Comparative Effectiveness Review
Number 188

Effective Health Care Program

Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia

Executive Summary

Background

Dementia severely erodes individuals' functioning and quality of life, creates burden and stress on the entire family, and is a major predictor of institutionalization. Although the age and sex standardized prevalence of dementia and the rates of incident dementia have fallen over the last several decades,[1, 2] the number of U.S. adults over 70 with dementia and mild cognitive impairment is rising.[3, 4] Additionally, dementia-related costs are high, exceeding even those of heart disease and cancer, and are often paid directly by families.[5] Given such enormous family and societal burdens, identifying interventions with potential to prevent or delay the onset of dementia is an urgent public health priority. Although many putative risk factors have been identified, the challenge is to identify any interventions that can lead to reductions in dementia incidence and make them more widespread.

The terminology used to describe dementia and cognitive impairment is inconsistent and changing, although the National Institute on Aging (NIA) and the Alzheimer's Association have jointly issued criteria and guidelines.[6] Diagnosis of a neurocognitive disorder due to Alzheimer's disease requires steadily progressive cognitive decline from a previous level, generally with

Objective

To assess the effectiveness of 13 interventions for preventing or delaying the onset of age-related cognitive decline, mild cognitive impairment (MCI), or clinical Alzheimer's-type dementia (CATD).

Key Messages

- Most interventions showed no evidence of benefit to delay or prevent age-related cognitive decline, MCI, and/or CATD.
- Some forms of cognitive training improve the performance of the specific target of training for adults with normal cognition, but little evidence supports transfer of benefits to other cognitive areas or reduced dementia incidence. Benefit for any form of cognitive training beyond 2 years is less certain.
- Some types of physical activity, and vitamin B12 plus folic acid, may benefit cognitive performance in some areas for adults with normal cognition.

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predominant early impairment in learning and memory that occurs outside the context of delirium and is not better explained by other mental disorders. If the decline interferes with independence in everyday activities, it is classified as major; if not, as mild. For this report, the term clinical Alzheimer's-type dementia (CATD) is used to recognize the clinical reality that a certain diagnosis of Alzheimer's disease is rarely possible in clinical settings and patients often have dementia from some unknown mix of etiologies. This term (CATD) is designed to be inclusive but does exclude several other forms of dementia (such as Lewy body disease, infectious disease, frontotemporal, traumatic brain injury, or isolated post-stroke dementia), including some that can otherwise be well-identified. Because the literature currently does not use the term CATD, we specified whenever the diagnosis of dementia was defined.

Some decline in cognition with aging is considered normal or inevitable, particularly for people past the age of 60 years. For example, reaction time and speed of processing are known to decline slowly throughout adulthood. Therefore, greater difficulty learning new information by 70 or 80 years old may not necessarily be a warning sign of neurocognitive disease in the absence of other signs or symptoms of cognitive difficulty. This type of normal cognitive aging is called age-related cognitive decline and is highly variable between individuals.[7] The relationship between age-related cognitive decline and dementia is unclear.

If the magnitude of cognitive decline exceeds a threshold (variously defined), the individual is said to have an intermediate form of cognitive impairment. This threshold may be defined symptomatically when the cognitive decline is recognized by the affected individual, caregiver, or health professional, and requires the individual to compensate using tools, such as lists, maps, or pill boxes, to continue to perform daily activities. This threshold also may be defined based upon formal cognitive testing scores below norms for younger populations, even if there are no changes in function. In 1995, Petersen et al. formally defined mild cognitive impairment (MCI) as the presence of subjective memory complaints and performance on memory testing 1.5 standard deviations below age-appropriate norms, in the setting of preserved activities of daily living.[8] Subsequently, the definition of MCI was broadened to include amnestic, multiple (cognitive) domain, and single non-memory domain subtypes.[9] MCI corresponds to mild neurocognitive disorder in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5).[10] Roughly half of people with MCI will progress to a more severe form of cognitive decline over about 3 years.[11]

A separate Institute of Medicine committee (not connected with this study) recently recognized that using a history of functional decline to distinguish between MCI and dementia is a problem,[7] because the presence of functional impairment depends on social factors independent of the underlying disease causing cognitive impairment. Recognizing and measuring cognitive and functional decline depends upon the life-circumstances of the individual and the source of information about cognitive and functional performance (e.g., self, caregiver, and employer). For example, minor forgetfulness for a retiree may have less impact on function and be reported differently than it would for the same person still in a cognitively challenging workplace. Likewise, modest loss of numeric skills may be unreported and insignificant for many older adults, but catastrophic for a scientist or an accountant.

Alzheimer's disease is the most commonly diagnosed dementia, but people may be affected by several types of dementia simultaneously. Individuals who meet the clinical criteria for Alzheimer's disease are more likely than others to have certain genetic markers, patterns on brain imaging (e.g., hippocampal atrophy), specific types of protein accumulation in the brain, or abnormal appearance of brain cells examined at autopsy. Yet, the relationship between these laboratory or imaging findings and measures of cognition are inconsistent and it is not clear whether some of these laboratory or imaging findings are causes of or caused by Alzheimer's disease. This type of uncertainty greatly complicates efforts to prevent or slow impairments in cognition that are a prelude to Alzheimer's disease.

A number of reviews have assessed the evidence of relationships between risk and protective factors and/or cognitive decline, MCI, and CATD, including the 2015 Institute of Medicine report on cognitive aging cited above[7] and a 2010 Agency for Healthcare Research and Quality (AHRQ) systematic review.[12] Nonmodifiable risk factors for CATD include age, sex, race/ethnicity, and family history. Certain medical conditions are associated with an increased risk of developing MCI and CATD, including depression, cancer, cardiovascular disease, diabetes, delirium, thyroid disorders, chronic kidney disease, and loss of hearing and/or vision. Modifiable risk or protective factors may include diet, physical activity, education and intellectual engagement, social engagement, alcohol, smoking, and substance abuse, medications, and vitamins. Interventions represent one way to establish the veracity of risk factors. If changing a putative risk factor changes the cognitive course, it will be seen as more salient.

Interventions have been developed to prevent or treat chronic diseases and to modify risk factors and protective factors. Multidomain interventions address multiple risk factors simultaneously, including nutrition, physical activity, cognitive training, social activity, and/or vascular risk factor management.[13]

Theories justifying various interventions to slow or prevent cognitive decline are diverse. If cognitive decline is due to natural age-related degeneration of the brain, the theory of neuroplasticity suggests that cognitive training could be useful to stimulate the brain to build additional neural pathways and to retain existing ones to build brain reserve against future decline. If brain degeneration and cognitive decline are due to toxins or lack of specific nutrients, changes in diet or nutritional supplements could be effective. If adequate blood flow to the brain is important in preventing cognitive decline, then medications and exercise that stimulate and maintain the health of the vascular system may be helpful. If inflammation is part of the disease process, anti-inflammatory drugs may be effective. These theories support prevention trials testing cognitive training, physical exercise, cardiovascular and other medications, diets, and nutraceuticals (products derived from food sources that are purported to provide extra health benefits). Preventive efforts can target people with any level of cognitive function, from normal, to age-related cognitive decline, to MCI, and finally, to dementia.

Research participants seeking to slow or prevent age-related cognitive decline, MCI, and CATD may have more than one risk factor. CATD may result from cumulative and possibly synergistic effects. Interventions may address one or multiple possible mechanisms with complex or multiple prevention strategies. Differential effects of interventions on subgroups defined on the basis of cumulative risk factors (both modifiable and nonmodifiable) may be of concern. Many studies testing the association of preventive factors or effectiveness of interventions for preventing dementia have looked at only the one-to-one relationship with a single risk factor or intervention. Few studies used multidomain interventions, and potentially none have explored the possibility of cumulative or synergistic effects.

Timing and measurement choices affect cognitive decline prevention studies. Researchers can recruit participants at any point along the cognitive continuum. Various proposed strategies target young and middle-aged adults with no evidence of cognitive decline, older adults worried about age-related changes, people with documented MCI, and those with major neurocognitive disorders. Common diseases that cause cognitive decline, especially CATD, progress slowly. Lengthy time periods are required between an intervention and the expectation of measurable cognitive decline or function in those not receiving an effective preventive intervention; the younger the participant, the longer the latency period. Short-term benefits on cognitive tests or biomarkers are uncertain predictors of long-term effects on cognition.

Proof that an intervention prevents or delays MCI or dementia ideally includes evidence that the intervention led to fewer individuals with a subsequent diagnosis of MCI or CATD. Such measures are rarely possible, due to the extended study length required (i.e., >10 years) or the extremely large number of participants (i.e., thousands) required, plus the complexity of measuring both cognition and functional abilities. Over shorter terms and in smaller studies, changes in cognitive function are assessed using validated neurocognitive tests addressing various domains of cognition. To assess changes in brain functional abnormalities earlier or with greater sensitivity than is possible with behavior-based testing or interviews, a variety of laboratory and brain imaging tests are used as biomarker measures to look for changes in specific biologic substances, structures, or processes. Improvement or slower deterioration from baseline biomarker measures could indicate a slowing of age- or disease-related decline as a result of an intervention, to the extent that the biomarker is an accurate reflection of brain capacity and activity. As noted before, there is a good deal of inconsistency regarding the relationship between biomarkers and cognitive function.

Scope and Key Questions

This systematic review is focused on intervention studies that target populations who are cognitively normal or may have age-related changes or MCI but do not yet have dementia. Specifically, this review examines the effectiveness of interventions to delay or slow cognitive decline or dementia, and did not examine the epidemiological literature on risk factors for cognitive decline or dementia. With the focus on CATD, the review does not include dementia due to specific, identifiable conditions such as Lewy body, infectious diseases, frontotemporal, and traumatic brain injury. The review does include studies addressing vascular components of mixed dementia, but clear post-stroke dementia is out of scope. Intermediate outcomes, such as measures of biomarkers and cognitive test performance, are included. However, since the review is focused on prevention, studies must be at least 6 months in duration to demonstrate some sustainability of the intervention effects. It is important to

note that this duration requirement by necessity eliminates many short-term studies in this field.

The review addresses two Key Questions (KQs) and the PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) framework that address the effects of interventions for delaying or slowing age-related cognitive decline and preventing, delaying or slowing MCI and clinical Alzheimer's-type dementia. The third KQ addresses the strength of association between various intermediate outcomes (e.g., biomarkers) with MCI and CATD.

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, slowing, or delaying the onset of MCI?
iii. 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 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?

Methods

Because of the overall plan for the use of this review given by our NIA sponsor, this project follows a unique model. The role of the Key Informants was filled by the National Academies of Sciences, Engineering, and Medicine (the National Academies) Committee on Preventing Dementia and Cognitive Impairment. The National Academies Committee will use the report to help develop its own report to the NIA on the state of knowledge on the efficacy, comparative effectiveness, and harms of interventions to prevent or delay the onset of age-related cognitive decline, MCI, or CATD. Because the National Academies Committee did not see the draft KQs, PICOTS, and analytic framework until the KQs were posted for public comment, a panel of content experts from Federal agencies acted as proxy Key Informants prior to posting. The content experts were drawn from the NIA, the National Institute of Neurological Disorders and Stroke, the Department of Veterans Affairs, the Administration for Community Living, and the Centers for Disease Control & Prevention. There was not a separate, independent Key Informant panel. The role of the Technical Expert Panel was then filled by the National Academies Committee.

A complete description of the methods can be found in the full report.

Literature Search Strategy

We searched Ovid Medline®, Ovid PsycINFO®, Ovid Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials (RCTs), nonrandomized controlled trials, and prospective cohort studies published and indexed in bibliographic databases between January 2009 and September 2016. We supplemented bibliographic database searches with backward citation searches of highly relevant systematic reviews and included studies.

Eligibility

We included randomized and nonrandomized controlled trials and observational studies published in English that examined one or more interventions to prevent, delay, or slow age-related cognitive decline, MCI, and CATD in adults with normal cognition and/or MCI, used a comparator group, and reported outcomes of interest in participants at least 6 months or more after the initiation of the intervention. Observational studies were included if they were prospective quasi-experimental cohort studies that had at least 250 participants per arm.

Two independent investigators independently determined study eligibility and resolved disagreements through discussions; when needed, a third investigator was consulted until consensus was achieved.

Data Extraction

We extracted data from included studies into evidence tables including author, year of publication, population, intervention, comparison, outcomes, timing, and setting. Results were extracted only from studies assessed as having low to moderate risk of bias. Initial data abstraction was quality checked by a second investigator.

Quality (Risk of Bias) Assessment of Individual Studies

The risk of bias of eligible studies was assessed by two independent investigators using an instrument based on AHRQ guidance.[14] Two investigators consulted to reconcile any discrepancies in overall risk of bias assessments and, when needed, a third investigator was consulted to reconcile the summary judgment. Overall summary risk of bias assessments for each study were classified as low, medium, or high based on the collective risk of bias inherent in each quality domain and confidence that the results are believable given the study's limitations.

Data Synthesis

We summarized results in summary tables and synthesized evidence for each unique population, intervention, comparison, and outcome and harm. We organized evidence tables and results by intervention type and population addressed. Subgroups, where possible, were examined and reported separately.

We reported summary results for primary and intermediate outcomes and harms. Intermediate cognitive outcomes were assessed using neuropsychological tests or biomarkers. Because studies used a highly varied set of tests, we opted to group them into categories to facilitate analysis. We categorized neuropsychological tests for extraction and analysis by their purpose and/or what they attempt to measure, such as specific cognitive domains (e.g., executive function, memory) (Appendix C of the full report). Since cognitive interventions often targeted individual cognitive functions, we reported on these domains in greater detail than was necessary for other sections of the report. The wide variety and inconsistency of tests used made it difficult to summarize the findings and prevented meta-analysis. For the cognitive training interventions we did use Cohen's D to estimate effect size where possible.

Strength of the Body of Evidence

We evaluated the overall strength of evidence for MCI or CATD incidence, or cognitive performance domains based on four strength of evidence domains: (1) study limitations (internal validity including risk of bias, either low or medium); (2) directness (single, direct link between the intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate) with the study limitations domain having considerable importance.[15] Study limitations were rated as low, moderate, or high according to study design and conduct. The possible strength of evidence grades were:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change the estimates.
- Moderate: Moderate confidence that the estimate reflects the true effect. Further research may change estimates and our confidence in the estimates.
- Low: Limited confidence that the estimate of effect lies close to true effect. Further research is likely to change confidence in the estimate of effect, and may change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.

Applicability

Applicability of studies was determined according to the PICOTS framework. Study characteristics that were evaluated to assess applicability included, but were not limited to, the population from which the study participants were enrolled, narrow eligibility criteria, baseline cognitive function, and patient and intervention characteristics different than those described by population studies.[16]

Results

We identified 9,448 unique references, 263 of which were eligible for our review. Table A provides a summary of the key messages from the results chapters detailing intervention results. Of the 13 classes of interventions examined, we found no high-strength evidence for any intervention to delay or prevent age-related cognitive decline, MCI, and/or CATD. A few specific interventions reached moderate strength evidence for no benefit in cognitive performance: vitamin E in women; and angiotensin converting enzyme and thiazide versus placebo and angiotensin receptor blockers versus placebo on specifically brief cognitive screening tests. We found low-strength evidence that the selective estrogen receptor modulator (SERM) raloxifene reduced risk of probable MCI. However, there was also low-strength evidence that estrogen replacement with or without progesterone therapy increased the risk of MCI and CATD.

A few intervention types show more potential than others at benefiting cognitive performance. We found moderate-strength evidence that cognitive training can improve cognitive function in the domain trained up to 2 years (low strength of evidence at 5 and 10 years), but generalization/transfer to other domains was rare. Although there was some evidence for improvement in instrumental activities of daily living (IADLs), these studies had design problems and short-term studies may not predict long-term

outcomes. Moreover, IADLs may be a benefit per se, but are not directly linked to dementia.

Although the evidence is less compelling, physical activity and perhaps vitamin B12 plus folic acid may also show potential benefit. While the majority of the results for physical activity showed little to no effect, the percent of results showing benefit in cognitive performance, particularly in resistance training and aerobic exercise, were unlikely to be explained solely by chance. Results for B12 plus folic acid are more spotty and so less persuasive; vitamin B12 and folic acid showed benefit in brief cognitive test performance and memory, but not for executive/attention/processing speed. There were also conflicting findings for B12 when used in combination with other B vitamins.

Notably, not all interventions for risk factors of interest were addressed by the eligible literature sufficiently for an assessment of these strategies to be made. For example, obesity is a risk factor of concern but it can be studied only in the context of prevention/intervention by assessing the impact of weight loss interventions. In the current systematic review, only one medium risk of bias trial specifically targeted weight loss. Some classes of interventions of interest were absent from the literature altogether, including interventions aimed at depression, smoking cessation, or community-level interventions. Other intervention types were represented by a literature set that was relatively sparse and likely did not represent a full range of possible interventions designs, such as sleep interventions. Lastly, with respect to the stroke prevention literature, although this study included the literature relevant to the vascular components of mixed dementias, it deliberately excluded dementia caused specifically by stroke. Thus, the findings may underestimate the effects of controlling blood pressure on dementias as a whole.

Table A. Summary of key messages by intervention class

Intervention	Key Message
Cognitive Training	• Most studies addressed intermediate outcomes 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 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.
Physical Activity Interventions	• Studies of physical activity interventions examined a wide variety of activities 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.
Nutraceutical Interventions	• Low-strength evidence suggests omega-3 fatty acids and ginkgo biloba did not reduce CATD incidence or improve cognitive performance in adults with normal cognition. • Evidence is insufficient to conclude whether resveratrol or plant sterol/stanol esters reduced CATD incidence or improved cognitive performance in adults with normal cognition. • Few studies examined the effects of nutraceuticals on adults with MCI.
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.

Table A. Summary of key messages by intervention class (continued)

Intervention	Key Message
Multimodal Interventions	• Evidence is insufficient to conclude whether most multimodal interventions offer benefits for cognitive performance or incidence of MCI or CATD, largely because few studies have examined interventions with similar components. • Low-strength evidence shows that a multimodal intervention composed of diet, physical activity, and cognitive training provides benefits in executive function/attention/processing speed. • Low-strength evidence shows that a multimodal intervention composed of lifestyle advice and drug treatment is not effective in reducing incidence of CATD or benefiting brief cognitive test performance or memory.
Hormone Therapy Interventions	• Hormone therapy shows mixed results of harm and benefit. • 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
Vitamin Interventions	• Moderate-strength evidence shows no benefit in cognitive performance for vitamin E in women. • There was some signal that B12 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 B12 (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 B12 (0.1-0.5 mg) versus placebo for executive/attention/processing speed. • Low-strength evidence for vitamin B12 (0.02=0.5 mg), B6 (3-10 mg), and folate (0.56-1 mg) shows no benefit for executive/attention/processing speed. • Low-strength evidence shows no benefit in cognitive performance for multivitamins, vitamin C (in women), vitamin D with calcium (in women), or beta carotene (in women). • Low-strength evidence shows no benefit in incident MCI or CATD for multivitamins or vitamin D with calcium. • In adults with MCI, low-strength evidence shows no benefit for vitamin E in incident CATD.
Antihypertensive Treatment	• 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.

Table A. Summary of key messages by intervention class (continued)

Intervention	Key Message
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.
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 followup after 1 to 3 years of use.
Antidementia Treatments	• Low-strength evidence shows AChEI antidementia drugs did not reduce the incidence of CATD in persons with MCI over 3 years; evidence is insufficient for persons with normal cognition. • Low-strength evidence shows AChEIs for 3 years provide no significant effect on cognitive performance in adults with MCI.
Diabetes Medication Treatment	• No studies reported on the effect of diabetes treatment on the risk of incident clinical diagnoses of MCI or CATD. • 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.
Other Interventions	• Evidence was insufficient for lithium, a nicotine patch, individual piano instruction, multitask rhythmic exercise to music, sleep interventions, and social engagement. • We found no relevant studies for depression treatments, smoking cessation, or community-level interventions.
Agreement of Biomarkers and Measures of Cognitive Performance	• Only a few (9) low or medium risk of bias studies for cognitive performance also used biomarkers; most of those used some form of brain scan. • The overall rate of agreement between biomarkers and cognitive testing was 57%, but 90% of that agreement resulted from both approaches showing no effect. When the biomarker showed a significant result, there was agreement in 25% of cognitive tests conducted.

AChEI= acetylcholinesterase inhibitor; CATD= clinical Alzheimer's-type dementia; IADL=instrumental activities of daily living; MCI=mild cognitive impairment; NSAIDs=nonsteroidal anti-inflammatory drugs

Discussion

Research on interventions to prevent or slow age-related cognitive decline, MCI, or CATD has focused largely on their effect on decline in measures of cognition. The reasons for this are many, including: 1) Meaningful investigation of dementia-onset requires either a long followup period or a large cohort of older individuals. 2) Long followups in the target population face serious attrition problems due to death or comorbidities. 3) The risk of selective attrition whereby the intervention might also affect mortality risk and hence create attrition bias if survivors have more health problems.

Interventions to slow or prevent age-related cognitive decline, MCI, or CATD are often chosen because of evidence from epidemiological studies that examine actions of individuals at higher or lower than expected risk for these conditions. In other cases, theories of brain function (e.g., neuroplasticity) justify the development and testing of experimental interventions. Not all such interventions would be expected to be found to be effective in controlled experiments. This systematic review cast a wide net and only a few interventions showed any evidence of an effect, all of which raise many questions. Most of the studies showed no benefit to those receiving interventions

compared to control groups. Four intervention classes show some positive results and seem the most promising for further study: cognitive training, physical activity, raloxifene, and vitamin B12 although the evidence for vitamin B12 and raloxifene is lower than the others. Problems with study designs make strong conclusions difficult. Assessing the strength of evidence for negative findings is a special challenge. There is a persistent concern about Type II errors.

Dementia Incidence

The preponderance of studies showed no effect. Raloxifene may reduce risk of MCI. However, in the case of estrogen therapy (with or without progesterone), the control groups did better than the experimental groups, suggesting a de facto harm.

Cognitive decline is almost always a precursor of dementia. Impairment below a designated threshold helps to define CATD and/or MCI. But not all individuals with cognitive decline develop CATD, and we do not know whether interventions that show effects on selected areas of cognitive performance can also stave off dementing conditions. Presumably, the broader the effect an intervention has on multiple cognitive domains, the more likely it will also have preventive effects. But improving (or slowing the decline of) performance in one given cognitive domain does not automatically imply protection against dementia. For example, some cognitive training does seem to improve performance in the specific area of the training, but the results do not generalize to improved performance in other cognitive domains. The strongest effect of cognitive training found in this analysis was in enhancing processing speed, but extrapolating that benefit to a reduced risk of CATD is not yet established. For example, improving a person's useful field of vision can help with driving a car, and it might facilitate some IADLs, but neither of those benefits necessarily slows the onset of CATD.

Cognitive Performance

The studies used a wide variety of instruments to assess cognitive performance. To facilitate analysis and interpretation, we categorized tests and measures into four groups (brief cognitive test performance, multidomain neuropsychological performance, executive function/ attention/ processing speed, and memory); some tests fit into more than one of these four groups.

Cognitive training studies were dominated by the ACTIVE trial, which investigated the effects of different types of group-based cognitive training on various cognitive performance outcomes for presumably cognitively healthy participants. For the most part, the training had sustained effects (up to 2 years) on cognitive performance in the domain trained but there was little evidence of generalization to other cognitive domains. There was an effort to assess the effects of booster training, but assignment to receive a booster was not random; participants with high initial compliance received most of the boosters. More work on cognitive training with longer followup is needed.

While the majority of results for physical activity showed no significant difference, resistance training and aerobic exercise produced some positive results in cognitive performance, although neither intervention shows an overwhelming or consistent effect.

While the overall findings for the remaining interventions showed little benefit, several studies of the treatment of hypertension showed improved cognitive functioning. Given that hypertension control is already a goal for the treatment of cardiovascular disease, these positive outcomes can be viewed as a potential additional benefit from efforts to control blood pressure. Ironically, if the hypertensive treatment lowered mortality, its benefits for dementia might be underestimated because of selective attrition.

Vitamin B12 and folic acid also showed benefit in brief cognitive test performance and memory, but not for executive/attention/processing speed. There were also conflicting findings for B12 when in combinations with other B vitamins. The other vitamins had no substantial benefit on cognition. Little or no benefit for cognitive performance was shown for multivitamins, vitamin C, vitamin D with calcium, or beta carotene (all low strength of evidence). Vitamins may work differently if given to a person to address an insufficiency compared to a megadose for a person with otherwise adequate basic vitamin intake. The participants varied widely in this and other respects.

The role of biomarkers as intermediate outcomes is unclear. Our results show a low level of agreement between the biomarker measures (which were primarily some form of brain scan) and various cognitive tests. More needs to be known about their ability to predict the clinical course of persons with various levels of cognitive function.

Limitations of the Review Process

This review encountered several limitations, including but limited to those stemming from the topic and our approach to address it. For example, (as requested) we deliberately excluded dementias with specific and clear etiologies, including stroke. By doing so, we may underestimate the importance of hypertension treatment. The outcomes of

interest were inconsistently defined in the literature, and there were numerous and widely varied interventions to address those outcomes. Other limitations arose from conceptual and methodologic issues with eligible studies. These included sample size, length of followup, measurement issues, and attrition. Our search strategy was challenging to design given the wide range of interventions and types of studies measuring cognitive outcomes as secondary outcomes. We designed a strategy to capture a wide variety of intervention types and outcomes with a degree of precision making the review process feasible and efficient. The scale and scope of the topic made identifying all relevant studies extremely difficult. We addressed this by supplementing our bibliographic database searches with citation searches.

To address the multiplicity of cognitive performance tests used, we arbitrarily clustered tests into domains. Because these domains were composites of various tests with different scoring systems, meta-analysis proved unwieldy to conduct. Instead we opted to simply show the proportion of tests.

Assessing and interpreting the strength of evidence for many studies that showed no difference was difficult, especially when we were unable to use meta-analysis to address small sample size issues. Several reviewers urged a clear distinction between the absence of strong evidence of an effect and strong evidence of no effect. We have tried to make that distinction whenever feasible.

Searches were difficult because key words could only identify studies that assessed cognitive performance outcomes as secondary outcomes if the study abstract listed the cognitive performance outcomes. Finding a balanced set of articles in cohort and add-on studies was difficult because the results were more likely to be noted in abstracts if they were positive.

Prioritizing Future Research

Effective use of scarce research dollars will require substantial investments in a limited number of well-designed trials of sufficient power and duration. Interventions selected to receive funding will need to be chosen carefully. The full effects of hypertension control should include attention to stroke. Priority should be given to interventions that already show some promise, most notably cognitive training and physical activity. However, the decision to exclude specific stroke-related dementia may underestimate the effect of antihypertension treatment. Although it cannot be said with complete certainty that other types of interventions have no effect, work examining NSAIDS, statins, nutraceuticals, and others has shown little promise. Moderate-strength evidence showing no benefit for some antihypertensive treatments and vitamin E for cognitive performance support assigning low priority to these areas.

Recommendations for Design and Methodology of Future Studies

Future trials such as RCTs or pragmatic trials using electronic health records from health systems should be designed intentionally to study methods of slowing and preventing age-related cognitive decline, MCI, and CATD incidence. Many studies originally designed for other purposes have added cognitive measures post-hoc. These "add-on" trials have frequently used less sophisticated measures, have not adequately evaluated baseline characteristics, and have not randomly assigned participants, all of which confound data and limit conclusions.

Another common limitation is that most trials have been too short to observe clinically meaningful change in cognitive function. Many were designed with an intervention period of one year or less with limited or no follow-up, making it impossible to draw conclusions about longer-term outcomes in most cases. Trials that address dementia incidence must be even longer. Designing trials of appropriate duration requires careful consideration of several key factors, including cohort characteristics (e.g., subject age, presence or absence of known risk factors of cognitive decline, cognitively normal versus MCI) and whether outcomes are intended to detect a delay in cognitive decline or a reduction in dementia incidence. Focusing on longitudinal investigations with followup periods of 10 years or more would greatly benefit the field and provide more insight about prevention. This will also require designing studies to actively minimize, or at least appropriately deal with, attrition. One way to accomplish this is by prioritizing enrollment of older cohorts although it is important to note that the most ideal age for intervention remains unknown and may vary by type of intervention. The danger of this strategy, however, lies in the possibility that treatment effects are stronger for persons in midlife than in late life. Epidemiological studies in hypertension point in this direction.

In addition to dedicated trials and longer intervention and followup periods, studies that assess dose-response relationships and underlying mechanisms of action are needed. Establishing the dose-response relationship can be done in two ways. Multiple arms of varying dosage could be used initially; alternatively, once an effect has been demonstrated, studies that assess dose-response relationships and underlying mechanisms of action could

be implemented. Finally, the vast majority of studies testing the effectiveness of interventions to delay or slow age-related cognitive decline or prevent onset of MCI or CATD have focused narrowly on a single intervention. Given that the causes of dementia are complex and multifactorial, studies should address interventions that modify multiple risk factors. Several such trials, focusing on multiple risk factors simultaneously (multi-domain interventions) have been initiated.[12] Three of these trials (FINGER, MAPT, PreDIVA) enrolled older adults and implemented multi-domain interventions with components addressing nutrition, physical activity, cognitive training, social activity, and/or vascular risk factor management. Of the two studies that have published results, while the more clinical multidomain PreDIVA trial did not find benefit,[17] results from the FINGER trial, which used a more lifestyle-based approach, were promising.[18] More studies assessing a combination of interventions would benefit the field. The key issue in designing such studies is choosing the best "package" of interventions. Current wisdom suggests that RCTs should use the most powerful combinations and leave the decisions about less potent versions to subsequent studies. The first critical question is whether a combination of strong interventions can achieve the goal.

Measurement

Consistent shortcomings across existing studies reveal many opportunities to improve the measurement techniques of future trials. Future research should employ a more consistent set of validated tests to assess cognitive performance. To date, cognitive outcomes have been measured using a wide array of neuropsychological tests. The sheer volume of cognitive measures used in the literature complicates comparisons across trials, particularly when an attempt is made to cluster or group tests into domains as most do not fit neatly into one category. Research in the field could be enhanced greatly through development of consensus guidelines that encourage investigators to use a common core standardized battery or batteries of tests in these trials. Although no one measure is adequate for all applications, movement towards the use of batteries with good psychometric qualities and already in common use in aging populations (such as those included in the National Alzheimer's Coordinating Center data set (https://www.alz.washington.edu/WEB/forms_uds.html) or drawn from the National Institutes of Health Toolbox (http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox)) could potentially help to narrow the field.

The baseline status of participants needs to be better measured and documented. Baseline cognitive status is variously described and often not tested. While some researchers measured baseline cognitive function as part of the trial design, the degree of measurement varied widely (e.g., brief cognitive screening versus more elaborate neuropsychological test performance). Finally, future research trials that include incident CATD as a study outcome should evaluate participants using formal diagnostic guidelines for Alzheimer's disease such as those from the NIA and the Alzheimer's Association.6 Including both measures of cognitive performance and CATD incidence as study outcomes would allow researchers to better understand how these two constructs are related. For trials that cannot include incident CATD as an outcome for whatever reason, more work is needed to define what degree of change in neuropsychological test performance is considered clinically meaningful. Consistently including objective and performance-based measures of everyday function (IADLs) in future trials may help address these questions.

Conclusion

At present, there is not sufficient strength of evidence to justify large-scale investing in public health activities aimed at preventing dementia; some results may be viewed as potential added benefits to already identified public health interventions. There was moderate-strength evidence that cognitive training improved performance in the trained cognitive domains, but not in domains not trained, and the evidence of an effect of cognitive training on reducing CATD incidence was weak. There was a mix of positive and negative findings, all of low strength, for physical activity, antihypertensives, NSAIDs, vitamin B12, nutraceuticals, and multimodal interventions. Signals seem more promising for resistance training and aerobic exercise, and vitamin B12.

The substantial work on modifiable risk factors would be better informed by testing interventions that address them to establish their putative causal role. A number of intervention areas, some of which have been identified as presumptive risk factors, do not seem fruitful avenues for further study; resources should be directed toward more promising interventions. Longer, larger, and better studies are needed. Future research on interventions should address methodological problems uncovered in this review, including using a variety of different outcome measures (cognitive tests) and short followups. For longer studies, attrition is a major problem. More work is needed to understand the relationship between intermediate outcomes like cognitive testing and the onset of dementia.

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Full Report

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