	Heart Outcomes Prevention Evaluation-3
HRS	Health and Retirement Study
HYVET	Hypertension in the Very Elderly Trial
IADL	instrumental activity of daily living
IHAMS	Iowa Health and Active Minds Study
IOM	Institute of Medicine
LIFE	Lifestyle Interventions and Independence for Elders trial
MAPT	Multidomain Alzheimer's Prevention Trial
MAX	Mental Activity and Exercise trial
MCI	mild cognitive impairment
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MMSE	Mini Mental State Exam
NIA	National Institute on Aging
NIH	National Institutes of Health
NMDA	N-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
ORIGIN	Outcome Reduction with Initial Glargine Intervention
PET	positron emission tomography
PREDIMED	Prevención con Dieta Mediterránea trial
PreDIVA	Prevention of Dementia by Intensive Vascular Care
PROGRESS	Perindopril Protection against Recurrent Stroke Study

RCT	randomized controlled trial
REGARDS	Reasons for Geographical and Racial Differences in Stroke study
RR	relative risk
SBP	systolic blood pressure
SCOPE	Study on Cognition and Prognosis in the Elderly
SPRINT	Systolic Blood Pressure Intervention Trial
SSRI	selective serotonin reuptake inhibitor
USPSTF	U.S. Preventive Services Task Force
WHIMS	Women's Health Initiative Memory Study
WHISCA	Women's Health Initiative Study of Cognitive Aging
WHO	World Health Organization

SUMMARY[1]

Individuals, families, and societies around the world are concerned about dementia and the other forms of cognitive impairment that affect many older adults. It is now known that brain changes typically begin years—if not decades—before people show symptoms, which suggests that a window of opportunity exists to prevent or delay the onset of these conditions. Furthermore, emerging evidence that the incidence and prevalence of dementia are declining in high-income countries offers hope that public health interventions can be effective in preventing cognitive decline and dementia. Although the evidence base on how to prevent or delay these conditions has been limited at best—despite the many claims of success made in popular media and advertising—a growing body of prevention research is emerging. The National Institute on Aging (NIA) initiated this study with the National Academies of Sciences, Engineering, and Medicine to take stock of the current state of knowledge on interventions for preventing cognitive decline and dementia, to help shape the messages NIA conveys to the broader public about these conditions, and to inform future actions and research in this area. Box S-1 provides definitions of the key terminology used in this report.

[1]This summary does not include references. Citations for the discussion presented in this summary appear in the subsequent report chapters.

BOX S-1
Key Terminology Used in This Report

This report considers several related conditions involving cognitive function in older adults for which many different terms and definitions are used. Developing clear, consistent terminology that accurately reflects the evidence is therefore challenging. Furthermore, the committee's task was to offer recommendations as to what can appropriately be communicated to members of the public, who generally are interested in staying cognitively healthy as they age and are unlikely to make the distinctions that are used in research.

When describing the overall goal addressed by this study, instead of specifying particular conditions or listing all relevant conditions repeatedly, the committee uses the shorthand umbrella term **preventing cognitive decline and dementia.** On the other hand, when discussing research results and associated conclusions and recommendations, the committee uses more specific terms for three conditions that can affect older adults:

Age-related cognitive decline (ARCD): Deterioration in cognitive performance that can be a normal part of aging. It is also sometimes referred to as **cognitive aging.**

Mild cognitive impairment (MCI): Cognitive impairment that has reached a level of deterioration from normal cognitive function identifiable by individuals, family members, or clinicians, but without significant functional impairment in daily activities (i.e., individuals may have mild functional impairments but can adapt to them).

Clinical Alzheimer's-type dementia (CATD): Cognitive impairment severe enough that an individual can no longer function independently. This impairment may be due to Alzheimer's disease (i.e., the abnormal build-up of amyloid and tau proteins in the brain) or to "mixed" causes of dementia, such as Alzheimer's disease combined with alpha-synuclein or TDP-43 proteins or with vascular disease in the brain. This term is not widely used in the field; the committee uses it here to reflect the increasing recognition of mixed dementia, which may be difficult to differentiate in a clinical setting.

As noted above, there is variability in the terms and definitions used for these conditions in the field. Furthermore, the conditions noted above are heterogeneous, and it is not possible at present to draw clear lines among them. However, understanding of these conditions will continue to evolve as a result of scientific and technological advances, and it is conceivable that the application of genomic

and other technologies in the clinic will enable better pairing of clinical interventions with particular populations of individuals.

To inform this committee's work, the National Institute on Aging (NIA) asked the Agency for Healthcare Research and Quality (AHRQ) to conduct a systematic review of the outcomes from intervention studies directed at the above three conditions. The committee relied on that analysis and uses these three terms in this report when summarizing findings and drawing conclusions about available evidence on specific interventions. Although the hope is that an effective intervention for ARCD would also benefit MCI and CATD, and the reverse, it is not yet known whether this is in fact the case. Therefore, this report does not make this extrapolation in either direction. Where the available evidence is specific to one condition (e.g., ARCD but not MCI or CATD), this is specified in the text. It is important to note, however, that given the overall paucity of data in this domain, the committee's conclusions may be due to a lack of evidence rather than a true difference.

This report refers to **preventing, delaying, or slowing MCI and CATD**, which encompasses both the onset of the disorders and the rate of change over time after onset. The report also considers evidence on **delaying and slowing ARCD**; prevention is not included in the discussion of ARCD since some level of decline is expected with aging.

A final consideration is that interventions may result in short-term improved performance on specific cognitive tests (e.g., memory or speed of processing) as compared with baseline. This improvement may be inherently valuable to some people, but it is not clear whether or how this short-term, specific benefit translates to general delaying or slowing of ARCD over the long term or to preventing, delaying, or slowing MCI and CATD. To describe such short-term, specific improvements, the committee uses the term **short-term improvements in cognitive performance.**

In addition to the above terms describing particular conditions, three more terms are used throughout this report. First, a **risk factor** is a characteristic or attribute that is associated with an increase or decrease in the likelihood of developing a condition. An **intervention** refers to any program or treatment applied to an individual (whether pharmacological or not) designed to modify the condition under investigation. Finally, the term **observational study** refers to a nonexperimental study design, that is, a design that does not use random assignment to an intervention. Examples of such studies include correlational, cohort, association, and epidemiological studies. In most cases, the committee relies on longitudinal population-based cohort studies when evaluating observational data; any use of case control studies is specifically noted.

A FRESH LOOK AT THE EVIDENCE

A systematic review published in 2010 by the Agency for Healthcare Research and Quality (AHRQ) and an associated "state of the science" conference at the National Institutes of Health (NIH) concluded that there was insufficient evidence to make recommendations about interventions to prevent cognitive decline and dementia. Since then, understanding of the pathological processes that result in dementia has significantly advanced, and a number of clinical trials of potential preventive interventions have been completed and published, with more under way or being planned.

Accordingly, NIA asked the National Academies to convene an expert committee to help inform the design of a new AHRQ systematic review, whose results then would be used by the committee as the primary evidence base for recommendations on the appropriate content for communicating with the public about steps that can be taken to prevent, delay, or slow the onset of mild cognitive impairment (MCI) and clinical Alzheimer's-type dementia (CATD) and delay or slow age-related cognitive decline (ARCD), as well as recommendations for future prevention research. Expert testimony provided during the public workshop held after the release of the draft AHRQ systematic review also was particularly useful in informing the committee's approach. The committee's full statement of task is provided in Chapter 1 of this report.

Consistent with its statement of task, the study did not specifically address the effectiveness of interventions in slowing the rate of decline among individuals already diagnosed with dementia, and some forms of dementia—frontotemporal dementia, Lewy body dementia, and those with a clear etiology (e.g., incident stroke, AIDS, traumatic brain injury)—were excluded from the analysis. Interventions targeting stroke risk factors were given particular attention because they may contribute to CATD, and conditions that coexist with CATD as components of mixed dementia, such as vascular contributions to dementia, were included in the study scope. However, cognitive impairment that is likely to be caused solely by vascular disease (pure vascular dementia) was excluded. The committee also was not asked to examine the potential of public health policies (e.g., access to education, clean air) to prevent cognitive decline and dementia.

There have been previous efforts to examine prevention in this domain, including a prior Institute of Medicine report titled *Cognitive Aging: Progress in Understanding and Opportunities for Action*. The present report incorporates the most recent evidence from a rapidly evolving field and stands out as uniquely focused on applying AHRQ's highly refined systematic review process to assess what evidence is available on the effectiveness of the interventions themselves—as opposed to focusing on potentially

modifiable risk factors—and examining how that evidence might serve as a basis for public health messaging.

The 2017 AHRQ systematic review, conducted by the Minnesota Evidence-based Practice Center (EPC), represents an extensive effort to summarize the state of the evidence in this area. It examines the evidence on the effectiveness, comparative effectiveness, and harms of interventions associated with preventing or delaying the onset or slowing the progression of CATD and MCI and delaying or slowing ARCD. The systematic review relies primarily on randomized controlled trials (RCTs) with a minimum 6-month follow-up period for intermediate outcomes; large prospective quasi-experimental cohort studies with comparator arms (n ≥250 per arm) were also included in the search conducted for the review, but little concrete evidence emerged from such studies.

Overall, the committee determined that, despite advances in understanding these conditions since the 2010 AHRQ systematic review was conducted, the available evidence on interventions derived from RCTs—the "gold standard" of evidence—remains relatively limited and has significant shortcomings. These shortcomings stem, in part, from the challenges inherent in conducting RCTs on interventions for conditions that may have a long latency period and are often comorbid with other late-life conditions. As described in more detail below, methodological shortcomings also contributed to the paucity of high-quality RCT data available to support recommendations on public health messaging. To supplement this evidence base, therefore, the committee considered additional evidence from observational nonexperimental studies—primarily longitudinal population-based cohort studies—as well as evidence from studies of risk factors and neurobiological studies that strengthen belief in the effectiveness of a class of interventions for which at least some supportive RCT data were identified. Although observational data are subject to their own limitations (e.g., risk of confounding, biases) and should be interpreted with caution, such studies are, if conducted using rigorous methods, an important complementary source of evidence when definitive RCT data are lacking. Knowledge of harms and costs, as well as potential benefits to noncognitive outcomes, was also considered.

COMMUNICATING WITH THE PUBLIC ABOUT INTERVENTIONS TO PREVENT COGNITIVE DECLINE AND DEMENTIA

The AHRQ systematic review identified no specific interventions that are supported by sufficient evidence to justify mounting an assertive public health campaign to encourage people to adopt them for the purpose of preventing cognitive decline and dementia. The systematic review did, however, find some degree of support for the benefit of three classes of intervention:

cognitive training, blood pressure management in people with hypertension, and increased physical activity.

The strength of evidence differs for these three interventions, and the evidence for each applies particularly to specific conditions. Cognitive training is supported by low- to moderate-strength RCT evidence, bolstered by observational study data, for delaying or slowing ARCD, although, as discussed below, these findings *cannot* be used to draw conclusions on the long-term cognitive benefits of commercial computerized cognitive training applications (i.e., "brain games"). RCT evidence for blood pressure management and increased physical activity is weaker. The suggestion that blood pressure management and increased physical activity be included among the interventions with some degree of support is not based primarily on RCT evidence from the AHRQ systematic review; rather, in the committee's judgment, there is sufficient complementary evidence from observational studies and neurobiological understanding to include them in communications with the public. This evidence supports blood pressure management for people with hypertension for preventing, delaying, or slowing CATD based on dementia incidence data, and increased physical activity for delaying or slowing ARCD based on cognitive test performance data.

Since many people are very interested in what they can do to prevent cognitive decline and dementia, and based on the totality of available evidence, the committee concluded that, when communicating with the public, these three classes of interventions can be described as supported by encouraging but inconclusive evidence. The finding of inconclusive evidence is driven largely by the lack of consistent results across RCTs for all three intervention domains and raises the possibility that future research may show that one or more of these interventions do not prevent cognitive decline or dementia but have only short-term or nonspecific effects. Moreover, although it is biologically plausible that the same interventions that help delay or slow ARCD would also be beneficial for the prevention of MCI and CATD, and the reverse, it is not known whether this extrapolation can be made in either direction. The public, however, will not draw fine distinctions among these conditions, and it will be challenging for NIA and others to convert these statements about the evidence into appropriate communications with the public.

Recommendation 1: Communicating with the Public

When communicating with the public about what is currently known, the National Institutes of Health, the Centers for Disease Control and Prevention, and other interested organizations should make clear that positive effects of the following classes of interventions are supported by encouraging although inconclusive evidence:

- ***cognitive training*—a broad set of interventions, such as those aimed at enhancing reasoning, memory, and speed of processing—to delay or slow age-related cognitive decline**
- ***blood pressure management for people with hypertension* to prevent, delay, or slow clinical Alzheimer's-type dementia**
- ***increased physical activity* to delay or slow age-related cognitive decline**

There is insufficient high-strength experimental evidence to justify a public health information campaign, per se, that would encourage the adoption of specific interventions to prevent these conditions. Nonetheless, it is appropriate for the National Institutes of Health and others to provide accurate information about the potential impact of these three intervention classes on cognitive outcomes in a place where people can access it (e.g., websites). It also is appropriate for public health practitioners and health care providers to include mention of the potential cognitive benefits of these interventions when promoting their adoption for the prevention or control of other diseases and conditions.

Cognitive Training

In the context of this report, the term *cognitive training* is used to denote a broad set of interventions, including those aimed at enhancing reasoning (e.g., problem solving), memory, and speed of processing (e.g., speed of identifying visual information on a screen). Such structured training exercises may or may not be computer based. Cognitively stimulating activities, for the purposes of this report, include such interventions as learning a new language and increasing proficiency in daily activities, such as playing bridge and doing crossword puzzles.

Cognitive training has engendered considerable interest and debate in both the academic and commercial sectors, particularly within the past 15 years. There is good evidence to show that cognitive training can improve performance on a trained task, at least in the short term, but debate has centered on evidence for long-term benefits and whether training in one domain (e.g., processing speed) yields benefits in others (e.g., memory, reasoning) and can translate to maintaining independence in instrumental activities of daily living, such as remembering to take medications and driving.

The AHRQ systematic review found that the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial provided moderate-strength evidence at 2 years (but low-strength evidence at 5 and

10 years) that cognitive training can improve cognitive function in the domain trained, but training in one cognitive domain generally did not lead to significant improvements in performance in other domains. Additionally, greater maintenance of independence in instrumental activities of daily living was reported for all intervention arms as compared with the control group at 10 years but not at earlier time points, with the exception of the reasoning training group, which also showed less decline in instrumental activities of daily living than controls at 5 years.[2] The ACTIVE trial was a long study (10 years) with a large sample size (N = 2,802) and a notable level of diversity (25 percent minority participants). The intervention included specific guidance on how to improve performance on a cognitive task during in-person and small-group training sessions with certified trainers over 5 to 6 weeks, as well as two follow-up "booster sessions." The booster training, however, was contingent on adherence to the initial training, complicating comparisons between booster and nonbooster groups. Other notable methodological limitations of the ACTIVE trial include the use of a no-contact control, high levels of attrition at the 5- and 10-year time points, and no direct comparison of the intervention arms. Given its complexity, additional research is needed to help tease out the effects of different aspects of the ACTIVE trial intervention (e.g., social aspects).

In conclusion, some RCT evidence, based largely on the ACTIVE trial, suggests that cognitive training can improve long-term cognitive function and maintenance of independence in instrumental activities of daily living in adults with normal cognition. Cognitive test results from other cognitive training RCTs meeting the systematic review criteria were mixed. Unlike the ACTIVE trial, however, all of these studies were of insufficient duration to support conclusions on the effects of such training on ARCD. Although inconclusive, this encouraging RCT evidence, bolstered by additional data from longitudinal cohort studies on the benefits of education and cognitively stimulating activities, supports public health communications about cognitive training as a tool for delaying or slowing ARCD. At present, however, there is no evidence to support the notion that the beneficial long-term cognitive effects suggested by the ACTIVE trial apply to computer-based "brain training" applications. The suite of cognitive training interventions in the ACTIVE trial—which included cognitive training and social engagement in a group setting—differ substantially from commercial computer-based "brain training" applications, the effects of which appear to be short term

[2]Tables summarizing effect sizes for the impacts of the ACTIVE trial cognitive training intervention on cognitive testing outcomes and instrumental activities of daily living (among other outcomes) at the 2-, 5-, and 10-year time points can be found in the 2017 AHRQ systematic review, *Interventions to prevent age-related cognitive decline, mild cognitive impairment, and clinical Alzheimer's-type dementia* (see Appendix A).

and apply only to the specific cognitive task that is rehearsed. Furthermore, the evidence discussed above is specific to ARCD. There is no evidence at this time to support a conclusion that cognitive training can prevent or delay MCI or CATD, and future research in this area will be important.

Blood Pressure Management for People with Hypertension

Multiple links exist among cerebrovascular disease, Alzheimer's disease, and dementia. A majority of dementia patients show evidence of cerebrovascular disease—including small vessel disease, large vessel disease, microbleeds, and white matter hyperintensities—often in combination with Alzheimer's pathology. Epidemiologic data also link cerebrovascular disease and dementia; both clinical stroke and subclinical cerebrovascular disease are important risk factors for dementia. Identification of hypertension and improved control of blood pressure in patients with hypertension have been linked to temporal declines in stroke incidence and mortality. It is plausible, then, that blood pressure management for people with hypertension—the most powerful tool for reducing the risk of stroke and subclinical cerebrovascular damage—would also reduce the risk of dementia and cognitive decline. The most widely used blood pressure–lowering strategies rely on medications, although lifestyle-based strategies such as diet, weight loss, and exercise also are effective. It may be that the actual control of blood pressure, rather than the specific medications used to achieve control, is what affects dementia risk, but there is insufficient evidence to determine whether certain classes of antihypertensives may be more beneficial with respect to cognitive decline and dementia.

Managing blood pressure for people with hypertension, particularly during midlife (ages generally ranging from 35 to 65 years), is supported by encouraging but inconclusive evidence for preventing, delaying, and slowing CATD. The AHRQ systematic review found that RCT data do not offer strong support for the use of blood pressure management in patients with hypertension to delay or slow ARCD or to prevent, delay, or slow MCI and CATD. Only one trial (Syst-Eur) of four measuring incident dementia as outcomes provided positive evidence of an impact, raising the possibility of a chance effect. Because of critical methodological limitations, however, the published trials may not accurately assess the effectiveness of blood pressure management in preventing cognitive decline and dementia. Moreover, when prospective cohort studies and knowledge of the natural history and biology of the disease are considered, effects of blood pressure management on incident CATD in patients with hypertension are consistent with a causal relationship.

It may never be possible to obtain a definitive answer in this area: given the known cardiovascular benefits of such treatment, it would not be

appropriate to test blood pressure management's cognitive effects directly with a control arm in which hypertensive individuals did not receive blood pressure management. In addition, the trend toward reduced cardiovascular risk factors, in part from improved identification and control of hypertension, complicates efforts to study this question. Nonetheless, the available evidence, together with the strong evidence for blood pressure management in preventing stroke and cardiovascular disease and the relative benefit/risk ratio of antihypertensive medications and lifestyle interventions, is sufficient to justify communication with the public regarding the use of blood pressure management, particularly during midlife, for preventing, delaying, and slowing CATD.

Increased Physical Activity

It is well documented that physical activity has many health benefits, and some of these benefits (e.g., stroke prevention) are causally related to brain health. The AHRQ systematic review found that the pattern of RCT results across different types of physical activity interventions provides an indication of the effectiveness of increased physical activity in delaying or slowing ARCD, although these results are not consistently positive. Reasons for the inconsistent results for physical activity across RCTs are unclear, but could be explained by variability in the types of physical activity interventions (e.g., resistance training, aerobic activity), duration, and frequency, as well as in the impact of such interventions across individuals. It is, of course, also possible that the inconsistent results are indicative of a lack of true effect on cognitive decline and dementia incidence.

As a supplement to the encouraging pattern of RCT results described in the AHRQ systematic review, the effects of increased physical activity on delaying or slowing ARCD are consistent with a causal relationship when prospective cohort studies and knowledge of neurobiological processes are considered, although reverse causality cannot be ruled out. In addition, physical activity has other known health benefits that may contribute to reduced rates of ARCD (i.e., lowering the risk of hypertension, stroke, midlife obesity, and symptoms of depression, which is expected to reduce rates of ARCD). These considerations led the committee to conclude that the evidence is sufficient to justify communicating to the public that increased physical activity for delaying or slowing ARCD is supported by encouraging but inconclusive evidence.

At this time, evidence is insufficient to conclude whether increasing physical activity prevents, delays, or slows MCI or CATD, as few studies examined these outcomes. Moreover, progression to MCI and CATD often occurs slowly, and therefore, it can be difficult to detect an effect on

these conditions in trials of short duration. Evidence also is insufficient to determine which specific types of physical activity are particularly effective.

METHODOLOGICAL IMPROVEMENTS

None of the interventions evaluated in the AHRQ systematic review met the criteria for being supported by high-strength evidence, based on the quality of RCTs and the lack of consistently positive results across independent studies. This limitation suggests the need for methodological improvements and additional research, both of which are discussed in this report. The absence of high-strength evidence supporting long-term beneficial cognitive effects for the interventions included in the AHRQ systematic review results in part from methodological limitations of past intervention studies. These include small sample sizes, short follow-up periods, relatively homogeneous study populations that may not have included the highest-risk groups, and use of suboptimal and heterogeneous outcome measures and assessment tools. Recognizing the limited pool of resources available for research on cognitive decline and dementia, future research investments in clinical trials will have the greatest impact if directed to a limited number of well-designed studies of sufficient power and duration. Accordingly, the committee suggests ways in which research methods in this field can be improved overall.

Foremost among the recommended methodological improvements is ensuring that interventions are evaluated in a diverse set of populations with variation across racial and ethnic backgrounds, socioeconomic status, age at time of intervention initiation, and risk of dementia. Some dementia risk factors linked to health disparities may be more prevalent in certain racial minority and underserved groups, yet little empirical evidence exists for these and other high-risk populations (e.g., those with a family history of dementia or high risk of vascular disease). Identifying and targeting interventions to high-risk populations may increase the likelihood of detecting a beneficial effect of an intervention and provide a more accurate assessment of its effectiveness. Additionally, interventions for cognitive outcomes are often initiated at later life stages that some research suggests may be outside the optimal window, indicating a need to also expand the age ranges of study participants to include midlife.

Given the significant cost and complexity of clinical trials, it is important as well to consider approaches to improving the evidence base while achieving greater efficiencies, making use, for example, of designs that embed research studies in clinical practice and community settings (e.g., pragmatic trials) and thoughtfully integrate cognitive outcomes into trials evaluating interventions for effects on other primary outcomes (e.g., cardiovascular risk). Long follow-up periods are needed to detect changes in cog-

nitive outcomes. However, inclusion of biomarkers that can be used to track responses to interventions and predict longer-term outcomes (ARCD, MCI, and CATD) has the potential to reduce significantly the length and cost of future clinical trials, although a change in a marker cannot automatically be assumed to indicate a change in risk of disease or improved outcomes. Finally, the strength of evidence for a given intervention is bolstered by consistency of results across independent studies. However, the multiplicity of tests used in the field to measure cognitive performance has hampered such assessments, and consistent cognitive outcome measures need to be developed to enable pooling of data in meta-analyses.

Recommendation 2: Methodological Improvements

When funding research on preventing cognitive decline and dementia, the National Institutes of Health and other interested organizations should improve the methodologies used in this field by supporting studies that to the extent possible

- **identify individuals who are at higher risk of cognitive decline and dementia and tailor interventions accordingly**
- **increase participation of underrepresented populations to study intervention effectiveness in these populations**
- **begin more interventions at younger ages and have longer follow-up periods**
- **use consistent cognitive outcome measures across trials to enable pooling**
- **integrate robust cognitive outcome measures into trials with other primary purposes**
- **include biomarkers as intermediate outcomes**
- **conduct large trials designed to test the effectiveness of an intervention in broad, routine clinical practices or community settings**

PRIORITIES FOR FUTURE RESEARCH

The absence of definitive data demonstrating the effectiveness of any of the interventions evaluated in the AHRQ systematic review underscores the need for future research on preventing cognitive decline and dementia. The above cross-cutting methodological recommendations should inform future research on the interventions included in Recommendations 3 and 4. Furthermore, emerging data from multimodal intervention studies suggest the potential for synergies when interventions are combined, indicating there may be value in evaluating each of these interventions both alone and

in an additive fashion. Such research should include efforts to optimize timing, dose, duration, and delivery schedule.

Highest Priorities for Future Research

Before developing public health strategies that strongly encourage the adoption of cognitive training, blood pressure management, and increased physical activity for the purpose of maintaining cognitive function, additional research is needed to further understand and gain confidence in the effectiveness of these interventions. Examples of research priorities for these three classes of interventions include evaluating the comparative effectiveness of different forms of cognitive training interventions and determining which specific intervention elements used in the ACTIVE trial (e.g., social aspects, links to instrumental activities of daily living) are responsible for the observed positive and long-term impacts on cognitive performance; determining whether there are optimal blood pressure targets and approaches across different age ranges; and comparing the effects of different forms of physical activity (e.g., aerobic, resistance training). Some large studies to this end are already under way.

Recommendation 3: Highest Priorities for Research
The National Institutes of Health and other interested organizations should support further research to strengthen the evidence base on the following categories of interventions, alone or in combination, which are supported by encouraging but inconclusive evidence:

- **cognitive training**
- **blood pressure management**
- **increased physical activity**

Other Priorities for Future Research

The AHRQ systematic review covered a large number of interventions for which the current evidence base from RCTs is insufficient to draw any conclusions regarding their impact on cognitive decline and dementia. As noted earlier, given this lack of RCT evidence, the committee considered data from observational prospective cohort and risk factor studies, as well as biological plausibility, in identifying other priorities for future research.

Recommendation 4: Additional Priorities for Research
The National Institutes of Health and other interested organizations should support research to strengthen the evidence base on

the following categories of interventions, alone or in combination, for which there is currently insufficient evidence to determine their effectiveness:

- **new antidementia treatments that can delay onset or slow disease progression**
- **diabetes treatment**
- **depression treatment**
- **dietary interventions**
- **lipid-lowering treatment/statins**
- **sleep quality interventions**
- **social engagement interventions**
- **vitamin B_{12} plus folic acid supplementation**

FINAL THOUGHTS

While the committee recognizes that well-conducted, rigorous, generalizable RCTs are the gold standard for demonstrating the effectiveness of interventions for preventing common conditions such as ARCD and CATD, there are references throughout this report to the challenges of implementing RCTs to test the value of interventions and behavioral changes for preventing or delaying such conditions. For example, the potential benefits of higher levels of education and socioeconomic well-being may have effects throughout the life course, from birth through the long process of brain aging, but these effects cannot be evaluated in an RCT. Alzheimer's-related brain changes are known to appear well before symptoms manifest and may even be present in young adults. Is there a conceivable way to study people this young for an illness that typically develops many decades later? An added challenge is that many of the interventions that show promise today, such as better control of hypertension and diabetes and regular physical activity, have widely accepted health benefits and are broadly prescribed. Similarly, while smoking has been shown to be a risk factor for dementia, it is difficult to imagine an ethically acceptable long-term RCT that would include an untreated control group and could meet the stringent quality criteria of the EPC. Potential solutions to these challenges include using evidence from life-course epidemiology cohort studies employing the most rigorous methods possible, and possibly from studies aimed at improving adherence to and adoption of such treatments as diabetes management in which the "control" group would be usual care. There are no easy answers to these challenges, and NIA and other institutes and organizations—in collaboration with researchers with expertise in cognitive decline and dementia—will need to continue to grapple with the question of what kinds

of research and outcomes constitute evidence rigorous enough to provide clear support for public health messaging.

The subject of this report is a vibrant, dynamic research area whose story is not complete. The fact that the report does not strongly support a public health campaign focused on actively promoting adoption of any type of intervention should not be taken to reflect a lack of progress or prospects for preventing, delaying, or slowing the discussed conditions. Although inconclusive, clinical trials and other studies have yielded encouraging data for some interventions, and the public should have access to this information to inform choices on how to invest time and resources to maintain brain health with aging. Despite the challenges noted above, RCT data will continue to form a critical source of evidence in this field. Trials in this area are under way and planned, funded by NIH and others, and more evidence is emerging all the time. As the results of these trials become available, it will be critical to assess them with an eye to updating the recommendations presented in this report for communicating with the public. Future intervention trials that build on advances in understanding of the biological basis of CATD and incorporate cutting-edge designs and the methodological recommendations presented herein will generate a more comprehensive, stronger evidence base. There is good cause for hope that in the next several years, much more will be known about how to prevent cognitive decline and dementia.

1

INTRODUCTION

Individuals, families, and societies around the world are concerned about dementia and other forms of cognitive impairment that affect many older adults. Recent advances in the science of aging have shown that brain changes typically begin years—if not decades—before people show symptoms, which suggests that a window of opportunity exists to prevent or delay the onset of these conditions (Bateman et al., 2012; Reiman et al., 2012; Ritchie et al., 2015; Sperling et al., 2011, 2014). Furthermore, emerging evidence that the incidence and prevalence of dementia are declining in high-income countries offers hope that public health interventions can be effective in preventing cognitive decline and dementia. Although the evidence base on how to prevent or delay these conditions has been limited at best—despite the many claims of success made in popular media and advertising—a growing body of prevention research is emerging.

The National Institute on Aging (NIA) initiated this study with the National Academies of Sciences, Engineering, and Medicine to take stock of the current state of knowledge on interventions for preventing cognitive decline and dementia, to help shape the messages NIA conveys to the broader public about these conditions, and to inform future actions and research in this area. The task for the committee charged with carrying out this study was to evaluate the existing evidence on interventions for preventing cognitive decline and dementia and, based on this evidence, to recommend the appropriate content for inclusion in public health messages, as well as priorities for future prevention research. NIA also asked the Agency for Healthcare Research and Quality (AHRQ) to commission and oversee a systematic review of the salient evidence, which was conducted

by the Minnesota Evidence-based Practice Center (EPC) (Kane et al., 2017). This extensive and thorough review provided the primary evidence base for the discussion and recommendations in this report.

An earlier AHRQ systematic review on this subject (Williams et al., 2010), published in 2010, concluded that there was insufficient evidence to make recommendations about interventions to prevent cognitive decline and dementia. Since then, the knowledge base—from interventional research but also from neurobiological studies on risk and compensatory factors for dementia, as well as mechanistic pathways—has advanced, and there is reason to believe that much more will be known about how to prevent cognitive decline and dementia in the next several years. Existing evidence also makes it possible to draw conclusions about what appears not to work. Even with recent advances, however, the available evidence from randomized controlled trials (RCTs)—the "gold standard" of evidence—is limited and has shortcomings. Therefore, the committee considered additional evidence from nonexperimental observational studies—primarily longitudinal population-based cohort studies—as well as studies of risk factors and neurobiological processes that support biological plausibility. Box 1-1 provides definitions of the key terminology used in this report.

SOCIETAL INTEREST IN PREVENTING DEMENTIA AND COGNITIVE IMPAIRMENT

Clinical Alzheimer's-type dementia (CATD) is common and costly, affecting approximately 4 to 5 million adults in the United States (Hebert et al., 2013; Plassman et al., 2007) at an annual estimated cost of more than $200 billion (Alzheimer's Association, 2015; Hurd et al., 2013). An even greater number of older Americans have mild cognitive impairment (MCI) without dementia (Plassman et al., 2008). Public health experts warn that the burden associated with Alzheimer's disease could nearly triple by 2050 as the number of adults over age 65 grows (Hebert et al., 2013), increasing annual costs to more than $1 trillion in the United States (Alzheimer's Association, 2015). Globally in 2015, 46.8 million people were living with dementia, costing an estimated $818 billion that year (Prince et al., 2015). In addition to CATD and MCI, cognitive changes in older adults, or age-related cognitive decline (ARCD), often occur as a typical part of aging (IOM, 2015).

Many people are very interested in what they can do to maintain their own and others' brain health (David and Gelfeld, 2014). Consequently, this topic is frequently covered by popular media, and unproven claims about brain health are commonplace in advertising. Many countries now support dementia research and are highly interested in what steps can be taken to prevent cognitive decline and dementia in their populations. In 2015, *The Lancet*, in partnership with academic institutions and other organizations,

convened an International Commission on Dementia Care to examine the evidence and make globally focused, evidence-based recommendations on dementia prevention and care (Livingston and Frankish, 2015). During the 2016 G7 summit in Japan, an array of national science academies highlighted global brain research as a critical priority, including a call for global programs on diagnosing, preventing, and treating brain disorders such as Alzheimer's and Parkinson's diseases (G-Science Academies, 2016). Similarly, the World Health Organization's (WHO's) 2016 draft *Global Action Plan on the Public Health Response to Dementia 2017-2025* includes prevention as an important action area for all countries (final version anticipated in 2017).

AN OPPORTUNITY TO TAKE A FRESH LOOK AT THE EVIDENCE

In 2010, NIA convened a state-of-the-science conference to evaluate the evidence on preventing Alzheimer's disease and cognitive decline. Like the current report, that conference was based largely on an AHRQ systematic review (Williams et al., 2010), supplemented by presentations and interactions among experts in the field. According to the consensus statement emerging from that process, no firm conclusions could be drawn about any interventions to prevent these conditions (Daviglus et al., 2010). Since then, a variety of other efforts have focused on the evidence in this domain. For example, the Alzheimer's Association recently examined the evidence on modifiable risk factors for cognitive decline and dementia (Baumgart et al., 2015). Likewise, a 2015 Institute of Medicine report took an in-depth look at the evidence on cognitive aging (IOM, 2015). Recently, AARP launched a Global Council on Brain Health to bring together scientists, health professionals, and others to develop evidence-based recommendations on lifestyle changes that may impact brain health (AARP, 2017).

This report incorporates the most recent evidence from a rapidly evolving field and stands out as uniquely focused on applying AHRQ's highly refined systematic review process to assess what evidence is available on the effectiveness of interventions themselves—as opposed to focusing on potentially modifiable risk factors—and examining how that evidence might serve as a basis for public health messaging. Since 2010, moreover, much research has provided significant evidence that the underlying pathophysiology of dementia is usually heterogeneous, entailing a mix of different pathologies. Furthermore, as noted above, it is now understood that the pathophysiologic processes of dementia begin to develop many years before symptoms manifest (Bateman et al., 2012; Jack et al., 2010; Kawas et al., 2015; Reiman et al., 2012; Sonnen et al., 2008; Sperling et al., 2011, 2014). This enhanced understanding can inform future clinical trials, including large-scale research now being planned.

BOX 1-1
Key Terminology Used in This Report

This report considers several related conditions involving cognitive function in older adults for which many different terms and definitions are used. Developing clear, consistent terminology that accurately reflects the evidence is therefore challenging. Furthermore, the committee's task was to offer recommendations as to what can appropriately be communicated to members of the public, who generally are interested in staying cognitively healthy as they age and are unlikely to make the distinctions that are used in research.

When describing the overall goal addressed by this study, instead of specifying particular conditions or listing all relevant conditions repeatedly, the committee uses the shorthand umbrella term **preventing cognitive decline and dementia.** On the other hand, when discussing research results and associated conclusions and recommendations, the committee uses more specific terms for three conditions that can affect older adults:

Age-related cognitive decline (ARCD): Deterioration in cognitive performance that can be a normal part of aging. It is also sometimes referred to as **cognitive aging.**

Mild cognitive impairment (MCI): Cognitive impairment that has reached a level of deterioration from normal cognitive function identifiable by individuals, family members, or clinicians, but without significant functional impairment in daily activities (i.e., individuals may have mild functional impairments but can adapt to them).

Clinical Alzheimer's-type dementia (CATD): Cognitive impairment severe enough that an individual can no longer function independently. This impairment may be due to Alzheimer's disease (i.e., the abnormal build-up of amyloid and tau proteins in the brain) or to "mixed" causes of dementia, such as Alzheimer's disease combined with alpha-synuclein or TDP-43 proteins or with vascular disease in the brain. This term is not widely used in the field; the committee uses it here to reflect the increasing recognition of mixed dementia, which may be difficult to differentiate in a clinical setting.

As noted above, there is variability in the terms and definitions used for these conditions in the field. Furthermore, the conditions noted above are heterogeneous, and it is not possible at present to draw clear lines among them. However, understanding of these conditions will continue to evolve as a result of scientific and technological advances, and it is conceivable that the application of genomic

and other technologies in the clinic will enable better pairing of clinical interventions with particular populations of individuals.

To inform this committee's work, the National Institute on Aging (NIA) asked the Agency for Healthcare Research and Quality (AHRQ) to conduct a systematic review of the outcomes from intervention studies directed at the above three conditions. The committee relied on that analysis and uses these three terms in this report when summarizing findings and drawing conclusions about available evidence on specific interventions. Although the hope is that an effective intervention for ARCD would also benefit MCI and CATD, and the reverse, it is not yet known whether this is in fact the case. Therefore, this report does not make this extrapolation in either direction. Where the available evidence is specific to one condition (e.g., ARCD but not MCI or CATD), this is specified in the text. It is important to note, however, that given the overall paucity of data in this domain, the committee's conclusions may be due to a lack of evidence rather than a true difference.

This report refers to **preventing, delaying, or slowing MCI and CATD**, which encompasses both the onset of the disorders and the rate of change over time after onset. The report also considers evidence on **delaying and slowing ARCD**; prevention is not included in the discussion of ARCD since some level of decline is expected with aging.

A final consideration is that interventions may result in short-term improved performance on specific cognitive tests (e.g., memory or speed of processing) as compared with baseline. This improvement may be inherently valuable to some people, but it is not clear whether or how this short-term, specific benefit translates to general delaying or slowing of ARCD over the long term or to preventing, delaying, or slowing MCI and CATD. To describe such short-term, specific improvements, the committee uses the term **short-term improvements in cognitive performance.**

In addition to the above terms describing particular conditions, three more terms are used throughout this report. First, a **risk factor** is a characteristic or attribute that is associated with an increase or decrease in the likelihood of developing a condition. An **intervention** refers to any program or treatment applied to an individual (whether pharmacological or not) designed to modify the condition under investigation. Finally, the term **observational study** refers to a nonexperimental study design, that is, a design that does not use random assignment to an intervention (Concato et al., 2000). Examples of such studies include correlational, cohort, association, and epidemiological studies. In most cases, the committee relies on longitudinal population-based cohort studies when evaluating observational data; any use of case control studies is specifically noted.

PREVALENCE AND TRENDS

As noted above, emerging evidence suggests that both the prevalence and incidence of dementia are declining in high-income countries. The Health and Retirement Study (HRS), a nationally representative prospective cohort study in the United States, found that dementia among those aged 65 and older declined between 2000 and 2012 by 2.8 percentage points, from 11.6 percent in 2000 to 8.8 percent in 2012 (Langa et al., 2017). This decline occurred despite the fact that the 2012 cohort had significantly higher rates of self-reported cardiovascular risk factors, including obesity, hypertension, and diabetes, all of which have been associated with an increased dementia risk (Deckers et al., 2015). Similarly, the Framingham Heart Study, a longitudinal cohort study, reported a 20 percent decline in dementia incidence between 1997 and 2008 even as body mass index, diabetes prevalence, and population age increased (Satizabal et al., 2016). The Cognitive Function and Ageing Study (CFAS) in the United Kingdom also reported declining incidence rates over the past 20 years across all age groups (Matthews et al., 2016). This decline was most pronounced in men, with incidence rates declining much less dramatically in women.

These studies confirm the findings of earlier studies in the United States and Europe of a decline in dementia prevalence (Grasset et al., 2016; Manton et al., 2005; Schrijvers et al., 2012). Results of a recent study in Switzerland also suggest a decline in the age-adjusted burden of amyloid deposition (Kovari et al., 2014), lending further support to the idea that the prevalence of Alzheimer's disease is declining. A recent study in the Netherlands, based on primary care records from 1992 to 2014, did not find evidence of a decline (van Bussel et al., 2017), but this may be due to increasing recognition and diagnosis of dementia by clinicians over the time period studied (Larson and Langa, 2017).

In contrast with the apparent trends in higher-income countries, the prevalence of Alzheimer's disease and dementia may not be declining in low- and middle-income countries (Chan et al., 2013; Gao et al., 2016; Wu et al., 2015). For example, there is some evidence that dementia prevalence appears to be increasing in some East Asian countries that are rapidly industrializing (Prince et al., 2016), whose populations show increased cardiovascular risk factors and rates of smoking, obesity, and metabolic diseases (Prince et al., 2016; Wu et al., 2015). However, it should be noted that these increases may be due in part to changes in diagnostic criteria (Prince et al., 2016), and that additional research is essential to inform understanding of future epidemiologic trends in dementia in this region given the rapidly changing socioeconomic environment and rise of noncommunicable diseases (Wu et al., 2015).

The apparent paradox that dementia prevalence is declining in higher-

income countries despite increases in cardiovascular risk factors could be explained, at least in part, by improvements in treatments for diabetes and heart disease and the decline of diabetes-related complications (Larson et al., 2013). Another factor correlated with a lower risk for dementia in both the HRS and the Framingham Heart Study is rising levels of education among U.S. adults (Federal Interagency Forum on Aging-Related Statistics, 2012). Other socioeconomic and environmental factors, including environmental exposures to toxins early in life, have been associated with dementia risk (Seifan et al., 2015) and could also explain the above paradox if overall trends mask disparities in dementia risk across subpopulations within higher-income counties. In the Framingham Heart Study, for example, a decline in dementia incidence was found only for those participants with at least a high school diploma (Satizabal et al., 2016). But education is a marker for socioeconomic status, making it challenging to disentangle the effects of each. Variation in risk by socioeconomic status also was demonstrated in analyses by Yaffe and colleagues (2013), which used data from the Health, Aging, and Body Composition study. The authors found that variation in dementia risk between white and black participants was no longer statistically significant when the analysis accounted for differences in socioeconomic status, a finding that underscores the inherent vulnerability of populations living in poverty in terms of both dementia risk and access to care (Yaffe et al., 2013).

Population-based estimates of the percentage of Alzheimer's cases attributable to a given factor suggest that seven potentially modifiable risk factors—diabetes, midlife hypertension, midlife obesity, insufficient physical activity, depression, smoking, and low educational attainment—may account for about one-third of cases in the United States and Europe. The same analysis indicated that even a modest 10 percent reduction in each of these risk factors could reduce the prevalence of Alzheimer's disease in these regions by about 8 percent by 2050 (Norton et al., 2014). These findings underscore the potential promise and importance of learning more about interventions that work to prevent cognitive decline and dementia.

It is important to note, however, that despite the trend toward declining age-specific incidence of dementia in high-income countries, increased longevity and the rise in the birth rate during the baby boom (1946 to 1964) mean that the overall number of people with dementia, and therefore its societal burden, will likely increase dramatically in the coming decades (Larson and Langa, 2017; Larson et al., 2013). This burden is felt most acutely among minority (Mayeda et al., 2016) and economically disadvantaged populations (Yaffe et al., 2013), as well as among the oldest old (Gardner et al., 2013). Among the latter population, specifically those aged 90 and older, dementia incidence has been shown to increase exponentially by age (Corrada et al., 2010).

STUDY CHARGE AND SCOPE

NIA asked the National Academies to convene an expert committee to evaluate current scientific evidence and make recommendations that could inform public health messaging on preventive interventions for cognitive decline and dementia, as well as recommendations for future research. Biographies of the committee members are in Appendix C. As noted above, the primary basis for the committee's work was a systematic review, commissioned and overseen by AHRQ and conducted by the Minnesota EPC, of the evidence on interventions that might prevent, delay the onset of, or slow MCI and CATD and delay or slow ARCD (see Appendix A). In accordance with the committee's statement of task (see Box 1-2), other, less common dementias, such as frontotemporal dementia and Lewy body dementia, were excluded from the analysis, as were dementias with a clear etiology (e.g., incident stroke, AIDS, traumatic brain injury), for which prevention efforts would be focused on avoidance of causative factors. Also in accordance with the statement of task, interventions targeting stroke risk factors were given particular attention since they may contribute to CATD, and conditions that coexist with CATD as components of mixed dementia, such as vascular contributions to dementia, were included within the study scope. However, cognitive impairment that is likely to be caused solely by vascular disease (pure vascular dementia) was excluded. The committee was asked to focus on prevention among cognitively healthy individuals and those with MCI; the study did not specifically address the effectiveness of interventions in slowing the rate of decline among individuals already diagnosed with dementia. In addition, as noted earlier, this study was focused on the effectiveness of *interventions*; the committee did not explicitly address the identification of risk factors, which have been examined in depth by other studies (e.g., IOM, 2015). The committee also did not examine the potential of public health policies (e.g., access to education, clean air) to prevent cognitive decline and dementia. While outside the scope of this study, the committee recognizes that the evidence base related to such societal-level interventions is inadequate, and interdisciplinary research to inform such policies would be valuable, particularly to benefit the most disadvantaged populations.

Of course, for any intervention to be effective, adherence is essential. One study of older adults in the United States found that as many as 50 percent of patients did not adhere to a regimen of chronic medications, incurring an estimated $100 billion in preventable costs (Osterberg and Blaschke, 2005). Indeed, the WHO (2003) has estimated that increasing adherence could have a far greater impact on health than improvements in medical treatments. Recognizing that there are many reasons why individuals discontinue treatments and other interventions (e.g., side effects),

BOX 1-2
Statement of Task

An ad hoc committee will examine the evidence on interventions for delaying or slowing age-related cognitive decline; preventing, slowing, or delaying the onset of mild cognitive impairment; and preventing, slowing, or delaying the onset of clinical Alzheimer's-type dementia. Other dementias such as frontotemporal dementia, Lewy body dementia, and dementias with a clear etiology, e.g., incident stroke, AIDS, traumatic brain injury will be excluded from the analysis. Interventions targeting stroke risk factors will be a priority in this study. The committee will make recommendations to inform public health strategies and messaging and recommendations for future research. The committee's work will be based on a systematic review commissioned by the Agency for Healthcare Research and Quality (AHRQ) and will take place in two phases: in the first phase the committee will provide input into the design of the AHRQ systematic review, and in the second phase the committee will use the review to make its recommendations.

Phase 1: The committee will convene to inform the development of an AHRQ systematic review. Responding to preliminary key questions and a preliminary study design developed by the National Institutes of Health (NIH), AHRQ, and the evidence-based practice center (EPC) that AHRQ will contract with to conduct the systematic review, the Institute of Medicine (IOM)[a] committee will provide advisory input to NIH, AHRQ, and the EPC in the form of a short (1-3 page) *data request* document that describes potential changes and considerations for the key questions and study design that would result in a systematic review that would be most informative for the committee's work during phase 2.

Phase 2: After the AHRQ/EPC systematic review is released, the committee will reconvene to consider the evidence found (based on the final key questions addressed in the systematic review). Interventions targeting stroke risk factors will be included. Based on the AHRQ systematic review and additional expert and public input, the committee will assess the quality of existing evidence and develop a short report that makes recommendations to inform the development of public health strategies and messaging (i.e., which preventive factors and interventions are supported by sufficient evidence to be incorporated into public health strategies and messages) and recommendations for future research.

The committee will hold an information-gathering workshop open to the public during the course of its work to seek input from stakeholders on the draft AHRQ report. The report will focus on the interventions outlined above, *not* on identifying risks for developing clinical Alzheimer's-type dementia, mild cognitive impairment, and age-related cognitive decline, as this has been the topic of significant previous research.

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[a]As of March 15, 2016, the Health and Medicine Division continues the consensus studies and convening activities previously undertaken by the Institute of Medicine.

designing effective messages and interventions to enhance adherence, while beyond the scope of this study, is an important aspect of preventing cognitive decline and dementia.

METHODS

The committee first met in December 2015 to provide input into the design of the AHRQ systematic review. This phase of the study included an open session in which NIA presented the charge to the committee, leaders from the Minnesota EPC review team provided a draft review protocol and discussed it with committee members, and other stakeholders were invited to comment (see Appendix B for the agendas of all open sessions). Following the meeting, the committee authored a brief letter report outlining its recommendations for the review design (NASEM, 2015).

In the following months, the EPC conducted the systematic review. The committee then reconvened in October 2016 after the draft review had been released. This second meeting included a day-long public workshop with presentations on the draft AHRQ systematic review by leaders from the EPC; individuals living with dementia; academic scientists; and representatives of government agencies, advocacy groups, and professional associations.

In January 2017, after the final AHRQ systematic review had been published, the committee met for a third and final time to develop its report. This meeting included a brief open session with leaders from the EPC and other interested parties to discuss the final version of the AHRQ systematic review.

AHRQ Systematic Review Design

The AHRQ systematic review represents the most up-to-date and thorough review of the RCT evidence available. The review relied primarily on RCTs with a minimum 6-month follow-up period for intermediate outcomes; large prospective quasi-experimental cohort studies with comparator arms (n ≥250 per arm) were also included in the search conducted for the review, but little concrete evidence emerged from such studies. Box 1-3 details the methodology of the review, the key questions addressed, and the inclusion criteria (the list of cohort studies and search details can be found in Appendix E of Kane et al. [2017]).[1] The AHRQ systematic review has several strengths: (1) it is the product of a systematic and extensive effort to summarize the state of the evidence; (2) it employed clear criteria

[1]Throughout this report, for easy visual identification, boxes that present material quoted directly from the AHRQ systematic review are presented with rounded corners.

for inclusion and exclusion of studies (see Box 1-3); and (3) it provides a helpful framework for cross-classifying the literature in three ways—by intervention, by population, and by outcomes (CATD, MCI, and ARCD).

A key step in the systematic review process was a quality assessment of the risk of bias for potentially eligible studies. The EPC created an instrument to assess the risk of bias from elements of study design including participant selection, method of randomization or selection, blinding, allocation concealment, and attrition.[2] Studies were classified as having a low, moderate, or high overall risk of bias based on the collective risk of bias inherent in each domain and confidence in the study results given the study limitations. Studies identified as having a high risk of bias generally were not included in the analysis for the AHRQ systematic review. However, such studies were still considered by the committee in identifying future research priorities, as the committee believed that less stringent criteria were appropriate for this purpose compared with those applied in identifying interventions to recommend for communications with the public. Where such studies are discussed in the following chapters, the committee notes that they were designated as having a high risk of bias.

Limitations of the Existing Randomized Controlled Trial Evidence

As noted earlier, the AHRQ systematic review was based almost exclusively on RCTs, generally regarded as the "gold standard" for providing evidence about the effectiveness of interventions. Yet it is particularly challenging to conduct RCTs for interventions that likely should be provided in midlife[3] for prevention of cognitive conditions that develop in older adulthood and often are highly comorbid with other later-life conditions. Indeed, the AHRQ systematic review makes clear that virtually all evidence on preventive interventions for such conditions has significant shortcomings: no interventions met the review's criteria for high-strength evidence of benefit based on the quality and design of the trials, and the review concluded that only a few RCTs can be used to inform recommendations on public health messaging.

These shortcomings stem partially from the challenges inherent in conducting RCTs on preventing cognitive decline and dementia. Examples of challenges that limit the strength of the evidence generated by existing studies include initiation of interventions at later life stages that may be

[2]More detailed information on the instrument used to assess risk of bias can be found in Appendix B of the 2017 AHRQ systematic review, *Interventions to prevent age-related cognitive decline, mild cognitive impairment, and clinical Alzheimer's-type dementia* (Kane et al., 2017) (see Appendix A).

[3]Different age windows are used in studies that enroll participants in midlife, generally ranging from ages 35 to 65.

BOX 1-3 DESCRIPTION OF THE AHRQ SYSTEMATIC REVIEW

Methodology

Objective. This review assessed evidence for interventions aimed at preventing or delaying the onset of age-related cognitive decline, mild cognitive impairment (MCI), or clinical Alzheimer's-type dementia (CATD).

Data sources. Ovid Medline, Ovid PsycINFO, Ovid Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) bibliographic databases; hand searches of references of prior reviews, eligible studies, grey literature; expert recommendations.

Review methods. Two investigators screened abstracts and full-text articles of identified references. Eligible studies included randomized and nonrandomized controlled trials and quasi-experimental observational studies published to September 2016, enrolling people with normal cognition and/or MCI. The Evidence-based Practice Center extracted data, assessed risk of bias, summarized results for studies without high risk of bias, and evaluated the strength of evidence for studies with sufficient sample size. Cognitive outcomes were grouped into domains to facilitate analysis; strength of evidence was assessed by MCI or CATD incidence and cognitive outcome domain.

The investigators identified 263 eligible studies addressing 13 classes of interventions: cognitive training, physical activity, nutraceuticals, diet, multimodal interventions, hormone therapy, vitamins, antihypertensive treatment, lipid-lowering treatment, nonsteroidal antiinflammatory drugs, antidementia drugs, diabetes treatment, and "other interventions."

Key Questions

KQ 1: In adults with normal cognition, what are the effectiveness, comparative effectiveness, and harms of interventions for:

i. Delaying or slowing age-related cognitive decline?
ii. Preventing, delaying, or slowing the onset of MCI?
iii. Preventing, delaying, or slowing the onset of clinical Alzheimer's-type dementia?

a. Do effectiveness, comparative effectiveness, and harms of interventions differ as a function of patient characteristics (i.e., age, sex, race/ethnicity, family history, education, socioeconomic status, risk factor status)?

KQ 2: In adults with MCI, what are the effectiveness, comparative effectiveness, and harms of interventions for preventing, slowing, or delaying the onset of clinical Alzheimer's-type dementia?

a. Do effectiveness, comparative effectiveness, and harms of interventions differ as a function of patient characteristics (i.e., age, sex, race/ethnicity, family history, education, socioeconomic status, risk factor status)?

KQ 3: What is the strength of association between outcome measures examined in KQs 1 or 2 including (but not limited to) cognitive test results, biomarkers, and brain imaging results and the incidence of MCI or clinical Alzheimer's-type dementia?

Inclusion Criteria

Category	*Criteria for Inclusion*
Study Enrollment	For KQ1: Adults with normal cognition. For KQ2: Adults with MCI. For KQ3: Adults with normal or abnormal cognition who have had testing such as cognitive tests, blood/CSF testing, or brain imaging used in intervention studies in KQ1 or KQ2.
Study Objective	For KQ1: To test the efficacy, comparative effectiveness, and harms of interventions to prevent, delay, or slow cognitive decline, onset of MCI, or clinical Alzheimer's-type dementia. For KQ2: To test the efficacy, comparative effectiveness, and harms of interventions to prevent, delay or slow clinical Alzheimer's-type dementia. For KQ3: To examine the association between biomarker outcomes and incidence of MCI of clinical Alzheimer's-type dementia.
Study Design	For KQ1-2: Randomized clinical trials (RCTs) of any size and large prospective quasi-experimental cohort studies with comparator arms (n ≥250 per arm). For KQ3: Studies identified in KQs 1 and 2.
Outcomes	Cognitive performance measured with validated instruments, biomarker measures associated with clinical Alzheimer's-type dementia, and incident MCI or clinical Alzheimer's-type dementia (pure vascular dementia including strokes is excluded).
Timing	For KQ1-2: Minimum follow-up of 6 months for intermediate outcomes. For KQ3: No minimum follow-up.
Publication Type	Published in peer-reviewed journals and grey literature with full text available (if sufficient information to assess eligibility and risk of bias are provided).
Language of Publication	English

SOURCE: Kane et al., 2017. For additional methodological detail, see Appendix A.

outside the optimal window; follow-up periods that are too short; high attrition (dropout and death); small sample sizes and studies underpowered to detect changes in incidence of MCI and CATD; heterogeneity in outcome measures and assessment tools; a focus on individual interventions when combinations of interventions may be most beneficial and, conversely, difficulty detecting which components of multimodal interventions are most effective in which combination(s); and difficulty identifying appropriate control groups. Chapter 3 describes these challenges in detail and examines opportunities to address them, including making greater use of new trial designs (e.g., adaptive trials) and analytic approaches for reducing biases related to attrition (e.g., methods for addressing missing data).

Use of Supplemental Evidence

Acknowledging the limitations of the evidence examined in the AHRQ systematic review, the committee supplemented that evidence by applying the judgment and expertise of its members to incorporate, when appropriate, information from a variety of other sources in developing the recommendations presented in this report. This supplemental evidence included

- available observational data—primarily from longitudinal population-based cohort studies—and evidence from neurobiological studies that address the effectiveness of a class of interventions;
- information from studies of risk factors;
- information about intervention effects on intermediate outcomes (e.g., changes in brain structure and function) that may predict ARCD, MCI, and CATD;
- knowledge about whether/how an intervention would benefit or harm other organ systems; and
- other general harms and costs potentially associated with an intervention.

In Chapter 2, which addresses communication with the public, the committee focuses on classes of interventions for which at least some supportive RCT data were identified, supplemented by the additional sources described above. Observational data and neurobiological knowledge are discussed more extensively in Chapter 4, which addresses priorities for future research. In addition to proposing further research on cognitive training, blood pressure management, and increased physical activity, which the committee found to be supported by encouraging but inconclusive evidence, Chapter 4 considers a number of interventions for which there was insufficient evidence and provides recommendations for future research priorities in these areas.

For well-known reasons, observational studies such as those cited in this report are imperfect and must be interpreted with caution. They demonstrate associations but not causation (Andrade, 2014). Confounding is a notable concern with observational studies, as it can result in misinterpretation of findings when an unmeasured factor affects both the outcome and the risk factor that is being examined, giving the false appearance of a causal relationship. Like RCTs, such studies also may be affected by subject selection bias and many other potential biases that are related to how studies are designed and reported, how participants are followed, and the accuracy of data collection (Viswanathan et al., 2012). Interpreting the findings from studies reporting associations with the incidence of cognitive decline may be further constrained by the use of a limited set of cognitive tests; changes in diagnostic thresholds and the frequency of diagnostic testing; changes in measures used to assess cardiovascular health, such as blood pressure; and changes in the use of self-reported versus informant-reported measures in both observational studies and RCTs (Glynn et al., 1999; Langa et al., 2017). Observational studies may be affected as well by changing recruitment and data collection strategies over time (Langa et al., 2017) and the difficulty of predicting trajectories of chronic diseases (Jones and Greene, 2013). Finally, while these studies suggest links between cognitive outcomes and modifiable risk factors, interventions (e.g., vitamin E supplementation, use of statins) targeting risk factors identified through observational studies have, in a number of cases, failed to translate into treatment benefit in RCTs conducted to date. Studies incorporating the full set of social, behavioral, and medical factors that may influence the risk of dementia are lacking (Langa et al., 2017), but this lack may never be remedied by studies that meet the evidence criteria of the AHRQ systematic review.

REPORT ORGANIZATION

This report is divided into four chapters. Following this introductory chapter, Chapter 2 provides the committee's analysis of the available evidence and recommendations regarding communicating with the public about the three interventions—cognitive training, blood pressure management for people with hypertension, and increased physical activity—supported by encouraging but inconclusive evidence. Chapter 3 presents recommendations for cross-cutting methodological improvements for future studies that would enhance the overall strength of evidence in this domain. Chapter 4 details future research priorities to enhance confidence in and tailoring of messages on the above three interventions, as well as others the committee deems potentially promising and worthy of prioritizing in future research. That chapter also summarizes the findings of the AHRQ system-

atic review regarding interventions for which there was some evidence of harm or low-strength evidence of no benefit.

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2

COMMUNICATING WITH THE PUBLIC ABOUT INTERVENTIONS TO PREVENT COGNITIVE DECLINE AND DEMENTIA

Ideally, communications with the public about interventions to delay or slow age-related cognitive decline (ARCD) and prevent, delay, or slow mild cognitive impairment (MCI) and clinical Alzheimer's-type dementia (CATD) would be informed primarily by evidence from randomized controlled trials (RCTs). However, the Agency for Healthcare Research and Quality (AHRQ) systematic review found—at best—modest RCT evidence for only a few classes of interventions (Kane et al., 2017). Accordingly, it is challenging to specify which intervention domains, if any, are supported by sufficient evidence to justify a public health messaging campaign. To supplement the AHRQ systematic review, the committee considered evidence from relevant studies using other methodologies, including observational studies[1] and neurobiological studies that support the biological plausibility of the effectiveness of a class of interventions; information from studies of risk factors; information about intervention effects on intermediate outcomes (e.g., changes in brain structure and function) that may predict cognitive decline and dementia; knowledge about whether and how an intervention would benefit or harm other organ systems; and information about other general harms and costs potentially associated with an intervention (see Chapter 1).

Based on this body of evidence, the committee identified three classes of interventions—cognitive training, blood pressure management for people

[1]The committee uses this term to refer to a study that did not employ random assignment to an intervention. Except where indicated, the committee relied on observational data from longitudinal population-based cohort studies.

with hypertension, and increased physical activity—as being supported by modest but inconclusive evidence at present. This strength of evidence does not, in the committee's judgment, warrant aggressive public health campaigns but does suggest information that should be made available to the interested public.

The strength of evidence differs for the three interventions. Cognitive training is suggested by the findings of the AHRQ systematic review, bolstered by data from observational studies of cognitively stimulating activities. The suggestion that blood pressure management and increased physical activity be included is not based primarily on evidence from the AHRQ systematic review. For cases in which strong experimental evidence does not exist, Bradford Hill proposed criteria[2] for evaluating whether credible causal inferences can be drawn when epidemiologic evidence suggests an association (Hill, 1965; Lucas and McMichael, 2005). Acknowledging that application of these criteria is subjective, the committee found them to be a useful tool for examining the body of evidence from non-RCT data when results from experimental studies were mixed. In the committee's judgment, when the Bradford Hill criteria are applied to blood pressure management and physical activity, there is sufficient evidence from observational studies and neurobiological understanding to include these interventions in communications with the public. Given the moderate-strength RCT evidence for cognitive training, the committee did not apply the Bradford Hill criteria to this intervention domain. The importance of further research on these interventions is discussed in Chapter 4.

Before proceeding to discuss each of the three interventions in turn, it is important to consider the challenges of making decisions about public health messaging, particularly in a domain so difficult to study and characterized by evidence that is modest at best.

First, different criteria and methodologies may be appropriate for different purposes. The AHRQ methodology is designed to support the work of the U.S. Preventive Services Task Force (USPSTF)—which informs health coverage determinations—and may not be optimally suited to guiding public health messaging on interventions for preventing cognitive decline and dementia or to informing agencies about prioritizing future research topics. Moreover, messaging aimed at encouraging people to adopt an intervention with compelling evidence would be stronger and would use different tactics

[2]The Bradford Hill criteria, described in more detail in the sections of this chapter on blood pressure management and physical activity, include strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy (Hill, 1965). Analogy is not relevant for the exercises described in this chapter, and experimental data are discussed in the context of the findings from the AHRQ systematic review. Thus, these two criteria are not discussed in the sections on assessing interventions against the Bradford Hill criteria.

relative to the messaging that public health practitioners and health care providers might use to inform individuals interested in taking action. The latter efforts, for example, might be focused more on improving scientific literacy (e.g., understanding of differences between association and causation) and public awareness to inform decision making among consumers and patients.

Second, it is important to emphasize that very little evidence exists about effectiveness in particular populations, such as underrepresented groups, people with a family history of or genetic susceptibility to dementia, and other high-risk groups. This issue may need to be considered in communications with the public about the state of the science and the need for individuals from such groups to participate in future research. Moreover, individual responses to these interventions will vary. These issues are discussed further in Chapter 3.

Third, in keeping with its statement of task (see Box 1-2 in Chapter 1), this study excludes some causes of dementia (e.g., stroke, traumatic brain injury) and therefore does not examine the behaviors that would potentially address these causes. It is widely recognized that CATD, especially late in life, often has mixed findings, including evidence of cerebrovascular disease, as well as neurodegenerative changes. When developing public health messaging, however, it will be important to remember that the public will not make fine distinctions based on specific causes and will want a sense of what could work to prevent any type of dementia.

Lastly, this report represents a snapshot of the state of the science in early 2017, but more data are constantly becoming available. Thus, it will be necessary to continually reassess whether new public health messages should be created or existing communication efforts should be revised.

COGNITIVE TRAINING

In the context of this report, the term *cognitive training* is used to denote a broad set of interventions, including those aimed at enhancing reasoning (e.g., problem solving), memory, and speed of processing (e.g., speed of identifying visual information on a screen). Such structured training exercises may or may not be computer based. Cognitively stimulating activities, for the purposes of this report, include such interventions as learning a new language and increasing proficiency in daily activities, such as playing bridge and doing crossword puzzles.

Cognitive training has engendered considerable interest and debate in both the academic and commercial sectors, particularly within the past 15 years (Simons et al., 2016). Recently, different groups have publicly released statements with conflicting conclusions on the benefits of cognitive training (Cognitive Training Data, 2015; Stanford Center on Longevity, 2014),

which may stem in part from differing opinions on what constitutes success. There is good evidence to show that cognitive training can improve performance on a trained task, at least in the short term (Simons et al., 2016), but debate has centered on the evidence for long-term benefits and whether training in one domain (e.g., processing speed) yields benefits in others (e.g., memory, reasoning) and can translate to maintaining independence in instrumental activities of daily living (IADLs), such as remembering to take medications and driving.

Findings from the AHRQ Systematic Review

Summary of the AHRQ Systematic Review Findings

The AHRQ systematic review identified 38 RCTs of cognitive training interventions, 11 of which were found to have sufficiently low risk of bias to be included in the analysis. The findings from the AHRQ systematic review on these cognitive training interventions are presented in Box 2-1.

BOX 2-1 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON COGNITIVE TRAINING INTERVENTIONS

- Most studies addressed intermediate outcomes[a] of cognitive training in terms of cognitive performance and a few measures of brain activity.
- The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial provided the strongest and most comprehensive design to assess the effect of cognitive training on cognitive performance for older adults with normal cognition. Its results provide moderate-strength evidence at 2 years (but low strength at 5 and 10 years) that cognitive training can improve cognitive function in the domain trained, but transfer to other domains was rare. There is some suggestion that processing speed training is associated with improved IADL [instrumental activity of daily living] performance, but longer-term studies were rated as low strength of evidence.
- Other than the ACTIVE trial, the few studies that examined CATD incidence or cognitive performance showed mixed results.

[a]In this context, the term intermediate outcomes refers to changes in cognitive performance (may be short or long term), in contrast to improvements in instrumental activities of daily living or progression to a particular diagnostic category.
SOURCE: Kane et al., 2017.

The AHRQ systematic review found no evidence to indicate that cognitive training can reduce the risk of CATD in individuals with normal cognition or those with MCI (Kane et al., 2017). The strongest evidence supporting the potential for cognitive training interventions to delay or slow ARCD was generated by the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial—a long-duration study (10 years) with a large sample size (N = 2,802) and a notable level of diversity (25 percent minority participants). This study showed long-term impacts on reasoning, speed of processing, and maintenance of independence in IADLs in older adults (aged 65 and older) with normal cognition at enrollment (Ball et al., 2002; Rebok et al., 2014; Willis et al., 2006).[3] Results from other cognitive training RCTs meeting the systematic review criteria were mixed but showed positive trends (Carretti et al., 2013; Klusmann et al., 2010; Miller et al., 2013; Stine-Morrow et al., 2014; Wolinsky et al., 2013). In each of these studies, significant short-term improvements in cognitive performance over controls were observed for at least one of the domains on which participants had been trained, but impacts on other domains (i.e., transfer effects) were rare. Only the Iowa Health and Active Minds Study (IHAMS), which used a modified version of the computer-based speed-of-processing training employed in the ACTIVE study, observed small but significant effects of training on tests used to evaluate a different cognitive domain (executive functioning) (Wolinsky et al., 2013). All of these studies were of short duration, however, with follow-up periods in the range of 6 to 12 months. The long follow-up period in the ACTIVE trial is an important aspect of that study, as it showed the sustained benefit of the intervention. In contrast, the majority of RCTs on computer-based "brain training" applications identified in the literature search were excluded from the AHRQ analysis because of follow-up periods that were too short to enable assessment of impacts on such long-term outcomes as age-related cognitive decline.

Given the prominence of the ACTIVE trial in the AHRQ systematic review and in the cognitive training literature more broadly, the intervention arms and results of this study—the largest RCT in this intervention domain to date—warrant more detailed description and analysis. It is important to note that the training model employed in the ACTIVE trial was far more complex than most computer-based "brain training" programs marketed commercially. ACTIVE trial participants were random-

[3]Tables summarizing effect sizes for the impacts of the ACTIVE trial's cognitive training intervention on cognitive testing outcomes and IADLs (among other outcomes) at the 2-, 5-, and 10-year time points can be found in the 2017 AHRQ systematic review, *Interventions to prevent age-related cognitive decline, mild cognitive impairment, and clinical Alzheimer's-type dementia* (Kane et al., 2017) (see Appendix A).

BOX 2-2
Cognitive Training Strategies of the ACTIVE Trial

Memory training was aimed at improving verbal episodic memory. The training utilized mnemonic strategies to help participants remember word lists and sequences of items, text material, and the central ideas and details of stories. Participants were provided instruction in a strategy or mnemonic rule, exercises, feedback on their performance in one-on-one and group settings, and a practice test. Participants were instructed, for example, in strategies for organizing word lists into meaningful categories and using visualization and mental associations to remember words and text. The exercises included laboratory-like memory tasks (e.g., remembering a list of objects, recalling a specific paragraph of text), along with memory tasks pertaining to cognitive activities of daily living (e.g., recalling a shopping list or the details of a prescription label).

Reasoning training was focused on solving problems that follow a serial pattern. Participants were instructed in strategies for pattern identification and were provided an opportunity to practice the strategies through individual and group exercises. The exercises involved laboratory-like tasks, such as identifying the pattern in a letter or number series, or understanding the pattern in an everyday activity such as prescription drug dosing or travel schedules.

Speed-of-processing training was aimed at improving visual search skills and timely identification and location of visual information in a divided-attention format. The complexity of computer-based speed tasks was increased incrementally each time a participant achieved criterion performance on a particular task by, for example, decreasing the duration of the stimuli, adding distractions (visual or auditory), increasing the number of tasks participants were asked to perform simultaneously, or presenting targets over a wider spatial area. The speed-of-processing training also included instruction in applications to instrumental activities of daily living, focused primarily on improving driving.

SOURCE: Adapted from Ball et al., 2002.

ized to one of three training arms—memory, reasoning, and processing speed—or a no-contact control. The intervention included specific guidance on how to improve performance on a cognitive task during in-person and small-group training sessions with certified trainers over 5 to 6 weeks, as well as follow-up "booster sessions" similar to the initial training, administered to participants who adhered to the intervention 11 months after the initial training and again after 3 years. Hence, there was a component of social interaction. Specific training strategies for the three intervention arms (described in Box 2-2) differed, but the intervention conditions shared key features (Jobe et al., 2001) that included

- providing strategies for solving problems, remembering, or responding rapidly to information;
- using trainers to demonstrate the strategy;
- including both individual and group exercises;
- providing feedback to participants on their performance;
- fostering self-efficacy with regard to performance (i.e., individuals' belief that they could improve their ability to carry out a specific task); and
- applying strategies to real-world tasks, such as recalling a shopping list, understanding medication dosing, and driving.

The ACTIVE trial was not designed to study the impact of cognitive training on the incidence of dementia, but an analysis conducted post hoc found no difference in incidence between intervention (all arms combined) and control arms[4] (Unverzagt et al., 2012). The primary outcome for the trial, as specified in the initial Request for Applications, was independence in cognitively demanding daily functions (performance-based and self-reported measures). Cognitive performance was measured as a short- and long-term outcome, and the study showed that participants improved from baseline on tests for the domain in which they had been trained, but not other domains. These domain-specific benefits were sustained for 10 years except in the memory group, where benefits were observed only at the 2- and 5-year follow-up periods (Rebok et al., 2014). Evidence from the 5- and 10-year follow-up periods was considered low strength in the AHRQ report because of high attrition. Importantly, participants with mild memory impairments at baseline profited from reasoning and speed training, indicating that mild impairment in one cognitive domain does not preclude training-related improvements in other domains (Unverzagt et al., 2007). It is difficult to assess the effect of the booster training in the ACTIVE trial since assignment to the booster group was contingent on adherence to the initial training.[5] Nonetheless, the results suggest that the periodic refreshing was beneficial for those compliant with the speed-of-processing and reasoning interventions. The beneficial effects of booster training for speed of processing also were observed in a study by Wolinsky and colleagues (2013), which did not condition the booster on compliance.

An unexpected finding from the ACTIVE trial was a substantial lag in the observed effect of training on measures of daily function. Greater

[4]The study had 80 percent power to detect a hazard ratio of 0.75 at a significance level of 0.05 assuming a 30 percent rate of loss to follow-up (Unverzagt et al., 2012).

[5]To be eligible to receive the booster, participants had to have attended at least 8 of the 10 initial training sessions. Only 20 percent of participants in the nonbooster group completed the initial training, so the two groups are not comparable (Rebok et al., 2014).

maintenance of independence in IADLs was reported for all intervention arms compared with the control group at 10 years but not at earlier time points (Rebok et al., 2014), with the exception of the reasoning training group, which also showed less decline in IADLs than controls at 5 years (Willis et al., 2006). While improvements are expected in the domain in which participants were trained, the observation of greater maintenance of independence in IADLs is a notable finding because it suggests that results are more broadly generalizable and that benefits of cognitive training are likely to be meaningful in the context of people's daily lives. This observation is supported by an analysis showing that at-fault motor vehicle collisions were reduced in the speed-of-processing and reasoning groups relative to controls at 6 years post-training (Ball et al., 2010).[6]

Limitations of the AHRQ Systematic Review Findings

The AHRQ systematic review finding of moderate-strength evidence for a beneficial effect of cognitive training on cognitive performance was drawn largely from a single large trial—the ACTIVE study. Data were insufficient to draw any conclusions regarding effects of cognitive training on the prevention, delay, or slowing of MCI and CATD. Results of the other RCTs meeting the inclusion criteria—short-duration studies with follow-up periods of 12 months or less—are consistent with expectations of short-term improvements in cognitive performance in the domain trained but do not add to the strength of evidence on long-term benefits of cognitive training and generalizability to other areas such as IADLs. The 5- to 10-year lag in training effects on functional outcomes observed in the ACTIVE trial underscores the importance of including long follow-up periods in study designs and highlights the challenge of research aimed at preventing cognitive decline and dementia.

The ACTIVE trial represents a promising model for subsequent studies on cognitive training interventions but still suffered from notable methodological limitations that need to be considered in the discussion of its results. One criticism is the use of a no-contact control, which may not control adequately for potential placebo effects related to motivation and expectations (Boot et al., 2013; Foroughi et al., 2016). One could argue that expectations would be similar across intervention arms, so if the conditions of the intervention rather than the training itself were responsible for the beneficial effects, the observed differences among the intervention arms

[6]It should be noted that the overall crash rate (at-fault and not-at-fault) was similar for the speed-of-processing and control groups, and, for the typical individual, the observed reduction in rates of at-fault crashes translates to approximately one fewer at-fault crash every 62.5 years (Simons et al., 2016).

would not be expected. However, the intervention arms were not directly compared, which is another limitation of the study design. Finally, booster training was contingent on adherence to the initial training, complicating comparisons between booster and nonbooster groups.

A number of questions remain regarding the critical components and optimal form of cognitive training interventions. The ACTIVE trial intervention was complex. Unlike some interventions in which participants completed training exercises while sitting alone at a computer, the intervention arms in ACTIVE included a social aspect. The relative contributions of the socialization and training components to the observed effects are unclear and require further study. A number of studies have suggested that social engagement may be important, independent of cognitive training (IOM, 2015). The effect of instructing participants on the relevance of the training exercises to daily activities that involve similar cognitive demands is also unclear.

Given the unique and complex nature of its intervention, the results from the ACTIVE trial *cannot* be used to draw conclusions on the cognitive benefits of computerized cognitive training applications (i.e., brain games) and other interventions that fall within this general domain but have different components and forms. Future research on cognitive training interventions (discussed in Chapter 4) may help tease out the effects of different aspects of the ACTIVE intervention and address other questions that arise from the literature included in the AHRQ systematic review, such as the optimal duration of the intervention, the effects of differing levels of participation in cognitively stimulating activities at baseline, and whether training would be better than taking up other cognitively stimulating activities (e.g., reading, chess).

Evidence from Observational Studies

Intervention studies have been focused largely on structured cognitive training activities (computer- and noncomputer-based), which lend themselves to clinical trials, but there also exists a wealth of observational data suggesting that higher levels of educational attainment, literacy, and participation in other cognitively stimulating activities are associated with maintenance of cognitive performance and reduced risk of cognitive impairment and dementia (IOM, 2015). For example, a recently published prospective cohort study of nearly 2,000 adults aged 70 and older with normal cognition at baseline found that participating in a variety of cognitively stimulating activities, including games, craft activities, computer use, and social activities, was associated with a lower risk of MCI in future years (Krell-Roesch et al., 2017). Similarly, Wilson and colleagues (2013) found that the frequency of both early- and late-life participation in cognitive

activities, such as visiting a library and reading books, was associated with slower cognitive decline in later life, even after accounting for the development of neuropathologic findings (e.g., beta-amyloid deposits, tau-positive tangles, neocortical Lewy bodies).

A large number of studies have examined the relationship of education (usually measured by years of formal schooling) to cognitive decline and dementia incidence. A recent systematic review found an association between lower educational attainment and worse cognitive outcomes in 18 of 27 prospective studies and 21 of 25 cross-sectional studies (Beydoun et al., 2014). The potential importance of education for dementia prevention is further underscored by the finding of an analysis focused on known modifiable dementia risk factors that low educational attainment is the single greatest contributor to the risk of Alzheimer's disease globally, accounting for nearly 20 percent of cases (Barnes and Yaffe, 2011; Norton et al., 2014). Although the mechanistic pathways are not well understood, one hypothesis is that education and sustained cognitive stimulation over the life course may help build "cognitive reserve" through alternative networks or pathways in the brain that enable individuals to better compensate for neurodegeneration and thereby maintain normal cognitive function longer (Meng and D'Arcy, 2012; Stern, 2012; Valenzuela, 2008). This has not been empirically demonstrated, however, and other factors may account for the association with cognitive outcomes.

Potential Harms and Costs

None of the published RCTs on cognitive training interventions reviewed by the committee found adverse effects, and there is little empirical evidence to suggest that participating in these activities has negative consequences. One consideration, however, that should feed into decision making for individuals interested in taking up activities that may help maintain cognitive function and reduce risk of dementia is cost. Opportunity cost is the time and money that could have been used for engaging in other activities (e.g., physical activity), some of which may also benefit cognition and have other positive health effects (e.g., reduced risk of cardiovascular disease). Commercially marketed cognitive training applications generally entail a purchase or subscription cost, which varies across manufacturers.

Conclusions About Cognitive Training

As a whole, the evidence for cognitive training impacts on maintenance of cognitive function is encouraging but inconclusive, and requires further study. Future research on cognitive training interventions, discussed in Chapter 4, may further strengthen the evidence base for the effectiveness

of cognitive training interventions and provide stronger support for specific activities, which need to be robustly evaluated for their effectiveness before they can be recommended to the public.

CONCLUSION: Some RCT evidence suggests that cognitive training can delay or slow ARCD, as measured by performance on cognitive tests and instrumental activities of daily living. This conclusion is based largely on the ACTIVE trial.

CONCLUSION: There is no RCT evidence at this time that cognitive training will prevent, delay, or slow MCI or CATD.

CONCLUSION: At present, there is no evidence to support the notion that the beneficial long-term cognitive effects suggested by the ACTIVE trial apply to computer-based "brain training" applications. The suite of cognitive training interventions in the ACTIVE trial—which included cognitive training and social engagement in a group setting—differ substantially from commercial computer-based "brain training" applications, the effects of which appear to be short term and apply only to the specific cognitive task that is rehearsed.

CONCLUSION: The encouraging evidence on cognitive training interventions from RCTs, bolstered by additional data from prospective observational cohort studies on the benefits of cognitively stimulating activities, supports communicating with the public about cognitive training as a tool for delaying or slowing ARCD. However, existing data did not allow the committee to draw conclusions regarding the relative effectiveness of different cognitive training approaches or techniques.

BLOOD PRESSURE MANAGEMENT FOR PEOPLE WITH HYPERTENSION

Lowering blood pressure in people with hypertension substantially reduces the risk of heart disease and stroke by slowing blood vessel changes that are the key causes of cardiovascular disease (Wang et al., 2005). The most widely used blood pressure management strategies, which aim to maintain blood pressures at levels specified by established clinical guidelines, rely on medications (antihypertensives), although lifestyle-based interventions such as diet, weight loss, and exercise are also effective and can be first-line strategies (Wexler and Aukerman, 2006). Different classes of medications are available for blood pressure management, with a typical

medication lowering systolic blood pressure (SBP) by about 5 to 10 points; greater decreases can be achieved through use of multiple medications (Law et al., 2009). It appears likely that the benefits of lowering blood pressure may relate not to the specific treatment approach or medication class but to the level of lowering achieved (Turnbull, 2003). Some network meta-analyses, however, have suggested that the cognitive benefits of antihypertensives may differ by drug class, with angiotensin receptor blockers possibly being considered most promising (Levi Marpillat et al., 2013). Nonetheless, evidence is insufficient to determine whether certain classes of antihypertensives may be more beneficial with respect to cognitive decline and dementia. Identification of hypertension and improved control of blood pressure in patients with hypertension through lifestyle changes and medication have been linked to temporal declines in stroke incidence and mortality in prospective cohort studies (Koton et al., 2014), and are doubtless key contributors to the major reduction in cardiovascular mortality seen over the last few decades (Ford et al., 2007). Yet of the almost one-third of Americans with hypertension, more than half lack adequate blood pressure control (National Center for Health Statistics, 2016), despite such efforts as those of the National High Blood Pressure Education Program to provide evidence-based guidance on blood pressure management to clinicians (NHLBI, 2004).

Multiple links exist among cerebrovascular disease, Alzheimer's disease, and dementia. A majority of dementia patients have pathologic (Kovacs et al., 2008, 2013; Rahimi and Kovacs, 2014) or radiographic (Debette and Markus, 2010) evidence of cerebrovascular disease (e.g., large vessel atherosclerosis, small vessel disease, microbleeds, white matter hyperintensities),[7] and these conditions are often seen in combination with Alzheimer's pathology (Iadecola et al., 2016). Moreover, vascular cognitive impairment and vascular dementia are defined cognitive disorders. Epidemiologic data also link cerebrovascular disease and dementia, as both clinical stroke and subclinical cerebrovascular disease (silent strokes) are important risk factors for dementia (Pendlebury and Rothwell, 2009; Vermeer et al., 2003). In addition, decreased cerebral blood flow resulting from cerebrovascular disease may increase the production, or decrease the clearance, of Alzheimer's disease proteins in the brain (Zlokovic, 2011). It is plausible, then, that antihypertensive treatments, which are the most powerful tools for reducing the risk of stroke and subclinical cerebrovascular disease, would also reduce the risk of dementia.

[7]Vascular pathologies are also common in the brains of older people without dementia (MRC CFAS, 2001).

Findings from the AHRQ Systematic Review

Summary of the AHRQ Systematic Review Findings

The AHRQ systematic review identified 16 unique RCTs of blood pressure management interventions in hypertensive populations, 13 of which were found to have sufficiently low risk of bias to be included in the analysis. Of the 16 RCTs identified, 8 compared antihypertensive treatments with placebo, 8 compared active treatments, and 1 compared intensive versus standard blood pressure management. A summary of the AHRQ findings on blood pressure management interventions is presented in Box 2-3.

The AHRQ systematic review found inconsistent evidence from RCTs for an effect of blood pressure management on cognitive decline and dementia in patients with hypertension. None of the included trials, however, were designed primarily to evaluate effects on cognitive decline and dementia. In secondary analyses, these RCTs demonstrated no effect of

BOX 2-3 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON ANTIHYPERTENSIVE TREATMENT[a]

- Generally, low-strength evidence shows that 3 to 4.7 years of antihypertensive treatment regimens versus placebo appear to have no benefit on cognitive test performance in adults with normal cognition.
- Moderate-strength evidence shows that angiotensin converting enzyme (ACE) plus thiazide versus placebo and angiotensin receptor blockers (ARBs) versus placebo have no benefit on brief cognitive screening tests.
- Low-strength evidence shows that intensive versus standard antihypertensive control shows no benefit on cognitive test performance.
- Low-strength evidence shows no benefit on cognitive test performance of any fixed antihypertensive treatment regimen versus another among those directly compared.
- Effects of stepped multiple agent antihypertensive medication regimens to reduce risk of dementia are inconsistent; one trial showed a positive effect but three other trials found no effect of antihypertensive treatment on CATD incidence.
- The only two trials that reported subgroup data found no differential effect of treatment group on cognition by participant age or other baseline characteristics.

[a]All studies of antihypertensive treatments included in the AHRQ systematic review were conducted in hypertensive populations.
SOURCE: Kane et al., 2017.

blood pressure management on global measures of cognitive performance (e.g., Brief Cognitive Test results), and data from domain-specific tests (e.g., executive function, attention, memory) were mixed. The review identified four placebo-controlled trials of antihypertensive medications in adults with normal cognition that measured incident dementia as a secondary outcome. Of these, only the Syst-Eur trial showed beneficial effects on dementia incidence (Forette et al., 1998), raising the possibility of a chance effect. The overall results of this trial convincingly demonstrated the efficacy of blood pressure reduction for the primary endpoint of fatal and nonfatal strokes combined. Active treatment reduced all strokes by 42 percent ($p = 0.003$) and nonfatal strokes by 44 percent ($p = 0.007$) (Staessen et al., 1997). In a substudy of this trial, 3,162 adults who were over age 60, had SBP ranging from 160 to 219 mm Hg, and were free of baseline cognitive impairment were randomized to placebo or stepped, multiple-agent active treatment targeting SBP below 150 mm Hg. After 2 years, active treatment had lowered SBP by 8 points and reduced dementia incidence by 50 percent (21 versus 11 patients; $p = 0.05$) relative to the control group, but no change in cognitive performance as measured by scores on the Mini Mental State Exam (MMSE) was noted in either group (Forette et al., 1998). Subsequent data gathered during an open follow-up phase of the main trial showed that the effect of active treatment on SBP (7-point reduction) and dementia incidence (55 percent risk reduction) persisted after a median of 3.9 years of follow-up (Forette et al., 2002).

The three negative blood pressure–lowering trials in cognitively normal adults that reported incident dementia as an outcome were the Study on Cognition and Prognosis in the Elderly (SCOPE) trial (N = 4,937) (Lithell et al., 2003), Action in Diabetes and Vascular Disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE) trial (N = 11,140) (Patel et al., 2007), and Hypertension in the Very Elderly Trial (HYVET)-Cog (N = 3,336) (Peters et al., 2008). Although the AHRQ systematic review did not include a meta-analysis of these trials, prior meta-analyses including similar trial populations demonstrated a positive effect on cognitive outcomes with the use of antihypertensive treatment (Levi Marpillat et al., 2013; Peters et al., 2008). In particular, when the Perindopril Protection against Recurrent Stroke Study (PROGRESS) (N = 6,105)—which compared variable-intensity antihypertensive treatments in a poststroke population (Tzourio et al., 2003)—was included, a meta-analysis of RCT results showed a borderline significant reduction in incident dementia ($p = 0.045$) (Peters et al., 2008). Another negative study—the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial—found no significant benefit of intensive blood pressure management over standard therapy at 40 months in patients with type 2 diabetes as

measured by cognitive test performance (Williamson et al., 2014). Of note, dementia incidence was not included as an outcome measure in this study.

As the AHRQ systematic review notes, the limitations of the existing experimental evidence stem from the fact that few studies have been explicitly designed to measure the impact of blood pressure management on cognitive impairment and dementia. Instead, these trials typically were designed to measure the impact of antihypertensive treatment on cardiovascular outcomes, with cognitive outcomes being addressed in secondary analyses. As a consequence, these trials tended to have limited statistical power, provide less than optimal cognitive assessments, and entail relatively short-duration follow-up. In addition, they were not designed to address the potential heterogeneity resulting from age differences among subjects at the time of treatment, baseline blood pressure and cognitive status, and class of drug.

Limitations of the AHRQ Systematic Review Findings

Although the AHRQ systematic review found the experimental evidence for the effect of antihypertensive treatment on dementia incidence to be inconsistent, the committee found the data from observational prospective cohort studies to be more consistently positive. Several important methodologic issues need to be considered to place these findings in context.

As noted earlier, RCTs are the gold standard for evaluating intervention efficacy. The trials analyzed in the AHRQ systematic review were not optimally designed to detect effects of blood pressure management on dementia incidence. For both SCOPE and ADVANCE, the difference in blood pressure control between study arms was likely too small to result in significant between-group differences in dementia incidence. In contrast, a substantial difference in blood pressure reduction between study arms was observed for the HYVET-Cog trial, but this study was stopped early for efficacy on a noncognitive endpoint; as a result, mean follow-up was only 2.2 years (Peters et al., 2008). It is unknown whether an effect on cognitive function would have been observed had the study continued longer. In addition, these four trials enrolled older patient cohorts and followed them for short durations; the longest mean duration of follow-up (in the ADVANCE trial) was 4.3 years. Based on evidence from observational studies, which suggests that the effects of lowering blood pressure may be greatest in midlife, the optimal trial to quantify the effect of antihypertension treatment on dementia incidence would likely involve enrolling a younger cohort. Given the low baseline risks of dementia in a midlife cohort (Brookmeyer et al., 1998) and the slow progression of neurodegenerative pathology (Bateman et al., 2012), a decade or more of follow-up may be required to identify whether there is a true effect of such treatment on dementia incidence. In

addition, the fact that the primary goal of these four trials was to assess cardiovascular effects may have made them less likely to detect cognitive effects. In ADVANCE, for example, outcomes included multiple cardiovascular events in addition to cognitive performance and dementia (Patel et al., 2007). The latter outcomes were secondary and not systematically assessed as rigorously as the primary cardiovascular outcomes. Moreover, most cognitive performance outcomes relied on such insensitive measures as the MMSE.

Results of these hypertension trials are further complicated by the potential for heterogeneity of treatment effects across different subpopulations, particularly across age strata. For example, the focus of prior trials on late-life hypertension treatment may have resulted in study populations at high risk of treatment-related harm (Protogerou et al., 2007). In the oldest old, for instance, late-life hypertension is associated with a reduced risk of dementia (Corrada et al., 2017). Low diastolic blood pressure may in fact lead to declining cognitive performance through hemodynamic mechanisms in a population with more preexisting small vessel disease. Comorbid conditions that themselves may be dementia risk factors, such as diabetes (Pobladador-Plou et al., 2014), pose additional challenges to intervention studies targeting dementia risk reduction through blood pressure management.

Assessing Antihypertensive Treatment Against the Bradford Hill Criteria for Causation

Although RCTs provide at best modest support for a role of blood pressure management in patients with hypertension for dementia prevention, other converging sources of evidence provide additional support. When assessed against the Bradford Hill criteria discussed earlier (Hill, 1965), blood pressure management for dementia prevention generally fares well.

Strength of the Association

Causal explanations are more likely when observational evidence suggests strong associations. The association between hypertension and dementia differs based on the age of the population that is studied (Qiu et al., 2005). Across multiple studies, midlife but not late-life hypertension is consistently associated with increased risk of dementia (odds ratio of 1.61 for midlife hypertension) (Barnes and Yaffe, 2011). The strength of the association between antihypertensive therapy and dementia is more modest based on RCT evidence, as discussed in the prior section. However, two meta-analyses of prospective cohort studies assessing the association between antihypertensive treatment and dementia have identified larger effect sizes

(relative risk [RR][8] = 0.84) (Chang-Quan et al., 2011; Levi Marpillat et al., 2013).

Consistency

Confidence in causal explanations for observed associations is enhanced when independent studies that test different study populations or use different methodologies produce similar results. While the experimental evidence on the effect on dementia incidence of blood pressure management in people with hypertension has varied, evidence from observational studies has shown a relatively consistent effect. In a recent systematic review, for example, 7 of 11 studies found that antihypertensive treatment was associated with reduced risk of dementia or Alzheimer's disease (Rouch et al., 2015). Meta-analyses of observational longitudinal data also have found a relatively consistent association between lowering blood pressure and improved outcomes on a variety of measures of cognition (Chang-Quan et al., 2011; Levi Marpillat et al., 2013).

Specificity

According to the Bradford Hill criteria, the association between an exposure and the potential outcome is more likely to be causal if the exposure influences predominantly outcomes that are on a hypothesized causal pathway. Animal studies have confirmed the etiological relationship among hypertension, vascular disease in the brain, and cognitive impairment. Spontaneously hypertensive rats develop cerebrovascular disease in a pattern similar to that of humans with vascular dementia and have more severe cognitive deficits than those without hypertension (Saito et al., 1995; Yamori et al., 1976), and antihypertensive treatment limits cognitive and behavioral abnormalities (Wyss et al., 2003). These animal findings suggest a causal link between hypertension and cognitive deficits that can be attenuated by antihypertensive treatment and are broadly concordant with results of observational studies in humans.

Temporality

Analyses using the Bradford Hill criteria assess temporality to demonstrate that an intervention or exposure occurred prior to the change in outcome measures and, therefore, that an observed statistical association

[8]RR, used to compare risk between two groups, is the ratio of the probability of a certain outcome in an exposed/treatment group to the probability of that outcome in an unexposed/no-treatment group.

does not result from reverse causality. In the present case, hypertension and antihypertensive treatment are clearly present prior to dementia in observational studies.

Biological Gradient

The demonstration of a dose–response effect lends additional support to a causal relationship. The degree of blood pressure lowering across RCTs has not varied substantially; thus, the trials offer little opportunity to determine whether differential blood pressure lowering is associated with differential risk of dementia. It is worth noting that the positive Syst-Eur trial (Forette et al., 1998) enrolled subjects with higher baseline SBPs (160 to 219 mm Hg) relative to those of subjects in the other trials. Moreover, several cohort studies have found evidence of a biological gradient, with greater associations between cognitive outcomes and blood pressure lowering among those with the most elevated blood pressures (Elias et al., 2007; Gottesman et al., 2014). In one cohort study with long-term follow-up, the incidence of dementia decreased as the duration of antihypertensive treatment increased (Peila et al., 2006). Similarly, in another long-term cohort study, individuals with more severe hypertension and stronger indications for blood pressure treatment at midlife showed less decline in a variety of long-term cognitive measures after treatment (Gottesman et al., 2014). Although the unpublished Heart Outcomes Preventions Evaluation-3 (HOPE-3) ancillary study showed no overall effect of blood pressure control on cognitive measures, blood pressure lowering was related to better cognitive performance among the subgroup in the highest tertile of baseline SBP (>145 mm Hg) (Bosch, 2016).

Plausibility/Coherence

Plausibility and coherence relate to how a causal explanation aligns with what is known regarding the biology and natural history of a disease. There are two converging arguments for the plausibility of blood pressure management reducing dementia incidence. First, blood pressure management in hypertensives may prevent dementia by preventing or delaying the progression of cerebrovascular disease. Blood pressure management is a powerful tool for preventing stroke (Wang et al., 2005), even in individuals with modest blood pressure elevations (Sipahi et al., 2012). Blood pressure management also reduces the risk of subclinical and silent cerebrovascular disease, such as white matter disease that is associated with small vessel disease (Dufouil et al., 2005). Both stroke and subclinical cerebrovascular disease are strong predictors of dementia (Debette and Markus, 2010; Pendlebury and Rothwell, 2009). Consequently, it is plausible that blood

pressure management may reduce dementia risk through prevention of symptomatic and asymptomatic cerebrovascular disease. Second, vascular disease may be an important causal factor in the neurodegenerative cascade underlying the most common forms of dementia, such as Alzheimer's disease (Zlokovic, 2011). In patients with MCI and dementia, both neurodegenerative and vascular pathology are commonly identified at autopsy (Kovacs et al., 2008, 2013; Rahimi and Kovacs, 2014; Saito and Murayama, 2007), and a variety of plausible pathophysiologic links between vascular disease and neurodegeneration have been proposed (Jellinger, 2007).

Overall Summary

When measured against the Bradford Hill criteria, the observational data indicating that blood pressure management reduces the risk of dementia are consistent with a causal relationship. Although RCT evidence is inconsistent, the observational data support management of hypertension as a plausible intervention for reducing dementia. As discussed in Chapter 4, opportunities exist for new RCTs focused on optimal targets (blood pressure levels and patient groups) and therapies to reduce risks for CATD that may avoid some of the potential shortcomings of observational studies (e.g., biases related to design and reporting) and add further support for this recommendation. However, given that blood pressure management, like physical activity (discussed below), is broadly recommended for primary, secondary, and tertiary prevention of many chronic conditions, the committee notes that it may not be possible to generate definitive evidence through prospective RCTs.

Other Known Health Benefits and Potential Harms and Costs

In addition to the efficacy and observational data discussed above, two other considerations are relevant to communications with the public on the potential benefits of blood pressure management for prevention of cognitive decline and dementia.

First, there is strong evidence indicating that effective blood pressure management substantially reduces the risk of fatal and nonfatal cardiovascular events and all-cause mortality in hypertensive patients (The SPRINT Research Group, 2015). While the proportion of Americans aware of their hypertension and receiving treatment has increased over time, both underrecognition and undertreatment remain common (Bromfield et al., 2014; Navar-Boggan et al., 2014). In addition, results of the recent Systolic Blood Pressure Intervention Trial (SPRINT) suggest that many patients already receiving antihypertensive treatment may benefit from more intense treatment in terms of cardiovascular outcomes (The SPRINT Research Group,

2015). Given the underutilization of antihypertensive treatment for blood pressure management, broader diffusion of such treatments would likely have important societal benefits with respect to the incidence of cardiovascular disease.

Second, the risks of antihypertensive treatment have been well studied and are generally modest in magnitude. Although some subgroups, including diabetics with low baseline blood pressure (Brunström and Carlberg, 2016), may be at risk for severe adverse events, the majority of patients treated in trials did not have a higher rate of severe adverse events relative to control groups. The four placebo-controlled trials of antihypertensive treatments for dementia prevention summarized above collectively enrolled more than 20,000 patients, and none of the four identified an increase in major cardiac events, microvascular events, or mortality. Importantly, given that these studies focused on late-life populations, they included the groups at highest risk for harm. While antihypertensive treatments do cause problematic idiosyncratic adverse events, these events are relatively rare and rarely severely disabling. For any given antihypertensive agent, approximately 3 to 6 percent of patients will discontinue the medication because of an adverse event, but the majority of these events do not result in irreversible harm (Ross et al., 2001). In addition to their relatively benign adverse event profile, antihypertensive treatments are relatively inexpensive, and their use is highly cost effective for the prevention of cardiovascular disease (Moran et al., 2015). In fact, the World Health Organization has categorized interventions for prevention of cardiovascular disease, including antihypertensive treatment, as one of their "best buys" for reducing noncommunicable diseases (WHO and World Economic Forum, 2011).

Conclusions About Blood Pressure Management

Hypertension is a well-documented risk factor for dementia. Intervention studies suggest the risk of dementia attributable to hypertension can be reduced through blood pressure management strategies, although further research (discussed in Chapter 4) is needed to optimize the effectiveness of this approach.

CONCLUSION: Blood pressure management for people with hypertension, particularly during midlife, is supported by encouraging but inconclusive evidence for preventing, delaying, and slowing CATD. The RCT data do not offer strong support for blood pressure management in patients with hypertension for delaying or slowing ARCD or preventing, delaying, or slowing MCI and CATD, although one trial provides some positive evidence of an impact on the risk of CATD. When prospective cohort studies

and knowledge of the natural history and biology of the disease are considered, however, effects of blood pressure management on incident CATD in patients with hypertension are consistent with a causal relationship. In addition, there are known cardiovascular benefits from blood pressure management.

INCREASED PHYSICAL ACTIVITY

Physical activity has been recognized as a key contributor to healthy aging, with benefits including both physical and cognitive function (IOM, 2015). Physical activity encompasses a diverse set of behaviors, alone or in combination, including aerobic activity (e.g., walking, dancing); resistance training (e.g., weightlifting); and stretching, toning, and balance (e.g., yoga, tai chi). A 2015 Institute of Medicine report identifies engaging in physical activity as one of the specific actions individuals should take to maintain and sustain their cognitive health (IOM, 2015). Importantly, individuals can change their behavior to become more physically active at any age, and doing so does not necessarily require adherence to a structured exercise program. Physical activity levels can be boosted by work or leisure (e.g., hiking) activities, and also may be influenced by community conditions (e.g., availability of neighborhood green space) (Dalton et al., 2016).

Physical activity has consistently been identified as one of the modifiable risk factors that could have the greatest impact on rates of cognitive impairment and dementia (Barnes and Yaffe, 2011; Beydoun et al., 2014). In 2011, Barnes and Yaffe (2011) estimated that nearly 4.3 million Alzheimer's disease cases globally and more than 1 million cases in the United States alone could be attributed to physical inactivity, and a 25 percent reduction in the prevalence of physical inactivity could potentially have prevented nearly 1 million cases globally and 230,000 in the United States. However, despite evidence accumulated over decades from observational studies showing the significant benefit of physical activity for reducing the risk of cognitive decline and dementia (Blondell et al., 2014; Brown et al., 2013), supportive data from intervention studies have been sparse, with meta-analyses reporting both no benefit (Young et al., 2015) and benefit (Northey et al., 2017; Zheng et al., 2016).

Findings from the AHRQ Systematic Review

Summary of the AHRQ Systematic Review Findings

The AHRQ systematic review identified 43 RCTs of physical activity interventions, 19 of which were rated as having a low or medium risk of

BOX 2-4 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON PHYSICAL ACTIVITY INTERVENTIONS

- Studies of physical activity interventions examined a wide variety of activities[a] potentially targeting different pathways to affect cognition.
- Evidence is insufficient to conclude whether physical activity interventions prevent MCI or CATD incidence.
- Low-strength evidence shows that multicomponent physical activity interventions offer no clear benefit in cognitive performance over attention control in adults with normal cognition.
- Evidence was insufficient to conclude whether other types of physical activity interventions had benefits for cognitive outcomes in adults with normal cognition.
- While the majority of results showed no significant difference, the pattern of results across very different types of physical activity interventions provides an *indication* of effectiveness of physical activity.

[a]The AHRQ systematic review classified physical activity interventions as aerobic activity, resistance training, Tai Chi, or multicomponent physical activity. Multicomponent physical activity interventions varied across studies but included flexibility, strength, balance, endurance, and/or aerobic components.
SOURCE: Kane et al., 2017.

bias and were included in the analysis. A summary of the AHRQ findings on physical activity interventions is presented in Box 2-4.

To date, no RCTs have demonstrated that physical activity can reduce the incidence of MCI or CATD, despite associations reported in observational studies (discussed in more detail below). Dementia and MCI incidence were rarely included as outcomes in physical activity trials analyzed in the AHRQ systematic review, and studies generally were not of sufficient duration or size to detect such changes. However, results from several RCTs of aerobic training interventions or interventions that included an aerobic training component in older adults with MCI suggest that physical activity can delay or slow cognitive decline in this population[9] (Baker et al., 2010; Lautenschlager et al., 2008; Suzuki et al., 2012). Langa and Levine (2014) identified two additional studies that provide further evidence supporting the beneficial effects of physical activity in individuals with MCI—Barnes

[9]The Baker et al. (2010) study is misclassified in the AHRQ report as having been conducted in adults with normal cognition.

et al. (2013) and Nagamatsu et al. (2012)—but these trials were excluded from the AHRQ analysis because of short follow-up periods (12 weeks) and a high risk of bias due to attrition, respectively.

Results from clinical trials of physical activity interventions in older adults with normal cognition at the time of enrollment have been mixed. The AHRQ systematic review found some instances of benefits for cognitive outcomes for aerobic activity (Antunes et al., 2015; Muscari et al., 2010) and resistance training (Cassilhas et al., 2007), but the effects were modest and may not be clinically meaningful (Kane et al., 2017). Evidence for both types of physical activity interventions was considered insufficient to conclude whether they were of benefit to adults with normal cognition. The largest physical activity trial, the Lifestyle Interventions and Independence for Elders (LIFE) study, featured a multicomponent intervention focused on walking, resistance training, and flexibility exercises targeting preservation of mobility in sedentary individuals aged 70-89 who had functional limitations (Pahor et al., 2014). Cognitive function, which was a preplanned secondary outcome for the trial, was not improved across 2 years, overall (Sink et al., 2015), although exploratory analyses provided some evidence for benefit among individuals who were relatively older, who had greater physical limitations, or who had diabetes (Espeland et al., 2017; Sink et al., 2015). These findings suggest that multicomponent physical activity interventions in older adults may be effective in preserving cognitive function only in subgroups of individuals. Although the AHRQ systematic review found that multicomponent physical activity interventions demonstrated no clear benefit for cognitive performance in adults with normal cognition, heterogeneity in the elements of multicomponent interventions limits the ability to generalize existing study results to all such interventions.

Limitations of the AHRQ Systematic Review Findings

The reasons for the mixed RCT data and the discrepancy between the results of RCTs and observational studies (discussed below) with respect to benefits of physical activity for reducing rates of cognitive impairment and dementia are not well understood. They may result in part from methodological limitations of physical activity intervention studies, such as insufficient study durations and follow-up periods, failure to include a proper control group, inconsistent and often subjective measures of physical activity, small sample sizes, and associated lack of power to determine efficacy for prevention of MCI or CATD. It is, of course, also possible that physical activity has no real effect on cognitive decline and dementia incidence and that the statistically significant effects on cognitive tests reported in some RCTs are the result of chance, with confounding potentially explaining the association between physical activity and cognitive outcomes in observa-

tional studies. However, with the exception of the LIFE study, all RCTs included in the AHRQ systematic review were of short duration (1 year or less). If the effect of increasing physical activity is to slow cognitive decline rather than increase cognitive performance, this is a relatively short period of time in which to observe decline reliably in most individuals, and any observed rates of change will vary depending on the population's risk factor profiles. One year or less is likely much too short a time in which to assess intervention effects on the risk of Alzheimer's disease and related dementias. Larger and longer-term studies are therefore needed to determine whether the short-term effects of physical activity translate into long-term cognitive benefits.

Additionally, given the multitude of potential interactions among pathways that may mediate cognitive decline and progression to dementia, the strength of the effect of any one intervention would be expected to vary across individuals. Further elucidation of the biological mechanisms mediating the protective effects of physical activity and the dose–response relationship may provide some additional explanation. The timing of initiation of interventions may be another factor, as there is increasing evidence that physical activity in midlife is important for reducing MCI and dementia risk in older adults (Hamer and Chida, 2009). These and other areas for future study are discussed further in Chapter 3.

Assessing Physical Activity Against the Bradford Hill Criteria for Causation

The pattern of positive results from RCTs included in the AHRQ systematic review provides an indication of short-term beneficial effects of physical activity, particularly in adults with MCI. However, physical activity interventions are not supported by sufficient evidence from clinical trials alone to justify public health messaging beyond the known physical benefits. Additional data supporting consideration of physical activity for public health messaging derive from the wealth of observational studies, including several large prospective studies (Larson et al., 2006; Lee et al., 2013; Scarmeas et al., 2009; Singh-Manoux et al., 2005; Yaffe et al., 2001), that have found that physical activity is associated with reduced rates of cognitive decline and dementia risk (Beydoun et al., 2014; Blondell et al., 2014; Hamer and Chida, 2009; Zhu et al., 2017). Absent strong experimental evidence, the committee again used the Bradford Hill criteria (Hill, 1965) to evaluate whether the large body of evidence from observational studies supports a causal relationship between physical activity and reduced rates of cognitive decline and dementia.

Strength of the Association

A recent meta-analysis of longitudinal studies demonstrated low- to moderate-strength inverse associations of physical activity with cognitive decline (see Figure 2-1) and dementia (see Figure 2-2), with overall RR

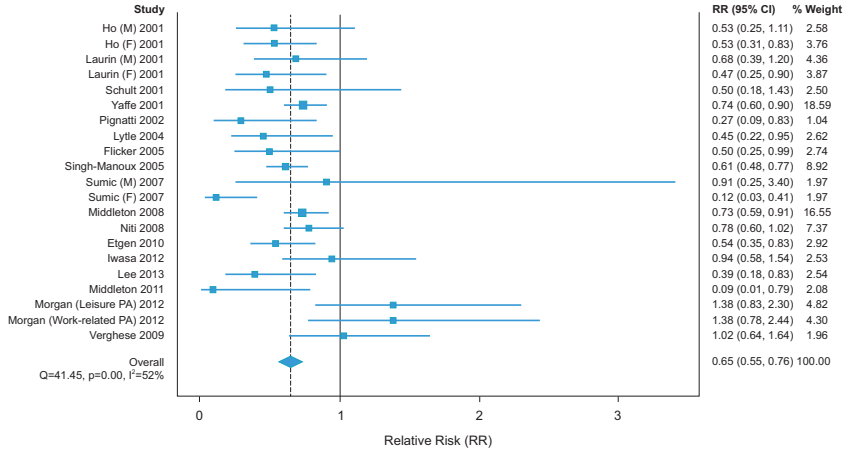

FIGURE 2-1 Forest plots showing the association between high physical activity and cognitive decline based on a meta-analysis of observational studies.
SOURCE: Blondell et al., 2014.

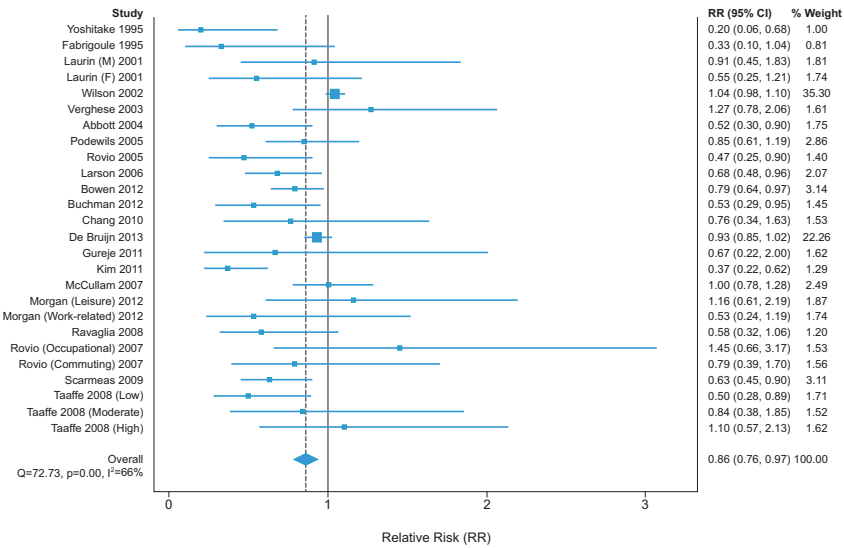

FIGURE 2-2 Forest plots showing the association between high physical activity and dementia based on a meta-analysis of observational studies.
SOURCE: Blondell et al., 2014.

estimates of 0.65 (95 percent confidence interval [CI] 0.55-0.76) and 0.86 (95 percent CI 0.76-0.97), respectively (Blondell et al., 2014).

Consistency

In the meta-analysis by Blondell and colleagues (2014), 18 of 21 studies had point estimates of reduced risk for cognitive decline, and 20 of 26 studies had point estimates of reduced risk for dementia. None of the 95 percent CIs for RR across all studies excluded benefit. In another recent systematic review, 21 of 24 cohort studies and 4 of 4 cross-sectional studies found an association between physical activity and cognitive outcomes (Beydoun et al., 2014). There also is a growing body of evidence showing that sedentary behavior is consistently associated with poor cognitive outcomes. A recent systematic review found that 6 of 8 observational studies reported significant negative associations between sedentary behavior and cognitive function (Falck et al., 2016). Some lack of consistency in findings on the beneficial cognitive effects of physical activity may be explained by methodological limitations and, perhaps, real differences in effects across individuals who have different risk factor profiles or are at different stages of cognitive decline (Tolppanen et al., 2015; Willey et al., 2016).

Specificity

It is difficult to establish specificity for how physical activity may reduce the risks for cognitive decline and dementia. As described in the section on plausibility below, there are many potential biological pathways through which physical activity may provide these benefits.

Temporality

In interpreting results from observational studies, the potential for an observed statistical association to result from reverse causality needs to be considered. In the present case, it is plausible that cognitive decline and dementia lead to reduced physical activity, thereby explaining the inverse relationship. However, RCT data showing improvement in cognitive outcomes in adults with MCI following physical activity interventions (Baker et al., 2010; Lautenschlager et al., 2008; Suzuki et al., 2012) suggest that reverse causality does not explain the association between physical activity and cognitive function (Ahlskog et al., 2011). Furthermore, Middleton and colleagues (2010) examined the effects of physical activity in women across the life course using a cross-sectional study design and found that the negative association between physical activity and late-life cognitive impairment was strongest for those who were physically active early in life. Finally, as discussed below, the temporal relationship between physical activity inter-

ventions and potential biological mediators of cognitive benefits, such as brain perfusion and brain structure, has been documented in some studies (Erickson et al., 2011).

Biological Gradient

Observational studies have provided only mixed evidence of a biological gradient for effects of physical activity on cognitive outcomes (Blondell et al., 2014). In their meta-analysis, Sofi and colleagues (2011) grouped studies according to the intensity level of physical activity (high and low to moderate) and found no indication of a dose–response relationship. However, several large prospective studies, including the Study for Osteoporotic Fractures (Yaffe et al., 2001) and the Reasons for Geographical and Racial Differences in Stroke (REGARDS) study (Zhu et al., 2017), found that objectively measured physical activity had a graded relationship for the risk of cognitive decline. The possibility of an intensity threshold has been raised but is not strongly supported by current evidence (Brown et al., 2013). One challenge to evaluating dose–response relationships is the use of subjective methods (e.g., questionnaires) to assess physical activity levels. The inadequate reliability of such methods can introduce bias into analyses. The use of objective measures of physical activity may help overcome this limitation and lead to evidence-based recommendations on target physical activity levels for cognitive benefit.[10] Indeed, when cardiorespiratory fitness was determined by objective measures, including peak oxygen consumption and treadmill exercise duration, Barnes and colleagues (2003) observed a graded association between cardiorespiratory fitness at baseline and level of performance on cognitive tests conducted 6 years later.

Plausibility/Coherence

The underlying mechanisms mediating changes in brain structure and function in response to physical activity are not well understood, but a number of hypotheses on possible direct and indirect effects have been proposed and are biologically plausible. These include increased brain perfusion, protection against brain volume loss (potentially mediated through such neurotrophic factors as brain-derived neurotrophic factor), reduction of inflammation, and reduction of brain beta-amyloid deposition. Indirectly, physical activity may prevent cognitive decline and dementia by reducing atherosclerosis and the associated risk of vascular disease (including stroke) (Ahlskog et al., 2011; Blondell et al., 2014; Brown et al., 2013).

[10]The American Heart Association (AHA, 2016) currently recommends 150 minutes of moderate physical activity per week, but this recommendation is not based on data from studies of cognitive benefit.

In addition to the RCT data summarized in the AHRQ systematic review and epidemiological studies discussed above, studies examining the effects of physical activity on biomarkers—neuroimaging studies in particular—provide additional evidence of the beneficial effects of physical activity on cognition (Ahlskog et al., 2011; Erickson et al., 2012). Brain shrinkage is a normal part of the aging process (Raz et al., 2005), and decreasing hippocampal volume has been associated with cognitive decline (O'Shea et al., 2016). In individuals with MCI, hippocampal atrophy is a predictor of progression to Alzheimer's dementia (Jack et al., 2010). Erickson and colleagues (2011) found that aerobic exercise was associated with an increase in hippocampal volume, while hippocampal volume decreased in a stretching control group over the same time period. Other intervention and observational studies have similarly found that aerobic exercise was associated with increases in brain matter volume in older adults (Colcombe et al., 2006; Erickson et al., 2010; Ruscheweyh et al., 2011). By attenuating and even reversing declines in brain volume, physical activity may help to protect cognitive function (Erickson et al., 2011) and reduce the risk of dementia (Tan et al., 2017), although the mechanisms for these effects have yet to be fully elucidated. A recent study emphasizes the importance of promoting physical activity in midlife to protect against brain volume loss observed later in life (Spartano et al., 2016). As discussed further in Chapter 3, however, the relationship between such biomarkers as brain volume and cognitive outcomes in intervention studies requires further study.

Overall Summary

When assessed against the Bradford Hill criteria, the existing body of evidence from observational studies lends some support, but is not conclusive, for a causal relationship between physical activity and cognitive decline and dementia. While many of the studies included in this analysis tried to adjust for confounding and assessed physical activity using standardized measures (Blondell et al., 2014), the committee recognizes that even with carefully conducted observational studies, there is a risk of confounding, bias, and reverse causality.

Other Known Health Benefits and Potential Harms and Costs

In considering public health messaging on interventions for reducing the risk of cognitive decline and dementia, it is important to weigh an intervention's other known health benefits, as well as risks and costs. Physical activity is an important factor in healthy aging (Hamer et al., 2014), with well-documented benefits extending to improvements in quality of life—

e.g., maintaining mobility and independence (Pahor et al., 2014)—and reduced risk of chronic conditions such as depression, hypertension, osteoarthritis, metabolic syndrome, diabetes, stroke, and coronary heart disease, as well as fall-related injuries (Chang et al., 2004; Howard and McDonnell, 2015; Lee et al., 2012).

While uncommon, it has been reported that physical activity may result in musculoskeletal injury and hospitalization in older adults (Marsh et al., 2016), although these risks in older adults do not appear to be greater than those for other age groups (Little et al., 2013), and for most individuals, the benefits are likely to far outweigh the risk of harm. Costs of physical activity interventions vary depending on the type of activity, but are typically minimal. Walking, for example, represents a low-cost, universally available form of physical activity that has been associated with maintaining cognitive performance in later life (Erickson et al., 2010).

The widely acknowledged public health benefits of physical activity beyond cognitive outcomes, along with the low risk of harm and minimal cost, are important factors that, combined with encouraging RCT data and strong epidemiological evidence of cognitive benefit, bolster the argument for public health messaging on interventions that increase physical activity. Even in the absence of RCT data showing positive long-term effects, there appears to be no clear detriment to public health messaging that promotes increased physical activity.

Conclusions About Increased Physical Activity

Physical activity has many known health benefits, some of which (e.g., stroke prevention) are causally related to brain health. There is growing evidence that among these health benefits is reduced risk of cognitive decline.

CONCLUSION: Increased physical activity is supported by encouraging but inconclusive evidence for delaying or slowing ARCD. The pattern of RCT results across different types of physical activity interventions provides an indication of the effectiveness of increased physical activity for delaying or slowing ARCD. These effects are consistent with a causal relationship when prospective cohort studies and knowledge of neurobiological processes are considered. In addition, increased physical activity has known cardiovascular and other health benefits.

CONCLUSION: There is insufficient evidence at this time to conclude that increased physical activity will prevent, delay, or slow MCI or CATD.

CONCLUSION: There is insufficient evidence to determine which specific types of physical activity are particularly effective for preventing cognitive decline and dementia.

RECOMMENDATION

The committee concludes that three classes of interventions—cognitive training, blood pressure management for people with hypertension, and increased physical activity—are supported by encouraging but inconclusive evidence. The lack of consistent results across RCTs for interventions in these three domains (i.e., effects reach statistical significance for some trials but not others) may be expected for interventions that have weak beneficial effects on cognitive outcomes, and the methodological limitations described in the sections above also may contribute to the inconclusive nature of the evidence base. However, it should also be acknowledged that future research may show that one or more of these interventions do not prevent cognitive decline or dementia, but have only short-term or nonspecific effects. Additionally, although it is biologically plausible that the same interventions that help delay or slow ARCD would also be beneficial for MCI and CATD, and vice versa, it is not known whether this extrapolation or generalization can be made in either direction. Therefore, the recommendation below is based on the available evidence. The public, however, will not draw fine distinctions among these conditions, and it will be challenging to convert these statements about the evidence into appropriate communications with the public.

Recommendation 1: Communicating with the Public

When communicating with the public about what is currently known, the National Institutes of Health, the Centers for Disease Control and Prevention, and other interested organizations should make clear that positive effects of the following classes of interventions are supported by encouraging although inconclusive evidence:

- ***cognitive training*—a broad set of interventions, such as those aimed at enhancing reasoning, memory, and speed of processing—to delay or slow age-related cognitive decline**
- ***blood pressure management for people with hypertension* to prevent, delay, or slow clinical Alzheimer's-type dementia**
- ***increased physical activity* to delay or slow age-related cognitive decline**

There is insufficient high-strength experimental evidence to justify a public health information campaign, per se, that would encourage the adoption of specific interventions to prevent these conditions. Nonetheless, it is appropriate for the National Institutes of Health and others to provide accurate information about the potential impact of these three intervention classes on cognitive outcomes in a place where people can access it (e.g., websites). It also is appropriate for public health practitioners and health care providers to include mention of the potential cognitive benefits of these interventions when promoting their adoption for the prevention or control of other diseases and conditions.

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3

METHODOLOGICAL IMPROVEMENTS

Chapter 2 identifies three classes of interventions[1]—cognitive training, blood pressure management in people with hypertension, and increased physical activity—that may be included when communicating with the public about interventions for delaying or slowing age-related cognitive decline (ARCD) and preventing, delaying, or slowing mild cognitive impairment (MCI) and clinical Alzheimer's-type dementia (CATD) (referred to throughout this report by the shorthand "preventing cognitive decline and dementia"). The strength of the evidence for the beneficial effects even of these most promising interventions, however, is low to moderate at best, in part because of methodological limitations noted in Chapter 1 and described in more detail below for many of the studies reviewed in the Agency for Healthcare Research and Quality (AHRQ) systematic review (Kane et al., 2017).

These limitations stem partially from inherent challenges associated with conducting randomized controlled trials (RCTs) on interventions to prevent cognitive decline and dementia. Examples of such challenges include initiation of interventions at later life stages that may be outside the optimal window; follow-up periods of insufficient duration; high attrition; small sample sizes and studies underpowered to detect changes in incidence of MCI and CATD; use of suboptimal and heterogeneous outcome measures and assessment tools; a focus on individual interventions when multiple

[1]As discussed in Chapter 1, the scope of the study was limited to individual-level interventions. Societal-level interventions, including public health policies (e.g., those related to access to education and clean air), were not evaluated.

interventions may be the most beneficial and, conversely, difficulty detecting which components in multimodal interventions are most effective in which combination(s); difficulty identifying appropriate control groups; and lack of knowledge regarding interactions between risk factors and interventions.

These methodological challenges limited the ability of the AHRQ systematic review to draw meaningful conclusions from many studies regarding the efficacy of interventions. To help ensure that future studies yield more definitive results, future investments in research on interventions for preventing cognitive decline and dementia would benefit greatly from efforts to rectify these common methodological shortcomings. One approach is to work toward common standards and protocols that might be applied across trials funded by the National Institute on Aging (NIA) and other institutes and interested organizations to make them more comparable. This chapter presents the committee's perspective on cross-cutting methodological modifications that would improve the utility of future research on preventing cognitive decline and dementia. The committee's recommendation in this area is presented at the end of the chapter, and draws on the conclusions in each of the sections below. Priority substantive areas for future research for specific intervention domains are identified in Chapter 4.

In addition to the more specific methodological recommendations described below, there are opportunities to make greater use of new adaptive designs for clinical trials. These include, for example, adaptive treatment strategies that permit valid comparisons when subjects are rerandomized to different or enhanced interventions based on their performance in the trial (Brown et al., 2009). Such designs may be highly useful in studying interventions that rely on adherence for success, as well as in multimodal studies, and are successful where reliable measures of outcome can be made during the trial. Other adaptive trial designs alter how participants are allocated to interventions over time, or expand to add new interventions, based on data emerging over the course of the study (Brown et al., 2009). Platform trials allow many therapies to be evaluated simultaneously and are designed with the flexibility to rapidly add, alter, and remove therapies in response to emerging measures of efficacy (Berry et al., 2015; EPAD, 2017).

IDENTIFY INDIVIDUALS WHO ARE AT HIGHER RISK OF COGNITIVE DECLINE AND DEMENTIA

Despite only modest successes in identifying interventions that can help prevent, delay, or slow MCI and CATD, dementia incidence has been decreasing in the United States (Langa et al., 2017; Rocca et al., 2011). As discussed in Chapter 1, the reasons for this decrease are not fully understood, but they parallel a decrease in cardiovascular morbidity and mortality that is the result of better prevention and treatment for heart disease

and stroke, the latter being a key determinant of dementia risk, including Alzheimer's and vascular dementias. The secular trend toward a decrease in dementia incidence may make it difficult to demonstrate that prevention strategies are effective because the control group in any study may be experiencing improvements in dementia incidence. Thus, it may be useful in future studies to target interventions to higher-risk populations that may not be affected by these secular trends—specifically, individuals who face the highest burden of disease and those for whom an intervention could have the greatest effect (e.g., APOE-4 positive individuals, people with a strong family history of dementia, those at high risk of vascular disease).

This approach is supported by findings from subgroup analyses in previous studies. In the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial, for example, which targeted vascular risk factors but failed to detect a reduction in all-cause dementia, the greatest effects were observed in those with uncontrolled blood pressure at baseline who adhered to the intervention (Moll van Charante et al., 2016). Most studies currently do not stratify or enrich according to these kinds of considerations, although it is worth noting that the Dominantly Inherited Alzheimer Network Trials Unit has launched the addition of new preventive treatment arms to its adaptive trial platform, now known as the Next Generation prevention trial, which targets those carrying deterministic gene mutations. It is hoped that by understanding the progression and prevention of the inherited form of the disease, the same treatments deemed effective for this high-risk group can be applied to those at risk of the more common, sporadic form of the disease (Alzheimer's Association, 2016). Biomarkers may, in the future, help identify other higher-risk populations that can be similarly targeted in intervention studies.

Identification of risk groups that could derive the greatest benefit from specific interventions would inform the tailoring of interventions so they would have the greatest possible impact on population health. For example, beginning interventions earlier in life may be particularly beneficial for those at risk of developing early-onset dementia. Individuals at higher risk for dementia may have the strongest incentive to adopt particular prevention strategies, and this may be an important consideration in public health messaging. This approach of considering individuals' risk profiles is consistent with the larger movement toward personalized medicine. It should be emphasized, however, that the committee does not mean to suggest that studies in populations not considered at high risk should be discontinued. Rather, the optimum strategy would be to undertake these two approaches in parallel. Lastly, it is worth examining whether the trend toward decreased dementia incidence varies by socioeconomic status, for which disparities across ethnic and racial groups are well documented in the United States (Fiscella et al., 2000; NRC, 2004; Williams, 1999; Williams et

al., 2010). If the secular trends are weaker for those of lower socioeconomic status, perhaps this population might also be considered at high risk for dementia and be a particular target for research on prevention.

CONCLUSION: Identifying and targeting interventions to high-risk populations may increase the likelihood of detecting a beneficial effect of an intervention and provide a more accurate assessment of its efficacy.

INCREASE PARTICIPATION OF UNDERREPRESENTED POPULATIONS IN INTERVENTION TRIALS

The population of older adults in the United States is not only growing but also becoming increasingly diverse (Johnson, 2016). By 2060, nearly one-half of U.S. adults aged 65 and older are expected to be from a nonwhite racial or ethnic background (U.S. Census Bureau, 2012). This demographic shift has significant implications for intervention research targeting cognitive outcomes, since it is well documented that some minority populations (e.g., African Americans, Latinos) have a higher risk of cognitive impairment and dementia (Mayeda et al., 2016; Mehta and Yeo, 2017; NRC, 2004; Steenland et al., 2016), as well as of vascular disease (Kurian and Cardarelli, 2007; Mozaffarian et al., 2016; Winkleby et al., 1998).

Historically, however, minorities have been underrepresented in biomedical research (Oh et al., 2015), and although the National Institutes of Health (NIH) mandates participation of minorities in research studies, clinical trials, including research on interventions for preventing cognitive decline and dementia, have experienced disappointing limits in their minority recruitment and participation. When race was incorporated at all among reported demographic factors in the studies included in the AHRQ systematic review, study populations often were found to be poorly representative of the diversity of the general population. Similar issues with underrepresentation can be observed with respect to such demographic characteristics as socioeconomic status and educational attainment. Education level, like race, is a well-recognized bias in study volunteer samples, with more highly educated individuals being more likely to volunteer (Cobb et al., 2014; Ganguli et al., 1998; Lindsted et al., 1996; Shavers et al., 2002). Importantly, education also is a key modifier in dementia studies (Evans et al., 1997; Fitzpatrick et al., 2004; Kukull et al., 2002; Ott et al., 1995; Stern et al., 1994). Further complicating the picture are the associations among race, education, and socioeconomic status, making it difficult to disentangle the effects of each. For example, an analysis by Yaffe and colleagues (2013) using data from the Health, Aging, and Body Composition study showed that variation in dementia risk between white and black participants was

no longer statistically significant when socioeconomic differences were accounted for during the analysis.

As a result of biases in the enrollment of study participants, the existing body of evidence may not accurately reflect the effectiveness of cognitive interventions in underrepresented populations. To ensure that public health messages promote interventions that are actually effective for the range of populations affected and can be targeted as appropriate, strengthening this evidence base by increasing the participation of underrepresented populations needs to be a priority in future research. Studies such as the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial that have achieved comparably higher levels of minority participation have shown, as is well documented in the literature, that greater success in recruiting representative populations can be realized by utilizing well-established community-based participatory research approaches that engage and empower minority populations to be more proactive with respect to their health (Ballard et al., 1993; Barnes and Bennett, 2014; Gauthier and Clarke, 1999; Hinton et al., 2010; Levkoff and Sanchez, 2003). Carefully designed observational studies may be more likely than RCTs to have representative distributions of race, ethnicity, education, and socioeconomic status and therefore represent an important opportunity to glean information on the impact of demographic characteristics on the effectiveness of various interventions.

Appropriate funding support for the kinds of studies needed to address these knowledge gaps and careful attention to tailoring outreach efforts and setting exclusion criteria will be key to increasing the participation of underrepresented populations. For example, exclusion of individuals with comorbidities may disproportionately disqualify minorities (Mount et al., 2012). Outreach will need to begin with engagement of the relevant communities to better understand their needs, concerns, and resource limitations. Attention also is necessary to developing interventions and messages that are culturally and linguistically appropriate (Johnson, 2016).

CONCLUSION: Recruiting study populations that better reflect the distributions of race, ethnicity, education, and socioeconomic status in the general population would help ensure the generalizability of clinical trial results to traditionally underrepresented populations.

BEGIN MORE INTERVENTIONS AT YOUNGER AGES AND HAVE LONGER FOLLOW-UP PERIODS

Although CATD is commonly understood to be a disease of older adults, an increasing body of evidence generated by epidemiologic studies

suggests that neurological changes associated with disease may in fact start in midlife, decades before the onset of symptoms (Ritchie et al., 2015). Thus, MCI and CATD develop over a long period of time, often in conjunction with other comorbid diseases. These findings indicate that intervention studies restricting enrollment to elderly cohorts may be misaligned with the optimum life-stage window for prevention, and interventions targeting risk factors for cardiovascular disease (e.g., blood pressure, diet, activity levels) may be more effective if initiated earlier in life. It should be acknowledged, however, that even if the preventive effects of an intervention are optimized when it is initiated in midlife,[2] the intervention could have other effects (e.g., stabilization or even reversal) when started at different life stages. Studies recruiting adults across a range of age groups could help elucidate these life-course effects.

The presumed latency period between onset of neurological changes and clinical symptoms has significant implications for the design of clinical trials, which if conducted in populations of middle-aged adults would require much longer follow-up periods to observe effects on CATD incidence and other cognitive outcomes. Indeed, the ACTIVE trial demonstrated the importance of long follow-up periods for evaluation of sustained intervention effects on cognitive performance, independent of measurements of disease incidence. In that trial, domain-specific improvements in cognitive function were measurable immediately following the intervention. However, there was a notable lag in the observable effects of cognitive training on instrumental activities of daily living—arguably one of the most meaningful types of measures for those concerned about cognitive decline—with differences from the control group apparent only 5 or 10 years later (Rebok et al., 2014; Unverzagt et al., 2012). The 10-year follow-up period employed in the ACTIVE trial was unusually good for this field.

Many of the studies analyzed in the AHRQ systematic review not only targeted older adults but were further limited by short (≤1 year) follow-up periods, which made it impossible to draw conclusions regarding the impact of the intervention under investigation on ARCD, MCI, and CATD. Recognizing that the optimal time to initiate an intervention aimed at preventing dementia is still unknown (and may vary across interventions) and that there is a nontrivial trade-off in terms of added costs and challenges arising from attrition, the committee believes that evaluating interventions in middle-aged adults and employing follow-up periods with durations similar to those used in the ACTIVE trial would benefit future studies and reduce the likelihood of falsely concluding that an intervention is not effective. Given the practical difficulties and barriers associated with conducting

[2]Different age windows are used in studies enrolling participants in midlife, generally ranging from ages 35 to 65.

longer studies, emphasis on integrating cognitive outcome measures into planned studies targeting other conditions that also represent dementia risk factors (i.e., add-on studies) from the beginning will be important. Inclusion of biomarkers as intermediate outcomes also may be of value when evaluating interventions initiated in midlife. Both of these strategies are discussed later in this chapter.

To address the concerns about attrition (mortality and loss to follow-up) that naturally arise with long-term studies, especially those on populations prone to dementia, such studies would benefit from taking full advantage of current knowledge regarding enhancing adherence to prevent attrition, as well as analytical methods for addressing the potential bias associated with higher attrition rates. Effective strategies for retaining study participants identified in recent reviews include offering incentives (often financial); using systematic methods for contacting subjects and scheduling visits (e.g., follow-up reminders); and offering alternative data collection methods, sites, or times for studies requiring in-person visits (Booker et al., 2011; Brueton et al., 2014; Robinson et al., 2007). Furthermore, such statistical methods as propensity scores, inverse probability weighting, multiple imputation, and modeling of nonresponse may prove to be useful in gauging the sensitivity of findings to lost follow-up (NRC, 2010). Many RCTs now routinely report results from such analyses. Mechanisms for including this information in evaluations of the quality of evidence from studies in systematic reviews would be of value.

Another important consideration in the design of longitudinal studies is the duration of the intervention itself. For some interventions—particularly those targeting healthier lifestyles, such as increased physical activity, improved diet, or participation in cognitively stimulating activities—it may be desirable for study participants to adhere to the intervention indefinitely. In such cases, follow-up at multiple testing points would require an assessment of adherence in addition to the measurement of outcomes. Statistical methods for assessing the mediating effects of adherence and sharpening the causal effects of an intervention may also be useful here (Emsley et al., 2010; Richiardi et al., 2013).

CONCLUSION: Starting interventions at younger ages and lengthening study follow-up periods may increase the likelihood of detecting a beneficial effect on preventing cognitive decline and dementia in future studies, as well as aid in identifying interventions that are not helpful.

USE CONSISTENT COGNITIVE OUTCOME MEASURES ACROSS TRIALS TO ENABLE POOLING

Variability in outcome measures employed across different studies has previously been recognized as a significant challenge to evaluating the effects of interventions on cognitive changes over time (IOM, 2015). As noted in the AHRQ systematic review, variability in the criteria used to define cognitive outcomes (e.g., scores on brief cognitive tests, self- or informant-reported complaints of cognitive impairment), as well as the multiplicity of tests used to measure cognitive performance,[3] complicates efforts to conduct meta-analyses and precludes quantitative pooling of results. The committee therefore concurs with the suggestion in the AHRQ systematic review that future research in the field would benefit from the use of formal diagnostic guidelines for measuring incident CATD and consistent batteries of validated tests for assessing cognitive function. Harmonizing test batteries, which would help support comparison and pooling across studies, without mandating the use of a single specific test is also a recommendation of the 2016 Alzheimer's Disease-Related Dementias (ADRD) Summit (NINDS, 2016). The AHRQ systematic review notes as a precedent the development of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), which is widely used in clinical trials with cognition as an outcome and has improved consistency of methodology across studies (Kane et al., 2017).

The appropriate analysis and interpretation of results of intervention studies depend on the collection of standardized measures at the time of study initiation to assess baseline cognitive status. Not only does this enable investigators to compare changes from baseline between intervention and control arms, but it also may inform the inclusion/exclusion of study participants. Since the effect and efficacy of interventions may differ in cognitively normal and cognitively impaired populations, interventions often are tested in these two populations separately. In a number of studies included in the AHRQ systematic review, however, baseline status was not assessed, or investigators relied on subjective (self- or informant) reports of cognitive status, which is a suboptimal substitute for objective measurements. Rigorous assessment of baseline status requires attention in future trials aimed at assessing the effect of interventions on preventing cognitive decline and dementia, particularly in the design of add-on studies.

[3]To facilitate analysis, the AHRQ systematic review grouped neuropsychological tests into broad categories based on what they were being used to measure (e.g., executive function, memory). However, these classifications were acknowledged to be somewhat arbitrary, as some tests could have been assigned to multiple domains.

CONCLUSION: The development and use of consistent cognitive outcome measures would enable comparison across studies and pooling of data in meta-analyses. Routine collection of baseline data using such measures is needed to properly assess the effectiveness of interventions.

INTEGRATE ROBUST COGNITIVE OUTCOME MEASURES INTO TRIALS WITH OTHER PRIMARY PURPOSES

Many of the targets for prevention of cognitive decline and dementia are also targets for prevention of cardiovascular and metabolic diseases (which themselves are known risk factors for dementia, as discussed in Chapter 2), creating opportunities to include cognitive outcome measures in clinical trials for interventions targeting these other conditions. The AHRQ systematic review does note a need for clinical trials explicitly designed to study interventions targeting the prevention, delay, and slowing of MCI and CATD. The committee agrees with this assessment but, recognizing the many practical reasons why large primary trials addressing cognition alone are unlikely to be undertaken (e.g., requirements for very long follow-up periods with associated risk of attrition and sample sizes large enough to enable detection of changes in disease incidence, as discussed above), believes that adding cognitive measures to other trials offers important opportunities to expand the evidence base. This view is consistent with the recommendation made at the 2016 ADRD Summit (NINDS, 2016). Yet while there are economic efficiencies to be gained from add-on studies relative to stand-alone cognition trials (e.g., avoidance of cohort recruitment costs), the addition of cognitive outcomes to a trial entails added cost and effort. Thus, there should be a compelling reason based on observational studies to think that the intervention being studied could also yield benefits for cognition.

In addition, a thoughtful, a priori study design is critical to the successful execution of add-on studies. Otherwise, the results for cognitive benefit may not be definitive, and there is a risk of detracting from the primary aim of the study. Challenges in interpreting results from add-on studies noted in the AHRQ systematic review—unsophisticated outcome measures, a lack of baseline measurements, failure to assign subjects randomly—generally arose from adding cognitive measures post hoc instead of building them carefully into the initial study design. Interinstitute communication within NIH and a standardized approach for a priori planning of cognitive add-on studies, including power considerations, would help overcome issues encountered in previous ancillary studies of cognition.

Cognitive outcome measures have been integrated into a number of antihypertension trials. For example, the Systolic Blood Pressure Interven-

tion Trial: Memory and Cognition in Decreased Hypertension (SPRINT-MIND) substudy of the Systolic Blood Pressure Intervention Trial (SPRINT) (discussed in Chapter 2), which prespecified secondary outcomes related to dementia and MCI (Ambrosius et al., 2014), could be considered a paradigm for future add-on studies. Although a study that included cognitive outcomes as an ancillary measure might not be sufficiently powered to detect dementia prevention effects, use of uniform cognitive measures (discussed earlier in this chapter) would enable pooling of results.

CONCLUSION: Integrating cognitive outcome measures into trials with other primary purposes is a cost-effective means of evaluating the effects of some interventions for preventing cognitive decline and dementia, but it is important to design such studies carefully a priori.

INCLUDE BIOMARKERS AS INTERMEDIATE OUTCOMES

Given the late onset and relative infrequency of dementia diagnoses in the population, long-duration studies with very large sample sizes are required to detect an effect of an intervention on dementia incidence (see Chapter 2). Therefore, the identification and use of biomarkers[4] (e.g., brain volume, brain amyloid accumulation) as intermediate outcomes predictive of cognitive decline and dementia is of significant interest, and may allow investigators to conduct smaller and shorter studies while also increasing confidence that an observed result is having a meaningful impact on brain function. To the degree that biomarkers can accurately reflect or predict cognitive function, improvement in biomarker measures could suggest that an intervention is slowing cognitive decline. It should be emphasized, however, that the relationship between biomarkers and clinical outcomes is not always transparent, and changes in biomarkers may not necessarily translate to observable cognitive benefits (Sano, 2016).

A wide range of biomarkers under development may be useful for identifying underlying pathologies across the continuum of dementia and enrich clinical trials (Mattsson et al., 2015). Blood-based biomarkers could be particularly useful since they would allow more frequent and inexpensive assessment in longitudinal studies (O'Bryant et al., 2017). Among the novel

[4]The term *biomarkers*, as used in the context of the AHRQ systematic review, refers to the biological targets of brain imaging and laboratory tests used to assess changes in brain structural characteristics and activity as proxies for functional abnormalities (Kane et al., 2017). Importantly, these are not necessarily biomarkers for Alzheimer's disease. All biomarkers reported in the studies included in the AHRQ systematic review were based on brain imaging techniques, specifically, magnetic resonance imaging (MRI) or positron emission tomography (PET) scans.

biomarkers under development—all of which have pros and cons for this purpose—are measures of tau deposition (Villemagne et al., 2015), hypometabolism (Mosconi et al., 2008), axonal damage (Mayo et al., 2017), synaptic dysfunction (Hellwig et al., 2015), neuronal damage (Tarawneh et al., 2012), inflammation (Gispert et al., 2016a,b), and changes in functional brain networks (Binnewijzend et al., 2014). Several Cochrane reviews of the literature have sought to systematically assess the use of biomarkers—cerebrospinal fluid beta-amyloid (Ritchie et al., 2014), cerebrospinal fluid tau (Ritchie et al., 2017), and positron emission tomography (PET) imaging (Zhang et al., 2014)—for accurately detecting and diagnosing future dementia in people with MCI. None of the biomarkers reviewed were found to be appropriate for current clinical practice, and all required additional research.

The utility of biomarkers as intermediate outcomes in clinical trials is an active and evolving area of research. Given the potential of valid biomarkers to reduce the length and size of clinical trials (with associated impacts on feasibility and cost), the committee supports continued efforts to further elucidate their relationship to cognitive outcomes. In fact, this is an objective of several studies currently under way, including the Mediterranean-Dietary Approaches to Stop Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) diet trial (Morris et al., 2014, 2015a,b) and the Exercise in Adults with Mild Memory Problems (EXERT) study on the effects of aerobic exercise in adults with mild memory impairment (NIA and Wake Forest University, 2017). Measuring a limited number of biomarkers in subsets of study participants can reduce the cost associated with data collection and analysis. The collection of numerous indicators is to be avoided without clear theoretical or empirical justification, as it not only would add significantly to the cost of trials but also would have implications for analysis in terms of correction for multiple comparisons. Given the current uncertainty regarding the value of biomarkers, drawing blood for future analysis would enable revisiting them as the field evolves.

CONCLUSION: The inclusion of biomarkers as intermediate outcomes has the potential to reduce significantly the length and cost of future clinical trials for interventions to prevent cognitive decline and dementia. However, this approach requires further development of a set of biomarkers that are useful for tracking response to an intervention or for predicting longer-term outcomes.

CONDUCT LARGE TRIALS IN ROUTINE CLINICAL PRACTICES OR COMMUNITY SETTINGS

The meta-analysis from the AHRQ systematic review provides an indication of intervention domains that offer the greatest promise for preventing cognitive decline and dementia. As discussed in Chapter 2, however, individual interventions within each of these domains were quite variable, and a number of questions remain regarding the effectiveness of specific interventions, including targets and components. Large RCTs that are conducted in clinical care or community settings—sometimes referred to as pragmatic trials[5]—lend themselves well to head-to-head comparisons of interventions already shown to have efficacy, and also offer an opportunity to assess dose–response relationships and optimal timing of delivery. The PreDIVA multidomain trial[6] (Moll van Charante et al., 2016) provides an example of how an intervention can be compared with standard care in the context of a pragmatic trial (in this case, a cluster randomized trial as entire primary care practices, not individuals, were randomized). Leveraging the existing clinical care infrastructure, including electronic medical records, allows for economic efficiencies, particularly in subject recruitment and follow-up. Additionally, because these trials are conducted with more inclusive cohorts, their results can be expected to be more generalizable than those of traditional RCTs (Patsopoulos, 2011), and may better inform clinicians and the public as to how an intervention will perform under their specific life conditions (e.g., in people on similar medication regimes). Pragmatic trials may therefore be an efficient means of addressing knowledge gaps raised in the AHRQ systematic review, such as optimal blood pressure targets in antihypertensive trials and the comparative effectiveness of specific cognitive training applications.

CONCLUSION: Large trials designed to test the effectiveness of an intervention in broad, routine clinical practices or community settings may be more cost effective than traditional RCTs for comparative effectiveness research for interventions that have already been shown to have beneficial effects on cognition.

[5]Unlike traditional RCTs, which assess the efficacy of interventions under highly controlled circumstances, pragmatic trials are designed to measure effectiveness, or how an intervention performs when used in usual conditions of care and in varied populations more reflective of the real world (Roland and Torgerson, 1998).

[6]In the PreDIVA trial, which is described in more detail in Chapter 4, the intervention group met three times per year with nurses who provided medical and nonmedical assistance to subjects to reduce vascular risk factors. The study's primary outcome was all-cause dementia (Moll van Charante et al., 2016).

RECOMMENDATION

CONCLUSION: The absence of high-strength evidence supporting beneficial effects on cognitive decline and dementia for interventions included in the AHRQ systematic review likely results in part from methodological limitations of past intervention studies. Recognizing the limited pool of resources available for research on ARCD, MCI, and CATD, future research investments will have the greatest impact if directed to a limited number of well-designed trials of sufficient power and duration.

Recommendation 2: Methodological Improvements

When funding research on preventing cognitive decline and dementia, the National Institutes of Health and other interested organizations should improve the methodologies used in this field by supporting studies that to the extent possible

- **identify individuals who are at higher risk of cognitive decline and dementia and tailor interventions accordingly**
- **increase participation of underrepresented populations to study intervention effectiveness in these populations**
- **begin more interventions at younger ages and have longer follow-up periods**
- **use consistent cognitive outcome measures across trials to enable pooling**
- **integrate robust cognitive outcome measures into trials with other primary purposes**
- **include biomarkers as intermediate outcomes**
- **conduct large trials designed to test the effectiveness of an intervention in broad, routine clinical practices or community settings**

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4

PRIORITIES FOR FUTURE RESEARCH

As discussed in previous chapters, none of the interventions evaluated in the Agency for Healthcare Research and Quality (AHRQ) systematic review met the criteria for being supported by high-strength evidence, based on the quality of randomized controlled trials (RCTs) and the lack of consistently positive results across independent studies (Kane et al., 2017). This underscores the need for further research on interventions that can delay or slow age-related cognitive decline (ARCD) and prevent, delay, or slow the development of mild cognitive impairment (MCI) and clinical Alzheimer's-type dementia (CATD) (referred to throughout this report by the shorthand "prevent cognitive decline and dementia").

In this chapter, the committee discusses priorities for future research on the three interventions highlighted in Chapter 2—cognitive training, blood pressure management, and increased physical activity—which is essential to enhance confidence in the effectiveness of these interventions and inform future communications with the public. The committee also identifies other interventions that, based on data from RCTs and observational studies, as well as a strong argument for biological plausibility, appear to be potentially promising and worth prioritizing in future research. In addition, this chapter identifies those specific interventions that the committee believes should be of lowest priority for future research because the AHRQ systematic review found no evidence of any benefit and some low-strength evidence to suggest that these interventions do not prevent cognitive decline or dementia or, in one case, some evidence of increased risk of harm.

It would be impractical for the committee to comment on every intervention that has been (or in the future could be) tested for its effect on cog-

nitive outcomes. Therefore, the discussion here is focused on those classes of interventions that appear to be promising. For ease of discussion, the identified research priorities are organized by class of intervention. However, the committee realizes that there are countless permutations of interventions that could fall within each of those domains. Recognizing that a number of intervention studies are planned or under way, far more research is needed to determine the optimal form (including dose and delivery schedule) of any specific intervention, as well as the potential for synergies when it is combined with other interventions. This chapter begins by addressing these cross-cutting considerations for intervention design, including the issue of adherence. It will be important for all future research on these interventions to attend to these design considerations in addition to the cross-cutting methodological recommendations presented in Chapter 3.

CROSS-CUTTING INTERVENTION DESIGN CONSIDERATIONS

In considering research priorities for specific intervention domains, the committee identified a number of recurring issues. Some, such as those related to optimal dose and schedule, apply to intervention research in all fields, but others are more particular to interventions focused on preventing cognitive decline and dementia. These cross-cutting issues are addressed in the sections below:

- Can combining interventions in a multimodal approach improve cognitive outcomes beyond what can be achieved through single interventions?
- For a given intervention, is there an optimal dose, delivery schedule, intervention duration, and timing that maximizes cognitive outcomes?
- How can adherence to an intervention best be promoted and measured?

As future research strategies are developed for the priority intervention domains discussed in this chapter, it will be important to incorporate each of these considerations.

Multimodal Approaches

Multimodal interventions utilize a combination of components—such as physical activity, diet, social engagement, and cognitive training—that target multiple dementia risk factors simultaneously. Although most available research on preventing cognitive decline and dementia reflects the quest for a single strong solution, multimodal approaches may be more effective than single-component interventions. ARCD, MCI, and CATD are

complex conditions with multiple, co-occurring risk factors (Etgen et al., 2011; Gottesman, 2016), and targeting several putative disease pathways simultaneously may result in synergistic effects and be more effective across a range of risk factor profiles relative to more narrowly focused interventions. This approach also may more closely resemble the real world, given that individuals are likely to engage in multiple activities that can help maintain cognitive function and reduce dementia risk (Verghese, 2016). At the same time, however, having interventions with multiple components makes it difficult to tease out the contributions of each and determine which are critical to its success.

Many multimodal RCTs conducted to date have been small and of short duration (Hars et al., 2014; Napoli et al., 2014; van de Rest et al., 2014), and thus not optimally designed for the measurement of long-term cognitive outcomes such as ARCD and CATD incidence. However, results from several larger and longer-duration multimodal studies have recently been reported. The most promising published data come from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a large trial of an intervention consisting of physical activity, nutrition counseling, cognitive training, and management of vascular risk factors that was carried out in a population of adults at risk for cardiovascular disease. Although the effect of the intervention on dementia incidence was not measured, the intervention group showed significantly improved cognitive performance after 24 months compared with an attention control group (Ngandu et al., 2015). In contrast, the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial, which had a median follow-up period of 6.7 years, failed to show that a multimodal intervention targeting the reduction of cardiovascular risk factors[1] improved cognitive performance or reduced dementia incidence in older adults (aged 70 to 78) with normal cognition (Moll van Charante et al., 2016). The Multidomain Alzheimer's Prevention Trial (MAPT), as described by Vellas and colleagues (2014), evaluated a multidomain intervention consisting of nutrition counseling, physical exercise, and cognitive stimulation, alone or in combination with omega-3 fatty acid (DHA) supplementation, in elderly people with memory complaints. Recently published results showed that after 3 years there were no significant differences in cognitive decline between intervention and placebo groups, but results from exploratory subgroup analyses suggest that the multimodal intervention may help slow cognitive decline in some high-risk groups (Andrieu et al., 2017).[2] Given that the effectiveness of a multimodal intervention will depend on the components it includes

[1]In this study, the intervention group met three times per year with nurses who provided advice on healthy lifestyle and optimized treatments for hypertension, dyslipidemia, and type 2 diabetes as needed (Moll van Charante et al., 2016).

[2]This information has been updated since the prepublication report was released.

and baseline levels of risk factors, as well as other factors (e.g., dose, adherence, schedule), multiple independent studies testing the same combination of component elements will be necessary before strong conclusions can be drawn regarding the effectiveness of any specific multimodal intervention.

Interest in multimodal approaches is likely to grow as more studies with positive results are published. For those single-component interventions that have shown promise (e.g., cognitive training, physical activity), multimodal studies can assess whether there is an added benefit in the presence of one or more other component interventions. Ongoing and future RCTs may provide a better understanding of the optimal combinations of component elements. Data from large observational studies, such as the Framingham Heart Study, which examines temporal trends in dementia incidence and identifies key risk factors (Satizabal et al., 2016), also may be helpful for informing the development of multimodal interventions that target multiple risk factors simultaneously.

Going forward, it will be important to design trials when possible in a way that allows for the separation of effects that result from the individual components. Studies that compare cognitive outcomes for interventions both alone and in combination with others in a multimodal format may help elucidate the potential for synergistic effects (Martin et al., 2007; Napoli et al., 2014). Studies with a factorial design, such as that used in the Mental Activity and Exercise (MAX) trial (Barnes et al., 2013), may yield results that are more informative regarding the value of multimodal versus single-component interventions. For some multimodal interventions, however, it may be more difficult to isolate the components. For example, the Baltimore Experience Corps intervention trial, which trained older adults to work as volunteers in elementary schools, was intentionally designed to boost a broad array of cognitive abilities (e.g., memory, planning, organizational skills), increase physical activity, and provide opportunities for social engagement in a complex, real-world environment (Carlson et al., 2008). The pilot study, which was not included in the AHRQ systematic review because of a high risk of bias from attrition, showed that the intervention group demonstrated improved memory and executive function, while declines were observed in a waitlist control group. It is not possible, however, to separate out the effects of increased cognitive stimulation, physical activity, and social engagement for this complex intervention, highlighting the potential challenges of a multimodal approach.

Dose, Delivery Schedule, Intervention Duration, and Timing

The optimization of dose, delivery schedule, and intervention duration is a common challenge for intervention research. The evaluation of multiple conditions for each of these parameters can rapidly increase the

complexity and cost of an RCT, but until multiple permutations have been tested, it is not clear whether a negative result is indicative of an ineffective intervention or one or more of these parameters being suboptimal. For some interventions, there may be a clear biological reason for the selection of ranges for each of these parameters; for others, however, the process is one of trial and error and requires consideration of feasibility. As discussed in Chapter 3, pragmatic clinical trial designs can offer a more efficient and cost-effective means of comparing such conditions as dose and delivery schedule for interventions that have already shown some promise.

The timing of an intervention relative to the onset of pathophysiological changes (which may occur at different ages in different people) also can have a large impact on the likelihood of observing a benefit. This parameter is especially relevant for interventions targeting cognitive decline and dementia given that degeneration occurs before symptoms manifest and, as discussed in Chapter 3, some interventions may need to be initiated long before symptoms are apparent (e.g., in midlife) to prevent or delay disease.

Adherence

One final cross-cutting consideration for future intervention research studies is the challenge of promoting adherence to interventions, as lack of adherence may reduce the observed effect of an intervention on cognitive outcomes. In several studies, the strongest effect for an intervention was observed in subgroups of individuals who were adherent (Moll van Charante et al., 2016; Singh et al., 2014), highlighting the challenges associated with poor adherence that affect assessment of efficacy in the study setting. This is an important issue not only for evaluating the effectiveness of an intervention in the context of a study but also for developing strategies for communicating with the public about the value of specific interventions.

Many factors may affect adherence, including opportunities for social interaction and even environmental conditions (Dalton et al., 2016). Cognitive impairment raises additional barriers, particularly for medication adherence (Campbell et al., 2012). A number of strategies can be used to improve adherence, including providing reminders, simplifying treatment regimens, and engaging family members as appropriate (Atreja et al., 2005). A recent intervention approach—just-in-time adaptive interventions, which are being used to drive health behavior changes and focus on providing the right type and amount of support at the right time by considering an individual's specific conditions (Nahum-Shani et al., 2016)—may have particular utility in addressing this challenge.

HIGHEST-PRIORITY RESEARCH NEEDS TO STRENGTHEN SUPPORT FOR COMMUNICATING WITH THE PUBLIC ABOUT INTERVENTIONS WITH ENCOURAGING EVIDENCE

The three classes of interventions discussed in Chapter 2—cognitive training, blood pressure management for people with hypertension, and increased physical activity—are supported by encouraging but inconclusive evidence. Before developing public health campaigns that strongly encourage the adoption of these interventions for the purpose of maintaining cognitive function, additional research is needed to further understand and gain confidence in their effectiveness. Research priorities specific to each of these intervention domains are discussed in the sections below.

Cognitive Training

A beneficial effect of cognitive training in delaying age-related cognitive decline is supported by moderate-strength evidence (Kane et al., 2017). As discussed in Chapter 2, however, the existing body of evidence is limited, and the AHRQ systematic review findings were based primarily on a single large and long-duration study—the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial.[3] Because of the many uncertainties about the ACTIVE trial (e.g., which components of the intervention were important, the high attrition for 10-year follow-up results, multiple comparisons), replication by additional trials (both costly and lengthy) may not be successful. Before embarking on replication, it is important to determine how the complex ACTIVE trial of a relatively short-duration intervention had such an apparently long-lasting effect in some domains but not others. This will be challenging to accomplish after the fact, but may be feasible using newer statistical methods developed for clinical trials with attrition and mediation effects provided adequate data are available. Moreover, given the data from observational studies suggesting that education (Beydoun et al., 2014) and less structured activities such as playing games, engaging in craft activities, and computer use (Krell-Roesch et al., 2017) also may prevent cognitive decline and dementia, comparative effectiveness studies of different types of cognitive training exercises, including those used in the ACTIVE trial and other cognitively stimulating activities, are needed. Recognizing that the robust kinds of long-term studies required to address current knowledge gaps are difficult to carry out, the committee

[3]This trial is described in more detail in Chapter 2, but briefly, participants were divided into reasoning, memory, and speed-of-processing groups and trained using different exercises over 5 to 6 weeks, with booster sessions similar to the initial training being administered 11 months after the initial training and again after 3 years. Participants were followed for 10 years (Jobe et al., 2001).

identified the following specific research questions that, if answered, would strengthen the evidence base for cognitive training interventions and inform the design of future trials. Answering these questions will require multidisciplinary research integrating social and behavioral science, psychology, and education.

- Which types of cognitive training activities are likely to have the greatest impact on ARCD? Do structured cognitive training interventions such as those used in the ACTIVE trial improve cognitive performance compared with other cognitively stimulating activities (e.g., reading, playing cards)?
- Which specific intervention elements, or combination of elements, used in the ACTIVE trial are responsible for the observed positive and long-term impacts on cognitive performance? For example, is it important to instruct participants in the relevance of training exercises to instrumental activities of daily living? Did the environment in which the training took place (e.g., at home alone or in a more social group setting) have an impact on the outcomes?
- Can cognitive training prevent, delay, or slow MCI and CATD in addition to delaying ARCD?
- What is the role of social engagement as part of a cognitive training intervention? Does a social aspect make cognitive training interventions more enjoyable and thereby have an effect on adherence?
- Are there any adverse effects of computer-based cognitive training applications similar to those that have been well documented in the computer gaming literature? For example, are the risks of addiction similar or reduced in an older-adult population?

Blood Pressure Management

As described in Chapter 2, the committee emphasizes that further research on the effectiveness of blood pressure management in preventing cognitive decline and dementia is a priority. A definitive answer may never be obtained through RCTs since a placebo-controlled trial may not be considered ethical in a hypertensive population, given the known cardiovascular benefits of blood pressure management. In addition, the large secular trend toward reduced dementia incidence and cardiovascular risk factors complicates efforts to study this question. Recent and ongoing RCTs, such as the Heart Outcomes Prevention Evaluation-3 (HOPE-3) (American College of Cardiology, 2016; Lonn et al., 2016), have included only relatively low-risk groups, making it challenging to power the trials adequately to identify a treatment effect. Moreover, blood pressure targets optimal for cardiovascular disease outcomes (e.g., prevention of stroke and/or heart

attack) likely will take precedence in such studies, and these targets may not be best for preventing cognitive decline and dementia (even vascular dementia). Ultimately, then, treatment recommendations may have to be based on data other than rigorous evidence derived from RCTs.

Despite these challenges, further research—and analyses of the results of studies already completed and under way—could, by improving understanding of populations most likely to benefit from treatment and guiding optimal blood pressure targets, help tailor clinical guidance and communications with the public. The question of an optimal blood pressure target for cognitive outcomes, for example, may be informed by the ongoing Systolic Blood Pressure Intervention Trial: Memory and Cognition in Decreased Hypertension (SPRINT-MIND) substudy of the Systolic Blood Pressure Intervention Trial (SPRINT), which is designed to examine the cognitive effects of more intensive antihypertensive therapy than is currently recommended for cardiovascular disease outcomes (The SPRINT Research Group, 2015). Given the documented problems with undertreatment for hypertension (Bromfield et al., 2014; Navar-Boggan et al., 2014), it will be particularly important to address adherence issues. Going forward, priority research questions include the following:

- Which populations would benefit most from blood pressure management? Are there some who might be harmed by treatment for hypertension?
- What is the optimal blood pressure management approach at different ages (e.g., midlife, late life, very late life) given the evidence on age-related heterogeneity in treatment effects?
- Is there an optimal treatment level (blood pressure target) for cognitive outcomes, and should targets differ among clinical subgroups?
- What is the comparative effectiveness of different classes of antihypertensive treatments (e.g., angiotensin II receptor blockers [ARBs] versus other treatments)?
- Does a focus on blood pressure in isolation from other vascular risk factors limit the impact on cognitive outcomes?

Increased Physical Activity

As described in Chapter 2, the data on the effects of increased physical activity on cognitive performance are promising. Most studies published to date have been of short duration, so one pressing research priority is to determine whether physical activity has long-term cognitive benefits in addition to the short-term benefits observed in some past RCTs. Moreover, it is unclear from existing studies whether there is an optimal form of physical activity (e.g., aerobic activity, resistance training, or both in combination)

for reducing the risk of cognitive decline and dementia, and whether some populations are more likely to benefit. The AHRQ systematic review found some indication that physical activity may reduce the rate of cognitive decline in individuals with MCI, but the data were not conclusive. The ongoing Exercise in Adults with Mild Memory Problems (EXERT) trial may further elucidate any benefit of aerobic activity in this population. Additional research addressing the following key questions would help strengthen and tailor communications with the public on the effects of increased physical activity on preventing cognitive decline and dementia:

- Which physical activity regimens are most promising for providing cognitive benefits?
- How does the beneficial effect of physical activity vary among subpopulations (e.g., adults with MCI or such comorbidities as diabetes)? Are there some groups for whom physical activity is ineffective, or even harmful, with respect to cognitive function?
- Are the cognitive benefits of physical activity sustained if the intervention is discontinued?

OTHER PRIORITY RESEARCH AREAS

There are a number of interventions discussed in the AHRQ systematic review for which the current evidence base from RCTs is insufficient to draw any conclusions regarding their impact on ARCD and the incidence of MCI and CATD. However, based on additional data from observational studies, knowledge of dementia risk factors, and/or a strong argument for biological plausibility, the committee identified the following intervention domains as priorities for future research:

- new antidementia treatments that can delay onset or slow disease progression
- diabetes treatment
- depression treatment
- dietary interventions
- lipid-lowering treatment
- sleep quality interventions
- social engagement interventions
- vitamin B_{12} plus folic acid supplementation

For each of these intervention domains, the sections below summarize the findings from the AHRQ systematic review, other relevant evidence suggesting that these interventions might be promising, and potential areas for future research. A summary of the evidence for other interventions not

identified by the committee as research priorities can be found in the AHRQ systematic review (see Appendix A).

The Search for New Antidementia Treatments to Delay Onset or Slow Disease Progression

Given the expected rise in dementia prevalence in some regions of the world and as life expectancy continues to increase (discussed in Chapter 1), there is a critical need for pharmacological treatments that, though not preventing disease, can delay onset of dementia or slow progression of cognitive impairment in those with ARCD or MCI. Although such treatments are not prevention interventions in the strict sense, they can be thought of as secondary or tertiary prevention. In the past decade, the emphasis of drug development for Alzheimer's disease has shifted from treatments that address symptoms (e.g., acetylcholinesterase inhibitors) to a search for such disease-modifying drugs, which currently is a very active area of research. However, no disease-modifying treatments have yet shown a significant drug–placebo difference in phase III studies (Siemers et al., 2016). A recent analysis of clinical trials registered on ClinicalTrials.gov found that of 24 agents being studied in phase III trials, 17 were being tested for disease-modifying effects and 7 for symptomatic effects, and among 45 agents in phase II trials, 30 were disease-modifying and 15 were symptomatic (Cummings et al., 2016a). The drugs currently being evaluated for disease modification across all phases of clinical trials target predominantly amyloid pathology. While the amyloid cascade hypothesis remains the dominant conceptual model of Alzheimer's disease pathogenesis (Hardy and Higgins, 1992), the lack of success of antiamyloid drugs has led many investigators in the field to question whether targeting other aspects of Alzheimer's disease pathophysiology might lead to additional mechanistically informed and more effective treatments (Cummings et al., 2016b; Hardy and De Strooper, 2017).

Future Research Questions and Directions

Antidementia treatments evaluated in studies included in the AHRQ systematic review were limited to acetylcholinesterase inhibitors, which were assessed for effects on cognitive performance in people with subjective complaints of cognitive loss or diagnosed MCI, and on progression from MCI to CATD. This class of antidementia treatments is discussed later in this chapter along with other interventions with some evidence suggesting no benefit. Future drug development aimed at delaying onset or slowing disease progression will be aided by a deeper understanding of the biological basis of Alzheimer's disease, including the multiple mechanistic

pathways that interact to give rise to the disease (Schadt et al., 2014). Ongoing efforts to identify biomarkers that can inform the development of disease-modifying therapies and identify high-risk populations that may be targeted with such treatments, along with increasingly sophisticated clinical trial methodologies that can enhance the trials' sensitivity and power (discussed further in Chapter 3), will help accelerate drug development. Such advances in knowledge and tools may help address the following priority research questions for antidementia treatments:

- Are there nonamyloid metabolic cascades that, if disrupted by a pharmacological agent, would halt, slow, or reverse disease progression in individuals with ARCD or MCI?
- At what stage in the process of neurobiological changes leading to cognitive decline and dementia do antidementia treatments need to be administered to optimize cognitive outcomes?

Diabetes Treatment

Diabetes is associated with an increased risk of dementia (Cheng et al., 2012; Ott et al., 1999; Rawlings et al., 2014). Moreover, high insulin levels, an important antecedent and companion of type 2 diabetes, may increase amyloid accumulation in the brain and thereby increase the risk of Alzheimer's disease (Craft and Watson, 2004). The evidence linking diabetes with ARCD, MCI, and CATD suggests that diabetes prevention in the general population and among those at risk (e.g., individuals with prediabetes), as well as good diabetes treatment in those who have been diagnosed (i.e., controlling glycemia, lipids, and blood pressure), may have a role in preventing cognitive decline and dementia (Luchsinger, 2010). According to a 2011 study, nearly 175,000 cases of Alzheimer's disease in the United States were attributable to diabetes, and a 25 percent reduction in diabetes prevalence could potentially have prevented 40,000 of these cases (Barnes and Yaffe, 2011). The prevalence of diabetes (and obesity), however, is increasing, threatening to reverse the apparent decline in dementia rates in some high-income countries (Larson et al., 2013).

Diabetes prevention and treatment include both nonpharmacologic and pharmacologic approaches. The former approaches use lifestyle changes (e.g., increased physical activity and reduced caloric intake) to induce weight loss. Medications used in diabetes treatment include those that increase insulin secretion or raise insulin levels (e.g., through treatment with insulin itself), as well as medications with insulin-sensitizing effects, such as metformin, pioglitazone, and rosiglitazone.

AHRQ Systematic Review Findings and Discussion

As summarized in Box 4-1, the AHRQ systematic review found little evidence from intervention studies to suggest that diabetes treatment in adults with MCI or normal cognition can prevent cognitive decline and dementia. Two RCTs evaluated the effectiveness of different insulin-sensitizing medications—pioglitazone treatment in obese older adults without diabetes (Hildreth et al., 2015) and metformin treatment in overweight nondiabetic and diet-controlled diabetic adults (Luchsinger et al., 2016)—versus placebo in a study population with MCI. Neither study found significant between-group differences in global measures of cognition or for the majority of domain-specific tests; however, these studies may have been too small and of inadequate duration to have observed an effect of the interventions. Two substantially larger RCTs—the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial (N = 12,537) and the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial (N = 2,977)—compared the effects of intensive and standard glycemic control methods on cognitive outcomes in diabetic adults presumed to have normal cognition (Cukierman-Yaffe et al., 2014; Launer et al., 2011; Seaquist et al., 2013). Both were substudies of trials designed with primary cardiovascular disease outcomes. The ORIGIN study found no difference in the risk of probable incident cognitive impairment after 6 years. Neither study found any difference in cognitive performance between treatment arms. However, less decline in brain volumes in individuals with intensive glycemic control was observed in the ACCORD study (Launer et al., 2011).

BOX 4-1 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON DIABETES MEDICATION TREATMENT

- No studies reported on the effect of diabetes treatment on the risk of incident clinical diagnoses of MCI or CATD.[a]
- In middle-aged older adults with diabetes and presumed normal cognition, low-strength evidence shows intensive versus standard glycemic control had no significant effect on cognitive performance.

[a]Clinically diagnosed MCI and CATD were not included as outcome measures in diabetes intervention studies that met AHRQ inclusion criteria, although one study reported on probable incident cognitive impairment as determined by cognitive test performance or finding of dementia diagnosis on case report forms.
SOURCE: Kane et al., 2017.

For the ORIGIN trial, there was little difference in high glycated hemoglobin A1c (HbA1c) levels—a measure of glycemic control—between intensive and standard glycemic control groups (Gerstein et al., 2012), potentially explaining the lack of observed differences in cognitive outcomes between the two study arms. This was not the case for the ACCORD trial, which was designed to test whether very tight glycemic control (glycated hemoglobin <6 percent) versus usual care improved cardiovascular outcomes among persons with diabetes (Gerstein et al., 2008). In that trial, the intervention group demonstrated significantly improved glycemic control but with no meaningful improvement in cognitive outcomes, although a reduced level of brain atrophy was observed at 40 months (Launer et al., 2011). Of note, however, the intensive glycemic control arm was stopped prematurely because of increased mortality, which to date has not been explained. It is possible that what caused this increased mortality in the intensive glycemic control arm could also have had a detrimental effect on cognition, although this possibility is speculative. Since the level of control targeted in the ACCORD trial is not the standard of care, it remains unknown whether glycemic control following the current guidelines of the American Diabetes Association (glycated hemoglobin less than 7 percent, or less than 8 percent in frail persons) (ADA, 2016) results in better cognitive outcomes. The results of one RCT of diabetes control using telemedicine versus usual care, which followed the guidelines of the American Diabetes Association for glycemic control, suggest that improved glycemic control leads to less decline in global cognition compared with usual care (Luchsinger et al., 2011). However, the AHRQ systematic review considered this study to be at high risk of bias (attrition was not clearly reported, and participants were not blinded), so it was excluded from the review.

Another important limitation of RCT data on diabetes interventions is the so-called legacy effect (Chalmers and Cooper, 2008), referring to the observation that some of the cardiovascular benefits of diabetes-related interventions take many years, if not decades, to become apparent after the intervention has ended. This observation may be true for cognitive outcomes as well, indicating that follow-up periods much longer than those in previous studies may be needed to observe a cognitive benefit (see the discussion of this issue in Chapter 3), and further highlighting the value of longitudinal observational studies.

Supplemental Information and Considerations

Although results of RCTs of diabetes treatment for preventing cognitive decline and dementia have not been encouraging, other sources of evidence indicate that further study of such interventions is warranted. A meta-analysis by Cheng and colleagues (2012) estimates that the risk of

incident Alzheimer's disease increases by almost 50 percent in individuals diagnosed with diabetes. Furthermore, peripheral high insulin levels caused by insulin resistance are common in people with obesity, those with prediabetes, and those with type 2 diabetes. Peripheral high insulin levels may lead to increased accumulation of amyloid in the brain, one of the main pathologies of Alzheimer's disease (Craft and Watson, 2004). Thus, it is biologically plausible that a decrease in insulin levels through pharmacologic (insulin-sensitizing drugs) or nonpharmacologic (diet and exercise leading to weight loss) means could prevent cognitive decline and dementia (Luchsinger, 2010).

Weight loss through reduced caloric intake and increased physical activity is recommended to treat overweight and obese individuals with type 2 diabetes (ADA, 2017). Although lifestyle interventions targeting weight loss in adults diagnosed with or at risk for type 2 diabetes have not resulted overall in improved cognitive outcomes (Espeland et al., 2014; Luchsinger et al., 2015; Rapp et al., 2017), one study provides some evidence that a long-term weight loss intervention may benefit cognition among individuals who are overweight, but not obese. The large Action for Health in Diabetes (Look AHEAD) RCT compared 10 years of a lifestyle intervention that resulted in weight loss with a control condition of diabetes support and education. In overweight adults (i.e., those with a body mass index of 25 to 30 kg/m^2), random assignment to the intervention was associated with better cognitive function and a trend toward lower rates of MCI and CATD, but no benefits were seen among heavier individuals (Espeland et al., 2014, 2017a; Rapp et al., 2017). In addition, the lifestyle intervention was associated with better markers of brain atrophy and cerebrovascular disease. The Look AHEAD trial did not assess cognitive function prior to delivery of the intervention. For this reason, the study did not meet inclusion criteria for the AHRQ systematic review, and further study and replication are needed.

Future Research Questions and Directions

Given that diabetes is consistently identified as a risk factor for MCI and CATD, considerable interest remains in evaluating diabetes treatment as a potential intervention for the prevention of cognitive decline and dementia. Priority areas for research include the identification of optimal treatment targets (given data showing that intensive treatment is not effective), the modifying effects of other risk factors (e.g., obesity), and the relative effectiveness of different diabetes medications. Some studies now under way may help address some of these questions. Low-dose pioglitazone, a medication with more powerful insulin-sensitizing and lowering effects relative to metformin, is being tested to delay onset of MCI due to Alzheimer's disease among nearly 3,500 cognitively normal, elderly individuals (Budur

et al., 2015). The Glycemic Reduction Approaches in Diabetes (GRADE) study (Nathan et al., 2013) is comparing insulin-sensitizing and other treatments for early diabetes, and is assessing cognition longitudinally. The committee identified the following specific areas in which additional research may lead to a better understanding of the impact of diabetes treatment on cognitive outcomes:

- Is there an optimal treatment target level? Does optimal glycemic control as currently recommended by the American Diabetes Association prevent cognitive decline among people with diabetes?
- Does a comprehensive approach to diabetes management that includes multiple treatment modalities (e.g., exercise, control of blood pressure) have a greater impact on cognitive outcomes than approaches relying on a single strategy?
- How do obesity-related factors modify the effects of diabetes interventions on cognitive outcomes?
- What is the comparative effectiveness of insulin-sensitizing versus non-insulin-sensitizing diabetes treatments?
- Can cognitive benefits of diabetes treatment be detected by starting interventions earlier in the life course and following participants for longer periods?

Depression Treatment

A number of studies and reviews have linked depression to cognitive decline (Butters et al., 2004; Goveas et al., 2014) and dementia (Byers and Yaffe, 2011; Diniz et al., 2013; Ownby et al., 2006). Although the association between late-life depression and cognitive decline and dementia may be attributed, in part, to reverse causality (that cognitive decline leads to depression, rather than the reverse) and the long prodromal stage of dementia, reverse causality does not provide a good explanation for the twofold increase in risk of cognitive impairment and dementia associated with depression in midlife (Byers and Yaffe, 2011). Barnes and Yaffe (2011) estimate that as many as 15 percent of Alzheimer's disease cases in the United States and more than 10 percent of cases worldwide may be attributable to depression. Depression treatments include both pharmacologic treatments and nonpharmacologic approaches employing psychotherapy.

The mechanistic pathways mediating the effects of depression on cognitive decline and dementia are not well understood, but plausibly relate to the links among depression, chronic inflammation, and cerebrovascular disease. Diniz and colleagues (2013) note that the risk of vascular dementia associated with depression is higher relative to the risk of Alzheimer's disease. Depression also is associated with elevated levels of the stress-related

hormone cortisol, which is linked to atrophy of the hippocampus, a region of the brain with a critical role in learning and memory (Lee et al., 2002).

AHRQ Systematic Review Findings and Discussion

As indicated in Box 4-2, the AHRQ systematic review identified no RCTs for depression treatment meeting the inclusion criteria. Similar to some other intervention domains (e.g., blood pressure management, diabetes treatment), RCTs for depression treatment are challenging to design since it may not be appropriate to randomize study participants with depression to a placebo control group, given the known benefits of treatment. Although active treatment comparisons and add-on studies can be designed, such studies are still logistically challenging because of the requirement for a large study population and long follow-up period to detect changes in MCI and CATD incidence. Moreover, there is significant heterogeneity in responsiveness to treatment, and in contrast to antihypertensive and diabetes treatments, the effectiveness of which can be measured through blood pressure and glycated hemoglobin, respectively, there is no clear marker for easily determining whether a patient is responding to depression treatment.

Supplemental Information and Considerations

The association between depression and cognitive decline and dementia suggests that depression treatment has the potential to prevent these conditions. The limited data from short-term RCTs and observational studies, however, have been inconclusive, and deleterious effects of treatment have been observed. Although one RCT found a significant improvement in cognitive function when elderly patients (aged 65 to 90) with recurrent depression were treated with a serotonin-norepinephrine reuptake inhibitor (Raskin et al., 2007), another RCT showed that treatment of depressed patients aged 75 and older with a selective serotonin reuptake inhibitor (SSRI) resulted in a decline in cognitive function for treatment

BOX 4-2 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON DEPRESSION INTERVENTIONS

No relevant studies for depression treatments were found.

SOURCE: Kane et al., 2017.

nonresponders relative to a placebo group (Culang et al., 2009). Both RCTs were too short (8 weeks), however, to permit conclusions regarding long-term effects of treatment. A large and long-duration prospective cohort study examining the effect of antidepressant use (SSRIs and tricyclic antidepressants) on the incidence of MCI and dementia in women aged 65 to 79 found a 70 percent increased risk of MCI for those being treated with antidepressants relative to nonusers, even after controlling for severity of depressive symptoms (Goveas et al., 2012). However, the study authors were unable to disentangle the relative contributions of depression and antidepressant use to the cognitive outcomes. These findings highlight the need for additional research, including trials on the effect of antidepressants on cognitive outcomes in individuals both with and without depression.

Future Research Questions and Directions

The link between depression and cognitive decline and dementia strengthens the argument for an aggressive, proactive, and ongoing approach to depression treatment. However, much remains unknown regarding the links between depression and cognitive decline and dementia and the impact of depression treatment on dementia risk. The following fundamental research questions are priorities for future studies:

- What are the biological mechanisms by which depression might lead to dementia?
- Does early identification and treatment of depression lower the risk of dementia?

Dietary Interventions[4]

Epidemiologic evidence links diet—primarily Mediterranean-style diets[5]—to prevention of Alzheimer's disease, and is supported by underlying biological mechanisms in the etiology of the disease (Singh et al., 2014; van de Rest et al., 2015). Further evidence suggests that diets targeting weight loss may address other dementia risk factors, such as diabetes and obesity. Despite evidence from observational studies linking diet to brain health, however, most RCTs examining effects of diet on the risk of Alzheimer's disease have been negative. To date, the majority of such RCTs have focused

[4]Consistent with the AHRQ systematic review, vitamins were considered separately from dietary interventions for the purposes of this report, and certain specific vitamins are addressed elsewhere in this chapter.

[5]The Mediterranean diet emphasizes consumption of fruits and vegetables, cereals, legumes, fish, and unsaturated fats (i.e., olive oil) and lower levels of saturated fats such as those found in meats and dairy products.

on either individual foods or high-dose nutrient supplements. Few have examined comprehensive diets, such as the Mediterranean diet, which is high in antioxidants and thought to protect against the primary biological mechanisms underlying Alzheimer's disease—oxidative stress and inflammation (Fitó et al., 2007; Mitjavila et al., 2013; Zamora-Ros et al., 2013).

AHRQ Systematic Review Findings and Discussion

Although the AHRQ systematic review initially identified six RCTs of the effect of diet-based interventions on cognitive function, all but two studies were excluded from the analysis because of a high risk of bias, and evidence from the two remaining trials was insufficient to permit any conclusions regarding efficacy (see Box 4-3). In adults with normal cognition, one small RCT (N = 65) showed that twice-daily consumption of a protein supplement drink had no effect on cognitive function in frail elderly adults after 24 weeks (van der Zwaluw et al., 2014b). Another small RCT (N = 107) in obese adults showed improvement in Brief Cognitive Test performance after 1 year for an energy-deficient diet intervention group compared with controls (Napoli et al., 2014). No eligible studies examined the effect of diet-based interventions on cognition in adults with MCI.

Supplemental Information and Considerations

Although RCTs of comprehensive diets (such as the Mediterranean diet) were excluded from the AHRQ systematic review because of a high risk of bias, promising data from observational studies indicate that additional research on such diets is needed. A number of observational studies have suggested the possibility that some types of diets can prevent cognitive decline and dementia (IOM, 2015; van de Rest et al., 2015). Specific diets found in these studies to be associated with improved cognitive function or reduced

BOX 4-3 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON DIET INTERVENTIONS

Evidence is insufficient to conclude whether protein supplementation or energy-deficit diets have an effect on cognitive performance or incidence of MCI or CATD.

SOURCE: Kane et al., 2017.

incidence of MCI or CATD include the Mediterranean diet (Scarmeas et al., 2009), the Dietary Approaches to Stop Hypertension (DASH) diet (Tangney, 2014; Tangney et al., 2014), and the Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND) diet—a hybrid of the Mediterranean and DASH diets designed to focus on foods that are specific to brain health (Morris et al., 2015a,b).

Observational data on the Mediterranean diet are bolstered by a post hoc analysis of cognitive outcomes from the PREDIMED (Prevención con Dieta Mediterránea) RCT, which evaluated the effect of the Mediterranean diet in a population at high vascular risk and found statistically significant improvements in cognition compared with a control group on a low-fat diet (Martinez-Lapiscina et al., 2013; Valls-Pedret et al., 2015). However, these studies were considered to be at high risk of bias because of high levels of attrition, and therefore were not considered in the AHRQ systematic review. Also, in the study by Martinez-Lapiscina and colleagues (2013), cognitive function was not assessed at baseline since the primary aim of the RCT was to evaluate the effect of the diet on incident cardiovascular disease.

Future Research Questions and Directions

As noted above, the majority of past dietary interventions have been focused on individual nutrient supplements (e.g., DHA) or single foods (e.g., fish, olive oil), not comprehensive diets that capture dietary components working in synergy. Intervention studies of such comprehensive diets (alone or in combination with other lifestyle interventions) are currently under way (Blumenthal et al., 2013) and, unlike studies evaluating single foods or nutrient supplements, will enable evaluation of entire dietary patterns and how they may impact neurodegeneration leading to changes in cognition. One recently funded trial of the MIND diet includes another methodological improvement over past diet trials in that only those with suboptimal diets for the foods included in the MIND diet will be randomized. Not only will this approach allow for a better contrast between the intervention and control groups, but it has the potential to help researchers define a target population for prevention and treatment studies. These and future studies may help address the following priority research questions regarding dietary interventions:

- Which foods are critical to brain health and should be included in diet-based interventions?
- Which populations are likely to benefit most from dietary interventions targeting prevention of cognitive decline and dementia?
- Do dietary interventions have a larger effect on late-life ARCD, MCI, and CATD if initiated in midlife?

Lipid-Lowering Treatment

Hyperlipidemia—particularly hypercholesterolemia—is associated with cognitive decline (Etgen et al., 2011; IOM, 2015). Moreover, cholesterol has been linked to the generation and deposition of beta-amyloid plaques (Pappolla et al., 2003; Puglielli et al., 2001), one of the hallmarks of Alzheimer's disease. Intervention studies of lipid-lowering treatments have been pursued based on the known effects of these drugs on vascular health, including stroke risk, which over time may also prevent cognitive decline and dementia. Most research on cognitive effects of lipid-lowering treatments has been focused on cholesterol-lowering statins (e.g., simvastatin, atorvastatin, lovastatin); far fewer studies have evaluated the efficacy of other lipid-lowering treatments, such as ezetimibe, which blocks cholesterol absorption.

AHRQ Systematic Review Findings and Discussion

The AHRQ systematic review found no evidence of cognitive benefit for lipid-lowering treatments in adults with normal cognition (see Box 4-4 for a summary of the AHRQ findings). Four RCTs, including the large (N = 20,536) and long-duration (5 years) Heart Protection Study (Heart Protection Study Collaborative Group, 2002), evaluated statins against

BOX 4-4 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON LIPID-LOWERING TREATMENT

- Evidence was insufficient to assess the effect of 5 years of statin treatment on the risk of incident CATD or for preventing MCI.
- Low-strength evidence shows a small, 6-month improvement in executive/attention/processing speed with placebo treatment that was not found with statin treatment, presumed to be due to practice effects and of uncertain clinical significance.
- Low-strength evidence shows no benefit on brief cognitive test performance, executive/attention/processing speed, or memory for statin plus fenofibrate versus statin plus placebo in adults with normal cognition.
- Evidence was insufficient to assess whether effects of statins on any cognitive outcomes differ by patient age, baseline lipid level, or other characteristics.

SOURCE: Kane et al., 2017.

placebo. Only the Heart Protection Study measured dementia incidence, and no between-group differences in dementia incidence or Brief Cognitive Test performance were identified for adults aged 40 to 80 with coronary disease, other occlusive arterial disease, or diabetes. Of the three other RCTs in adults with very high cholesterol levels, one found no between-group difference in cognitive performance (Santanello et al., 1997), and the other two found statistically significant increases in cognitive performance for the placebo group (Muldoon et al., 2000, 2004); these may have resulted from practice effects (Kane et al., 2017). One very small study (N = 34) showed that statins combined with ezetimibe resulted in slightly improved cognitive performance at 1 year as compared with placebo (Tendolkar et al., 2012), but these between-group differences were small and may not be clinically meaningful (Kane et al., 2017). A combination therapy consisting of statins and fenofibrate (another lipid-lowering drug) did not improve cognitive performance beyond statins alone in the ACCORD-MIND trial (Williamson et al., 2014). No studies included in the AHRQ systematic review evaluated the efficacy of statins in adults with MCI, so conclusions cannot be drawn regarding the ability of these drugs to prevent or delay dementia in this subpopulation.

Although results from the limited number of RCTs included in the AHRQ systematic review are not very promising, it should be noted that follow-up periods were short (6 months) for all but the Heart Protection Study and may not have been sufficient to show beneficial cognitive effects of statins and other lipid-lowering treatments. The longer Heart Protection Study was originally designed to measure cardiovascular outcomes (cognitive outcomes were added on) and did not include a baseline measure of cognition.

Supplemental Information and Considerations

In contrast to the RCT data reviewed in the AHRQ report, many observational studies suggest that statins could have the potential to prevent cognitive decline and dementia (Haag et al., 2009; Steenland et al., 2013; Wolozin et al., 2000; Zissimopoulos et al., 2016). The Rotterdam Study found that the risk of developing CATD was reduced by nearly 50 percent in study participants taking statins (Haag et al., 2009). As is the case with hypertension (discussed in Chapter 2), hyperlipidemia in midlife may be an important risk factor for cognitive decline (Kivipelto et al., 2001; van Vliet, 2012; Whitmer et al., 2005), suggesting that RCTs with longer follow-up periods are needed to evaluate the effects of lipid-lowering treatment on cognitive outcomes. Some inconsistent evidence suggests possible differential effects in older (more than 80 years of age) individuals (Harrison et al., 2015).

In addition to lowering lipids, statins may work via amyloidogenic pathways involved in the development of CATD (Barnard et al., 2014). This may, in part, explain why Haag and colleagues (2009) observed reduced CATD risk associated with the use of statins, but not other cholesterol-lowering drugs. The lipid transport molecule Apolipoprotein E4 increases the risk of CATD via amyloidogenic pathways, and basic research evidence supports this notion (Puglielli et al., 2003).

Future Research Questions and Directions

Promising observational data, a strong argument for biological plausibility, and significant limitations of past RCTs support the need for additional research on the effects of statins and other lipid-lowering treatments in preventing cognitive decline and dementia. Intervention studies on statins have been conducted largely in populations with normal cognition and high vascular risk. Conducting future studies in other populations, such as adults with MCI and those at low vascular risk (e.g., normal cholesterol levels), and initiating interventions at midlife may expand understanding of the cognitive effects of lipid-lowering drugs. Moreover, little is known regarding the cognitive effects of other (nonstatin) lipid-lowering drugs, such as ezetimibe and fenofibrate, and this is another area in which more research may be valuable. The committee identified the following priority research questions:

- Which populations (considering, for example, age, cholesterol level and overall vascular risk, and baseline cognitive status) may benefit most from lipid-lowering treatments? Are any age groups at risk of being harmed by lipid lowering?
- Do other classes of lipid-lowering treatments, alone or in combination with statins, show potential to prevent cognitive decline and dementia if tested in studies that are sufficiently powered and of adequate duration?

Sleep Quality Interventions

Sleep disturbances, including difficulty falling or staying asleep, fragmented sleep, sleep-disordered breathing, and circadian rhythm disturbances, are common among the elderly and have been associated with cognitive decline (Yaffe et al., 2014). Among individuals with Alzheimer's disease, sleep disruptions can be especially severe (Bliwise, 1993), and elevated brain beta-amyloid burden is associated with worse sleep quality (Brown et al., 2016; Spira et al., 2013, 2014).

Multiple factors associated with poor sleep quality also are associated

with cognitive decline and Alzheimer's disease, including metabolic and inflammatory changes that lead to cardiovascular disease and diabetes (Landry and Liu-Ambrose, 2014; Mullington et al., 2009) and primary sleep disorders such as sleep apnea (Emamian et al., 2016). Chronic inflammation increases the risk for circadian dysregulation and cognitive decline (Landry and Liu-Ambrose, 2014), and intermittent hypoxia associated with sleep-disordered breathing may lead to neurodegeneration (Yang et al., 2013). Moreover, sleep plays a role in memory consolidation (Diekelmann and Born, 2010). Through the glymphatic system, sleep also plays an important role in clearing toxins such as beta-amyloid and tau from the brain (Cedernaes et al., 2016; Xie et al., 2013). Taken together, these converging lines of research suggest that interventions aimed at improving sleep quality and circadian regulation could have a role in preventing or slowing the progression of cognitive decline and dementia (Landry and Liu-Ambrose, 2014). Empirical evidence, however, is lacking, and the potential for reverse causality needs to be explored.

AHRQ Systematic Review Findings and Discussion

As summarized in Box 4-5, the AHRQ systematic review concluded that insufficient evidence exists to support the use of sleep interventions to prevent cognitive decline and dementia. However, only two RCTs of sleep interventions were identified in the AHRQ systematic review, and neither of these studies met the criteria for low to medium risk of bias. Furthermore, the interventions tested did not include sleep restriction and stimulus control, two components of behavioral interventions for insomnia that are considered the gold standard of insomnia treatment (McCurry, 2016).

Supplemental Information and Considerations

Although the AHRQ systematic review did not find sufficient evidence to indicate whether sleep interventions can prevent cognitive decline and

BOX 4-5 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON SLEEP QUALITY INTERVENTIONS

Evidence was insufficient for sleep interventions.

SOURCE: Kane et al., 2017.

dementia, the substantial body of data supporting a link between sleep and cognition suggests that improving sleep quality could improve cognitive performance. A recent study using polysomnography to assess biophysical changes during sleep found that better sleep quality, when measured objectively, is associated with improvements in executive function in adults with insomnia (Wilckens et al., 2016). Cognitive-behavioral therapy for insomnia (CBTI) is among the most well-studied sleep interventions, but its effect on cognitive outcomes has not been well studied. Other potential interventions that have been evaluated in patients with dementia for improving sleep and cognitive function include light therapy (Forbes et al., 2014) and use of melatonin (Wade et al., 2014; Zisapel, 2001). Whether these interventions would have a role in preventing cognitive decline and dementia has not been determined.

Future Research Questions and Directions

Accumulating evidence from observational studies in humans and experimental studies in animal models supports a link between sleep disruptions and the pathogenesis of Alzheimer's disease (Cedernaes et al., 2016), although reverse causality is a potential factor to be considered in future research. Given the urgency of identifying interventions that may prevent, slow, or delay the development of CATD, additional studies on this potential therapeutic approach are needed. A key question is whether the observed benefits of sleep for cognition translate into the delay or slowing of cognitive decline and the prevention, slowing, or delay of MCI and CATD. Answering this question will require the use of accurate, sensitive, and standardized measures of sleep quality and a better understanding of which cognitive domains to assess. Future research questions that can then be answered regarding sleep-based interventions include the following:

- Do interventions designed to improve sleep quality delay or slow cognitive decline in the long term and prevent dementia?
- What kinds of interaction effects are important to consider in studies of sleep interventions? How might the effect of improved sleep be accounted for in studies of other interventions that have known effects on cognition and sleep (e.g., physical activity)?
- How does sleep quality in midlife affect late-life cognitive outcomes?

Social Engagement Interventions

A growing body of evidence suggests that engaging in social activities may help prevent cognitive decline and dementia (IOM, 2015). Such evidence stems from observational studies on the cognitive impacts of social

isolation and loneliness (Holwerda et al., 2014; O'Luanaigh et al., 2012; Shankar et al., 2013), as well as observational (Brown et al., 2012) and intervention (Mortimer et al., 2012) studies on the cognitive benefits of participation in social activities. A variety of different mechanisms by which social engagement may be linked to cognitive decline and dementia have been proposed. They include direct neurobiological effects (e.g., neuroplasticity), as well as indirect effects such as diminished sleep quality, reduced physical activity, and increased risk of depression in those who are socially isolated (Cacioppo and Hawkley, 2009). Studies on social engagement can be challenging to design, as measurement of social activity is often subjective, and it is difficult to isolate the social aspects of activities from other aspects (e.g., cognitive stimulation) that also may affect cognition.

AHRQ Systematic Review Findings and Discussion

As summarized in Box 4-6, the AHRQ systematic review found that insufficient evidence exists to support a conclusion on the efficacy of interventions targeting social engagement in preventing cognitive decline and dementia. The one intervention study identified in this domain was designed to evaluate the effect of cognitive group social interactions (board games, discussions of newspaper articles) in adults with MCI, but this study was determined to be at high risk of bias.

Supplemental Information and Considerations

Although it is particularly difficult to disentangle the effects of social engagement from those of cognitively stimulating activities, studies have suggested that social interactions have positive effects on cognitive outcomes (Mortimer et al., 2012). One study comparing the effects of reasoning-based cognitive training and an intervention aimed at fostering creative problem solving in a socially complex, team-based competitive environment

BOX 4-6 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON SOCIAL ENGAGEMENT INTERVENTIONS

Evidence was insufficient for social engagement interventions.

SOURCE: Kane et al., 2017.

showed that both approaches can improve cognitive performance, but in different cognitive domains (Stine-Morrow et al., 2014).

Future Research Questions and Directions

Priority research questions with respect to the potential role of social engagement interventions in preventing cognitive decline and dementia include the following:

- Which kinds of social activities might have the greatest impact on long-term cognitive outcomes?
- Are there specific interventions targeting increased social activity that reduce the risks for cognitive decline and dementia?

Vitamin B_{12} Plus Folic Acid Supplementation

Supplemental B vitamins (B_6, B_{12}, and folate) are of interest as possible interventions for preventing cognitive decline and dementia based on their ability to lower blood homocysteine levels, which, when elevated, are associated with increased risk of cardio- and cerebrovascular disease, as well as poor cognitive outcomes (Beydoun et al., 2014; IOM, 2015). Blood homocysteine levels are known to increase with age and declining kidney function, but are determined largely by dietary B vitamin intake (Beydoun et al., 2014). Despite evidence linking vitamin B_{12} deficiency with cognitive impairment (Moore et al., 2012), a previous review did not find strong evidence for benefits of B_{12} supplementation (alone or in combination with other B vitamins) for cognitive function (Ontario Health Technology Advisory Committee, 2013).

AHRQ Systematic Review Findings and Discussion

Results from studies of B vitamin interventions included in the AHRQ systematic review were mixed for adults with normal cognition. As summarized in Box 4-7, the review found some indication of short-term improvement in Brief Cognitive Test performance for intervention groups in two RCTs (total N = 3,819) receiving vitamin B_{12} plus folic acid compared with placebo (van der Zwaluw et al., 2014a; Walker et al., 2012). However, effect sizes were small, and follow-up periods were limited to 2 years, so the long-term implications of these results are unclear. The study by Walker and colleagues (2012) also found benefits for memory for two of three cognitive tests. Neither study showed benefits for performance in the areas of executive function, attention, and processing speed. Of note, in the study by van der Zwaluw and colleagues (2014a), adults with elevated homocysteine

BOX 4-7 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON B VITAMINS

- There was some signal that B_{12} plus folic acid may benefit brief cognitive test performance and memory but not executive function/attention/processing speed.
- Low-strength evidence for folic acid (0.4 mg) plus vitamin B_{12} (0.1-0.5 mg) shows benefit in brief cognitive test performance and memory.
- Moderate-strength evidence shows no benefit for folic acid (0.4 mg) plus B_{12} (0.1-0.5 mg) versus placebo for executive/attention/processing speed.
- Low-strength evidence for vitamin B_{12} (0.02-0.5 mg), B6 (3-10 mg), and folate (0.561 mg) shows no benefit for executive/attention/processing speed.

SOURCE: Kane et al., 2017.

levels were specifically recruited, so the study population had a higher risk of vitamin B deficiency relative to the general population. Two other studies in adults with normal cognition failed to show any benefit of vitamin B_{12} combined with vitamin B_6 and folate compared with placebo (Andreeva et al., 2011; McMahon et al., 2006).

Supplemental Information and Considerations

Biomarker data also suggest a potential benefit of vitamin B_{12} supplementation in individuals with a deficiency. An RCT published by Smith and colleagues (2010) showed that supplementation with B vitamins slowed the rate of brain atrophy in adults with MCI. The study used only surrogate neuroimaging markers and therefore was not included in the AHRQ systematic review, but those markers moved in a direction consistent with a favorable effect.

Results of the studies of Smith and colleagues (2010) and van der Zwaluw and colleagues (2014a), along with decades of negative trials in unselected populations, suggest that an approach targeting individuals with higher homocysteine levels may have value. Not only are elevated homocysteine levels associated with vascular risk, but they also may portend a subset of the population that is at higher risk for development of B_{12} deficiency over time. It is well known that the prevalence of pernicious anemia and B_{12} deficiency increases with age and that left untreated, they can cause neurodegeneration, including cognitive impairment (Andres and Serraj, 2012;

Kifle et al., 2009; Moore et al., 2012; Toh et al., 1997). Other studies that did not involve targeting a higher-risk group likely were offering treatment to individuals who, because of adequate nutrition and absorption of B_{12} in particular, would not be likely to show a B vitamin–mediated beneficial effect. Given evidence from research on B_{12} and folate showing the importance of accounting for initial deficits in these vitamins, it is important for future research on dietary supplements to control for baseline levels.

Future Research Questions and Directions

Future research on vitamin B_{12} plus folic acid supplementation may be of most value if it can clarify whether the effects on cognitive performance generally are limited to those at higher risk of a deficiency. A higher-risk population could be selected for future studies based on higher measured homocysteine levels—for example, the top half of the distribution or potentially the top third or quartile to target an even higher-risk group. An alternative approach would be a simple but large pragmatic trial based on screening a large population in a real-world clinical setting and randomizing only those at risk of deficiency to receive vitamin B_{12} plus folic acid or placebo. The following are priority questions for this research:

- Are cognitive outcomes associated with vitamin B_{12} plus folic acid supplementation improved in a population at risk for a deficiency as compared with a population not at risk?
- Do the short-term improvements in cognitive performance observed for vitamin B_{12} plus folic acid supplementation translate into delay or slowing of cognitive decline and reduced risk of dementia?

LOWEST-PRIORITY INTERVENTIONS FOR FUTURE RESEARCH

This section provides a brief overview of those interventions for which the AHRQ systematic review found no evidence of any benefit and some low-strength evidence indicating that the intervention does not prevent cognitive decline or dementia and, in one case, may in fact increase the risk of MCI or dementia. Based on these findings, the committee believes these interventions should be the lowest priority for future research.

Interventions with Evidence Suggesting Detrimental Effects on Cognition

For most hormone therapy interventions included in the AHRQ systematic review, evidence on cognitive impacts is insufficient to draw conclusions regarding their priority for future research. However, estrogen-containing hormone therapy interventions were given special consideration in the

BOX 4-8 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS ON HORMONE THERAPY

- Low-strength evidence suggests that estrogen therapy may slightly increase the risk of probable MCI and CATD when the two diagnostic categories are examined together.
- Low-strength evidence suggests that estrogen plus progestin therapy may slightly increase the risk of probable CATD.
- Low-strength evidence suggests that raloxifene may decrease the risk of MCI but not the risk of CATD or of a combined outcome of MCI or CATD compared to placebo.
- In addition to these outcomes, hormone therapy has been associated with serious adverse events, including increased risk of certain cancers and cardiovascular disease.

SOURCE: Kane et al., 2017.

AHRQ systematic review because of their observed detrimental effects on cognition in women aged 65 or older (as summarized in Box 4-8).

Much of the evidence on the cognitive effects of hormone replacement therapy originates from substudies of the large and long-duration Women's Health Initiative RCT. The Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative Study of Cognitive Aging (WHISCA) examined effects of hormone replacement therapies that included conjugated equine estrogen on cognition in women aged 65 or older. These studies found that such medications increased the overall risk of dementia by 76 percent and resulted in a small average relative deficit in cognitive function that persisted for years after the cessation of therapy (Espeland et al., 2017b; Shumaker et al., 2004). Furthermore, significantly lower frontal lobe volumes (a marker of brain atrophy) were observed in women assigned to hormone therapy in the WHIMS study. Conjugated equine estrogen therapies may be particularly harmful for older women with diabetes (Espeland et al., 2015a,b). In addition to these cognitive effects, increased risk of stroke was observed in the parent Women's Health Initiative clinical trial (Manson et al., 2013).

Three recent well-powered RCTs have examined whether various hormone therapy regimens affect cognitive function in women nearer to the time of their menopausal transition: the Women's Health Initiative Study of Younger Women (Espeland et al., 2013, 2017b), the Kronos Early Estrogen Prevention Study (Gleason et al., 2015; Kantarci et al., 2016), and the Early vs. Late Intervention Trial with Estradiol (Henderson et al., 2016). None

of these studies found any cognitive benefit of any of the hormone therapy regimens, and there was some evidence of increased brain atrophy linked to one hormone preparation (Kantarci et al., 2016). Of note, no studies have examined whether hormone therapy, if begun during the menopausal transition rather than following menopause, affects cognitive function.

In conclusion, although hormone therapy remains the recommended treatment for menopausal symptoms, current evidence is that it provides no cognitive benefit for younger women, and therapies based on conjugated equine estrogen may be harmful for women aged 65 or older, increasing their risk for dementia and brain atrophy. In addition, a number of studies have found that hormone therapies may increase women's risk for stroke. The current evidence suggests that hormone therapies based on estrogen or estrogen plus progestin should be deprioritized in future research aimed at identifying interventions that prevent cognitive decline and dementia in older women.

Interventions with Some Evidence Suggesting No Benefit

Some low-strength evidence from RCTs suggests that nonsteroidal anti-inflammatory drugs, vitamin E, gingko biloba, and medications belonging to the class of antidementia drugs known as acetylcholinesterase inhibitors do not prevent or delay dementia or improve cognitive function. Key findings from the AHRQ systematic review for each of these interventions are summarized in Box 4-9. Although the limitations of existing studies make it difficult to definitively rule out possible benefits of these interventions under certain conditions (e.g., in specific subpopulations or in combination with other interventions), the committee believes that priorities for future intervention research are the more promising areas described above.

With regard to the nutritional supplements included in Box 4-9—gingko biloba and vitamin E—the committee notes that these supplements are widely marketed, with manufacturers claiming a variety of potential health benefits. While a review of health effects attributable to these supplements outside of the cognitive domain is beyond the scope of this report, and there is little evidence to suggest they may be harmful, the nontrivial cost of their purchase may not be justified if their intended use is to prevent cognitive decline or bolster cognitive performance. As discussed earlier in this chapter, however, the committee supports additional study of the cognitive effects of diet more broadly, even if attempts to tease out the potential benefits of individual nutritional components have been largely unsuccessful.

Intervention studies on acetylcholinesterase inhibitors have failed to provide any evidence that these drugs are effective at preventing further cognitive decline and progression to dementia in people with MCI. There

BOX 4-9 AHRQ SYSTEMATIC REVIEW: SUMMARY OF FINDINGS RELATED TO INTERVENTIONS THAT SHOWED SOME EVIDENCE SUGGESTING NO BENEFIT

Acetylcholinesterase Inhibitor (AChEI) Antidementia Drugs[a]

- Low-strength evidence shows AChEI antidementia drugs did not reduce the incidence of clinical Alzheimer's-type dementia (CATD) in persons with MCI over 3 years; evidence is insufficient for persons with normal cognition.
- Low-strength evidence shows AChEI for 3 years provides no significant effect on cognitive performance in adults with MCI.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- No evidence was available for the effect of low-dose aspirin on MCI or CATD incidence.
- Low-strength evidence shows no benefit for low-dose aspirin on brief cognitive screening tests, multidomain neuropsychological performance, or memory, even with 10 years of use.
- Low-strength evidence shows no benefit for NSAIDs, including both selective and nonselective cyclooxygenase-2 (COX-2) inhibitors, to reduce CATD incidence, or to benefit multidomain neuropsychological performance or memory, with 8 years of follow-up after 1 to 3 years of use.

Gingko Biloba

- Low-strength evidence suggests omega-3 fatty acids[b] and gingko biloba did not reduce CATD incidence or improve cognitive performance in adults with normal cognition.

Vitamin E

- Moderate-strength evidence shows no benefit in cognitive performance for vitamin E in women.
- In adults with MCI, low-strength evidence shows no benefit for vitamin E in incident CATD.

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[a]Please see general discussion of antidementia drugs in previous section.

[b]The committee believes that the randomized controlled trial data suggesting lack of benefit from omega-3 fatty acid supplementation is weak and counterbalanced by encouraging evidence from observational studies and preliminary results from ongoing studies such as the Multidomain Alzheimer's Prevention Trial (MAPT) discussed earlier in this chapter.

SOURCE: Kane et al., 2017.

are currently five drugs approved by the U.S. Food and Drug Administration to treat the cognitive symptoms of Alzheimer's disease—four cholinesterase inhibitors[6] and memantine, an N-methyl-D-aspartate (NMDA)-receptor antagonist (Cummings et al., 2014). None of these drugs treats the underlying cause of Alzheimer's disease, nor do they slow disease progression (Cummings et al., 2016a; Schneider and Sano, 2009). No new Alzheimer's drug has been approved since 2003 (Cummings et al., 2014). However, as discussed earlier in this chapter, the search for new antidementia treatments that can delay onset or slow progression of cognitive impairment and dementia remains a priority for future research.

RECOMMENDATIONS

CONCLUSION: Before public health messaging strongly encourages adoption of cognitive training, blood pressure management for people with hypertension, and increased physical activity solely for the purpose of maintaining cognitive function, additional research is needed to further understand and gain confidence in the effectiveness of these interventions. Emerging data from multimodal intervention studies suggest there may be value to evaluating each of these interventions alone and in combination. Some large studies already under way may help address these questions.

Recommendation 3: Highest Priorities for Research
The National Institutes of Health and other interested organizations should support further research to strengthen the evidence base on the following categories of interventions, alone or in combination, which are supported by encouraging but inconclusive evidence:

- **cognitive training**
- **blood pressure management**
- **increased physical activity**

CONCLUSION: There is insufficient evidence with which to assess the effectiveness of the following interventions in preventing cognitive decline and dementia: diabetes treatment, dietary interventions, depression treatment, lipid-lowering treatment, sleep quality interventions, social engagement interventions, and vitamin B_{12} plus folic

[6]Only three cholinesterase inhibitors are commonly used to treat dementia symptoms, as one—tacrine—has been associated with toxicity and significant adverse effects (Winker, 1994).

acid supplementation. Emerging data and/or biological arguments suggest that these interventions could be considered, but additional research is needed before a decision can be made as to whether they should be included in public health messaging. Emerging data from multimodal intervention studies suggest there may be value to evaluating each of these interventions alone and in combination. In addition, it will be important to explore new targets—beyond amyloid and tau—for antidementia drug development.

Recommendation 4: Additional Priorities for Research

The National Institutes of Health and other interested organizations should support research to strengthen the evidence base on the following categories of interventions, alone or in combination, for which there is currently insufficient evidence to determine their effectiveness:

- **new antidementia treatments that can delay onset or slow disease progression**
- **diabetes treatment**
- **depression treatment**
- **dietary interventions**
- **lipid-lowering treatment/statins**
- **sleep quality interventions**
- **social engagement interventions**
- **vitamin B_{12} plus folic acid supplementation**

FINAL THOUGHTS

While the committee recognizes that well-conducted, rigorous, generalizable RCTs are the gold standard for demonstrating the effectiveness of interventions for preventing common conditions such as ARCD and CATD, there are references throughout this report to the challenges of implementing RCTs to test the value of interventions and behavioral changes for preventing or delaying such conditions. For example, the potential benefits of higher levels of education and socioeconomic well-being may have effects throughout the life course, from birth through the long process of brain aging, but these effects cannot be evaluated in an RCT. Alzheimer's-related brain changes are known to appear well before symptoms manifest and, like the unexpected coronary artery disease seen in autopsies of Korean War veterans (Enos et al., 1953), may even be present in young adults. Is there a conceivable way to study people this young for an illness that typically develops many decades later?

An added challenge is that many of the interventions that show prom-

ise today, such as better control of hypertension and diabetes and regular physical activity, have widely accepted health benefits and are broadly prescribed. Similarly, while smoking has been shown to be a risk factor for dementia, it is difficult to imagine an ethically acceptable long-term RCT that would include an untreated control group and could meet the stringent quality criteria of the evidence-based practice center. Potential solutions to these challenges include using evidence from life-course epidemiology cohort studies employing the most rigorous methods possible, and possibly from studies aimed at improving adherence to and adoption of such treatments as diabetes management in which the "control" group would be usual care. There are no easy answers to these challenges, and the National Institute on Aging and other institutes and organizations—in collaboration with researchers with expertise in cognitive decline and dementia—will need to continue to grapple with the question of what kinds of research and outcomes constitute evidence rigorous enough to provide clear support for public health messaging.

The subject of this report is a vibrant, dynamic research area whose story is not complete. The fact that the report does not strongly support a public health campaign focused on actively promoting adoption of any type of intervention should not be taken to reflect a lack of progress or prospects for preventing or delaying the discussed conditions. Although inconclusive, clinical trials and other studies have yielded encouraging data for some interventions, and the public should have access to this information to inform choices on how to invest time and resources to maintain brain health with aging. Despite the challenges noted above, RCT data will continue to form a critical source of evidence in this field. Trials in this area are under way and planned, funded by the National Institutes of Health and others, and more evidence is emerging all the time. As the results of these trials become available, it will be critical to assess them with an eye to updating the recommendations presented in this report for communicating with the public. Future intervention trials that build on advances in understanding of the biological basis of CATD and incorporate cutting-edge designs and the methodological recommendations presented herein will generate a more comprehensive, stronger evidence base. There is good cause for hope that in the next several years, much more will be known about how to prevent cognitive decline and dementia.

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A

AGENCY FOR HEALTHCARE RESEARCH AND QUALITY (AHRQ) SYSTEMATIC REVIEW

The AHRQ systematic review, *Interventions to Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia*, can be found here: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2417 (accessed May 22, 2017).

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B

PUBLIC MEETING AGENDAS

Committee on Preventing Dementia and Cognitive Impairment

First Committee Meeting
Open Sessions: December 15-16, 2015

National Academy of Sciences Building
2101 Constitution Avenue, NW | Washington, DC 20418

DAY ONE—TUESDAY, DECEMBER 15

11:00 a.m. **Welcome and Introductions**

Alan Leshner, Chair, Committee on Preventing Dementia and Cognitive Impairment
CEO Emeritus, American Association for the Advancement of Science

11:05 a.m. **Delivery of Study Charge and Q&A/Discussion with Committee**
Objectives:

- Receive study background and charge from the National Institute on Aging (NIA), discuss task with the sponsor, and determine scope of committee's work (i.e., what is in and what is out).
- Receive an overview of the Agency for Healthcare Research and Quality (AHRQ) process for systematic reviews.
- Receive an update from the evidence-based practice center (EPC) on progress to date and areas for committee input.
- Clarify issues identified by the committee and seek answers to questions.
- Discuss report audience and expected products.

Delivery of Charge
Richard Hodes, Director, NIA
Overview of AHRQ Process
Kim Wittenberg, Health Scientist Administrator, AHRQ
Overview of EPC progress to date and areas for committee input
Robert Kane, Director, Minnesota Evidence-based Practice Center

Discussion

12:30 p.m. **Lunch**

1:15 p.m. **Follow-Up Q&A/Discussion to Clarify Remaining Questions by the Committee on the Study Charge**

Alan I. Leshner, Chair, Committee on Preventing Dementia and Cognitive Impairment
CEO Emeritus, American Association for the Advancement of Science

Richard Hodes, Director, NIA
Kim Wittenberg, Health Scientist Administrator, AHRQ
Robert Kane, *Mary Butler*, and *Howard Fink*, Minnesota Evidence-based Practice Center

2:30 p.m. **Public Comment Period**

3:15 p.m. **Adjourn Open Session**

DAY TWO—WEDNESDAY, DECEMBER 16

10:15 a.m. **Follow-Up Discussion/Q&A Regarding the Systematic Review**
Objective: Discuss any remaining issues, questions, or points of clarification for the systematic review.

Alan I. Leshner, Chair, Committee on Preventing Dementia and Cognitive Impairment
CEO Emeritus, American Association for the Advancement of Science

Marie A. Bernard, Deputy Director, NIA
Kim Wittenberg, Health Scientist Administrator, AHRQ
Robert Kane, *Mary Butler*, and *Howard Fink*, Minnesota Evidence-based Practice Center

11:15 a.m. **Adjourn Open Session**

Preventing Dementia and Cognitive Impairment: A Workshop
Open Session: October 25, 2016

National Academy of Sciences Building
2101 Constitution Avenue, NW | Washington, DC 20418

Background: Many organizations and individuals worldwide are interested in the state of the science on preventing Alzheimer's disease and related dementias, mild cognitive impairment (MCI), and age-related cognitive decline (ARCD). To develop a better understanding of current scientific evidence, implications for public health messaging, and future research needs, the National Institute on Aging (NIA) asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to convene an expert committee to make recommendations that inform public health strategies and messaging on preventive interventions and recommendations for future research. To aid the committee in its work, NIA has asked the Agency for Healthcare Research and Quality (AHRQ) to commission and oversee a systematic review—conducted by the Minnesota Evidence-based Practice Center (EPC)—of the evidence on interventions associated with preventing, slowing, or delaying the onset of clinical Alzheimer's-type dementia and MCI, and delaying or slowing ARCD. Other dementias such as frontotemporal dementia, Lewy body dementia, and dementias with a clear etiology, e.g., incident stroke, AIDS, traumatic brain injury will be excluded from the analysis. Interventions targeting stroke risk factors are a priority in this study. To help inform the National Academies committee's recommendations, this public workshop will bring together key stakeholders to provide input to the committee on the draft AHRQ report. The National Academies committee's report is expected to be released in June 2017.

Workshop Objectives:

- Collect reactions to the draft EPC systematic review on preventive interventions that might reduce the risk of developing clinical Alzheimer's-type dementia and mild cognitive impairment, and slow or delay age-related cognitive impairment/decline.
- Explore the current state of evidence on preventive interventions and discuss areas where public health messaging might be warranted.
- Discuss promising, emerging data on interventions that did not meet the evidentiary standard of the systematic review, and identify gaps and areas for future research.

8:00 a.m. **Welcome and Overview of Workshop**
Alan Leshner, CEO Emeritus, American Association for the Advancement of Science, *Committee Chair*
Story Landis, Director Emeritus, National Institute of Neurological Disorders and Stroke, *Committee Vice-Chair*

8:05 a.m. **Background and Overview of the Committee's Charge**
Marie A. Bernard, Deputy Director, National Institute on Aging

8:15 a.m. **Overview of the Draft EPC Systematic Review**
Robert Kane, Director, Minnesota Evidence-based Practice Center

9:00 a.m. Discussion with Committee Members
Additional Respondents: *Mary Butler* and *Howard Fink*, Minnesota Evidence-based Practice Center

10:00 a.m. BREAK

10:15 a.m. **Making Decisions About Areas for Public Health Messaging**

- Discuss criteria and best practices for selecting areas for public health communication efforts. Questions may include: What strength of evidence is needed to justify public health messaging? What should be taken into account when considering developing messages about interventions that may apply only to specific subgroups?
- Discuss evidence-based approaches to public health messaging (e.g., focusing on the benefits of interventions versus the consequences of not acting)

Brian Southwell, Program Director, Science in the Public Sphere, Center for Communication Science, RTI International

10:45 a.m. Discussion with Committee Members

SESSION I: PUBLIC HEALTH MESSAGING AND FUTURE RESEARCH—PERSPECTIVES FROM ACADEMIA

Session Objectives:

- Reflect on the current state of evidence on preventive interventions (*not risk factors*) and where public health messaging might be warranted.
- Discuss promising, emerging data on interventions that did not meet the evidentiary standard of the systematic review.
- Identify gaps and priorities for future research.

11:00 a.m. Session Overview
Ronald Petersen, Director of the Alzheimer's Disease Research Center and Mayo Clinic Study of Aging, Mayo Clinic

11:05 a.m. **Public Health Trends: Understanding the Impact of Individual and Societal Factors on Delaying or Preventing the Risk of Dementia and Cognitive Impairment**
Walter Rocca, Professor of Neurology and Epidemiology, Mayo Clinic

Panel I: Perspectives from Academia

11:20 a.m. **Interventions on Co-Existing Conditions** (e.g., blood pressure control, depressive symptoms, diabetes prevention and control, and obesity and weight loss)

Vascular Factors, Diabetes, and Obesity
Rebecca Gottesman, Associate Professor of Neurology, Johns Hopkins University
Jeff Williamson, Interim Chair of Internal Medicine; Program Director of the Sticht Center on Aging; Professor of Gerontology and Geriatric Medicine, Neurology, Epidemiology & Prevention, and Translational Science Institute, Wake Forest Baptist Health

Multimodal Interventions
Edo Richard, Neurologist, University of Amsterdam, Academic Medical Center; Radboud University Medical Center

11:50 a.m. Discussion with Committee Members
Including questions on interventions using drugs and supplements (e.g., aspirin/nonsteroidal anti-inflammatory drugs, drugs for memory, hormone therapies, nutraceuticals, and vitamins)

12:30 p.m. LUNCH

1:30 p.m. **Interventions on Lifestyle and Social Support Factors** (e.g., cognitive stimulation and training, diet, physical activity, sleep quality and disorder, and substance use)

Diet and Physical Activity
Joe Verghese, Professor of Neurology and Medicine, Director of the Division of Cognition and Motor Aging, Director of the Jack and Pearl Resnick Gerontology Center, Albert Einstein College of Medicine

Cognitive Training and Computer-Based Brain Games
Sherry Willis, Research Professor, Department of Psychiatry and Behavioral Sciences, University of Washington

Sleep Quality and Disorders
Susan McCurry, Research Professor and Vice Chair of Research of Psychosocial and Community Health, University of Washington

2:15 p.m. **Methodological Considerations Pertaining to the Prevention of Dementia** (e.g., life course perspective, timing of interventions, and characteristics of people living with dementia)
Mary Sano, Professor of Psychiatry and Director of the Alzheimer's Disease Research Center, Mount Sinai School of Medicine

2:30 p.m. **Individual Characteristics: Interventions Conducted in Minority Populations**
Julene Johnson, Professor of Cognitive Neuroscience; Professor and Associate Director at the University of California, San Francisco, Institute for Health & Aging

2:45 p.m. Discussion with Committee Members

3:30 p.m. BREAK

SESSION II: PERSPECTIVES FROM PEOPLE LIVING WITH DEMENTIA, ADVOCACY ORGANIZATIONS, AND PROFESSIONAL SOCIETIES

Session Objectives:

- Comment on which preventive interventions and outcomes are of most interest to people living with dementia and their caregivers.
- Collect input from advocacy organizations and professional societies' on the EPC draft systematic review, the current state of evidence on preventive interventions and where public health messaging might be warranted, and areas for future research.

3:45 p.m. Session Overview
Marilyn Albert, Professor of Neurology and Director of the Division of Cognitive Neuroscience, Johns Hopkins University School of Medicine

3:50 p.m. **Panel II: Comments from Alzheimer's Disease/Dementia Advocates**
Michael Ellenbogen, Alzheimer's Disease/Dementia Advocate (video recording)
Brian LeBlanc, National Public Speaker/Alzheimer's Advocate

4:10 p.m. **Panel III: Perspectives from Advocacy Organizations**
Matthew Baumgart, Senior Director of Public Policy, Alzheimer's Association
Sarah Lenz Lock, Senior Vice President-Policy in Policy Strategy & International Affairs, AARP
Stacy Pagos Haller, President and Chief Executive Officer, BrightFocus Foundation

4:25 p.m. Discussion with Committee Members

4:40 p.m.	**Panel IV: Perspectives from Professional Societies** *James Appleby*, Chief Executive Officer and Executive Director, The Gerontological Society of America *Mary Ann Forciea*, Clinical Professor of Geriatric Medicine, University of Pennsylvania Perelman School of Medicine; American College of Physicians *Lisa Shulman*, Eugenia Brin Professor of Parkinson's Disease and Movement Disorders, Director of the University of Maryland Movement Disorders Center, University of Maryland; Treasurer, American Academy of Neurology *Regina Davis Moss*, Associate Executive Director of Public Health Policy and Practice, American Public Health Association
5:00 p.m.	Discussion with Committee Members
5:15 p.m.	Public Comment Period
5:25 p.m.	Closing Remarks *Alan Leshner*, Committee Chair *Story Landis*, Committee Vice-Chair
5:30 p.m.	Public Session Adjourns

Third Committee Meeting
Open Session: January 31, 2017

Meeting Objective:

- Discuss significant changes from the draft to the final AHRQ systematic review, which forms the predominant basis for the work of the National Academies' Committee on Preventing Dementia and Cognitive Impairment.

9:00-9:05 a.m. **Welcome**
Alan Leshner, CEO Emeritus, American Association for the Advancement of Science, *Committee Chair*

Brief Remarks
Richard Hodes, Director, NIA
Marie A. Bernard, Deputy Director, NIA

9:05-9:25 a.m. **Overview of Changes from the Draft to the Final AHRQ Systematic Review**
Robert Kane, Director, Minnesota Evidence-based Practice Center

9:25-10:00 a.m. **Discussion with Committee Members**
Additional Respondents: *Mary Butler* and *Howard Fink*, Minnesota Evidence-based Practice Center

10:00 a.m. **Adjourn open session**

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BIOSKETCHES OF COMMITTEE MEMBERS

Alan I. Leshner, M.S., Ph.D. (*Chair*), is chief executive officer, emeritus, of the American Association for the Advancement of Science (AAAS) and former executive publisher of the journal *Science*. Previously, Dr. Leshner was director of the National Institute on Drug Abuse at the National Institutes of Health (NIH). He also served as deputy director and acting director of the National Institute of Mental Health (NIMH) and in several roles at the National Science Foundation. Before joining the government, Dr. Leshner was professor of psychology at Bucknell University. He is an elected fellow of AAAS, the American Academy of Arts and Sciences, the National Academy of Public Administration, and many other professional societies. He is a member of and served on the governing Council of the National Academy of Medicine. He was appointed by President Bush to the National Science Board in 2004, and then reappointed by President Obama in 2011. Dr. Leshner received Ph.D. and M.S. degrees in physiological psychology from Rutgers University and an A.B. in psychology from Franklin and Marshall College. He has been awarded seven honorary doctor of science degrees.

Story Landis, Ph.D. (*Vice Chair*), is director, emerita, of the National Institute of Neurological Disorders and Stroke (NINDS). She received her undergraduate degree from Wellesley College and her Ph.D. from Harvard University. After postdoctoral work at Harvard University, she served on the faculty of the university's Department of Neurobiology. In 1985, she joined the faculty of Case Western Reserve University School of Medicine, where she created the Department of Neurosciences that, under her leadership, achieved an international reputation for excellence. Dr. Landis joined

NINDS in 1995 as scientific director and worked to reengineer the Institute's intramural research program and fostered the growth of a trans-NIH neuroscience community that led to the construction of the Porter Neuroscience Building on the NIH campus. From 2003 to 2014, she served as NINDS director, overseeing an annual budget of $1.6 billion that supported research by investigators in its intramural program and public and private institutions across the country. Together with NIMH and National Institute on Aging (NIA) directors, she co-chaired the NIH Blueprint for Neuroscience Research, a roadmap-like effort to support trans-NIH activities in the brain sciences. In 2013 and 2014, she and Dr. Tom Insel played a key role in launching the NIH BRAIN Initiative. Dr. Landis currently serves on the scientific advisory boards of the Vollum Institute at Oregon Health & Science University and the Neurological Research Institute at Baylor College of Medicine, as well as the scientific review boards of the Howard Hughes Medical Institute and the Wellcome Trust. Throughout her research career, she has made fundamental contributions to the understanding of how functionally appropriate synapses form during development and the role of neurotrophins in peripheral nervous system. She is an elected fellow of the National Academy of Medicine, the Academy of Arts and Sciences, and the American Association for the Advancement of Science, and is the 2015 recipient of the Ralph W. Gerard Prize from the Society of Neuroscience for outstanding contributions to neuroscience throughout her career.

Marilyn Albert, Ph.D., is a professor of neurology at Johns Hopkins and director of the Division of Cognitive Neuroscience. She received her Ph.D. in physiological psychology from McGill University in Montreal and completed a fellowship in neuropsychology at Boston University School of Medicine. She served on the faculty of the Harvard Medical School for more than 22 years. Dr. Albert focuses on the cognitive and brain changes associated with aging and Alzheimer's disease (AD). Her work has delineated the cognitive changes associated with aging and early AD, along with potential methods of early identification of AD. She has also identified lifestyle factors that promote maintenance of mental abilities with advancing age. Dr. Albert's research currently focuses on the early identification of AD and potential ways of monitoring the progression of disease to permit early intervention.

Lisa L. Barnes, Ph.D., is a professor in the departments of Neurological Sciences and Behavioral Sciences at Rush University Medical Center and a cognitive neuropsychologist in the Rush Alzheimer's Disease Center. She earned her Ph.D. in biopsychology from the University of Michigan and completed postdoctoral training in cognitive neuroscience at the University of California, Davis, before joining the faculty at Rush in 1999. Her research focus is

on racial disparities in chronic diseases of aging. She is principal investigator of several community-based cohort studies of older African Americans and director of the Rush Center of Excellence on Disparities in HIV and Aging. Dr. Barnes is nationally recognized for her contributions to minority aging and health disparities, and has published extensively on risk factors for cognitive aging and dementia in older African Americans. She is an advocate for Alzheimer's disease awareness in the minority communities in which she serves.

Dan G. Blazer, M.P.H., M.D., Ph.D., is former dean of medical education and currently J.P. Gibbons professor emeritus of psychiatry and behavioral sciences at Duke University in Durham, North Carolina. He is a professor of community and family medicine. He also serves as adjunct professor in the Department of Epidemiology, School of Public Health, at the University of North Carolina. Dr. Blazer received his M.D. degree from the University of Tennessee and his M.P.H. and Ph.D. degrees from the University of North Carolina at Chapel Hill. He was elected to the National Academy of Medicine in 1995, where he chaired the membership committee for 2 years (2005-2007). He was awarded the Walsh McDermott Award from the Institute of Medicine (IOM) in 2014 for distinguished lifetime service to the institute. He currently serves on the editorial board of the *Archives of General Psychiatry* and as chair of the Board on the Health of Select Populations. He chaired the IOM committee on the public health aspects of cognitive aging, whose report released in 2015.

Mark A. Espeland, Ph.D., is a professor of public health sciences at the Wake Forest School of Medicine, where he was founding chair of its Department of Biostatistical Sciences. Trained as a biostatistician and an expert in statistical analysis, in the last decade Dr. Espeland has directed much of his research toward conducting clinical trials of strategies to preserve physical and cognitive function during later life. He has authored/co-authored more than 260 methodological and biomedical journal articles and has received awards for his research from the American Heart Association and American Diabetes Association. He has held leadership positions in more than two dozen coordinating centers for major studies and is a frequent consultant to NIH and industry. He has served on or chaired dozens of data safety monitoring boards (DSMBs) for NIH and industry and currently serves on the NIA Clinical Trials Advisory Panel.

J Taylor Harden, R.N., Ph.D., is executive director, National Hartford Center of Gerontological Nursing Excellence, at the Gerontological Society of America (GSA). She is a social and behavioral nurse scientist with expertise in aging. Prior to her current position, she was affiliated with the

Building Academic Geriatric Nursing Capacity Initiative at the American Academy of Nursing and NIA. At NIA she served as both Assistant to the Director for Special Populations (1997-2011) and Acting Deputy Director (2008). Prior to joining NIA in 1994, she was a tenured associate professor at the University of Texas Health Science Center at San Antonio where she taught in both graduate and undergraduate programs. Dr. Harden has wide-ranging research and administrative expertise in aging research, with emphases in research administration, clinical interventions, risk and resilience in older women, minority health/health disparities, recruitment and retention of older adults, and mentoring and career development of early career scientists. She earned her B.S. and M.S. degrees from the University of Maryland at Baltimore and her Ph.D. in nursing from The University of Texas at Austin.

Claudia H. Kawas, M.D., Al and Trish Nichols chair in clinical neuroscience and professor of neurobiology and behavior and neurology, University of California, Irvine, is a geriatric neurologist and researcher in the areas of aging and dementia. Her work is concentrated on the epidemiology of aging and Alzheimer's disease, the determinants of successful aging, longitudinal and clinical pathological investigations, clinical trials, and most recently studies of cognitive and functional abilities of the oldest old (over 90 years of age). Dr. Kawas is a graduate of Swarthmore College, and completed her medical studies at the University of Louisville and her neurology residency training and a fellowship in dementia and aging at Albert Einstein College of Medicine. After 15 years on the faculty of the Johns Hopkins University School of Medicine, Dr. Kawas moved to the University of California, Irvine (UCI), in 2000, where she is principal investigator of The 90+ Study and associate director of the UCI Institute for Memory Impairments and Neurological Disorders. She serves on committees for NIH and the scientific advisory boards of several organizations, including the Medical and Scientific Advisory Council of the National Alzheimer's Association, The Dana Foundation, and the Food and Drug Administration.

Nan M. Laird, Ph.D., is the Harvey V. Fineberg research professor of biostatistics in the Harvard School of Public Health. Dr. Laird has contributed to methodology in many different fields, including longitudinal data analysis, missing data, meta-analysis, and family-based association studies in genetics. She has coauthored two popular textbooks, on longitudinal data analysis and on statistical genetics. She has received numerous awards, including the Florence Nightingale David award and the Samuel S. Wilkes Award, both from the American Statistical Association.

Kenneth M. Langa, M.D., Ph.D., is the Cyrus Sturgis professor of medicine in the Division of General Medicine, Veterans Affairs Health Services Research and Development (HSR&D) Center for Clinical Management Research, Institute for Social Research, Institute for Healthcare Policy and Innovation, and Institute of Gerontology, University of Michigan. He is also associate director of the Health and Retirement Study (HRS), an NIA-funded longitudinal study of 20,000 adults in the United States. Dr. Langa received an M.D. and a Ph.D. in public policy at the University of Chicago as a fellow in the Pew Program for Medicine, Arts, and the Social Sciences. He is a board-certified general internist with an active clinical practice treating adult patients, and is an elected member of the American Society for Clinical Investigation (ASCI). His research focuses on the epidemiology and costs of chronic disease in older adults, with an emphasis on Alzheimer's disease and other dementias. He has published more than 200 peer-reviewed articles on these topics. He is currently studying population trends in dementia prevalence, and the relationship of common cardiovascular risk factors, as well as acute illnesses such as sepsis and stroke, to cognitive decline and dementia. In 2007 and 2015, Dr. Langa served as a visiting professor at the Institute of Public Health, University of Cambridge, and in 2015, he was also a visiting professor at the World Health Organization in Geneva, Switzerland, where he continued work on cross-national comparisons of the epidemiology and outcomes of dementia in the United States, England, and other countries around the world.

Eric B. Larson, M.D., M.P.H., is executive director of Kaiser Permanente Washington Health Research Institute and vice president for research and health care innovation at Kaiser Foundation Health Plan of Washington. A graduate of Harvard Medical School, he trained in internal medicine at Beth Israel Hospital in Boston, completed a Robert Wood Johnson Clinical Scholars and M.P.H. program at the University of Washington (UW), and then served as chief resident of University Hospital in Seattle. He served as medical director of the University of Washington Medical Center and associate dean for clinical affairs, 1989-2002. Dr. Larson's research spans a range of general medicine topics and has focused on aging and dementia, and includes a long-running study of aging and cognitive change set in the Group Health Cooperative—the UW/Group Health Alzheimer's Disease Patient Registry/Adult Changes in Thought Study. He has served as president of the Society of General Internal Medicine, chair of the Office of Technology Assessment/Department of Health and Human Services Advisory Panel on Alzheimer's Disease and Related Disorders, and chair of the Board of Regents (2004-2005) of the American College of Physicians. He is an elected member of the National Academy of Medicine.

José A. Luchsinger, M.P.H., M.D., is an associate professor of medicine and epidemiology at Columbia University Medical Center. He is a general internist and epidemiologist whose main research focus has been the study of modifiable risk factors and prevention of cognitive disorders, including Alzheimer's dementia. He is the principal investigator of two R01s from NIA focused on risk factors for Alzheimer's disease, and grants from the National Institute on Nursing Research (NINR) and the Patient-Centered Outcomes Research Institute (PCORI) focused on the health of caregivers of persons with dementia. Dr. Luchsinger is the leader of the cognitive coordinating center of the Diabetes Prevention Program Outcomes Study (DPPOS) and the Glycemia Reduction Approaches in Diabetes study (GRADE), funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). He is editor-in-chief of the journal *Alzheimer Disease & Associated Disorders*. He received his M.D. from the Universidad Central de Venezuela and his M.P.H. from Columbia University.

Ronald C. Petersen, M.D., Ph.D., is director of the Mayo Clinic Alzheimer's Disease Research Center and the Mayo Clinic Study of Aging. He received a Ph.D. in experimental psychology from the University of Minnesota and graduated from Mayo Medical School in 1980. He completed an internship in medicine at Stanford University Medical Center and returned to Mayo Clinic to complete a residency in neurology. He then completed a fellowship in behavioral neurology at Harvard Medical School/Beth Israel Hospital in Boston. Dr. Petersen joined the staff of Mayo Clinic in 1986 and became a professor of neurology in 1996. His current research focuses on the study of normal aging, mild cognitive impairment, and Alzheimer's disease. Dr. Petersen consults for the Federal Trade Commission. He formerly was chair of the Alzheimer's Association Medical and Scientific Advisory Council and is now on its board of directors. He was a member of the National Advisory Council on Aging and the Board of Scientific Counselors of NIA and is the chair of the Advisory Council on Alzheimer's Research, Care and Services for the National Alzheimer's Project Act, and serves on the World Dementia Council.

Ralph L. Sacco, M.S., M.D., is the chairman of neurology; Olemberg Family chair in neurological disorders; Miller Professor of neurology, epidemiology and public health sciences, human genetics, and neurosurgery; executive director of the Evelyn McKnight Brain Institute, Miller School of Medicine, University of Miami; and chief of the neurology service at Jackson Memorial Hospital. A graduate of Cornell University in bioelectrical engineering and a cum laude graduate of Boston University School of Medicine, he also holds an M.S. in epidemiology from the Columbia University Mailman

School of Public Health. Dr. Sacco completed his neurology residency training and postdoctoral training in stroke and epidemiology at Columbia Presbyterian in New York. He was previously professor of neurology, chief of Stroke and Critical Care Division, and associate chairman, Columbia University. He is principal investigator of the NINDS-funded Northern Manhattan Study, the Florida Puerto Rico Collaboration to Reduce Stroke Disparities, and the Family Study of Stroke Risk and Carotid Atherosclerosis, as well as co-investigator of multiple other NIH grants. He has also been the co-chair of international stroke treatment and prevention trials. Dr. Sacco has published extensively with more than 425 peer-reviewed articles and 102 invited articles in the areas of stroke prevention, treatment, epidemiology, risk factors, vascular cognitive impairment, human genetics and stroke recurrence. His research has also addressed stroke and vascular disparities. He has been the recipient of numerous awards including, the Johann Jacob Wepfer Award from the European Stroke Conference, the American Heart Association's Golden Heart Award, the Feinberg Award of Excellence in Clinical Stroke, the Chairman's Award from the American Heart Association, the NINDS Javits Award in Neuroscience, and been elected to the American Association of Physicians. He has lectured extensively at national and international meetings. Dr. Sacco is a fellow of the Stroke and Epidemiology Councils of the American Heart Association, the American Academy of Neurology, and the American Neurological Association. He has been a member of the World Stroke Organization since 2008 and currently chairs the research committee, and is on the board of directors. He currently serves as president elect of the American Academy of Neurology and as a member of the National Advisory NINDS Council. He was the first neurologist to serve as the president of the American Heart Association, 2010-2011.

Sudha Seshadri, M.D., is a professor of neurology at the Boston University School of Medicine and a senior investigator of the Framingham Heart Study (FHS), where she leads the neurology and neurogenetics cores. As a board-certified neurologist, she has been diagnosing and treating patients with dementia and mild cognitive impairment for more than two decades. She is also principal investigator on five NIH grants that fund dementia surveillance, magnetic resonance imaging (MRI), and amyloid and tau positron emission tomography (PET) imaging, neuropsychological testing and brain autopsies on FHS participants. Her research focuses on risk prediction; temporal trends; primary prevention; and the lifestyle, vascular, metabolic, biomarker, and genetic risk factors underlying dementia, stroke, Alzheimer's disease, vascular cognitive impairment, and healthy brain aging. She has more than 200 peer-reviewed publications, has authored or edited 3 books

and 10 chapters, serves on the editorial board of *Neurology*, *Stroke*, and *Journal of Alzheimer's Disease*, and chairs an NIH Study Section. She leads the neurology working group within the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium, is a founding principal investigator of the International Genomics of Alzheimer Project and the Alzheimer Disease Sequencing Project, and currently is vice-chair of the METASTROKE consortium. In addition to numerous genetic analyses, she is undertaking collaborative research with other cohorts exploring a possible protective role of diabetes and hypertension treatments in cognitive decline and dementia risk and of physical activity in cognitive decline.

Leslie B. Snyder, Ph.D., is professor and interim department head of communication at the University of Connecticut (UConn). She holds master's and Ph.D. degrees in communications from Stanford University and was director of the Center for Health Communication and Marketing, a Centers for Disease Control and Prevention (CDC) Center of Excellence, at UConn, 2006-2013. Dr. Snyder conducts research on media effects, communication campaigns, health, and international communication. Her research includes design and evaluation of communication-based interventions, meta-analyses of campaign effects, population-based surveys, and experimental work on messaging and communication channels. She has received more than $7 million in research funding from NIH, CDC, and other sources, and regularly consults on national health campaigns. In 2008, she received the American Public Health Association's Rogers Health Communication Award for her research. Recent studies have examined mobile media, mobile devices, games, and traditional media across a range of topics, including tobacco, alcohol, HIV/AIDS, family planning, maternal/child health, physical activity and sedentary behaviors, food marketing, and nutrition. Dr. Snyder co-edited *The Sage Sourcebook of Advanced Data Analysis Methods for Communication Research*. She served on the Institute of Medicine Committee on the Public Health Dimensions of Cognitive Aging.

Kristine Yaffe, M.D., is a professor of psychiatry, neurology, and epidemiology and Roy and Marie Scola endowed chair and vice chair of research in psychiatry at the University of California, San Francisco (UCSF). She attended Yale University for her undergraduate degree, received her medical degree at the University of Pennsylvania, and completed residencies in neurology and psychiatry at UCSF. In her research, clinical work, and mentoring, she has directed her efforts toward improving the care of patients with cognitive disorders and other geriatric neuropsychiatric conditions. Dr. Yaffe serves on the Council of the German Center for Neurodegenerative Diseases and the Alzheimer's Association Medical & Scientific Advisory

Council, and was the co-chair of the Institute of Medicine's Committee on the Public Health Dimensions of Cognitive Aging. As the current principal investigator of seven NIH grants, as well as several other Department of Defense and Department of Veterans Affairs grants, Dr. Yaffe's research focuses on the epidemiology of dementia and cognitive aging.