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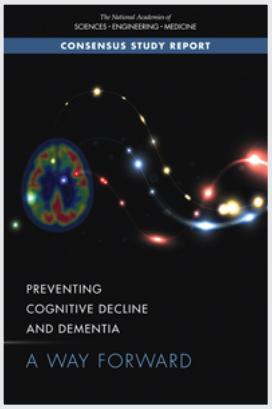

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Preventing Cognitive Decline and Dementia: A Way Forward (2017)

DETAILS

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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.

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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

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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.

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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

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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:

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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:

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- ***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

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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).

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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

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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

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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-

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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

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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

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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

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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.

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