

Draft Systematic Review

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

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies. The National Institute on Aging of the National Institutes of Health requested this report from the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program. The report was presented October 25, 2016, at the Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine public meeting on Preventing Dementia and Cognitive Impairment: A Workshop.

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

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

Structured Abstract

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

Data sources. We searched Ovid Medline, Ovid PsycINFO, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials, nonrandomized controlled trials, and prospective cohort studies published and indexed in bibliographic databases between January 2009 and March 2016. We contacted experts and reviewed prior reviews. We searched the grey literature.

Review methods. We explored a wide variety of potential interventions including: aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs); cardiovascular and cerebrovascular disease treatments (medications and nonpharmacologic interventions); cognitive stimulation and training; community-level interventions (built environment); depression treatments (medications and nonpharmacologic interventions); diabetes treatments (medications and nonpharmacologic interventions); diet types (Mediterranean, low fat, vegetarian, etc.); hormone therapies (estrogen, selective estrogen receptor modulators, testosterone); music-based interventions (dancing, playing music); nutraceuticals (gingko biloba, fish oil); obesity treatments (medications and nonpharmacologic interventions); pharmacologic (statins, cholinesterase inhibitors, nicotine); physical activity (aerobic, resistance training, balance, dancing); sleep disorder treatments (medications and nonpharmacologic interventions); smoking cessation; social engagement (network, social activities); and vitamin supplements (multivitamins, vitamin D).

We first reviewed titles and abstracts to identify appropriate studies. They were reviewed and abstracted. We assessed risk of bias using standard criteria and summarized those studies not judged to have high risk of bias. We summarized results in summary tables and synthesized evidence for each unique population, intervention, comparison, and outcome and harm. Because a highly varied set of tests was used across the studies, we opted to group them into domains to facilitate analysis. We used a standard method to rate the strength of evidence for those studies that had sufficient sample size.

Results and Discussion. We identified 8,433 unique references, 205 of which were eligible for our review.

Of the 13 classes of interventions we examined (cognitive training, physical activity, nutraceuticals, diet, hormone therapy, vitamins, antihypertensive treatment, lipid lowering treatment, nonsteroidal anti-inflammatory drugs, anti-dementia drugs, and diabetes treatment), we found no high-strength evidence for the effectiveness of interventions to delay or prevent age-related cognitive decline, mild cognitive impairment, and/or clinical Alzheimer's-type dementia. However, a few intervention types merit further study:

- Cognitive Training: Moderate-strength evidence indicates that cognitive training in adults with presumed normal cognition produces sustained benefit over 2 years for the specific

cognitive performance area that was the target of training (memory, reasoning or processing speed), but there is little evidence of diffusion of benefits to other cognitive areas. The strength of evidence is low for longer follow up periods largely because of high attrition. Likewise, evidence of any effect on dementia incidence is sparse and weak. Efforts to adapt studies not originally designed to address dementia incidence were plagued by problems, such as inadequate sample sizes, inconsistent determination of dementia onset, and lack of intact cohorts for substantial time periods. Future research on CATD incidence will require addressing these issues.

- Physical Activity: Aerobic exercise offers low-strength evidence for benefits in cognitive performance in some areas for adults with normal cognition. Given the responses to quite different forms of exercise, the underlying mechanism is unclear. Future studies need to employ control groups that address potential confounding effects such as socialization.
- Vitamin B: In adults with normal cognition, a small proportion of vitamin B studies showed benefit in some brief cognitive test performance, executive/attention/processing speed, and memory (low strength of evidence) versus placebo.

A few other interventions (e.g., nutraceuticals, antihypertensives, and NSAIDs) showed at least one positive finding, some reaching low strength of evidence, but these were more than offset by negative findings.

In order to be able to address evidence gaps that exist across the intervention types, common problems with study design/methodology and measurement need to be addressed:

- Trials should be designed intentionally to study preventing MCI and CATD with a priori cognitive measures. The designs will require longer-term cohorts, employing all necessary steps to maintain the integrity of those cohorts.
- Research should utilize an agreed upon set of measures and definitions of dementia. The wide variety of cognitive measures that are currently used complicate summarization and comparison of results across studies.
- Future intervention research will best employ multiple intervention arms that assess combinations of interventions to address the complexity of the potential mechanisms.
- Studies should be planned at the outset to use adequate followup periods to detect dementia incidence and demonstrate persistence of cognitive effects. Such studies need to include active steps to retain the integrity of the study cohorts.

Conclusions. A number of intervention areas 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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Chapter 1. Introduction

Background

Neurocognitive disorders, typically referred to as dementia and cognitive impairment, are a grave concern. Although the incidence of dementia has fallen over the last several decades,¹ the number of people with dementia and cognitive impairment among adults over 70 in the United States is rising.^{2,3}

Dementia severely erodes individuals' functioning and quality of life, creates burden and stress on the entire family, and is a major predictor of institutionalization. Additionally, costs associated with dementia are high, exceeding even those of heart disease and cancer, and are often paid directly by families.⁴ 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. The challenge is to identify those interventions with positive influences and make them more widespread.

Cognitive Impairment

Dementia – Definitions and Diagnostics

Research on dementia has been affected by changes in nomenclature and classification. Most published work was done under the Fourth Edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-4), but the Fifth Edition (DSM-5) published in 2013 made substantive changes to the language describing cognitive impairment. It laid out a set of six distinct neurocognitive domains, some of which are associated with specific parts of the brain. These changes can affect the way various elements of dementia are diagnosed and viewed. Other tests, such as blood tests or radiologic images, are often performed to rule out different diagnoses. The term dementia is slowly being replaced by the DSM-5 defined phrase major neurocognitive disorder, which is more inclusive than dementia. For example, the earlier definition of dementia excluded those with only loss of ability to express or understand speech due to a stroke, while DSM-5 would include such individuals in its more broadly defined syndrome.

Even beyond the shift from DSM-4 to DSM-5, the terminology used to discuss dementia and cognitive impairment is inconsistent and changing. Several criteria are available to diagnose dementia, including criteria described by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) in 1983.⁵ Specific etiologies of neurocognitive disorders include Alzheimer's disease and other less common conditions (e.g., frontotemporal lobar degeneration, Lewy body disease, traumatic brain injury, etc.).⁶ Diagnosis of a neurocognitive disorder due to Alzheimer's disease requires steadily progressive cognitive decline, generally with predominant impact on the cognitive domain of learning and memory, from a previous level occurring outside the context of delirium not better explained by other mental disorders; if the decline interferes with independence in everyday activities, it is classified as major; if not, mild. Other tests, such as blood tests or radiologic images, are often performed to rule out different diagnoses. For this report, the term clinical Alzheimer's-type dementia (CATD) is used to recognize the clinical reality that a precise diagnosis of Alzheimer's disease is

rarely available and clinicians are often working with patients with dementia from some unknown mix of etiologies. This term is designed to be inclusive but does exclude types of dementia that can otherwise be well-defined (such as Lewy body disease or infectious disease; see Table 1.1 below). Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Age-Related Cognitive Decline and Mild Cognitive Impairment – Definitions and Diagnostics

Some subtle decline in cognition associated with aging is considered normal or inevitable, particularly past the age of 60 years. For example, by 70 or 80 years old, having greater difficulty with learning a new language or with remembering names would not be considered warning signs of neurocognitive disease in the absence of other signs or symptoms of cognitive difficulty.

If the extent of decline crosses a threshold (variously defined), the individual is said to have some intermediate form of cognitive impairment. One way of defining this threshold is when the decline in cognition is recognized by an 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. Another way cognitive impairment has been defined is based upon formal cognitive testing scores below norms for younger populations, even if there are no changes in function. After a variety of terms were proposed for such early or minimal changes in cognition, in 1988 the term mild cognitive impairment (MCI) was coined.⁷ Roughly half of people with MCI will progress to a more severe form of cognitive decline over about 3 years.⁸ The relationship between progression from overall cognitive decline to dementia is less clear.

Petersen's criteria are typically used to diagnose MCI as characterized by a subjective decline in cognition and objective neurological testing threshold without a loss of function. MCI corresponds to mild neurocognitive disorder in the DSM-5.⁹ In contrast, cognitive aging that is the process of normal changes that occur as individuals age is called age-related cognitive decline and is highly variable.¹⁰

Distinguishing Between Mild Cognitive Impairment and Dementia

An Institute of Medicine (IOM) committee has recently recognized potential problems with using cognitive and functional decline elements of the definition for dementia and MCI.¹⁰ They note, "The natural history that leads to Alzheimer's-type dementia could be summarized as follows: persons with normal cognition start developing deterioration in their cognitive performance of slow onset and progression. When this deterioration achieves a 'clinically significant' level of cognitive deterioration that is documented objectively, this level of deterioration may be called cognitive impairment. This cognitive impairment may or may not be accompanied by subjective cognitive complaints. If the cognitive impairment is not accompanied by significant functional impairment (i.e., persons can live independently despite cognitive impairment), the cognitive impairment can be termed *mild cognitive impairment* or *cognitive impairment without dementia*. If deterioration in cognitive performance continues to the point where a person cannot maintain independent function, the

cognitive impairment is called *dementia*. Given this natural history, cognitive performance is recognized as a patient-centered outcome.” The problem with using such criteria to define dementia and MCI is that functional impairment depends on social factors independent of the underlying disease causing cognitive impairment. Recognizing and measuring cognitive and functional decline depend 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.

Causes of Cognitive Impairment

Dozens of specific diseases can cause major neurocognitive disorder (Table 1.1). Alzheimer’s Disease is the most common diagnosis in this set. 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. atrophy), excess or abnormal proteins in the brain, or abnormal appearance of brain cells examined at autopsy. Yet, the relationship between these findings and measures of cognition are inconsistent and not constant. We do not know 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 cognitive decline due to Alzheimer’s Disease. In this report, we use the term CATD to exclude most of the conditions italicized in Table 1.1.

Table 1.1: DSM-5 underlying causes of major neurocognitive disorders

Cause
<i>Frontotemporal lobar degeneration</i>
<i>Lewy body disease</i>
<i>Traumatic brain injury</i>
<i>Substance/medication use</i>
<i>HIV infection</i>
<i>Prion disease</i>
<i>Parkinson’s disease</i>
<i>Huntington’s disease</i>
<i>Another medical condition</i>
Alzheimer’s disease
Vascular disease
Multiple etiologies
Unspecified

Source: American Psychiatric Association (2013). Neurocognitive Disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association.

Interventions to Prevent or Slow Cognitive Decline

Interventions and Underlying Theories

A number of reviews have assessed the evidence linking risk factors and protective factors to CATD and MCI, including a 2015 Institute of Medicine report on cognitive aging¹⁰ and a 2010 Agency for Healthcare Research and Quality (AHRQ) systematic review.¹¹ Several risk factors are correlated with incident CATD, some modifiable and

others not. Nonmodifiable risk factors 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 address chronic disease status and modifiable risk factors as well as protective factors. Table 1.2 lists a number of interventions that have either been explored or suggested. More comprehensive intervention programs address multiple risk factors simultaneously with multi-domain interventions with components addressing nutrition, physical activity, cognitive training, social activity, and/or vascular risk factor management.¹²

Table 1.2. Interventions aimed at preventing age-related cognitive decline, MCI, and/or CATD

Interventions (examples)
Aspirin/nonsteroidal anti-inflammatory drugs (NSAIDS)
Cardiovascular and cerebrovascular disease treatments (medications and nonpharmacologic interventions)
Cognitive stimulation and training
Community-level interventions (built environment)
Depression treatments (medications and nonpharmacologic interventions)
Diabetes treatments (medications and nonpharmacologic interventions)
Diet Types (Mediterranean, low fat, vegetarian, etc.)
Hormone therapies (estrogen, selective estrogen receptor modulators, testosterone)
Music-based interventions (dancing, playing music)
Nutraceuticals (gingko biloba, fish oil)
Obesity treatments (medications and nonpharmacologic interventions)
Pharmacologic (statins, cholinesterase inhibitors, nicotine)
Physical activity (aerobic, resistance training, balance, dancing)
Sleep disorder treatments (medications and nonpharmacologic interventions)
Smoking cessation
Social engagement (network, social activities)
Vitamin supplements (multivitamins, vitamin B, vitamin D)

Interventions cannot change nonmodifiable risk factors. However, age, sex, race/ethnicity, and family history are relevant to intervention effectiveness because they can modify the effect of interventions. Further, provider perceptions of and attitudes toward nonmodifiable risk factors may themselves be modifiable. Genetic factors (i.e., ApoE status) have been shown to modify the degree to which risk factors and interventions correlate with cognitive decline.¹⁰

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 pathways and 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 are reasonable. If inflammation is part of the 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 any time point on the cognitive spectrum, which spans from healthy cognition to the normal age-related cognitive decline that everyone experiences to abnormal and subclinical cognitive decline to MCI, and finally, to AD and other dementias.

Research subjects 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. Rarely have studies used multidomain interventions, and potentially none have explored the possibility of cumulative or synergistic effects.

Methods to Measure Intervention Impact - Measuring Cognitive Function and Biomarkers

Timing and measurement choices affect cognitive decline prevention studies. Researchers can recruit subjects 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 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. The range of testing includes both simple tests performed in a primary care clinic (such as drawing a clock face and remembering three words) and hours-long, comprehensive cognitive testing performed by a neuropsychologist that measure multiple domains of cognition.¹³

To assess changes in brain functional abnormalities earlier or with greater sensitivity than is possible with paper-based testing or interviews, a variety of laboratory and brain imaging tests are used; collectively these are called biomarkers. Examples include total brain and hippocampal volumes; white matter hyperintensity volume;¹⁴ uptake with fluorodeoxyglucose positron emission tomography (PET) in key areas of the brain (e.g.,

temporomedial lobes); accumulation of brain amyloid ascertained with brain PET; and cerebrospinal fluid levels of tau, phosphorylated-tau, and amyloid beta.

Improvement or slower deterioration from baseline biomarker measures could indicate a slowing of cognitive 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. However, studies have included or focused on measures of biomarkers.

Scope and Key Questions

This systematic review is focused on studies that target populations who are cognitively normal or may have age-related changes or MCI but do not yet have 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 (see Table 1.2). The review does include studies addressing vascular components of mixed dementia, but post-stroke dementia is out of scope.

Key Questions

The review addresses two key questions (KQ) and PICOTS (populations, interventions, comparisons, outcomes, timing, and setting; Table 1.3) 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.

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, socio-economic 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, socio-economic 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?

Table 1.3. Populations, Interventions, Comparators, Outcomes, Timing, and Settings (PICOTS)

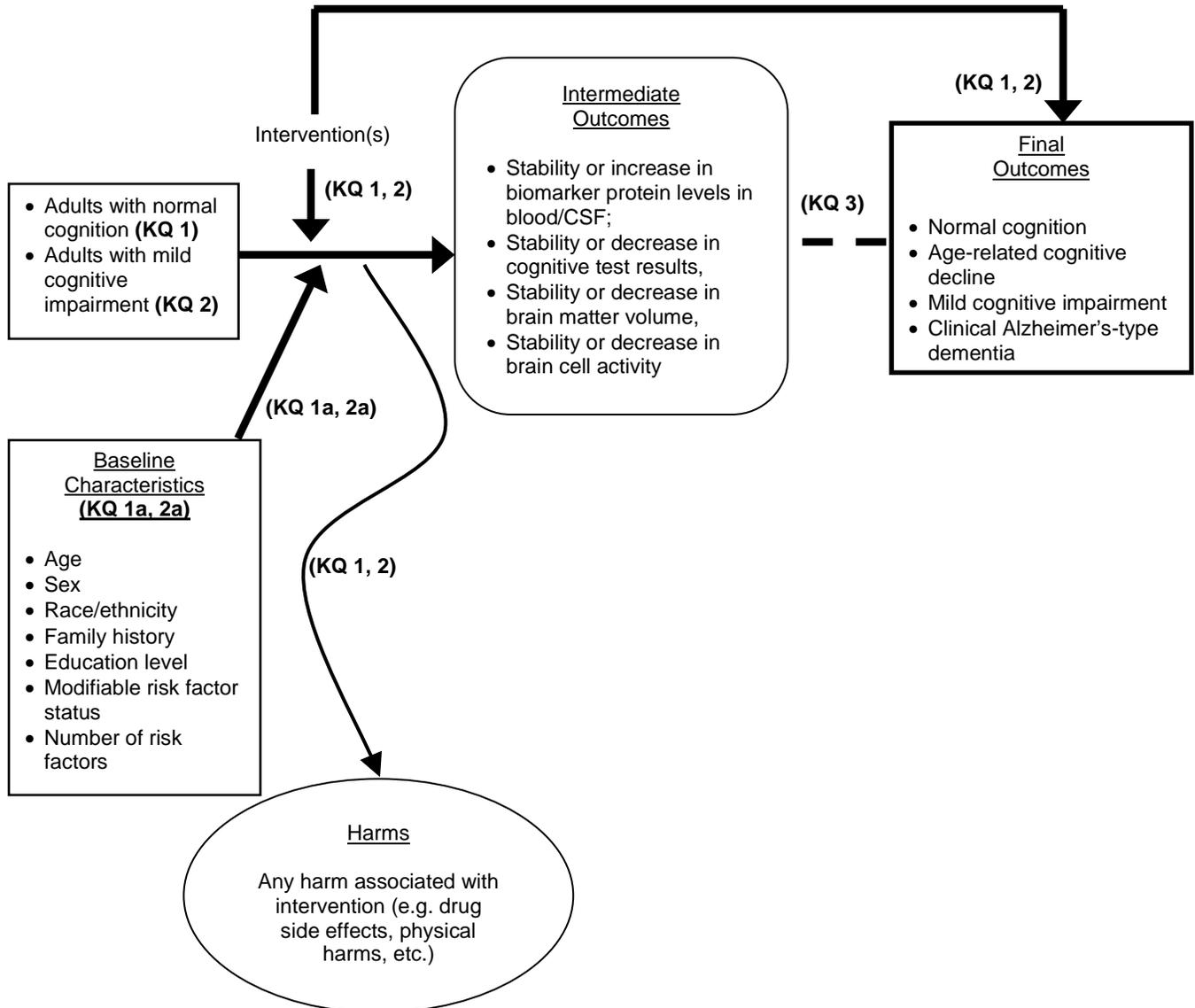
PICOTS	KQ 1	KQ 2	KQ3
Population	Adults with normal cognition	Adults with MCI	Adults with normal cognition or MCI
Intervention	Interventions aimed at preventing, delaying, or slowing the development of age-related cognitive decline, incident MCI or CATD	Interventions aimed at preventing, delaying, or slowing the development of CATD	The analysis will be limited to intermediate outcomes uncovered in KQs 1-2
Comparators	Placebo Usual care Waitlist Information or attention control Active control	Placebo Usual care Waitlist Information or attention control Active control	NA
Outcomes	<p>Final health or patient-centered outcomes: normal cognition, age-related cognitive decline, incident MCI or CATD</p> <p>Intermediate outcomes: Biomarker protein level(s) Cognitive test results Brain matter volume Brain cell activity level</p> <p><u>As determined by:</u> Blood/CSF tests, Validated cognitive test results, and Brain scans Structural imaging - CT, MRI; PET Functional Imaging – PET, fMRI Molecular imaging – PET, fMRI, SPECT</p> <p>Adverse effects of intervention(s): Pharmacologic side effects, Psychological, Financial, Physical</p>	<p>Final health or patient-centered outcomes: Incident CATD</p> <p>Intermediate outcomes: Biomarker protein level(s) Cognitive test results Brain matter volume Brain cell activity level</p> <p><u>As determined by:</u> Blood/CSF tests, Validated cognitive test results, and Brain scans Structural imaging - CT, MRI; , PET Functional Imaging – PET, fMRI Molecular imaging – PET, fMRI, SPECT</p> <p>Adverse effects of intervention(s): Pharmacologic side effects, Psychological, Financial, Physical</p>	Final health or patient-centered outcomes: Incident MCI or CATD
Timing	Minimum followup of 6 months for intermediate outcomes	Minimum followup of 6 months for intermediate outcomes	None
Settings	Community-dwelling adults, including assisted living	Community-dwelling adults, including assisted living	Community-dwelling adults, including assisted living

CATD = Alzheimer’s-type dementia; CFS = cerebrospinal fluid, CT = computerized tomography; fMRI = functional magnetic resonance imaging; KQ=key questions; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography

Analytic Framework

Figure 1.1 is a traditional analytic framework, illustrating the relationship of intermediate and final outcomes. It should be noted, however, that the outcomes listed as intermediate may be measured at several times over an extended period and several themselves contribute to the diagnosis of MCI or CATD.

Figure 1.1. Analytic framework for interventions to prevent cognitive decline, mild cognitive impairment and clinical Alzheimer’s-type dementia



Report Organization

This report is organized in several chapters. Following the Methods chapter, we present the overall search results in Chapter 3 and syntheses conducted for each class of prevention interventions in Chapters 4A through 4M. Chapter 4A presents the systematic review of literature for cognitive training, Chapter 4B for physical activity Interventions, and so on through Chapter 4M for other interventions. Since the introduction and the methods used applied to all the interventions, we present that material in separate chapters rather than duplicating them in each results chapter. Each of Chapters 4A through 4M presenting results is otherwise intended to stand on its own; therefore, each includes discussions specific to the intervention of interest. Next, Chapter 4N provides information on the linkages between biomarkers, cognitive performance, and incident MCI or dementia. The report finished with a discussion of overarching themes (Chapter 5), overall conclusions with a summary of key findings (Chapter 6), and suggested future research (Chapter 7).

Chapter 2. Methods

Protocol Development

Because of the overall design from our National Institute on Aging (NIA) sponsor, this project follows a unique model. The role of the Key Informants was filled by the Health and Medicine Division (HMD) Committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) that will use the report to help develop its own recommendations report on the state of knowledge on the efficacy, comparative effectiveness, and harms of interventions to protect cognitive health and prevent cognitive decline and dementia to NASEM and the NIA. (An overview of the NASEM conflict of interest policies can be found at <http://nationalacademies.org/studyprocess/index.html>; detailed information is available at http://www8.nationalacademies.org/cp/information.aspx?key=Conflict_of_Interest.) Because the HMD committee would not see the draft key questions, 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 and Prevention. There was not a separate, independent Key Informant panel. The role of the Technical Expert Panel was then filled by the HMD committee.

Criteria for Inclusion/Exclusion of Studies in the Review

We included studies that met our inclusion criteria based upon the PICOTS framework outlined above and the study-specific inclusion criteria described in Table 2.1.

Table 2.1 Study 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 and brain imaging outcomes and incidence of MCI of clinical Alzheimer's-type dementia.
Study Design	For KQ1-2: RCTs 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, biomarkers associated with clinical Alzheimer's-type dementia, and incident MCI or clinical Alzheimer's-type dementia
Timing	For KQ1-2: Minimum followup of 6 months for intermediate outcomes. For KQ3: No minimum followup.
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

CSF=Cerebrospinal fluid; MCI=Mild cognitive impairment; RCTs= Randomized controlled trials

Literature Search Strategies

We searched Ovid Medline, Ovid PsycINFO, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials (RCT), nonrandomized controlled trials, and prospective cohort studies published and indexed in bibliographic databases between January 2009 and March 2016. We will update this search and incorporate newly identified studies while the draft report undergoes peer review. We identified eligible studies published prior to 2009 using the previous AHRQ review, including the excluded study bibliography.¹¹ Our search strategy (Appendix A) included relevant medical subject headings and natural language terms for two concepts: 1) the conditions of dementia, MCI, cognitive decline, and 2) interventions—a wide variety of intervention types. These concepts were combined with filters for relevant intervention study designs. We supplemented bibliographic database searching with citation searches of recent relevant systematic reviews. To confirm that we identified all high-quality, quasi-experimental studies, we supplemented our bibliographic database search for potentially relevant publications using a list of longitudinal studies provided by the HMD Committee. We will update searches while the draft report is under public/peer review.

A significant challenge to developing our bibliographic database search strategy was the wide variety of interventions that have been suggested to influence cognitive decline and the fact that many of these interventions have a primary purpose other than preventing this decline. Our search strategy to identify intervention studies with cognitive outcomes measured as secondary to the purpose of a given study must acknowledge the risk of identifying a biased set of studies because dementia results will be more likely noted in abstracts if they are positive. For example, intervention studies with the primary goal of reducing blood pressure or managing diabetes are more likely to mention cognitive outcomes in titles or abstracts when those results are significant. Therefore, our search strategy was more likely to identify studies with significant results and unlikely to identify all studies measuring cognitive outcomes. This issue is especially challenging when secondary outcomes may only be identified during a full text review. It was not feasible to screen the full text of all publications of studies evaluating any intervention suggested to benefit cognitive outcomes. To address this challenge, we revisited the larger evidence base for specific interventions where cognitive outcomes were likely secondary to the primary purpose of the intervention when synthesized results clearly suggested a benefit from that intervention to preventing cognitive decline.

Bibliographic database search results were downloaded to EndNote. Titles and abstracts were reviewed by two independent investigators to identify publications of studies potentially relevant to our inclusion criteria. Two investigators independently screened full-text of those studies identified to determine if inclusion criteria were met. Differences in screening decisions were resolved by consultation between investigators, and, if necessary, consultation with a third investigator. Exclusion reasons of citations undergoing full-text screening were documented.

During the public review period, we will continue searching grey literature sources to identify relevant completed and ongoing studies using ClinicalTrials.gov. These results will be used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and inform future research needs. Results of search and screen of grey literature resources will be incorporated into results of update bibliographic databased search in October, 2016.

Data Abstraction and Data Management

Studies meeting inclusion criteria were distributed among investigators for data extraction. We extracted author, year of publication, population, intervention, comparison, outcomes, timing, and setting. Results were extracted from studies assessed as having low to moderate risk of bias. Summary tables were created and reviewed by a second investigator, checking for accuracy.

Assessment of Methodological Risk of Bias of Individual Studies

We created an instrument to assess risk of bias components specific to study design to assess risk of bias of eligible studies based upon AHRQ guidance (Appendix B).¹⁵ Relevant components included participant selection, method of randomization or selection, blinding, allocation concealment, and attrition. Two investigators independently assessed risk of bias for all eligible studies and consulted with each other to reconcile discrepancies in overall risk of bias. Overall risk of bias assessments for each study were classified low, moderate, or high based on the collective risk of bias inherent in each domain and confidence that the results were 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 by their purpose and/or what they attempt to measure, such as specific cognitive domains (i.e., executive function, memory) (Appendix C) for extraction and analysis. Since cognitive interventions were specifically targeting cognitive functions, we reported on a more complete set of cognitive domains for cognitive interventions. Changes in neuropsychological test scores were difficult to interpret. While cognitive function declines as we age, it is difficult to understand the level of change that is concerning. Reliable change indices have been identified for many commonly used instruments assessing cognitive function. These serve to identify meaningful changes in test scores for individuals.¹⁶ Methods for calculating reliable change indices ensure that the degree of change is not due to chance or measurement error; later refined to also account for practice effects, and regression to the mean.¹⁶ However, such scores were not developed to assess meaningful differences between groups of individuals, the comparisons of interest to systematic reviewers. We identified published reliable change indices for many commonly used instruments (Appendix C) and used these to facilitate interpretation of statistically significant results. For outcomes measured with instruments lacking established thresholds to measure improvement, we calculated standard effect sizes and required a small effect size ($d \geq 0.2$) to conclude efficacy or comparative effectiveness.

We assessed clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.²⁷ Clinical and methodological heterogeneity precluded quantitative pooling of results.

Grading the Strength of Evidence for Major Comparisons and Outcomes

When sufficient data were available (more than one study or one large study [$n \geq 500$]), the overall strength of evidence for select outcomes within each comparison was evaluated based on five required domains: 1) study limitations (risk of bias); 2) directness (single, direct link between intervention and outcome); 3) consistency (similarity of effect direction and size); 4) precision (degree of certainty around an estimate); and 5) reporting bias.²⁸ Based on study design and risk of bias, study limitations were rated as low, medium, or high. Consistency was rated as consistent, inconsistent, or unknown/not applicable (e.g., single study) based on whether intervention effects were similar in direction and magnitude, and statistical significance of all studies. Directness was rated as direct or indirect based on whether inference required observations across studies. That is, more than one step was needed to reach the conclusion. Precision was rated as precise or imprecise based on the degree of certainty surrounding each effect estimate or qualitative finding. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For outcomes found to have at least moderate or high strength of evidence, we assessed reporting bias by evaluating the potential for publication bias, selective outcome reporting bias, and selective analysis reporting bias by comparing reported results with those mentioned in the methods section and assessment of the grey literature to assess potentially unpublished studies. Other factors we considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association. Assessing strength of evidence for studies with null findings is especially challenging because several strength of evidence are designed to address differences. We tried to separate statements about the scientific quality of the evidence from those addressing the nature of the findings themselves. Due to the large number of comparisons with null findings (i.e. intervention and comparison yielded results that were not statistically different from each other), we assessed strength of evidence and formulated results cautiously. When assessing precision, it was important to identify the level of precision that provided confidence of no effect.

Based on these factors, the overall strength of evidence for each outcome was rated as:

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias, with consistent, direct, and precise domains. We assessed strength of evidence for key final health outcomes measured with validated scales.

Tables presenting summary strength of evidence for conclusions drawn from the data synthesis are provided in each Results chapter that had at least one intervention type with sufficient evidence to arrive at a strength of evidence rating. Tables were not created for intervention types for which all outcomes for the intervention type for a given population (adults with normal cognition or adults with MCI) was either too limited (only one study with fewer than 500 participants) or nonexistent.

Assessing Applicability

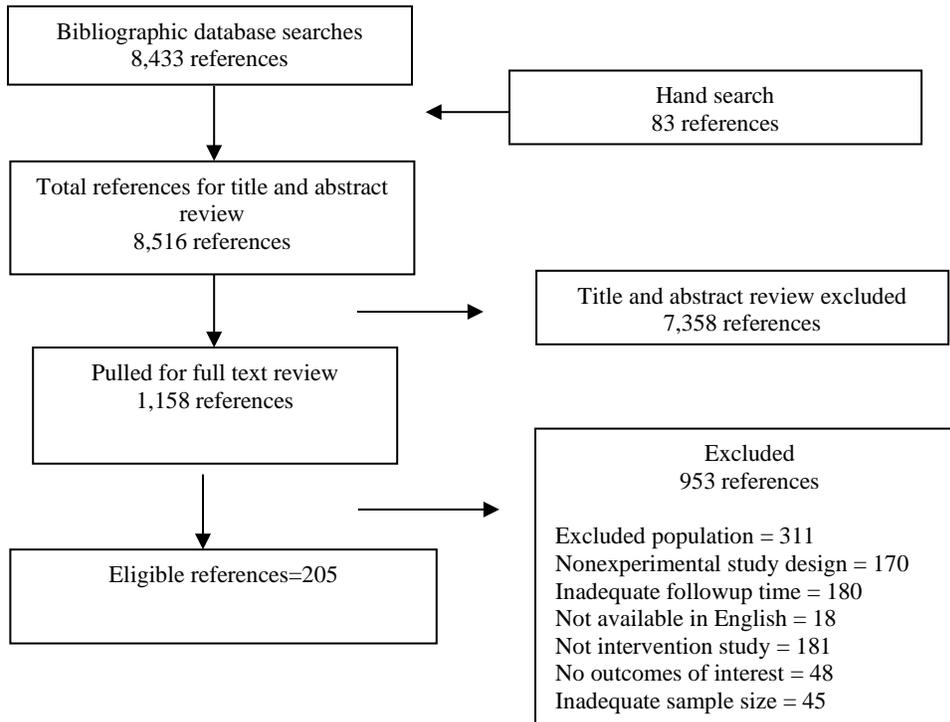
Applicability of studies was determined according to the PICOTS framework. Study characteristics that were evaluated to assess applicability included, but were not limited to, the population from which the study participants were enrolled, narrow eligibility criteria, baseline cognitive function, and patient and intervention characteristics different than those described by population studies.²⁹ Applicability issues are addressed in Chapter 5.

Chapter 3. Search Results

Literature Search Results

Bibliographic database searches identified 8,433 unique references (Figure 3.1). Hand searching identified an additional 85 references. Title and abstract screening of these yielded 1,158 references for full text review. Full text review yielded 205 references eligible for our review. Common exclusion reasons included ineligible populations (n=311; i.e., individuals with dementia), ineligible study designs (n=170; i.e., nonexperimental designs), ineligible interventions (n=181; interventions not intended to prevent dementia), and inadequate followup time (n=180; i.e., followup less than 6 months). Appendix D provides a list of excluded studies and reasons for exclusions. Appendix E provides a list of prospective cohort studies related to health and aging topics that were subjected to special searches in an attempt to find relevant articles.

Figure 3.1. Literature Flow Diagram



Studies were categorized and results analyzed by the intervention types addressed (Table 3.1). Several studies are grouped in multiple intervention types because they addressed more than one intervention type in multiple arms. As Table 3.1 shows, not all interventions expected as per the protocol were informed by published studies.

Table 3.1. Eligible publications by intervention type

Report Intervention type	Protocol type	Eligible articles
Cognitive interventions	Cognitive stimulation and training	37
Physical activity/exercise	Physical activity	31
Nutraceuticals	Nutraceuticals	21
Diet types	Diet types	7
Multimodal interventions	Not included	16
Hormone therapy	Hormone therapies	30
Vitamins	Vitamin supplements	22
Antihypertensive treatment	Cardiovascular and cerebrovascular disease treatments	24
Lipid lowering treatment	Cardiovascular and cerebrovascular disease treatments	9
Nonsteroidal anti-inflammatory drugs	Aspirin/NSAIDS	7
Acetylcholinesterase inhibitors	Pharmacologic	12
Diabetes medication treatment	Diabetes treatments	7
<i>Other interventions</i>		
Other drugs	Pharmacologic	2
Social engagement	Social engagement	2
Sleep disorder treatments	Sleep disorder treatments	2
Depression treatments	Depression treatments	0
Music-based interventions	Music-based interventions	2
Obesity treatments	Obesity treatments	0
Smoking cessation	Smoking cessation	0
Community-level interventions	Community-level interventions	0
TOTAL INTERVENTIONS		230
	Minus duplicates (publications in more than 1 intervention type)	-25
TOTAL PUBLICATIONS		205

Chapter 4A. Results: Cognitive Training

Key Messages

- 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 diffusion to other domains was rare.
- Other than the ACTIVE trial, the few studies that examined clinical Alzheimer's-type dementia (CATD)* incidence (one study for adults with MCI) or patient-reported memory function (three for adults with MCI) showed mixed results.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

Out of the 38 studies of cognitive training interventions that met inclusion criteria after review of full text, only 11 studies (12 articles) had medium or low risk of bias. Appendix F provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

We assessed strength of evidence based on a best-evidence approach, using the trial best designed to test the question of interest. Other relevant trials are then presented in followup sections as context for and consistency with best-evidence.

The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Trial

The ACTIVE trial is the most ambitious study to date to test alternative forms of cognitive training. It has received wide attention and serves as a model for subsequent work. Its findings have been interpreted differently by various groups of investigators.^{14,30}

We discuss four ACTIVE publications, three of which reported the results for proximal and primary outcomes, as described in the ACTIVE protocol, at 2 years,³¹ 5 years,³² and 10 years.³³ The fourth study looked at incident dementia at 5 years.³⁴ Although assessing dementia was not part of the original ACTIVE protocol and was rated as having high risk of bias, we include the latter study because this outcome is of particular interest for our review.³⁴ We include three publications that have high risk of bias because of the salience of the topic.³¹⁻³³ Conclusions based on the ACTIVE trial are provided in Table 4A.1.

Table 4A.1. Conclusions: Cognitive Training in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Cognitive training	Dementia	Data insufficient to draw conclusions	Insufficient (high study limitations, imprecise)
	MCI	Data insufficient to draw conclusion	Insufficient (high study limitations, imprecise)
	Reasoning	Improvement with reasoning training (ES=0.26). No significant differences with memory or speed of processing training. (n=2832; 2 year).	Moderate (medium study limitations, indirect, precise)
		Improvement remained at 5 (ES=0.26) and 10 years (ES=0.23) but not at 10 years.	Low (high study limitation, indirect, precise)
	Processing Speed	Improvement with speed of processing training (ES=0.87). No significant differences with reasoning or memory training. (n=2832; 2 year)	Moderate (medium study limitations, indirect, precise)
Improvement remained at 5 (ES=0.76) and 10 years (ES=0.66)		Low (high study limitation, indirect, precise)	
Memory	Improvement with memory training intervention (ES=0.17). No significant differences with reasoning speed of processing training. (n=2832; 2 year)	Moderate (medium study limitations, indirect, precise)	
	Improvement remained at 5 (ES=0.23) but not 10 years.	Low (high study limitation, indirect, precise)	

Between March 1998 and October 1999, 2,832 adults aged 65 years or older whose MMSE scores were ≥ 23 , and who were living independent of formal care were enrolled in the trial at one of the five ACTIVE field centers. Participants were randomized to one of three training arms or a no-contact control arm. Each of the training arms targeted a different domain: memory, reasoning, or processing speed. Proximal outcomes (changes on cognitive testing), primary outcomes (changes in functioning, everyday problem solving, driving), and secondary outcomes (health service utilization, mobility, quality of life) were evaluated. Because each arm focused on a different domain, we can contrast the specific effects of training with more generalizable effects (“spillover” into other domains).

The three intervention arms: 1) provided strategies for solving problems, remembering, or responding quickly to information; 2) used trainers to demonstrate the strategy; 3) incorporated individual and group exercises; 4) provided feedback on performance; 5) fostered self-efficacy with regard to performance; and 6) applied strategies to real-world tasks. In all three conditions, the first five sessions focused on strategy instruction and exercises to practice the strategy, while the last five sessions provided additional practice exercises but introduced no new strategies. Content for each of the 10 sessions was scripted in a trainer’s manual. Initial training was conducted between May 1998 and December 1999. The reasoning and speed of processing arms, but not memory, were tailored to participant baseline performance.³⁵

Memory was evaluated using three paper/pencil tests (Hopkins Verbal Learning Test, Rey Auditory-Verbal Learning Test, and Rivermead Behavioral Memory Test). Reasoning was evaluated using three paper/pencil tests (word series, letter series, letter sets). Speed was evaluated using two paper-pencil tests (Digit Symbols Substitution, Digit Symbols Copy) and one computer-based test (Useful Field of View).

Findings from the four studies are summarized in Table 4.2. Only the 2-year outcome study³¹ had a medium risk of bias. As noted above, the 5-year and 10-year outcome studies had a high risk of bias due to attrition but are retained here because of the scarcity of long-term followup studies. Attrition at 5 years was 33 percent (attrition rates were essentially the same for all arms including controls); attrition at 10 years was 57 percent (55 percent attrition for reasoning and speed arms, 58 percent for memory arm, and 60 percent for control arm), but only about a quarter of the sample loss at 5 years was attributable to death. Thus, much of the sample loss was unexplained. By 10 years death accounted for about 15 percent of the attrition. Participant factors that predicted 10-year attrition included: being older, male, or unmarried; having physical or mental health concerns; consuming more alcohol; and exhibiting worse performance on cognitive outcomes. Predictors of attrition were reported as similar across arms. Efforts were made to assess the impact of attrition, including using linear mixed methods, multiple imputation, survival analysis, and sensitivity analysis, but none of these efforts completely excluded attrition effects. Further, the studies did not indicate whether those who withdrew by virtue of self-reported or proxy-reported dementia were assigned to the worse cognitive category. Finally, the booster effect was also biased, because 80 percent of those receiving boosters had a compliance rate on the initial training of 80 percent or better. We rated the strength of evidence for the 2-year outcomes as moderate, but for the reasons discussed above, we rated the 5- and 10-year outcomes as low.

The ACTIVE study was not designed to study the incidence of dementia. No psychometrically or clinically valid measures of dementia were included. Regular contact with the cohorts was not maintained, and reasons for sample loss were not well established. In the Unverzagt study the determination of dementia relied on three different sources (MMSE, a decrease in the cognitive composite measure of 1.5 SD, or a report from a proxy or the subject that the subject had dementia). For the purpose of this analysis, dementia was defined as the first occasion of measurement (immediate post-test, 1-year, 2-year, 3-year, and 5-year followup) in which a participant had any of these outcomes: 1) Memory composite 1.5 SD below the ACTIVE sample baseline mean; and Reasoning composite, Speed composite, or Vocabulary 1.5 SD below the mean; and functional impairment defined as MDS IADL Total Performance at or below the 10th percentile of the ACTIVE sample baseline; 2) first visit in which MMSE<22 and all subsequent visits are MMSE<22 or are missing; 3) interval self- or proxy-report of diagnosis of dementia or Alzheimer disease during the followup; 4) interval self- or proxy-report of institutionalization during the followup; or 5) deactivation from the study due to the family refusing access to the subject. Because some subjects who were lost to followup were inferred to have dementia, the purported dementia rates are confounded by the attrition rates. A sensitivity analysis that assigned all those assumed to have dementia and who were not retested to a low performance level on cognitive tests could provide one estimate of long-term effects, although the dementia may not have affected all areas of performance equally. We rated the strength of evidence for this aspect of the ACTIVE portfolio as insufficient.

Table 4A.2 Key ACTIVE Studies

	Ball, 2002³¹	Willis, 2006³²	Unverzagt, 2012³⁴	Rebok, 2014³³
Risk of Bias	Medium	High	High	High
N completed / randomized	2,244/2,832	1,879/2,832	1,879/2,832	1,220/2,832
Attrition (%)	21%	33%	33%	57%
Followup Duration	2 years	5 years	5 years	10 years
Design	For all three arms, the intervention was administered in a small-group setting (3-4 preferred, 5 maximum) by a certified trainer. Participants received 10, 60- to 70-minute trainings over 6 weeks. Sixty percent of the compliant initial sample (those attending at least 8 of the 10 sessions) were randomly chosen to receive two booster training interventions at about 1 year and 3 years. Each booster included four sessions that were similar in content and structure to the initial training.			
Testing Outcomes	Cognitive Testing in Domains Related to Training (Memory, Reasoning, Speed)	None	Cognitive Testing in Domains Related to Training (Memory, Reasoning, Speed)	Cognitive Testing in Domains Related to Training (Memory, Reasoning, Speed)
Primary Outcomes	Everyday Problem Solving, Everyday Speed, IADL/ADL, Driving Habits	Dementia Diagnosis	Everyday Problem Solving, Everyday Speed, IADL/ADL,	Everyday Problem Solving, Everyday Speed, IADL/ADL,
Key Findings	<ul style="list-style-type: none"> • Participants improved on tests related to the domain in which they were trained and not the other domains • Broader outcomes (e.g. everyday problem-solving, functioning, and driving) were not affected by trainings 	<ul style="list-style-type: none"> • Hazard model (based on original sample of 2,832) to assess risk of incident dementia over five year period • Cases of incident dementia did not differ between intervention (combined) and control arms • Incidence of dementia was higher for people with diabetes, heart failure and stroke/TIA 	<ul style="list-style-type: none"> • Participants improved on tests related to the domain in which they were trained and not the other domains • Reasoning training (not memory or speed) improved IADLs at 5 years 	<ul style="list-style-type: none"> • Participants in speed and reasoning arms sustained improvement on tests related to the domain in which they were tested but not the other domains • Memory improvement was no longer sustained for participants in memory arm • Participants in each intervention group reported less difficulty with self-reported instrumental activities of daily living

ADL= Activities of Daily Living; IADL=Instrumental Activities of Daily Living; TIA= Transient Ischemic Attack

Overall, as shown in Table 4A.3, at 2 and 5 years participants did better in the domain for which they received training and not the other domains (except speed positively affects reasoning at 5 years). These advantages are sustained for up to 10 years for two of the three domains (reasoning and speed of processing training). The effect sizes for memory and reasoning are modest. The effect size for speed of processing training is medium to large. (Bear in mind that high attrition in all arms could create bias.)

Table 4A.3. Effect of domain specific training on 2-, 5- and 10-year cognitive outcomes (reported as effect sizes)**

Timing	Outcomes	Memory	Reasoning	Speed of Processing
2-year Outcomes	Memory	0.17*	0.03	0.05
	Reasoning	0.05	0.26*	0.02
	Speed of Processing	-0.03	-0.04	0.87*
5-year Outcomes	Memory	0.23*	0.05	0.05
	Reasoning	0.01	0.26*	0.02
	Speed of Processing	0.01	.015*	.076*
10-year Outcomes	Memory	0.06	0.11	0.05
	Reasoning	0.02	0.23*	0.06
	Speed of Processing	0.07	0.01	.66*

*p<.01; **Effect size = (group mean-control mean at time point) – (group mean at baseline) divided by intrasubject standard deviation

Table 4A.4 shows the mean change in test score by treatment arm. These should be interpreted in the context of the score range of the domain scores. Statistically significant improvements in the memory and reasoning arms are not associated with large changes in actual mean scores. For example, at 5 years the memory training group showed a mean change of one point on a 132-point scale. By contrast, speed of processing showed a gain of 240 points out of a possible 1500. By 10 years, that gain, while still significant, had fallen to 24 points. The other arms, by contrast, showed actual losses in performance. All of these findings must be viewed while recognizing the attrition rates.

Table 4A.4. Effect of domain specific training on 5- and 10- year cognitive testing outcomes (mean changes in test score from baseline)

Timing	Outcome	Memory	Reasoning	Speed of Processing	Control
5-year Outcomes	Memory (possible range 0-132)	-1.0	-4.8	-5.3	-4.0
	Reasoning (possible range 0-75)	4.3	8.1	4.2	5.2
	Speed of Processing (possible range 0-1500)	79.1	119.6	241.8	-96.1
10-year Outcomes	Memory (possible range 0-132)	-10.6	-11.2	-12.7	-9.4
	Reasoning (possible range (0-75)	-3.5	-0.1	-3.9	-3.0
	Speed of Processing (possible range 0-1500)	-144.4	-126.2	24.3	-123.3

As shown in Tables 4A.5, compared to participants who did not receive reasoning training, participants who received reasoning training and were assessed at five years showed significant benefits in IADLs, but no changes in incident dementia were observed at 5 years. By the 10-year

assessment all subjects showed significant benefits in IADLs. Again, the high attrition rates need to be considered.

Table 4A.5. IADL 2-, 5-, and 10-year outcome

Timing	IADL Outcome	Memory	Reasoning	Speed of Processing
2-year Outcomes	Every day problem solving	0.07	9.03	0.03
	ADL/IADL	0.02	0.06	0.07
	Everyday speed	0.01	0.03	0.01
	Driving Habits	0.09	0.03	0.08
5-Year Outcomes	Every day problem solving	0.15	0.08	0.05
	ADL/IADL	0.20	0.29*	0.26
	Everyday speed	0.04	0.09	0.08
	Driving Habits	NR	NR	NR
10-year Outcomes	Every day problem solving	0.00	0.02	0.01
	ADL/IADL	0.48*	0.38*	0.36*
	Everyday speed	0.02	0.00	0.05
	Driving Habits	NR	NR	NR

*p<.01 **Effect sizes = (group mean-control-mean at time point) – (group mean – control mean at baseline) divided by intrasubject standard deviation. NR = not reported

Other Studies

Effect of Training on Adults with Normal Cognition

Five of the included trials tested the effect of cognitive training interventions on older adults with normal cognition.³⁶⁻⁴⁰ Three of the five trials for older adults with normal cognition used computer-based interventions;³⁶⁻³⁸ two of which used computer programs directly targeting specific cognitive domains and administered the training individually;^{36,37} one trial used a more general- or activity- based approach to cognitive training by teaching participants how to perform basic tasks on a personal computer in groups of 12 participants.³⁸ Two trials used a noncomputer-based intervention.^{39, 40} Table 4A.6 describes the included trials that tested the effects of cognitive interventions for older adults with normal cognition.

Table 4A.6. Training interventions for older adults with normal cognition

Author, Year Risk of Bias	N completed/ randomized Attrition (%) Followup	Domains trained	Mode	Intensity	Testing outcomes	Patient-centered outcomes; Other outcomes	Key Findings
Wolinsky, 2013 ³⁶ Low	620/681 9% 1 year	Speed of processing	Individual, computer-based training	10 hours over 5 weeks, booster at 11 months	Primary outcome = Useful Field of View (UFOV) test	None	<ul style="list-style-type: none"> Used same tool as ACTIVE, speed of processing arm Found significant changes on domain trained using UFOV test Administered 9 other tests, mixed results on these secondary testing outcomes
Miller, 2013 ³⁷ Medium	69/84 18% 6 months	Short- & long-term memory, language, visual/spatial processing, reasoning, calculation	Individual, computer-based training	13 hours over 8 weeks	Delayed memory, immediate memory, & language	None	<ul style="list-style-type: none"> Computer program trained 5 domains Only 2 of the 5 domains (or 3 of 6 depending on how you count long vs. short term memory) were formally tested Only delayed memory showed improvement (immediate memory and language not significant) Individual tests combined in results to present a "domain score"
Klusmann, 2010 ³⁸ Medium	230/259 11% 6 months	None specifically trained	Group, computer-based training	112.5 hours over 6 months of in-class instruction (90 minutes per session)	Delayed memory, immediate memory, & executive attention	None	<ul style="list-style-type: none"> Computer training resulted in statistically significant improvements in story recall (immediate and delayed), free recall (long delay), and one of the two tests of executive functioning/ attention (TMT B/A). Computer training did not improve free recall (short delay), verbal fluency, or executive functioning (as measured with the Stroop test) Effect sizes for statistically significant improvements were small
Carretti, 2013 ³⁹ Medium	36/40 4% 6 months	Working memory	Individual, computer-based training	2.5-3.5 hours over 2 weeks (50-70 minutes per session, 3 sessions total)	Working memory, listening comprehension, reading comprehension, and fluid intelligence.	None	<ul style="list-style-type: none"> Participants who received working memory training showed improvements in working memory, and listening comprehension compared with controls. Working memory training did not improve reading comprehension or fluid intelligence compared with control.

Stine-Morrow, 2014⁴⁰ Medium	395/461 14% 8 months	Reasoning (cognitive training arm), divergent thinking (engagement arm)	Group, non-computer based or individual, non-computer based	24 hours over 16 weeks of formal engagement, with 15 hours per week of work related to team-based project in engagement arm	Processing speed, verbal episodic memory, visual/spatial processing, reasoning and divergent thinking	None	<ul style="list-style-type: none"> • Participants did better in domain for which they were trained (reasoning for training arm, divergent thinking for engagement arm) • Spillover effects were not observed, engagement or training did not improve processing speed, visual-spatial, or verbal episodic memory compared with waitlist controls.
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ACTIVE=Advanced Cognitive Training for Independent and Vital Elderly; TMT B/A = Trail making test B and A; UFOV=Useful Field of View

The Iowa Health and Active Minds Study (IHAMS) used a version of the speed of processing tool from the ACTIVE trial.³⁶ Six hundred eighty-one adults with normal cognition were randomized separately based on their age at baseline (50-64 year-olds vs. 65 or older). The authors used a university-based attention control activity (computerized crosswords) compared with one of two active intervention arms (visual speed of processing training at the university or the same visual speed of processing training at home on the participant's personal computer). Ten hours of training was provided over 5 weeks (similar to ACTIVE). Outcomes were assessed at baseline and at 6 months and 1 year post-training. Similar to the ACTIVE design, a booster was provided to a pre-randomized group at 11 months. The primary outcome was determined using the Useful Field of View (UFOV) test. Similar to the ACTIVE trial, the IHAMS found the visual speed of processing intervention positively affected tests of performance in that domain up to 1 year post-intervention (effect size 0.32 onsite, 0.37 at home, and 0.58 with booster). Nine additional cognitive tests were administered: Trail Making (Trails) A and B Tests, Symbol Digit Modalities Test (SDMT), Stroop Color and Word Tests, Controlled Oral Word Association Test (COWAT), and the Digit Vigilance Test (DVT). Significant effects of training on these secondary outcomes were found on TMT A and B, SDMT, and Stroop-Word, but not Stroop-Color, COWAT or DVT. Effects sizes were smaller than the trained domain (.2-.3). These additional tests appeared to be related to higher-order cognitive domains (e.g. executive functioning) than what the training specifically targeted. They suggest more spillover effects than seen with the ACTIVE study.

The study by Miller was much smaller, enrolling just 84 participants.³⁷ The intervention was an individual-level, computerized, brain-training program focusing on six domains (short- and long-term memory, language, visual spatial processing, reasoning, and calculation). Presumably cognitively normal participants were asked to use the program 20-25 minutes a day, 5 days a week, for 8 weeks. Outcomes were evaluated by domain-specific tests of delayed memory, immediate memory, and language (visual spatial processing, reasoning, and calculation not evaluated). Outcomes were evaluated at baseline and at 2 months and 6 months. Individual tests were combined and only overall domain scores were reported. Only one of the three domains showed significant improvement (delayed memory). Measures of overall cognition were not reported.

The Klusmann trial was conducted in Berlin, Germany, and enrolled 259 nondepressed women with over the age of 70.³⁸ Participants were randomized to a computer-based intervention, a physical activity intervention, or a nonintervention control arm. The cognitive intervention was a group computer courses taught approximately three times per week, 90 minutes per class, for 6 months. Course activities included: learning to email and use the internet, taking and editing pictures or videos, playing games, word processing, or drawing. Neuropsychological testing was conducted using paper-pencil tests at baseline and at 6 months post-intervention. Tests measured: immediate and delayed story recall (RBMT), short and long delay free word recall (FCSRT), semantic verbal fluency, and executive functioning (Stroop, TMT B/A). Six months of computer classes significantly improved immediate and delayed story recall, free recall (long delay), and one of the two tests of executive functioning/attention (TMT B/A), compared with a no intervention control. Computer training did not improve free recall (short delay), verbal fluency, or the other measure of executive functioning (as measured with the Stroop test). In this Cognitive Training Chapter of our report, we are only interested in comparisons between the cognitive intervention arm and the no contact control. However, it is notable that the exercise and cognitive interventions resulted in significant changes on the exact

same tests at followup, compared with no contact controls. Klusmann et al. argue that the pathway may be through “management of new complex situations,” not training mental “muscles,” as may be supposed for domain-specific training.

The study by Carretti et al. was a small trial, enrolling just 40 participants.³⁹ The intervention was individual-level working memory training using audio recordings for word recall and computers for text recall. Participants in the intervention group were asked to complete three training sessions, 50-70 minutes each, over a 2-week period with 2 days between each session. The control group also attended three sessions with experimenters where they filled out paper-and-pencil questionnaires. Outcomes were evaluated at baseline, after completing training, and at 6 months. Outcomes were evaluated by tests of working memory, listening comprehension, reading comprehension, and fluid intelligence. Participants receiving working memory training showed significant improvements in working memory and listening comprehension compared with those in the control group. No significant differences were observed between groups for reading comprehension or fluid intelligence.

Another pathway through which group activities may affect cognitive outcomes is through engagement. The Stine-Morrow et al. study aims to test the differential effects of domain-specific cognitive training and engagement activities that may broadly stimulate the mind.⁴⁰ This study enrolled 461 adults with normal cognition over the age of 60 who were doing less than 15 hours of scheduled activity (work or volunteering) per week. Subjects were randomized to a group intervention aimed at engagement and problem-solving, an individual intervention with cognitive training in inductive reasoning, or a waitlist control. In the engagement arm, participants were put in teams, practiced weekly, and competed in the Odyssey of the Mind—a tournament-style competition in which teams are judged on their ability to develop a solution to a novel problem without preparation and on their ability to present a solution to a problem that they have prepared in advance. The training arm consisted of paper-pencil weekly lessons and activities focused on inductive reasoning. Both active intervention arms were 16 weeks. The authors state the intervention went through fall semester and into spring, with breaks for winter holidays and weather-related cancelations. Posttests were conducted between 30 and 32 weeks. Five cognitive domains were assessed before and after the intervention: processing speed (Letter and Pattern Comparison, Finding As), reasoning (Letter Sets, Number Series, Letter Series, Word Series, everyday problem-solving), visual-spatial processing (card rotation, hidden patterns), divergent thinking (alternate uses task, opposites task), verbal episodic memory (Hopkins Verbal Learning Test, total number of words over three trials, delayed recall score, and immediate sentence free-recall). The authors refer to these domains as “fluid abilities.” Participants in the training arm showed greater improvement in reasoning (the skill to which they were trained) than the engagement or control arms. Improvements in reasoning between the engagement and control arms did not differ. Participants in the engagement arm showed greater improvements in the divergent thinking arm (also the skill they practiced) than the training and waitlist arms. However, spillover effects from either intervention arm were not observed. No significant differences were seen in processing speed, visual-spatial, or verbal episodic memory between study arms.

Effect of Training on People with Mild Cognitive Impairment

Five included studies (six articles) enrolled participants with MCI or memory complaints (Table 4A.7). The studies used group interventions that were not computer-based.

Table 4A.7. Cognitive testing interventions for adults with mild cognitive impairment

Author, Year Risk of Bias	N completed/ randomized Attrition (%) Followup	Domains trained	Mode	Intensity	Testing outcomes	Patient-centered outcomes; Other outcomes	Key Findings
Buschert, 2012 ⁴¹ Forster, 2011 ⁴² Medium	18/24 21% 28 months	Mnemonic memory training	Small group (12 participants)	12 hours over 6 weeks	Brief cognitive test performance/ Multidomain neuropsychological test performance (ADAS-cog & MMSE), Immediate & delayed memory (RBANS), Trail Making Tests A & B	Conversion to CATD; Glucose uptake (PET scans)	<ul style="list-style-type: none"> • Intervention improved one of the two global measures of cognition (ADAS-cog), but not the other (MMSE) • One of the four domain-specific tests was significantly improved (RBANS immediate memory); RBANS delayed memory and Trail Making Tests A and B were not significantly improved by the intervention • Forster study reports results of FDG-PET scans: intervention showed no decline in uptake during the 6-month study period, while those who did not receive the intervention showed widespread declines in uptakes. • Half of the control/ delayed intervention group converted to CATD during the 28 month followup, but none of the early intervention group converted to CATD
Rapp, 2002 ⁴³ Medium	16/19 16% 6 months	Memory	Small group (Size not reported)	12 hours over 6 weeks	Word list (immediate and delayed). shopping list (immediate and delayed), names and faces (immediate and delayed), paragraph (immediate and delayed)	Self-rated memory (Memory Functioning Questionnaire)	<ul style="list-style-type: none"> • No significant effects of training at 6 months on the eight objective measures of memory • Present memory self-rated higher in intervention group at 6 months
Vidovich, 2015 ⁴⁴ Low (1 year outcome only)	154/160 38% 24 months (reported 12 months)	Attention, memory, executive processes	Small group (6-9 participants)	15 hours over 5 weeks	Brief cognitive test performance/ Multidomain neuropsychological test performance (CERAD, MMSE, CAMCOG-R), Memory (CVLT-II), Attention or Processing (Digit Span, Symbol Search, Trail Making B), executive (COWAT, Trail Making A)	Perception of memory (Memory Functioning Questionnaire)	<ul style="list-style-type: none"> • 1 of 9 cognitive assessments (digit span forward) showed slightly significant effects of intervention at 1 and 2 years • No differences in Brief cognitive test performance/ Multidomain neuropsychological test performance measures or perceptions of memory were found

Kwok, 2012⁴⁵ Medium	197/223 12% 12 months	Attention/ processin g speed, memory, reasoning	Small-group (3-5 participants)	18 hours over 12 weeks	Brief cognitive test performance/Multidomain neuropsychological test performance (Chinese MMSE & Chinese Mattis Dementia Rating Scale)	Subjective memory complaints	<ul style="list-style-type: none"> • Intentionally uses same domains as ACTIVE, but different tools used to assess • Although they were using global measures of cognition, only domain scores reported in results section (unclear from which tools domains originated) • Training did not affect domain scores overall, but did improve scores for those subgroup with less education
Herrera, 2012⁴⁶ Medium	22/22 No attrition reported 6 months	Recognitio n, working memory, recall	Individual, computer- based	24 hours over 12 weeks	Recognition (Doors Recognition Sets A and B, DMS48), Working memory (digit span, forward and backward), Recall (BEM- 144 12-word-list, 16-Item free and cued, MMSE- 3 words, Rey's complex figure)	None	<ul style="list-style-type: none"> • Results were mixed • 1 of 3 recognition tests improved at 6 months • 1 of 2 working memory tests improved at 6 months • 2 of 4 recall tests improved at 6 months

ADAS-Cog; CATD= clinical Alzheimer's-type disease; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CAMCOG-R=Cambridge Cognitive Examination-Revised; CVLT-II=California Verbal Learning Test- Second Edition; MMSE= Mini Mental Status Examination; PET=Positron Emission Test;

In one trial, 24 participants were randomized to receive either 12 hours of cognitive training, including formal mnemonic memory training and informal activities to foster cognitive and social engagement, or a control condition that involved monthly paper-pencil activities.^{42,47} A crossover design was used. The intensity and duration of the intervention was similar to the ACTIVE and IHAMS trials: 2 hours a week for 6 weeks. The target in this study was brief cognitive test performance/multidomain neuropsychological test performance as measured by the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and MMSE. However, three other domain-specific tests were also used to evaluate the effectiveness of the intervention: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trail Making Test (TMT). Conversion to CATD was also evaluated. The intervention improved one of the two global measures of cognition (ADAS-cog), but not the other (MMSE), and these results were sustained for 22 months post-intervention. One of the four domain-specific tests was significantly improved (RBANs immediate memory); RBANs delayed memory and Trail Making Tests A and B were not significantly improved by the intervention. The author argues these null findings on the domain-specific tests over time support the case for their intervention to have a "true" impact and not merely a byproduct of attention or practice effects. In this small sample, half of the control or delayed intervention group converted to CATD during the 28-month followup, but none of the early intervention group converted to CATD. Even the trial authors are cautious to avoid overstating this finding, given the size of the study. For one outcome, FDG-PET scans measure declines in uptake of glucose as a marker of disease progression. People with MCI who received the intervention showed no decline in uptake during the 6-month study period, while people with MCI who did not receive the intervention showed widespread declines in uptakes.

Another small trial randomized 19 participants to either a cognitive training intervention (n=9) or a no intervention control (n=10).⁴³ The group intervention, which ran 2 hours per week for 6 weeks, involved a combination of coping skills education (moderating mood, sleep, relaxation) and training of specific memory techniques (chunking, categorization, cueing). Results from eight objective measures of memory and nine subjective measures of memory were reported. The objective measures included: word list (immediate and delayed), shopping list (immediate and delayed), names and faces (immediate and delayed), and paragraph (immediate and delayed). The nine subjective measures of memory originated from one tool, the Memory Functioning Questionnaire (MFQ). Individual subjective measures/domains reported included: present ability, frequency of forgetting, retrospective functioning, general functioning, perceived impact of memory functioning, seriousness, memory skill use, inevitable decline, and effort utility. No significant effects of training were seen at 6 months on the eight objective measures of memory. Participants in the intervention group self-rated their memory more positively than those in the control group at 6 months (1/9 subjective measures).

The Promoting Healthy Ageing with Cognitive Exercise (PACE) trial randomized 160 adults with MCI to a cognitive activity intervention or an educational control.⁴⁴ Participants in the intervention and control arms met in small groups for 90 minutes, twice a week, for five weeks. The intervention arm received strategies specific to improving attention, processing speed, executive functioning, memory, and language. The educational (control) arm received information and participated in small group discussions about physical activity, stress, depression, sleep, and expectations for retirement. Participants in both arms received a telephone call at 6 months. Participants in the intervention arm completed 30 minutes of cognitive exercises prior to this booster call. Three measures of brief cognitive test performance/

multidomain neuropsychological test performance (Consortium to Establish a Registry for Alzheimer's Disease [CERAD]; MMSE; Cambridge Cognitive Examination-Revised), three measures of attention or processing speed (Digit Span, Symbol Search, Trail Making Test A), two measures of executive functioning (Trail Making Test A, Controlled Oral Word Association Test), and one measure of memory (California Verbal Learning Test- Second Edition) were used at baseline, after 1 year, and 2 years post-intervention. Only one of these nine assessments showed a slightly significant effect of the intervention (Digit Span Forward), which the authors state is of questionable clinical significance. Kwok enrolled 223 adults over the age of 65 with “subjective memory complaints” but no dementia (>19 on the Chinese MMSE).⁴⁵ The intervention used in the Kwok trial is based on the ACTIVE trial intervention and focused on the same three domains: attention/processing speed, memory, and reasoning. Training was conducted 1.5 hours per week for 12 weeks (twice as long as ACTIVE). The control condition was a health lecture each week for the same 12-week period. Assessments were conducted at baseline, and 12 weeks and 9 months post-intervention. Outcomes included: subjective memory complaints (Chinese Memory Symptom Scale) and brief cognitive test performance/multidomain neuropsychological test performance (a screening tool—Chinese MMSE, and a more neuropsychological measure, Chinese Mattis Dementia Rating Scale). Overall, no significant improvements in cognition were found post-intervention or at 1 year, although some subgroup analyses by education level showed significance (training was more effective for those with less education).

The Herrera et al. trial is different from the other cognitive training trials targeting people with existing MCI because it is an individual, computer-based intervention. Twenty-two people with MCI were randomized to cognitive training or cognitive activity (control) 60 minutes, twice a week, for 12 weeks.⁴⁶ The cognitive training involved a number of memory and attention training tasks on the computer, such as memorizing a group of pictures or a group of words spoken by the computer for later identification, or testing the time it took for participants to identify a target image. Participants in the control arm completed various computer-based cognitive activities including matching countries and capitals, organizing items into groups, finding similarities and differences, and reading comprehension. Verbal memory was assessed using the digit span test, the 12 word list recall (BEM-144), the 16 item free and cued reminding test, and the memory subscore of the MMSE. Visual memory was assessed using Doors and People, DMS48 test, and the Rey-Osterrieth Complex Figure recall. In the results section, these tests are organized under the headings: recognition (Doors Recognition Sets A and B, DMS48), working memory (Digit Span Forward and Backward), and recall (BEM-144 12-word list, 16 item free and cued, MMSE-3 words, Rey’s complex figure). Results were mixed. One of 3 recognition tests improved at 6 months compared to control condition (only Doors, Set A); 1 of 2 working memory tests improved (digit span forward); and 2 of 4 recall tests improved (BEM-144 and MMSE improved).

Interpreting the Findings

The overall results are summarized in Tables 4A.8 and 4A.9. The ACTIVE trial showed most clearly that cognitive training could improve performance on the domain being trained but there was little spillover to other domains. There was also no difference in dementia diagnosis at 5 years. There may be an IADL effect at 10 years but there was high attrition. CATD results are hard to interpret because the design was *post hoc*.

When reviewing the larger literature set, in contrast to the ACTIVE trial, most of the other studies showed mixed results; at times one test for a domain is significant and the other is not. A few studies show sustained improvement in the domain that was trained, similar to ACTIVE. The intensity of domain-specific training was relatively consistent (10-18 hours over 5-12 weeks). This extent of treatment seems to continue to show an effect 5-10 years later. The booster effect in ACTIVE is hard to assess because the sampling was not random. Effect sizes are mostly small; however, speed of processing effect sizes are larger.

Overall, the results are consistent with a theoretical base that assumes various areas of the brain can be trained to perform better (or lose ability less quickly) but this training has little effect on other areas.

Table 4A.8. Summary of overall results of cognitive training for older adults with normal cognition

Author, Year	Domains trained	Group/ Individual	Computer/ No Computer	Intensity	Testing Outcomes	Other Outcomes	Tools Used to Assess
Ball, 2002 ³¹	Memory, reasoning, speed of processing	Group	Computer	10-12 hours over 6 weeks, booster at 11 months	<ul style="list-style-type: none"> • Speed (only for Attn/ Speed Arm, ES=.87) • Memory (only for Attn/ Speed arm, ES=.17) • Reasoning (only for Reasoning Arm, ES=.26) 	<ul style="list-style-type: none"> • NS Everyday problem solving • NS IADL • NS Everyday Speed Habits 	<ul style="list-style-type: none"> • Memory (Hopkins Verbal Learning Test, Rey Auditory-Verbal Learning Test, and Rivermead Behavioral Memory Test) • Reasoning (word series, letter series, letter sets) • Speed (Digit Symbols Substitution, Digit Symbols Copy, Useful Field of View)
Wolinsky, 2013 ³⁶	Speed of processing	Individual	Computer	10 hours over 5 weeks, booster at 11 months	<ul style="list-style-type: none"> • Speed (ES=.32-.58 depending on booster) • NS Executive? (+ TMT A and B, SDMT, and Stroop-Word, NS Stroop-Color, COWAT or DVT) 	None	<ul style="list-style-type: none"> • Speed (Useful Field of View) • Executive (Trail Making A and B Tests, Symbol Digit Modalities Test, Stroop Color and Word Tests, Controlled Oral Word Association Test, and the Digit Vigilance Test)
Miller, 2013 ³⁷	Short- and long-term memory, language, visual spatial processing, reasoning, and calculation	Individual	Computer	13 hours over 8 weeks	<ul style="list-style-type: none"> • Delayed memory • NS Immediate memory • NS language • (Other domains not reported) 	None	<ul style="list-style-type: none"> • Delayed (Delayed Buschke-Fuld, Delayed Rey-Osterrieth. VP) • Immediate (Buschke-Fuld Total, Rey-Osterrieth Copy, VP Total) • Language (FAS, Animal Naming, Boston Naming)
Carretti, 2013 ³⁹	Working memory	Individual	Computer	2.5-3.5 hours over 2 weeks (50-70 minutes per session, 3 sessions total)	<ul style="list-style-type: none"> • Delayed memory • NS Immediate memory • NS language • (Other domains not reported) 	<ul style="list-style-type: none"> • Listening comprehension (True/False, Map Drawing) • NS Reading Comprehension • NS Fluid Intelligence 	<ul style="list-style-type: none"> • Working Memory (Categorization Working Memory Span Test, Working Memory Updating Word Span Test) • Listening Comprehension (True/False Questions, Map Drawing) • Reading Comprehension (Adapted from Nelson-Denny Reading Test) • Fluid Intelligence (Cattell Culture Fair Test, Scale 3)

Klusmann, 2010 ³⁸	None, general computer instruction	Group	Computer	112.5 hours over 6 months of in-class instruction	<ul style="list-style-type: none"> • Delayed Memory • NS Immediate Memory • NS Executive Attention • NS Verbal Fluency 	None	<ul style="list-style-type: none"> • Immediate and delayed story recall (Rivermead Behavioral Memory Test) • Short and long delay free word recall (FCSRT) • Semantic verbal fluency • Executive functioning (Stroop, TMT B/A)
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COWAT=Controlled Oral Word Association Test; DVT=Digit Vigilance Test; ES=effect size; FAS=verbal fluency test using words starting with F, A, and S; FCSRT=Free and Cues Selective Reminding Test; IADL= Instrumental Activities of Daily Living; NS=Not significant; SDMT=Symbol Digit Modalities Test; TMT=Trail Making Trial (A & B); VP=verbal proficiency

Table 4A.9 Summary of overall results of cognitive training for cognitively impaired older adults

Author, Year	Domains trained	Group/ Individual	Computer/ No Computer	Intensity	Testing Outcomes	Other Outcomes	Tools Used to Assess
Buschert, 2012 ⁴⁷ Forster, 2011 ⁴²	Mnemonic memory training	Group	No Computer	12 hours over 6 weeks	<ul style="list-style-type: none"> • NS Global Cognition (+ ADAS cog, NS MMSE, ES=.26) • NS Immediate & Delayed Memory (+ immediate, NS delayed) • NS Executive/Attention 	<ul style="list-style-type: none"> • Conversion to CATD • Glucose uptake 	<ul style="list-style-type: none"> • Brief cognitive test performance/ Multidomain neuropsychological test performance (ADAS-cog & MMSE) • Immediate & Delayed Memory (RBANS) • Executive/Attention (Trail Making Tests A & B)
Kwok, 2012 ⁴⁵	Memory, reasoning, speed of processing	Group	No Computer	18 hours over 12 weeks	<ul style="list-style-type: none"> • NS Attention • NS Initiation/ preservation • NS Construction • NS Conceptualization • NS Memory 	Subjective Memory Complaints (results not reported)	<ul style="list-style-type: none"> • Attention, initiation/ preservation, construction, conceptualization, and memory (Domains from Chinese Mattis Dementia Rating Scale) • Subjective memory complaints (Chinese Memory Symptom Scale)
Rapp, 2002 ⁴³	Memory	Group	No Computer	12 hours over 6 weeks	<ul style="list-style-type: none"> • NS Memory 	Present self-rated memory improved	Word list (immediate and delayed), shopping list (immediate and delayed), names and faces (immediate and delayed), paragraph (immediate and delayed)

Vidovich, 2015⁴⁴	Attention, memory, executive processes	Group	No Computer	15 hours over 5 weeks	<ul style="list-style-type: none"> • NS Global Cognition • NS Memory • NS Executive • Attention or Processing (+ digit forward, NS digit backward, symbol search, and Trail Making Test B) 	No differences in perception of memory	Brief cognitive test performance/ Multidomain neuropsychological test performance (CERAD, MMSE, CAMCOG-R), Memory (CVLT-II), Attention or Processing (Digit Span, Symbol Search, Trail Making B), executive (COWAT, Trail Making A)
Herrera, 2012⁴⁶	Memory, executive, attention, processing speed Note: authors classify as recognition, working memory and recall	Individual	Computer	24 hours over 12 weeks	<ul style="list-style-type: none"> • Recognition (+ Doors Set A, NS Doors B and DSM48) • Working memory (+ digit span forward, NS digit span backward) • Working memory (+BEM-144 12-word list and MMSE 3 words, NS 16-Item free and cued and Rey's complex figure) 	NR	Recognition (Doors Recognition Sets A and B, DMS48), Working memory (digit span, forward and backward), Recall (BEM-144 12-word-list, 16-Item free and cued, MMSE- 3 words, Rey's complex figure)

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BEM; CAMCOG-R; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CATD=Alzheimer's disease; COWAT=Controlled Oral Word Association Test; CVLT=California Verbal Learning Test; MMSE=Mini-Mental State Examination; NS=Not significant; RBANS=Repeat Battery for the Assessment of Neuropsychological Status; TMT=Trail Making Trial (A & B)

Chapter 4B. Results: Physical Activity Interventions

Key Messages

- 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 prevents MCI or clinical Alzheimer's-type dementia (CATD)* incidence.
- Low-strength evidence shows that neither multicomponent physical activity nor resistance training offers clear benefit in cognitive performance over attention control in adults with normal cognition.
- While the majority of the results showed little to no effect for resistance training, there were several instances of improvement in cognitive outcomes for resistance training compared with attention control.
- Low-strength evidence shows benefits in cognitive outcomes with aerobic training interventions when compared to attention control in adults with normal cognition.

* Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified 28 eligible publications reporting 27 unique studies of physical activity interventions to prevent age-related cognitive decline, MCI, or CATD.^{38,48-74} Eleven were assessed as high risk of bias and not used in our analysis. We analyzed the efficacy and comparative effectiveness of physical activity interventions separately for adults with normal cognition and those with MCI. Appendix G provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Physical Activity Interventions

Many observational studies and systematic reviews have identified a correlation between physically active lifestyles and decreased rates of CATD. Generally, the selection bias inherent in observational studies precludes adequate testing of correlations for causal relationships; however, experimental studies designed to test the nature of the correlation between physical activity and reduced dementia risk suggest potential mechanisms of action justifying a potential causal relationship (Table 4B.1 and 4B2). Many justify the relationship by citing previous research. Authors only sometimes proposed mechanisms of action, which included enhanced blood flow and neuronal connectivity,^{62,68} increased brain volume,^{62,68,74} potential reductions in β -amyloid deposition,⁶⁸ reductions in chronic disease risk,^{48,71} anxiety and depression (which are associated with cognitive function), and lowered blood viscosity (which improves aerobic capacity and cognition).⁴⁸

Table 4B.1. Logic of proposed physical activity interventions in adults with normal cognition

Intervention	Study	Hypothesized Logic or Mechanism of Action
Multicomponent physical activity	Sink, 2015 ⁶⁸ Williamson, 2009 ⁷⁴	<ul style="list-style-type: none"> Improvements in cerebral blood flow and neuronal connectivity; maintenance or improvement in brain volume; favorable changes in brain-derived neurotrophic factor and neurogenesis; potential reduction in β-amyloid deposition.
	Napoli ,2014 ⁶⁴	<ul style="list-style-type: none"> Previous research suggesting weight loss and/or exercise may improve cognition.
	Taylor-Piliae, 2010 ⁷¹	<ul style="list-style-type: none"> Previous research suggesting exercise, such as walking or calisthenics, improves cardiorespiratory endurance, muscle strength, flexibility, balance, and cognitive functioning. Improvements in blood pressure, lipid profiles, and heart-rate variability, may improve cognitive function.
Resistance	van de Rest, 2014 ⁷³	<ul style="list-style-type: none"> Previous research showing that resistance training combined with aerobic exercise improved cognition more than aerobic exercise alone.
	Cassilhas, 2007 ⁵²	<ul style="list-style-type: none"> Previous research showing physical activity decreasing chronic disease risk, anxiety and depression and aerobic exercise improving cognition in older adults. Previous research suggesting resistance training may increase cognitive performance.
Aerobic training	Antunes, 2015 ⁴⁸	<ul style="list-style-type: none"> Cumulative physical and psychological of long-term aerobic training showing mitigation of changes in cognitive function. Previous research showing that physical activity is inversely related to cognitive decline in older adults and the correlation between physical fitness and aerobic capacity and cognitive function. Hypothesize a decrease in blood viscosity by improving aerobic capacity, improves blood circulation in the brain, improving cognition.
	Muscari, 2010 ⁶²	<ul style="list-style-type: none"> Previous research showing that physical activity improves cerebral blood flow, neurotransmitters and growth factors.
Tai-Chi	Taylor-Piliae, 2010 ⁷¹	<ul style="list-style-type: none"> Previous research suggesting exercise, such as walking or calisthenics, improves cardiorespiratory endurance, muscle strength, flexibility, balance, and cognitive functioning. Improvements in blood pressure, lipid profiles, and heart-rate variability, may improve cognitive function. Eastern forms of exercise (Tai Chi) may provide benefits beyond traditional exercise because of the focus on mindfulness and relaxation and integration of mental concentration and breathing control.
Comparative effectiveness	Eggenberger, 2015 ⁵³	<ul style="list-style-type: none"> Previous research linking physical activity with healthy brain aging and protection from cognitive decline and dementia.
	Napoli, 2014 ⁶⁴	<ul style="list-style-type: none"> Previous research suggesting that weight loss and/or exercise may improve cognition. Hypothesize interventions work best in frail, obese older adults.
	Cassilhas, 2007 ⁵²	<ul style="list-style-type: none"> Previous research linking physical activity to healthy aging by decreasing chronic disease risk, anxiety, and depression and research showing correlation between aerobic training and cognitive function.
	Baker, 2010b ⁴⁹	<ul style="list-style-type: none"> Previous research showing physical activity contributes to glucose regulation and cardiovascular health, which, when compromised, may threaten cognitive integrity. Previous research suggesting that aerobic exercise ameliorates age-related brain volume loss especially in regions supporting executive control and memory.
	Taylor-Piliae, 2010 ⁷¹	<ul style="list-style-type: none"> Previous research suggesting exercise, such as walking or calisthenics, improves cardiorespiratory endurance, muscle strength, flexibility, balance, and cognitive functioning. Improvements in blood pressure, lipid profiles, and heart-rate variability, may improve cognitive function. Eastern forms of exercise (Tai Chi) may provide benefits beyond traditional exercise because of the focus on mindfulness and relaxation and integration of mental concentration and breathing control.

Table 4B.2. Logic of proposed physical activity interventions in adults with MCI

Intervention	Study	Hypothesized Logic or Mechanism of Action
Aerobic training	Hildreth, 2015 ⁵⁶	<ul style="list-style-type: none"> • Previous research showing type 2 diabetes increases the risk of cognitive impairment and dementia. • Previous research showing insulin resistance strongly associated with central obesity and cognitive decline and CATD. • Insulin is present in the brain, where it helps to support normal cognitive function, and abnormalities in insulin concentrations and activity have been observed in the brains of individuals with CATD. • Interventions that target insulin resistance may delay or prevent further cognitive decline in individuals with MCI. • Endurance exercise training is effective in improving insulin resistance. Previous research suggests that endurance exercise may improve some aspects of cognitive adults with MCI.
	Lautenschlager, 2008 ⁵⁹	<ul style="list-style-type: none"> • Previous research showing correlation between physical activity, reduced risk of cognitive decline, and dementia.
	Law, 2014 ⁶⁰	<ul style="list-style-type: none"> • Previous research showing that physical activity improves cognitive function in older adults with MCI. • “Research has found that spatial learning or exposure to an enriched environment can rescue the newly generated immature cells and promote their long-term survival and functional connection with other neurons in the adult brain. Animal studies have also shown that a combination of exercise and an enriched environment induces a greater increase in neurogenesis than either exercise or environmental enrichment alone.”
	Nagamatsu, 2013 ⁶³	<ul style="list-style-type: none"> • Previous research showing that resistance and aerobic training improves cognitive function and results in “functional plasticity in healthy older adults.” • Emerging evidence also suggests that physical activity has cognitive benefits in older adults with MCI. • “While research on the effects of resistance training on cognitive function has been limited, preliminary evidence suggests that different forms of exercise (e.g., aerobic versus resistance) alter distinct cognitive processes.” • Previous research suggests that resistance training increases levels of serum IGF-1 while aerobic training increased levels of brain-derived neurotrophic factors.
	Suzuki, 2012 ⁷⁰ Suzuki, 2013 ⁶⁹	<ul style="list-style-type: none"> • Proposed association between regular physical activity, especially aerobic, and a variety of cognitive benefits. • Previous research showing effects of physical activity on cognitive function in older adults with MCI. • Neuroimaging studies showing aerobic exercise increased “hippocampal volume, and gray and white matter regions including the cingulate cortex, supplementary motor cortex, inferior frontal gyrus, and superior temporal gyrus.”

Adults with Normal Cognition

Efficacy: Physical Activity Versus Inactive Control

Seven RCTs reported in eight publications with low to medium risk of bias compared physical activity interventions to inactive controls in adults with normal cognition.^{48,52,62,64,68,71,73,74} Total sample sizes ranged from 42 to 1,635. Most interventions were multicomponent.^{64,68,71,74} Single component physical activity interventions consisted of resistance training,^{52,73} aerobic exercise/endurance,^{48,62} and Tai Chi.⁷¹ Inactive comparisons included usual care, information, and/or attention controls (i.e., health education). Results are presented by type of physical activity intervention. Conclusions are summarized in Table 4B.3 and individual study results in Table 4B.4.

Table 4B.3. Conclusions: Physical activity versus inactive comparisons in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Multicomponent physical activity vs. attention control	Dementia	Data insufficient to draw conclusion.	Insufficient (medium study limitations, unknown consistency, imprecise)
	MCI	Data insufficient to draw conclusion	Insufficient (medium study limitations, unknown consistency, imprecise)
	Brief cognitive test performance	No benefit in brief cognitive test performance with multicomponent physical activity versus attention control (n=155; 6 months to 1 year).	Low (medium study limitations, indirect, imprecise)
	Multidomain neuropsychological performance	No benefit in brief cognitive test performance with multicomponent physical activity versus attention control (n=1635; 2 years).	Low (medium study limitations, indirect, unknown consistency)
	Executive Function	No benefit in brief cognitive test performance with multicomponent physical activity versus attention control (n=1885; 6 months to 1 year).	Low (medium study limitations, indirect, imprecise)
	Memory	No benefit in brief cognitive test performance with multicomponent physical activity versus attention control (n=1836; 6 months to 1 year).	Low (medium study limitations, indirect, imprecise)
Resistance training vs. attention control	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No data available	Insufficient (no data)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive Function	No benefit in brief cognitive test performance with resistance training versus attention control (n=120; 6 months).	Low (medium study limitations, indirect, imprecise, inconsistent)
	Memory	No benefit in brief cognitive test performance with resistance training versus attention control (n=120; 6 months).	Low (medium study limitations, indirect, imprecise, inconsistent)
Aerobic training vs. attention control	Dementia	Limited data	Insufficient (limited data)
	MCI	No data available	Insufficient (no data)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
	Brief cognitive test performance/ Multidomain neuropsychological performance	Aerobic training interventions improve brief cognitive test performance/multidomain neuropsychological performance compared to attention control (n=290; 6 months to 1 year)	Low (medium study limitations, indirect)
	Executive Function	Data insufficient to draw conclusion	Insufficient (indirect, imprecise, inconsistent)
	Memory	Data insufficient to draw conclusion	Insufficient (indirect, imprecise, inconsistent)
Tai Chi vs attention control	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No data available	Insufficient (no data)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive Function	Limited data	Insufficient (limited data)
	Memory	No data available	Insufficient (no data)

Multicomponent Physical Activity

Multicomponent physical activity interventions included flexibility, strength, balance, endurance, and/or aerobic components.^{64,68,71,74} Enrollment criteria varied by trial. One trial enrolled sedentary adults over 70;^{68,74} another enrolled adults over 60⁷¹ and the last enrolled frail obese older adults.⁶⁴

Only the large 2-year trial (n=1635) reported diagnostic outcomes, finding no difference between multicomponent physical activity and attention control in diagnosis of MCI or CATD.⁶⁸ Evidence was insufficient to conclude whether a multicomponent physical activity intervention prevents MCI or CATD over a 2-year time period when compared with attention control in adults with normal cognition.

Two trials (n=1,688) assessed cognition with brief cognitive tests.^{64,74} After the intervention, one trial found no statistical difference between multicomponent physical activity and attention control in changes from baseline (n=102),⁷⁴ and one (n=53) showed a statistically significant improvement in Modified Mini-Mental State Examination (3MS) scores.⁶⁴ However, the difference in mean change from baseline between intervention and control was three points (95% CI: 1.5 to 4.5). The mean 3MS score in the control group remained nearly the same from baseline (96.3 of 100 possible) to 12 months and the mean score in the moderate physical activity group improved by nearly three points from baseline (94.9 of 100 possible). This three-point change is not likely clinically meaningful given that identified reliable change indices for this instrument range from 5 to 10 points. Low-strength evidence shows that multicomponent physical activity interventions with durations of 6 months to 1 year have no significant effect on brief cognitive test performance when compared to attention control in older sedentary adults.

The large 2-year trial showed no statistical difference with multicomponent physical activity versus attention control in multidomain neuropsychological performance.⁶⁸ These two trials constitute low-strength evidence that multicomponent physical activity interventions with duration of 2 years have no significant effect on multidomain neuropsychological performance when compared with attention control in older sedentary adults.

Four trials (n=1,885) used 13 tests to measure the effects of multicomponent physical activity on executive function/attention/processing speed.^{64,68,71,74} Only two of the 13 tests showed a

statistically significant improvement with multicomponent physical activity compared with attention control. These two trials constitute low-strength evidence that multicomponent physical activity interventions lasting 6 months to 2 years have no significant effect on executive function, attention, or processing speed when compared with attention control in older sedentary adults.

Two trials (n=1,688) also reported results of six memory tests; only one test result showed a statistical difference favoring the intervention.^{64,68} Napoli et al. showed greater improvements from baseline with multicomponent physical activity than attention control.⁶⁴ Participants improved their verbal fluency (naming animals) by a mean of over 4.1 with multicomponent physical activity, but decreased by 0.8 with attention control, for a mean difference of 4.9. This improvement is not likely clinically meaningful given an identified reliable change index of over 10. These two trials constitute low-strength evidence that multicomponent physical activity interventions lasting 6 months to 2 years have no significant effect on memory when compared to attention control in older sedentary adults.

No study of multicomponent physical activity interventions in adults with normal cognition reported other cognitive outcomes, biomarkers, or adverse effects.

Subgroup Effects

Sink et al. reports subgroup effects by sex, age, baseline MMSE and baseline Short Physical Performance Battery scores.⁶⁸ Subgroup effects were tested on four outcomes. Two instruments assessed three cognitive domains (executive function, processing speed, and verbal memory) and two composite scores assessed executive function and global cognitive function (according to authors). Physical activity led to better effects on the composite executive function score than health education (attention control) in participants aged 80 to 89. There were no other subgroup differences in executive function.

Resistance Training

Two studies compared resistance training to attention control or placebo.^{52,73} Van de Rest, et al. enrolled adults over 65⁷³ and Cassilhas enrolled sedentary men between 65 and 75.⁵² Cassilhas randomized participants to one of three groups (attention control, high-resistance training, and low-resistance training).

Neither trial reported diagnoses or overall cognitive performance outcomes. Van de Rest reported 11 tests of executive function, attention,⁷³ and processing speed and Cassilhas et al. reported seven (making comparison for each of the intervention groups to attention control).⁵² Evidence was insufficient to draw conclusions about the effects of resistance training on executive function/attention/processing speed or memory. However, the pattern of evidence shows mixed results. Eight of the 25 comparisons showed a statistically significant improvement in executive function/attention/processing speed with resistance training versus attention control or placebo. Only one of the eight comparisons tested in van de Rest et al. showed a statistically different improvement with resistance training compared to placebo control.⁷³ Cassilhas et al. showed improvements in four of seven tests of executive function, attention, and/or processing speed with high resistance training and three of seven tests of executive function, attention, and/or processing speed with moderate resistance training compared with attention control, scores on digit span, forward; Corsis block-tapping, backward; and similarities improved with high resistance training compared with attention control.⁵² Scores on digit span, forward; Corsis block-tapping, backward; and similarities improved with moderate resistance training compared

with attention control.⁵² Van de Rest reported six measures of memory⁷³ and Cassilhas et al. reported two.⁵² Van de Rest showed no statistical differences between resistance training and attention control in any memory score.⁷³ Cassilhas et al. showed improvements in one of two memory scores with resistance training; both high and moderate intensity resistance training improved compared with attention control.⁵²

Neither resistance training intervention study reported adverse effects.

Subgroup Effects

Van de Rest et al. examined the effect of frailty on the effect of resistance training on reaction time.⁷³ Treatment-time interaction was not significant for any of the five reaction time measures compared.

Aerobic Activity

Three trials with low to medium risk of bias compared aerobic or endurance programs to an attention control.^{48,59,62} Antunes et al. enrolled sedentary older men;⁴⁸ Muscari et al. enrolled healthy older adults;⁶² and Lautenschlager et al. enrolled adults having difficulty with memory and MMSE scores of 24 or greater.⁵⁹

Only Lautenschlager et al. reported dementia diagnosis outcomes and found that aerobic training was less likely to lead to a diagnosis than attention control.⁵⁹ Evidence was insufficient to conclude whether aerobic training offers benefits related to preventing dementia.

Two other trials reported either brief cognitive or multidomain neuropsychological test performance. Muscari et al. showed that brief cognitive test performance was better with aerobic training⁶² and Antunes et al. found that multidomain neuropsychological test performance was better with aerobic training.⁴⁸ Evidence was insufficient to conclude whether aerobic training offers benefits related to brief cognitive or multidomain neuropsychological test performance.

Other domains of cognitive performance were also reported. Executive function/attention/processing speed were better with aerobic training in 2 or 4 tests and memory was better in 6 of 15 tests. Evidence was insufficient to conclude whether aerobic training offers benefits related to executive function, attention, and/or processing speed, or memory.

Tai Chi

One trial compared Tai Chi to an attention control.⁷¹ Executive function, attention, and/or processing speed were better with Tai Chi than with the attention control. Evidence was insufficient to conclude whether Tai Chi offers benefits related to executive function, attention, and/or processing speed.

Table 4B.4 Results Overview: Physical activity versus inactive comparisons in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Multicomponent Physical Activity							
Sink, 2015⁶⁸ Multicomponent physical activity vs. attention control n=1635 2 years	NS [Dementia]			NS [DSy]	NS [HVLt-R, immediate recall]	1 of 15 favor I	NR
	NS [MCI]		MNP NS [Global composite ^a]	NS [N-Back, 1 back]	NS [HVLt-R, delayed recall]		
	NS [Dementia or MCI]			NS [N-Back, 2 back]	NS [HVLt-R, composite ^b]		
				NS [Reaction time on task switching, No]			
				NS [Reaction time on task switching, Yes]			
				I>C [Reaction Time on Flanker Test, Congruent] NS [Reaction Time on Flanker Test, Incongruent]			
				NS [Composite of Flanker test scores ^c]			
Napoli, 2014⁶⁴ Multicomponent physical activity vs. attention control			BCT I>C [3MS]	NS [TMT A]	I>C [Word List Fluency]	2 of 4 favor I	NR
				NS			

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
n=53 1 year				[TMT B]			
Taylor-Piliae, 2010 ⁷¹ I ₁ Multicomponent physical activity vs. attention control n=95 6 months				NS [DS Forward]		0 of 2 (no differences)	NR
				NS [DS Backward]			
Williamson, 2009 ⁴ Multicomponent physical activity vs. attention control n=102 1 year			BCT NS [3MS]	NS [Stroop]	NS [RAVLT]	0 of 4 (no differences)	NR
					NS [DSST]		
Multicomponent Physical Activity Results Summary	0 of 3 (no difference)	NR	BCT 1 of 2 favors I MNP 0 of 1 (no difference)	1 of 13 favor I	1 of 6 favor I	3 of 25 favor I	NR
Resistance Training							
van de Rest, 2014 ⁷³ Resistance-type exercise program vs. usual care n=55 6 months				I>C [DS Forward]	NS [Word Learning Test, Immediate Recall-75 Words]	2 of 17 favor I	NR
				NS [DS Backward]	NS [Word Learning Test, Delayed Recall-15 Words]		
				NS [TMT A]	NS Word Learning Test, Decay]		
				NS [Stroop 1]	NS [Word Learning Test,		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
					Recognition, 30 Words]		
				NS [Stroop 2]	I>C ^z [Attention and Working Memory Composite]		
				NS [Stroop Inference]	NS ^z [Episodic Memory Composite]		
				NS [Reaction Time Uncued]			
				NS [Reaction Time Cued]			
				NS [Word Fluency-Letter]			
				NS ^z [Processing Speed Composite]			
				NS ^z [Executive Functioning Composite]			
Cassilhas, 2007 ⁵² High resistance training (I1) vs. attention control N=43 males 6 months				I ₁ >C [DS Forward]	NS [RCFT, Copy]	5 of 9 favor I	NR
				NS [DS Backward]	I ₁ >C [RCFT, Immediate Recall]		
				NS [Corsi Block, Forward]			
				I ₁ >C [Corsi Block, Backward]			
				I ₁ >C [Corsi Block, Similarities]			
				NS			

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
				[Toulouse-Pieron, Cancellations Numbers]			
				I ₁ >C [Toulouse-Pieron, Errors]			
Cassilhas, 2007 ⁵² Moderate resistance training (I2) vs. attention control N=42 males 6 months				I ₂ >C [DS Forward]	NS [RCFT, Copy]	4 of 9 favor I	NR
				NS [DS Backward]	I ₂ >C [RCFT, Immediate Recall]		
				NS [Corsi Block, Forward]			
				I ₂ >C [Corsi Block, Backward]			
				I ₂ >C [Corsi Block, Similarites]			
				NS [Toulouse-Pieron, Cancellations Numbers]			
				NS [Toulouse-Pieron, Errors]			
Resistance Training Results Summary	NR	NR	NR	8 of 25 favor I	3 of 10 favor I	11 of 35 favor I	NR
Aerobic Training							
Antunes, 2015 ⁴⁸ Multicomponent physical activity vs. usual care n=46 older males				I>C [Picture Arrangement, WAIS-III]	NS [Verbal Paired Associates, Trial 1, Easy Pair]	7 of 16 favor I	
				I>C	I>C		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
6 months				[Corsi Block-tapping, Forward]	[Verbal Paired Associates, Trial 1, Hard Pair]		
				NS [Corsi Block-tapping, Backward]	NS [Verbal Paired Associates, Trial 2, Easy Pair]		
					I>C [Verbal Paired Associates, Trial 2, Hard Pair]		
					NS [Verbal Paired Associates, Trial 3, Easy Pair]		
					I>C Memory [Verbal Paired, Trial 3, Hard Pair]		
					NS [Verbal Paired Associates, Recall Test, Easy Pair]		
					NS [Verbal Paired Associates, Recall Test, Hard Pair]		
					I>C [Free Word Recall. Total Words Recalled (Non- Semantic)]		
					I>C [Free Word Recall, Total Words Recalled (Semantic)]		
					NS [Free Word Recall,		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
					Intrusions]		
					Unclear [Free Word Recall, Repetitions]		
					Unclear [Free Word Recall, Preservations]		
Muscari, 2010⁶² Endurance training vs. information control n=120 1 year			BCT I>C [MMSE]			1 of 1 favor I	NR
Lautenschlager, 2008⁵⁹ Home-based physical activity vs. information control n=170 6 months			MNP I>C [ADAS-Cog]	NS [DSy]	NS [Word List, Immediate Recall]	3 of 5 favor I	NS [Cardiovascular problem]
	I>C [Clinical Dementia Rating, Sum of Boxes (diagnosis estimate)]				I>C [Word List, Delayed Recall]		NS [Stroke] NS [Shoulder operation]
Aerobic Training Results Summary	1 of 1 favors I	NR	BCT 1 of 1 favor I MNP 1 of 1 favor I	2 of 4 favor I	6 of 15 favor I	10 of 21 favor I	0 of 3 (no differences)
Tai Chi							
Taylor-Piliae, 2010⁷¹ I ₂ Tai Chi vs. attention control n=93 6 months				I ₂ >C [DS Backward]		1 of 2 favor I ₂	NR
				NS [DS Forward]			

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Tai Chi Results Summary	NR	NR	NR	1 of 2 favor I	NR	NR	NR
Physical Activity vs. Inactive Control Results Summary	1 of 4 (25%)	NR	BCT 2 of 3 favors I (67%) MNP 1 of 2 favors I (50%)	11 of 44 favor I (25%)	10 of 31 favor I (36%)	25 of 84 favor I (30%)	0 of 3 (0%)

^a mean global composite z score composed of Digit Symbol Coding, HVLT immediate and delayed recall, n-back task, and reaction time on task switching and Flanker tasks; ^b composite z score of HVLT-R immediate and delayed word recall; ^c composite z score of Flanker congruent and incongruent reaction times

3MS=Modified Mini-Mental State Examination; BCT=Brief cognitive test performance; C=inactive control; DS=Digit Symbol; DSST=Digit Symbol Substitution Test; DSy=Digit Symbol Coding; HVLT-R=Hopkins Verbal Learning Test; I₁=first intervention; I₂=second intervention; MNP=Multidomain neuropsychological performance; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; RCFT= Rey-Osterrieth Complex Figure Test; Stroop=Modified Stroop; TMT=Trail-Making Test

Comparative Effectiveness: Physical Activity Versus Active Comparison

Five studies compared physical activity interventions to active interventions.^{50,52,53,64,71} Individual study results are provided in table 4B.5. Eggenberger et al. (n=89) compared 6-months of virtual reality dance video game with treadmill walking combined with verbal memory training in adults over 70.⁵³ Napoli et al. (n=54) compared exercise with an exercise and diet program.⁶⁴ Baker et al. (n=34) compared 6-months of an aerobic exercise program with stretching.⁵⁰ Taylor-Piliae et al. (n=132) compared multicomponent physical activity with Tai Chi.⁷¹ Cassilhas et al. (n=39) compared a high intensity resistance training with a lower intensity resistance training.⁵²

None of the eligible studies reported diagnoses outcomes. Three comparative effectiveness trials showed no statistical differences in any cognitive category, despite examining many comparisons.^{52,53,64} These trials are likely underpowered for comparative effectiveness.

Baker et al. showed that executive function/attention/processing speed (measured with four different instruments) improved with aerobic exercise compared with stretching in 3 of the 4 tests.⁵⁰ They found no statistically significant difference in memory with aerobic exercise versus stretching.

Taylor-Piliae et al. showed that executive function/attention/processing speed (measured with two different instruments) improved more with Tai Chi than multicomponent physical activity in one of two tests.⁷¹

Evidence on comparative effectiveness was insufficient due to the heterogeneity in interventions, comparisons, and outcomes examined, resulting in either limited data (n<500 for single studies), or no data.

Table 4B.5. Results Overview: Physical activity versus active comparisons in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Eggenberger, 2015 ⁵³ Dance/treadmill memory training vs. treadmill n=89 6 months				NS [Trails A]	NS [Story Recall]	0 of 9 (no differences)	NR
				NS [Trails B]	NS [Paired Associates Learning]		
				NS [Executive Control Trask]			
				NS [Digit Forward]			
				NS [Age Concentration Test A]			
				NS [Age Concentration Test B]			
				NS [Digit Symbol Substitution]			
Napoli, 2014 ⁶⁴ I ₁ Exercise vs. I ₂ diet+exercise n=54 1 year			BCT NS [3MS]	NS [Trails A]	NS [Word List Fluency]	0 of 4 favor (no difference)	NR
				NS [Trails B]			
Baker, 2010 ⁵⁰ Aerobic exercise (I ₁) vs. stretching (I ₂) n=34 6 months				I ₁ >I ₂ [Trails B]	NR [Story Recall]	3 of 7 favor I ₁	NR
				I ₁ >I ₂ [Task Switching]			
				I ₁ >I ₂ [Stroop Inference]			
				NS [Self-Ordered Point Test]			
				NS [Verbal Fluency]			

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Taylor-Piliae, 2010 ⁷¹ I ₁ Multicomponent physical activity vs. I ₂ Tai Chi n=70				I ₂ >I ₁ [Digit Span Backwards]		1 of 2 favor I ₂	
				NS [Digit Span Forwards]			
Cassilhas, 2007 ⁵² High resistance training (I1) vs. Moderate resistance training (I2) n=39 6 months				NS [Digit Span, Forward]	NS [Rey Osterrieth Figure, Copy]	0 of 9 (no differences)	NR
				NS [Digit Span, Backward]	NS [Rey Osterrieth Figure, Immediate Recall]		
				NS [Corsi Block, Forward]			
				NS [Corsi Block, Backward]			
				NS [Corsi Block, Similarites]			
				NS [Toulouse-Pieron, Cancellations Numbers]			
				NS [Toulouse-Pieron, Errors]			

C=inactive control; I=intervention; I₁=first intervention; I₂=second intervention; NS=not significant

Adults with MCI

Conclusions are provided in Table 4B.6 and individual study results in Table 4B.7.

Table 4B.6. Conclusions: Physical activity versus inactive comparisons in adults with MCI

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Multicomponent physical activity vs. attention control	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	Data insufficient to draw conclusion	Insufficient (medium study limitations, indirect, imprecise)
	Multidomain neuropsychological performance	Limited data	Insufficient (limited data)
	Memory	Data insufficient to draw conclusion	Insufficient (medium study limitations, indirect, imprecise)
Aerobic training vs. attention control	Dementia	Limited data	Insufficient (limited data)
	MCI	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No data available	Insufficient (no data)
	Multidomain Neuropsychological Performance	Data insufficient to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
	Executive Function	Data insufficient to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise)
	Memory	Data insufficient to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise)

Efficacy: Physical Activity Versus Inactive Control

We identified four reports of three unique studies comparing physical activity interventions to inactive controls in older adults with MCI.^{56,59,69,70} Lautenschlager et al. (n=170) compared a 24-week home-based exercise program with usual care.⁵⁹ Hildreth et al. (n=78) compared a 6-month endurance exercise program with placebo in obese older adults with MCI.⁵⁶ Suzuki et al. compared a 6-month multicomponent physical activity program to attention control in older adults with MCI or amnesic MCI.⁶⁹

All three trials reported multidomain neuropsychological test performance measured with the ADAS-Cog. Lautenschlager et al. showed improvements with the home-based physical activity program versus usual care.⁵⁹ Hildreth et al. showed no statistical difference with endurance exercise versus placebo.⁵⁶ Suzuki et al. showed no statistical difference with a 6-month multicomponent physical activity program versus attention control.⁶⁹ Lautenschlager et al. showed no difference in executive function/ attention/processing speed with home exercise versus usual care compared using two different measures.⁵⁹ Hildreth et al. used four tests to measure executive function/attention/processing speed and found no differences in any measure.⁵⁶ Suzuki et al. showed no difference in memory with multicomponent exercise versus attention control measured with two different measures.⁶⁹

We identified six reports of five unique studies comparing physical activity interventions to active interventions in older adults with MCI.^{50,58,60,63,75} All were assessed high risk of bias.

Interpreting the Findings

These results do not show a clear and consistent benefit of physical activity interventions in preventing cognitive decline. However, the number of positive results exceeds what would be expected by chance alone; providing a signal of a possible relationship. Given that many of these physical activity intervention studies enrolled older sedentary adults and had followup times as short as 6 months, substantial benefits to cognition might be unlikely. It likely involves a more long-term investment in lifestyles thought to be protective of cognitive function to reverse a lifetime of exposure to risk factors. Longer term studies enrolling younger adults would greatly benefit the field and provide more insight on prevention.

Table 4B.7. Results Overview: Physical activity interventions versus inactive comparisons for adults with MCI

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Multicomponent Physical Activity							
Suzuki, 2013 ⁶⁹ Multicomponent physical activity vs. attention control n=100 6 months		NS [MTA-ERC]	BCT NS [MMSE]		NS [WMS-LM I]	0 of 6 (no differences)	NS [Falls and hospitalizati on for illness]
		NS [WBS]	MNP NS [ADAS-cog]		NS [WMS-LM II]		
Suzuki, 2012 ⁷⁰ Multicomponent physical activity vs. attention control (sMCI subgroup of Suzuki 2013) n=50 6 months 12 months			MNP I>C [MMSE, 6 months]	NS [SCWT-I]	I>C [WMS-LM I, 6 months]	2 of 9 favor I	
			NS [MMSE, 12 months]	NS [SCWT-II]	NS [WMS-LM I, 12 months]		
				NS [DSy, WAIS-III]	NS [WMS-LM II]		
				NS [LVFT]			
Multicomponent Physical Activity Results Summary	NR	0 of 2 (no differences)	BCT 1 of 3 favor I MNP 0 of 1 (no difference)	0 of 4 (no difference)	1 of 5 favors I	2 of 15 favor I	0 of 1 (no difference)
Aerobic Training							
Hildreth, 2015 ⁵⁶ Endurance training vs. usual care + placebo n=53 6 months			MNP NS [ADAS-cog]	NS [WMS-R Visual Reproduction II]	NS ^a [Memory Composite]	0 of 11 (no differences)	Unclear [Musculo- skeletal Complaints]
				NS [Picture Completion, WAIS-R]	NS [WMS-R, LM II]		
				NS ^b	NS		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
				[Executive Function Composite]	[RAVLT]		
				NS [TMT B]			
				NS [Digit Symbol Test, WAIS-R]			
				NS [SCWT]			
				NS [DS, WAIS-III]			
Lautenschlager, 2008 ⁵⁹ Home-based physical activity vs. information control n=100 6 months	NS [Clinical Dementia Rating, Sum of Boxes (diagnosis estimate)]		MNP I>C [ADAS-Cog]	NS [DSy]	NS [Word List, Immediate Recall]	1 of 5 favor I	NS [Cardiovasc ular Problem] NS [Stroke] NS [Shoulder Operation]
					NS [Word List, Delayed Recall]		NS [Shoulder Operation]
Aerobic Training Results Summary	0 of 1 (no difference)	NR	MNP 1 of 2 favors I	0 of 8 (no differences)	0 of 5 (no differences)	1 of 16 favor I	0 of 4 (no difference)
Physical Activity vs. Inactive Control Results Summary	0 of 1 (no difference)	0 of 2 (no differences)	BCT 1 of 3 favor I (33%) MNP 1 of 3 favor I (33%)	0 of 12 (no differences)	1 of 10 favor I (10%)	3 of 31 favor I (10%)	

^a=Scaled score for domain: visual reproduction II, logical memory II, RAVLT; ^b= Domain scaled score: Trails B, Digit Symbol Test; ADAS-Cog= AD Cooperative Studies AD Assessment Scale - Cognitive Subscale; BCT=Brief cognitive test performance; C=inactive control; DS=Digit Symbol; DSy=Digit Symbol Coding; I₁=first intervention; I₂=second intervention; LVFT= Letter verbal fluency test; MNP=Multidomain neuropsychological performance; MTA-ERC=Medial temporal areas including the entorhinal cortex; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; Stroop=Modified Stroop; SCWT= Stroop Color and Word Test; TMT=Trail-Making Test; WBC= Whole brain cortices; WMS=Wechsler Memory Scale

Chapter 4C. Results: Nutraceutical Interventions

Key Messages

- Low-strength evidence suggests omega-3 fatty acids and ginkgo biloba did not improve clinical Alzheimer’s-type dementia (CATD) incidence or cognitive performance in adults with normal cognition.
- Evidence is insufficient to conclude whether resveratrol or plant sterol/stanol esters improved CATD incidence or cognitive performance in adults with normal cognition.
- Few studies examined the effects of nutraceuticals on adults with MCI.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified 21 eligible publications reporting 20 unique studies of nutraceutical interventions to prevent age-related cognitive decline, MCI, or CATD.^{51,76-95} Six were assessed as high risk of bias and not used in our analysis. We analyzed the efficacy and comparative effectiveness of nutraceutical interventions separately for adults with normal cognition and those with MCI. Appendix H provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Nutraceuticals Interventions

The logic underlying nutraceuticals varies with the nutraceutical. Targeted pathways include reducing oxidative stress and chronic inflammation, improving vascular function, and supplementing macronutrients found in brain tissue and used in brain function.

Adults with Normal Cognition

Conclusions are summarized in Table 4C.1 and individual study results in Table 4C.2.

Table 4C.1. Conclusions: Nutraceuticals in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Omega-3 fatty acids vs. inactive control	Dementia	No statistically significant difference in dementia diagnosis with omega-3 fatty acids versus placebo in long term (n=12,536; 6 years; adults with diabetes or glucose intolerance).	Low (high study limitation of composite outcome with component of unequal importance, one of which is not clinical diagnosis and may be achieved due to chance, unknown consistency)
	MCI	No data available	Insufficient (no data)
	Biomarkers	Limited data	Insufficient (limited data)
	Brief cognitive test performance	No benefit in brief cognitive test performance with omega-3 fatty acids versus placebo in long term (n=16,431; up to 6 years).	Low (medium study limitation, indirect, imprecise)
	Multidomain neuropsychological performance	No benefit in multidomain neuropsychological performance with omega-3 fatty acids versus placebo in long term (n=744; 2 years).	Low (medium study limitation, indirect, imprecise, unknown consistency)
	Executive/Attention/Processing Speed	No benefit in executive/attention/processing speed with omega-3 fatty acids versus	Low (medium study limitation, indirect, imprecise)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
		placebo in long term (n=5,079; up to 6 years).	
	Memory	No benefit in memory with omega-3 fatty acids versus placebo in long term (n=3,428; up to 4 years).	Low (medium study limitation, indirect, imprecise)
Omega -3 fatty acids vs. Vitamin B	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief cognitive test performance	No benefit in brief cognitive test performance with omega-3 fatty acids versus vitamin B in long term (n=885; 4 years).	Low (medium study limitations, indirect, imprecise, unknown consistency)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)
	Memory	No benefit in memory with omega-3 fatty acids versus vitamin B in long term (n=885; 4 years).	Low (medium study limitations, indirect, imprecise, unknown consistency)
Omega-3 fatty acids vs. Vitamin B + Omega-3 fatty acids	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief cognitive test performance	No benefit in brief cognitive test performance with omega-3 fatty acids versus omega-3 fatty acids plus vitamin B in long term (n=877; 4 years).	Low (medium study limitations, indirect, imprecise, unknown consistency)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)
	Memory	No benefit in memory with omega-3 fatty acids versus omega-3 fatty acids plus vitamin B in long term (n=877; 4 years).	Low (medium study limitations, indirect, imprecise, unknown consistency)
Ginkgo biloba vs. inactive control	Dementia	No statistically significant difference in dementia diagnosis with ginkgo biloba versus placebo in long term (n=5,407; 6 years; adults over 70).	Low (medium study limitations, direct, imprecise, consistent)
	MCI	Limited data	Insufficient (limited data)
	Biomarkers	No data available	Insufficient (no data)
	Brief cognitive test performance	No data available	Insufficient (no data)
	Multidomain neuropsychological performance	No benefit in multidomain neuropsychological performance with ginkgo biloba versus placebo in long term (n=3069; 6 years, adults over 70).	Low (medium study limitation, indirect, imprecise, unknown consistency)
	Executive/Attention/Processing Speed	No benefit in executive/attention/processing speed with ginkgo biloba versus placebo in long term (n=5079; 6 years, adults over 70).	Low (medium study limitation, indirect, imprecise)
	Memory	No benefit in memory with ginkgo biloba versus placebo in long term (n=3,187; up to 6 years, adults over 70).	Low (medium study limitation, indirect, imprecise)

MCI=Mild cognitive impairment

Omega-3 versus Placebo

Seven RCTs with low to medium risk of bias enrolling a total of 21,027 adults compared some form of omega-3 fatty acids versus placebo in adults.^{76,78,82,90,92,94,95} Total sample sizes ranged from 65 to 11,685. Yurko-Mauro et al. used only docosahexaenoic acid (DHA),⁹⁴ all

others used some combination of eicosapentaenoic acid (EPA) plus DHA. Geleijnse et al. also used alpha-linolenic acid (ALA) as another omega-3 study arm.⁸² Only the ORIGIN study (n=15,077) allowed adults already using omega-3 supplementation to participate in the study.⁹⁵ All studies assessed baseline cognition; six reported baseline MMSE score of at least 28^{78,82,90,92,94,95} while one study used the Isaacs Set Test (35.8).⁷⁶ However, only three studies specified a baseline cognition inclusion criterion.^{78,90,94} Populations studied included adults with diabetes or impaired glucose tolerance,⁹⁵ a history or ischemic heart disease,⁷⁶ coronary patients,⁸² or healthy adults.^{78,90,92,94}

No study reported incident diagnosis of dementia or MCI as determined solely by clinical diagnosis. The ORIGIN study, a large multinational study of adults with diabetes or impaired glucose tolerance, used a combination of clinical diagnosis or an MMSE score less than 24 and found no difference in probable dementia incidence between EPA+DHA or placebo groups for the median duration of 6.2 years (HR 0.93 [0.86 to 1.0]).⁹⁵

Overall, the studies provide low-strength evidence suggesting that omega-3 fatty acids do not improve cognitive performance between adults with normal cognition as compared to placebo. (Table 4C.2) None of four studies (n=16,431) found a statistical improvement in brief cognitive test performance, such as the MMSE;^{76,82,94,95} likewise, one study that assessed multidomain neuropsychological performance using a global composite also found no statistical difference between groups.⁷⁸ Of 32 tests to assess executive function in 5 studies (n=5,079), 29 tests did not find a significant difference between groups, with a maximum followup of 6 years.^{78,90,92,94,95} The two tests with significant differences that favored the omega-3 fatty acid group were based on 548 participants and for only a 6 month followup.^{92,94} Similarly, of 25 tests to assess memory in 5 studies (n=3,428),^{76,78,90,92,94} 22 did not find a significant difference between groups, with a maximum followup of 4 years. The three tests with the omega-3 fatty acid group performing better than the placebo group were from a single 6 month study that used 6 memory tests (n=483).⁹⁴

No studies found significant differences in adverse events for omega-3 supplementation.

Four studies examined the effects of the omega-3 fatty acid interventions versus placebo on several subgroups. No significant differences in effect were found for age,^{76,82,90,95} sex,^{82,90,95} or inclusion criteria disease condition.^{82,95}

Andreeva et al. used a 2X2 factorial design, assigning adults with a history of ischemic heart disease to four groups: placebo, omega-3, vitamin B, or omega-3 plus vitamin B.⁷⁶ Results noted above collapsed the four arms into one group with any omega-3 assignment versus one group without omega-3 assignment. Results when comparing the omega-3 alone group with the vitamin B alone group also found no significant differences between groups for any outcome. Likewise, the omega-3 alone versus omega-3 plus vitamin B did not result in significant differences between groups.

Ginkgo Biloba Extract

Three RCTs (four publications) with low to medium risk of bias enrolling a total of 5,559 older adults with presumed normal cognition compared 240 mg/day of ginkgo biloba versus placebo in adults.^{79,80,88,91} Total sample sizes ranged from 118 to 3,069. All studies assessed baseline cognition, two reporting baseline MMSE scores of at least 27.6^{80,91} while one reported baseline 3MS of 93 and ADAS-Cog of 6.5.^{79,88} All studies specified a baseline cognition inclusion criterion.^{78,90,94} Age inclusion criterion were ≥ 70 ,⁹¹ ≥ 75 ,^{79,88} and ≥ 85 .⁸⁰

Two studies provide low-strength evidence suggesting that ginkgo biloba does not affect incidence of probable CATD compared to placebo.^{79,88,91} Both studies assessed probable CATD according to DSM-IV criteria by adjudication panels of clinical experts (Table 4C.2).

Overall the studies also provide low-strength evidence that ginkgo biloba does not improve cognitive performance as compared to placebo. One study that assessed multidomain neuropsychological performance using the 3MS and the ADAS-Cog found no statistical difference between groups.⁸⁸ Likewise, no differences between groups were found in either executive function⁸⁸ or memory.^{80,88}

All studies reported adverse events. No studies found significant differences in adverse events for omega-3 supplementation. The two larger studies found no differences in adverse events between groups (n=5,437).^{79,88,91} Dodge et al., who recruited 122 adults 85 years and older with normal cognition, reported a larger number of strokes and TIAs in the ginkgo biloba group (7 vs 0, p=.01).⁸⁰

Two studies explored the effects of the ginkgo biloba interventions versus placebo on several subgroups. Vellas et al. found differences in effect in men, people who consumed alcohol at baseline, and adults who continued the intervention for at least four years.⁹¹ The authors also advised caution in interpreting the results since they assessed 13 planned subgroups (including age, APOE-E4, MMSE ≤ 27 at baseline, hypertension, diabetes, hypercholesterolaemia, body mass index (BMI) ≥ 27 , and failing leg balance test) and did not adjust for multiple testing (all 3 groups showing differences would have been nonsignificant with a Bonferroni correction).⁹¹ In contrast, the GEM study did not find significant effect modification for sex. They also did not find differences for age, sex, race, APOE-E4 status, education, or MCI at baseline. However, CVD at baseline did show a significant treatment by group interaction (p=.02).

Other Nutraceuticals

Two additional RCTs examined the effects of nutraceuticals on cognition. Resveratrol, a member of a group of plant compounds called polyphenols with possible antioxidant properties, was examined in one study. In this 6 month study on the use of resveratrol in 46 healthy overweight people aged 50-80 years, people assigned to resveratrol performed better on 2 of 6 memory tests and showed significant increases in functional connectivity of the hippocampus to frontal, parietal, and occipital areas of the brain when compared to placebo.⁹³ No significant changes between groups in total gray matter volume or in the volume or microstructure of the hippocampus were noted. Schiepers et al. (n=57) compared cognition in 57 adults assigned to consume margarines enriched with plant sterol or stanol esters with those using a control margarine and found no differences between groups.⁸⁶ No adverse effects were reported in either study. Due to the evidence base of single studies with small sample sizes, strength of evidence was not assessed.

Table 4C.2. Results Overview: Nutraceuticals in adults with normal cognition

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychologi cal test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Omega-3 Efficacy							
Cukierman-Yaffe 2014⁹⁵ Omega-3 (EPA 465 mg+ DHA 375 mg daily) n=15077 Median 6.2 years	NS [incident probable cognitive impairment = reported dementia or an MMSE score of < 24] (n=12536)		BCT NS [MMSE] (n=11685)	NS [DSS – WAIS] (n=3392)		0 of 2 favor I	
Witte 2014⁹² Omega-3 (fish oil LC-n3-FA) 2.2 grams daily vs placebo n=65 6 months		I>C [MRI - gray matter volume]		I>C [executive composite: phonemic & semantic fluency, TMT A&B, Stroop parts 1-3]	NS [memory composite: AVLT learning, delayed recall, recognition, digit span backward]	2 of 6 favor I	
		NS [MRI - white matter integrity]		NS [sensorimotor speed composite: TMT part A, Stroop A & B]			
				NS [digit span forward]			
Geleijnse 2012⁸² Omega-3 (EPA- DHA 400 mg/d) vs placebo n=2522 40 months			BCT NS [MMSE]			0 of 3 (no differences)	
			BCT NS [risk of moderate/severe cog decline, MMSE] ^a				
			BCT NS [risk of severe cog				

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychologi cal test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
			decline, MMSE ^b				
Geleijnse 2012 ⁸² Omega-3 (ALA 200 mg/d) vs placebo n=2522 40 months			BCT NS [MMSE]			0 of 3 (no differences)	
			BCT NS [risk of moderate/severe cog decline, MMSE] ^a				
			BCT NS [risk of severe cog decline, MMSE] ^b				
Andreeva 2011 ⁷⁶ Omega-3 (EPA- DHA 600 mg/d in a 2:1 ratio) vs placebo n=1741 4 years			BCT NS [F-TICS-m overall score]		NS [F-TICS-m attention & semantic memory subscore]	0 of 3 (no differences)	
					NS [F-TICS-m recall/repetition subscore]		
Dangour 2010 ⁷⁸ Omega-3 (EPA 200 mg/d + DHA 500 mg/d) vs placebo n=744 2 years			MNP NS [global composite] ^c	NS [executive composite: CVLT delayed recall, location memory delayed recall, story recall delayed]	NS [CVLT – words correct]	0 of 17 (no differences)	NS [hospitaliz ation for stroke or MI]
				NS [processing speed composite: letter cancellation, simple RT, choice RT, symbol-letter substitution]	NS [CVLT - delayed recall]		

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychologi cal test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
				NS [letter search/ cancellation]	NS [memory composite: CVLT sum of words, CVLT delayed recall, location memory & delayed, story recall & delayed]		
				NS [symbol letter modality]	NS [global delay composite: CVLT delayed recall, location memory delayed recall, story recall delayed]		
				NS [reaction time, simple]	NS [story recall - immediate]		
				NS [reaction time, choice]	NS [story recall - delayed]		
				NS [digit span forward]	NS [spatial memory - immediate]		
				NS [digit span backward]	NS [spatial memory - delayed]		
Yurko-Mauro 2010⁹⁴ Omega-3 (DHA 900 mg/d) n=483 6 months			BCT NS [MMSE]	I>C [CANTAB Stockings of Cambridge]	I>C [CANTAB PAL battery]	4 of 8 favor I	NS [infection]
					NS [CANTAB VRM – free recall]		NS [musculos keletal]
					I>C [CANTAB VRM - immediate recall]		NS [gastrointe stinal]
					I>C [CANTAB VRM - delayed recall]		NS [nervous system]
					NS [CANTAB SWM]		

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychologi cal test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
					NS [CANTAB PRM - delayed]		
Van de Rest 2008⁹⁰ Omega-3 (EPA- DHA 400 mg/d) vs placebo n=196 6 months				NS [executive composite: TMT A & B, Stroop Part 3: (part 1 + part 2/2), word fluency animals & letter]	NS [memory composite: word learning immediate, delayed, & recognition, digit span backward]	0 of 13 (no differences)	
				NS [attention composite]	NS [word learning - immediate recall]		
				NS [digit span forward]	NS [word learning - delayed recall]		
				NS [digit span backward]	NS [word learning - recognition]		
				NS [TMT A]			
				NS [TMT B]			
				NS [Stroop Part 1]			
				NS [Stroop Part 2]			
				NS [Stroop Part 3: (part 1 + part 2/2)]			
Van de Rest 2008⁹⁰ Omega-3 (EPA- DHA 1800 mg/d) vs placebo n=199 6 months				NS [executive composite (same as immediately above)]	NS [memory composite (same as immediately above)]	0 of 13 (no differences)	
				NS [attention composite]	NS [word learning, immediate recall]		
				NS	NS		

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychologi cal test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
				[digit span forward]	[word learning, delayed recall]		
				NS [digit span backward]	NS [word learning, recognition]		
				NS [TMT A]			
				NS [TMT B]			
				NS [Stroop Part 1]			
				NS [Stroop Part 2]			
				NS [Stroop Part 3: (part 1 + part 2/2)]			
Omega 3 fatty acids efficacy Results Summary	0 of 1 (no differences)	1 of 2 favor I	BCT 0 of 9 (no differences) MNP 0 of 1 (no differences)	2 of 31 favor I	3 of 25 favor I	6 of 68 favor I (9%)	0 of 4 (no differences)
Ginkgo biloba Efficacy k=3; n=6041							
Vellas 2012 ⁹¹ Ginkgo biloba extract (EGb761) 120 mg twice daily vs placebo n=2820 5 years	NS [incidence of probable CATD, each year for 5 years]					No intermediate outcomes reported	NS [stroke, haemorrhagic events, cardiac disorders]
Snitz 2009 ⁸⁸ DeKosky 2008 ⁷⁹ Ginkgo biloba extract 120 mg	NS [all dementia]		MNP NS [composite: 3MS & ADAS-Cog]	NS [executive composite: TMT B & Stroop color/word test]	NS [memory composite: CVLT & recall conditions - Modified Rey Osterrieth figure test]	0 of 9 (no differences)	NS [mortality, CHD, stroke, major

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychologi cal test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
twice daily n=3069 (normal cog & MCI, cognitive test results) n=2587 (incident AD/dementia) Median 6.1 years							bleeding]
	NS [CATD without vascular dementia]			NS [attention & psychomotor speed composite: WAIS-R digit span & TMT A]	NS [CVLT])		
	NS [CATD with vascular dementia]			NS [TMT B]	NS [recall conditions - Modified Rey Osterrieth figure test]		
	NS [total CATD]			NS [TMT A]			
	NS [vascular dementia without CATD]			NS [Stroop color/word test]			
				NS [WAIS-R digit span]			
Dodge 2008 ⁸⁰ Ginkgo biloba extract 80 mg three times daily n=118 3 years 6 months	NS [MCI diagnosis estimate: progress from CDR 0 to CDR 0.5]				NS [CERAD word list delayed recall]	0 of 2 (no differences)	C>1 [stroke/TI A] [AEs in treatment group]
							NS [cardiac, renal, falls, other]
Ginkgo biloba efficacy Results Summary	0 of 11 (no differences)	NR	BCT NR MNP 0 of 1 (no differences)	0 of 6 (no differences)	0 of 4 (no differences)	0 of 11 (no differences)	All serious AEs NS except C>1 [stroke/

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychologi cal test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
							TIA]
Resveratrol Efficacy							
Witte 2014⁹³ Resveratrol 200 mg daily n=46 6 months (Resveratrol is a member of a group of plant compounds called polyphenols with possible antioxidant properties)		NS [total gray matter volume]			I>C [memory composite: AVLT retention, delayed recall, recognition, learning ability, 5th learning trial]	5 of 11 favor I	
		NS [HC microstructure]			I>C [AVLT retention]		
		I>C [functional capacity, HC frontal]			NS [AVLT delayed recall]		
		I>C [functional capacity, HC parietal]			NS [AVLT recognition]		
		I>C [functional capacity, HC occipital]			NS [AVLT learning ability]		
					NS [AVLT fifth learning trial]		
Resveratrol efficacy Results Summary	NR	3 of 5 favor I	NR	NR	2 of 6 favor I	5 of 11 favor I	NR
Plant sterols or plant stanols efficacy							
Schiepers 2009⁸⁶ Margarines				NS [simple information processing speed]	NS [composite: Visual Verbal Word Learning Task total]	0 of 4 (no differences)	No adverse effects

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
enriched with plant sterol esters (2.5 g/d) or plant stanol esters (2.5 g/d) n=57 1.6 years (85 weeks)				composite: Stroop 1 & 2, concept shifting tests A & B]	free recall, delayed recall, recognition]		reported
				NS [complex speed composite: Stroop 3, complex shifting test]			
				NS: [letter digit substitution]			
Plant sterols/stanols efficacy Results Summary	NR	NR	NR	0 of 3 (no differences)	0 of 1 (no differences)	0 of 4 (no differences)	NR
Omega 3 vs. Vitamin B							
Andreeva 2011 ⁷⁶ Omega-3 (EPA-DHA 600 mg/d in a 2:1 ratio) vs Vit B n=885 4 years			BCT NS [F-TICS-m]		NS [F-TICS-m memory subscore]	0 of 3 (no differences)	
					NS [F-TICS-m recall subscore]		
Omega-3 versus Vitamin B comparative effectiveness Results Summary	NR	NR	BCT 0 of 1 (no differences) MNP NR	NR	0 of 2 (no differences)	0 of 3 (no differences)	NR

Cognitive test abbreviations: 3MS=Modified Mini Mental Status Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; AVLT=Auditory Verbal Learning Test; BCT=brief cognitive test; CVLT=California Verbal Learning Test; CANTAB=Cambridge Neuropsychological Test Automated Battery Paired Associated Learning Test; CANTAB PAL=Cambridge Neuropsychological Test Automated Battery Paired Associated Learning Test; CDR=Change in Dementia Rating; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; COWA= Controlled Oral Word Association; DSS-Digit Symbol Substitution; F-TICS=French version, Telephone Interview Cognitive Status; HVLT-R=Hopkins Verbal Learning Test-Revised; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological test; RT=reaction time; SWM=Spatial Working Memory; PRM=Pattern Recognition Memory; TICS=Telephone Interview Cognitive Status; TICS-m=Telephone Interview Cognitive Status-Modified; TMT=Trails Making Test (A & B); VRM=Verbal Recognition Memory; WAIS=Wechsler Adult Intelligence Scale; WMS= Wechsler Memory Scale
Other abbreviations: CATD=Alzheimer's disease; cog=cognitive; DSM= Diagnostic and Statistical Manual of Mental Disorders (DSM); HC=hippocampus; NINCDS-

ADDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; RCT=Randomized Controlled Trial

^aDecrease of 3 or more MMSE points or, if missing, incidence of cognitive decline or dementia.

^bDecrease of 5 or more MMSE points or, if missing, incidence of cognitive decline or dementia.

^cComposite: CVLT sum of words recalled, CVLT delayed recall, prospective memory test 1, prospective memory test 2, story recall, story recall delayed, verbal fluency, letter cancellation, location memory, location memory delayed, symbol-letter substitution, digit span forward & backward, simple reaction time, choice reaction time]

Adults with MCI

Nutraceuticals versus Inactive Control

Three (3) RCTs compared nutraceuticals to inactive controls in older adults with MCI.^{79,81, 83} Summaries of study results are detailed in Table 4C.3.

Lee et al. (n=36) examined the effects of daily omega-3 fatty acids (fish oil supplementation, DHA 430 mg and EPA 150 mg) on cognitive function in people aged 60 and older with MCI.⁸³ After 1 year, no significant change in MMSE scores was observed. However, people taking omega-3 performed better than those on placebo on 1 of 3 tests of executive function/attention/processing speed, and better on 3 of 5 memory tests. No serious adverse effects were reported. Evidence to draw conclusions was insufficient due to limited data (single study with n<500) or no data.

Two (2) studies compared the effects of ginkgo biloba to placebo in people with MCI.^{79,81} Follow-up periods in the studies varied, with Gavrilova's study lasting 6 months⁸¹ and median follow-up in DeKosky et al. lasting 6.1 years.⁷⁹

DeKosky et al. examined diagnostic outcomes.⁷⁹ Of 5 categories of dementia, no significant differences were found between ginkgo and placebo groups. Gavrilova et al. included 2 objective measures of cognition, both related to the executive function/attention/processing speed domain. In both tests, participants taking ginkgo performed significantly better than those taking placebo.⁸¹

Gavrilova et al. reported no serious adverse effects.⁸¹ DeKosky et al. found no significant differences between ginkgo and placebo groups in rates of serious adverse effects, including death, bleeding, coronary heart disease (CHD), and stroke.⁷⁹ Evidence to draw conclusions was insufficient due to limited data (single study with n<500) or no data.

Interpreting the Findings

The results do not show a benefit for the nutraceuticals that have been examined. Some nutraceuticals, such as resveratrol, have not been sufficiently studied to provide sufficient evidence from which to draw conclusions. Most nutraceuticals are based on doses an individual could derive from diet, and are hypothesized to be much less likely to have adverse effects than "therapeutic" doses. However, this also means the interactions with metabolic, environmental, and other nutrition intake may overwhelm possible small effects related to nutritional doses. Designing studies to take such complexity into account is challenging.

Table 4C.3. Results Overview: Nutraceutical interventions in adults with MCI

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Omega 3 Efficacy							
Lee 2013{Lee, 2013 #506} Omega 3 fatty acids (DHA 430 mg and EPA 150 mg) daily n=36 1 year			BCT NS [MMSE]	NS [Composite: Clock Drawing Test, Digit Span Forward]	I>C [Composite: Vr I, Vr II, RAVLT – Immediate & Delayed Recall, Digit Span Backward]	4 of 9 favor I	No serious AEs reported
				NS [Digit Symbol Substitution Test]	I>C [Vr I]		
				I>C [Digit Span Forward & Backward]	NS [Vr II]		
					NS [RAVLT, Immediate Recall]		
					I>C [RAVLT, Delayed Recall]		
Omega 3 vs placebo	NR	NR	BCT 0 of 1 (no differences) MNP NR	1 of 3 favor I	3 of 5 favor I	4 of 9 favor I (44%)	NR
Ginkgo biloba Efficacy							
Gavrilova 2014 {Gavrilova, 2014 #504} Ginkgo biloba (240 mg) daily n=160 6 months				I>C [TMT A]		2 of 2 favor I	No serious AEs reported
				I>C [TMT B]			

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
DeKosky 2008 {DeKosky, 2008 #502} Ginkgo biloba extract 120 mg twice daily n=482 (MCI sub- sample) Median 6.1 years	Ns [All Dementia]						Serious AEs reported:
	Ns [CATD Without Vascular Dementia]						death, bleeding, CHD, stroke.
	Ns [CATD With Vascular Dementia]						No statistically significant differences
	NS [Total Ad]						between groups.
	NS [Vascular Dementia Without CATD]						
Ginkgo biloba efficacy	0 of 5 (no differences)	NR	NR	2 of 2 favor I	NR	2 of 2 favor I (100%)	NR

Abbreviations: CATD: clinical Alzheimer's-type dementia; MMSE=Mini-Mental State Examination; RAVLT: Rey's Auditory Verbal Learning Test; RCT: randomized controlled trial; TMT=Trails Making Test (A & B); VR=visual reproduction

Chapter 4D. Results: Diet Interventions

Key Messages

- Evidence is insufficient to conclude whether protein supplementation or energy-deficit diets have an effect on cognitive performance or incidence of MCI or clinical Alzheimer's-type dementia (CATD)*.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified seven eligible publications reporting six unique studies evaluating the effect of diet interventions to prevent age-related cognitive decline, MCI, or clinical Alzheimer's-type dementia (CATD).^{64,96-101} Four studies were high risk of bias and not used in our analysis. All eligible studies enrolled participants with normal cognition. Appendix I provides evidence tables and summary risk of bias assessments.

Logic of Diet Interventions

Several mechanisms are suggested to link diet to cognitive function and then to age-related cognitive decline, MCI, and CATD. Among these include the link between obesity and CATD with a dietary intervention leading to weight loss and decreased risk.^{64,96} Another proposed mechanism involves the effect of antioxidants (diets rich in these foods) on oxidative stress and vascular impairment, decreasing risk.¹⁰⁰

Adults with Normal Cognition

No conclusion table is provided since evidence to draw conclusions was insufficient due to limited data (single study with n<500) or no data.

Protein Supplement Versus Placebo

Van der Zwaluw et al. compared a protein supplement drink versus a placebo.¹⁰¹ Sixty-five older adults were randomized to receive either 15mg of protein twice daily or a placebo drink for 24 weeks. No diagnoses outcomes were reported. Despite administering numerous cognitive tests, no statistically significant differences were found in change in executive function/attention/processing speed or memory function. Individual study results are summarized in Table 4D.1. Evidence was insufficient (limited data) to conclude whether protein supplementation has an effect on cognitive outcomes when compared to placebo.

Energy-deficit Diet Versus Inactive Control

Napoli et al. reported a single RCT with medium risk of bias enrolling a total of 107 adults that compared a diet intervention with inactive controls in adults with normal cognition.⁶⁴ The intervention consisted of an energy-deficit diet (500-750 kcal per day) while setting weekly behavioral goals and attending weekly weigh-in sessions. A weight-loss goal of approximately 10 percent was to be achieved at 6 months, followed by weight maintenance for the remaining 6

months. (Weight loss of -9.7 ± 5.4 kg was reported for the diet group while the control group weight was reported as stable.) The control comparisons consisted of diet education with a prohibition on participating in any weight-loss or exercise program. Individual study results are summarized in Table 4D.1. Evidence was insufficient (limited data) to conclude whether energy-deficit diets have an effect on cognitive outcomes when compared to attention control.

Adults with MCI

No studies address adults with MCI.

Interpreting the Findings

Diet interventions are challenging to study as demonstrated by the proportion of eligible studies that were high risk of bias.

Table 4D.1. Results Overview: Diet interventions in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/Mu ltidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Protein supplement vs. placebo							
van der Zwaluw, 2014 ¹⁰¹ Protein drink (15mg of protein) twice daily vs. placebo n=65 24 weeks					NS [WLT, immediate]	0 of 16 (no difference)	NR
					NS [WLT, delayed]		
					NS [WLT, recognition]		
				NS [DS Forward]			
				NS [DS Backward]			
				NS [TMT A]			
				NS [Stroop 1]			
				NS [Stroop 2]			
				NS [Stroop 3]			
				NS [Reaction Time test]			
				NS [TMT B/A]			
				NS [Word Fluency, animals]			
				NS [Word Fluency, letter P]			
			NS [composite]				
			NS [composite]				
			NS [composite]				
Protein supplement vs. placebo Results Summary				0 of 13 (no difference)	0 of 3 (no differences)		
Energy restriction vs. inactive control							
Napoli, 2014⁶⁴			Brief cognitive			2 of 3 favor I	NR

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/Mu ltidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Energy deficit of 500–750 kcal/d from daily requirements vs. control n=53 1 year			test performance I>C [3MS]				
				NS [TMT A]			
				NS [TMT B]			
Energy restriction vs. inactive control Results Summary			1 of 1 favors I	0 of 2 (no difference)			

C=placebo/control; COWA=Controlled Oral Word Association; I=intervention; NS=no statistically significant difference; WMS=Wechsler Memory Scale

Chapter 4E. Results: Multimodal Interventions

Key Messages

- Evidence is insufficient to conclude whether most multimodal interventions offer benefits for cognitive performance or incidence of MCI or clinical Alzheimer’s-type dementia (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.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified 16 eligible publications that reported unique studies of multimodal interventions to prevent age-related cognitive decline, MCI, or CATD.^{53,64,73,75,97,102-109,110,111,112} Nine were assessed as high risk of bias and not used in our analysis.^{75,102-109} We analyzed the efficacy and comparative effectiveness of multimodal interventions separately for adults with normal cognition and those with MCI. Appendix J provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Multimodal Interventions

Studies that examine multimodal interventions theorize that an integrated approach to addressing multiple risk factors for CATD may be more successful than single component interventions in producing benefits.^{53,110,111} Multimodal interventions often include components like physical activity, changes to diet, and cognitive training. Several of the studies included in this review have suggested mechanisms for the relationship between individual components like physical activity^{48,62} or cognitive training³¹ and reduced dementia risk.

Table 4E.1 lists the components included in the seven studies that had low to medium risk of bias. Six of the seven studies included physical activity as part of the multimodal intervention. The two most frequent combinations across the seven studies were physical activity with changes to diet and physical activity with cognitive training. Other components include protein supplementation and goal setting.

Table 4E.1. Components of multimodal interventions for low/medium risk of bias trials

Study	Physical Activity	Diet	Cognitive Training	Protein Supplementation	Goal Setting
Clare, 2015 ¹¹⁰					•
Eggenberger, 2015 ⁵³	•		•		
Ngandu, 2015 ¹¹¹	•	•	•		
Hars, 2014 ¹¹²	•		•		
Napoli, 2014 ⁶⁴	•	•			
van de Rest, 2014 ⁷³	•			•	
Martin, 2007 ⁹⁷	•	•			

Adults with Normal Cognition

Efficacy: Multimodal Interventions versus Inactive Control

Six studies with low to medium risk of bias enrolling a total of 1,606 adults compared multimodal interventions with inactive controls in adults with normal cognition.^{64,73,97,110-112} All were RCTs. Total sample sizes ranged from 24 to 1,260. Most interventions included physical activity as a component. Inactive comparisons included health information and maintaining lifestyle habits. Conclusions are summarized in Table 4E.2 and individual study results in Table 4E.3.

Table 4E.2. Conclusions: Multimodal interventions versus inactive comparisons in adults with normal cognition

Intervention Components	Outcome	Conclusion	Strength of Evidence (justification)
Physical Activity and Diet	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	Limited data	Insufficient (limited data)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive Function	Data insufficient to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
	Memory	Limited data	Insufficient (limited data)
Physical Activity and Cognitive Training	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	Limited data	Insufficient (limited data)
	Multidomain Neuropsychological Performance	Limited data	Insufficient (limited data)
	Executive Function	No data available	Insufficient (no data)
	Memory	No data available	Insufficient (no data)
Physical Activity, Diet, and Cognitive Training	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No data available	Insufficient (no data)
	Multidomain Neuropsychological Performance	Intervention composed of diet, physical activity, and cognitive training improves multidomain neuropsychological test performance; unclear if improvement is clinically meaningful (n=1260; 2 years).	Low (indirect, unknown consistency)
	Executive Function	Intervention composed of diet, physical activity, and cognitive training improves multidomain neuropsychological test performance; unclear if improvement is clinically meaningful (n=1260; 2 years).	Low (indirect, unknown consistency)
	Memory	Data insufficient to draw conclusion.	Insufficient (indirect, imprecise, inconsistent)
Physical Activity and Protein Supplementation	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No data available	Insufficient (no data)
	Multidomain Neuropsychological	No data available	Insufficient (no data)

Intervention Components	Outcome	Conclusion	Strength of Evidence (justification)
	Performance		
	Executive Function	Limited data	Insufficient (limited data)
	Memory	Limited data	Insufficient (limited data)
Goal Setting and Mentoring	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	Limited data	Insufficient (limited data)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive Function	Limited data	Insufficient (limited data)
	Memory	Limited data	Insufficient (limited data)

Physical Activity and Diet

Two trials (n=79) compared physical activity and diet with inactive controls.^{64,97} Both enrolled overweight or obese adults. Napoli et al. randomized individuals to an intervention consisting of calorie-restriction diet and multicomponent exercise for 90 minutes, 3 times per week for one year.⁶⁴ Martin et al. randomized overweight young to middle aged adults to a calorie restriction diet and structured exercise for 6 months.⁹⁷

Neither trial reported diagnostic outcomes or multidomain neuropsychological test performance. Napoli et al. reported brief cognitive test performance for one measure (3MS) and found a statistically significant improvement with the physical activity and diet intervention compared with attention control.⁶⁴ Martin et al. reports 11 measures of memory, none of which differed between physical activity with diet and attention control.⁹⁷ Limited data prevented assessment of strength of evidence for brief cognitive test performance or memory.

Napoli et al. reported two measures of executive function/attention/processing speed,⁶⁴ and Martin et al. reported eight.⁹⁷ Napoli et al. showed statistically significant improvement in Trail Making Test A from baseline to 1 year in the multimodal intervention group compared with the health information group.⁶⁴ The remaining nine measures from Napoli et al. and Martin et al. showed no statistically significant difference with multimodal intervention compared with attention control.^{64,97} Evidence was insufficient to determine whether a multimodal intervention consisting of physical activity and diet improves executive function/attention/processing speed.

Physical Activity and Cognitive Training

Hars et al. (n=134) compared physical activity and cognitive training with an inactive control.¹¹² Adults who were frail or had an increased risk of falling were randomized to a structured, music-based exercise or their usual lifestyle habits.¹¹² The intervention involved weekly 60-minute structured music-based multitasking exercise classes for 6 months.

One measure of brief cognitive test performance (MMSE) showed no statistically significant improvements with the intervention compared with the control. Hars et al. also reported two measures of executive function.¹¹² Overall, the Frontal Assessment Battery showed no statistically significant improvements with the intervention compared with the control; however, the Sensitivity to Inference subtest of the battery showed statistically significant improvements with the intervention. Limited data prevented assessment of strength of evidence for brief cognitive test performance or executive function. The trial reported on no other diagnoses, cognitive outcomes, biomarkers, or harms.

Physical Activity, Diet, and Cognitive Training

Ngandu et al. (n=1,260) compared physical activity, diet, and cognitive training with an inactive control.¹¹¹ Adults at risk for cardiovascular disease were randomized to a multimodal intervention (nutritional counseling, multicomponent exercise, cognitive training, and management of metabolic and vascular risk factors) or an attention control. The intervention involved 1 to 3 aerobic exercise sessions per week; 2 to 5 resistance training sessions per week; both group and individual cognitive training; and management of vascular risk factors with lifestyle changes for 2 years.

One measure of multidomain neuropsychological test performance was reported. The Neuropsychological Test Battery was significantly higher with multimodal intervention compared with control at 6 months. Low-strength evidence shows that a multimodal intervention consisting of physical activity, diet, and cognitive training improves multidomain neuropsychological performance when compared to attention control.

Three of four subtests (two executive function, two memory) of the Neuropsychological Test Battery showed statistical improvement with intervention compared with control at 6 months. Both executive function measures showed improvement; only one of the memory measures showed improvement. Low-strength evidence shows that a multimodal intervention consisting of physical activity, diet, and cognitive training improves executive function when compared to attention control.

Ngandu et al. reported no other diagnoses, cognitive outcomes, biomarkers, or harms.¹¹¹

Physical Activity and Protein Supplementation

Van de Rest et al. (n=58) compared physical activity and protein supplementation with usual care.⁷³ Pre-frail and frail adults were randomized to resistance type exercise with protein supplementation or usual care (no exercise) and placebo for 6 months. The trial reported 11 measures of executive function. Only a composite score of processing speed showed a statistically significant difference between intervention and control groups at 6 months. The same trial also reported six measures of memory, none of which showed a statistically significant difference between groups at 6 months. This trial was likely underpowered. Evidence was insufficient to conclude whether physical activity and protein supplementation improves executive function or memory due to limited data.

Van de Rest et al. reported on no other diagnoses, cognitive outcomes, biomarkers, or harms.⁷³

Multimodal Goal Setting

Clare et al. (n=75) compared goal setting (with and without mentoring) with attention control.¹¹⁰ Functionally independent community-dwelling older adults participated in setting and discussing goals related to a variety of risk factors, then randomized to goal-setting alone or goal-setting with mentorship. Goal-setting involved an interview and identification of five goals; mentorship involved bi-monthly phone calls to discuss progress towards goals. Duration was 6 months.

Brief cognitive test performance (Montreal Cognitive Assessment), was better with the interventions compared to control. The trial also reported statistically significant improvements for the Trail-Making Test (executive function) and the Immediate Recall sub-test of the CVLT (memory) with intervention compared with control. However, the Delayed Recall subtest of the CVLT showed statistically significant improvements with attention control. Evidence was insufficient to conclude whether goal setting with mentoring improves cognitive outcomes due

to limited data. The trial reported on no other diagnoses, cognitive outcomes, biomarkers, or harms.

Table 4E.3. Results Overview: Multimodal interventions versus inactive comparisons in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Physical Activity and Diet							
Napoli, 2014⁶⁴ Physical activity and diet vs. health information n=55 1 year			BCT I>C [3MS]	I>C [TMT A]		2 of 3 favor I	NR
				NS [TMT B]			
Martin, 2007⁹⁷ Physical activity and diet vs. weight maintenance n=24 6 months				NS [CPT-II, Beta (response style)]	NS [RAVLT, Trial I-V]	0 of 19 (no difference)	NR
				NS [CPT-II, Omissions]	NS RAVLT, Trial B]		
				NS [CPT-II, Detectability]	NS [RAVLT, Trial VI]		
				NS [CPT-II, Reaction time]	NS [RAVLT, Delayed Recall]		
				NS [CPT-II, RT Std. Error]	NS [RAVLT, Recognition]		
				NS [CPT-II, Commissions]	NS [ACT, 9 sec]		
				NS [CPT-II, Perseverations]	NS [ACT,, 18 sec]		
				NS [CPT-II, RT Block Changes]	NS [ACT, 36 sec]		
					NS [BVRT, Correct Deviation]		
					NS		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
					[BVRT, Error Deviation]		
					NS [BVRT, Correct Deviation]		
Physical Activity and Diet Results Summary	NR	NR	BCT 1 of 1 favors I	1 of 10 favors I	0 of 11 (no difference)	2 of 22 favor I	NR
Physical Activity and Cognitive Training							
Hars, 2014^{II2} Physical activity and cognitive training vs. usual lifestyle n=134 6 months			BCT NS [MMSE]	NS [FAB] I>C [Sensitivity to Inference Sub-test, FAB]		1 of 2 favors I	NR
Physical Activity and Cognitive Training Results Summary	NR	NR	BCT 0 fo1 (no difference)	1 of 2 favors I	NR	1 of 3 favors I	NR
Physical Activity, Diet, and Cognitive Training							
Ngandu, 2015^{III} Physical activity, diet, and cognitive training vs. health information n=1260 2 years			MNP I>C [NTB, Total Score]	I>C NTB, Executive Functioning] I>C NTB, Processing Speed]	NS [NTB, Memory] I>C [NTB, Abbreviated Memory]	4 of 5 favor I	Unclear [Musculosk eletal pain]
Physical Activity, Diet, and Cognitive Training Results Summary	NR	NR	MNP 1 of 1 favors I	2 of 2 favors I	1 of 2 favors I	4 of 5 favors I	
Physical Activity							

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
and Protein Supplementation							
van de Rest, 2014⁷³ Resistance-type exercise program vs. usual care n=58 6 months				NS [DS Forward]	NS [Word Learning Test, Immediate Recall-75 Words]	1 of 17 favor I	NR
				NS [DS Backward]	NS [Word Learning Test, Delayed Recall-15 Words]		
				NS [TMT A]	NS Word Learning Test, Decay]		
				NS [Stroop 1]	NS [Word Learning Test, Recognition, 30 Words]		
				NS [Stroop 2]	NS [Attention and Working Memory Composite]		
				NS [Stroop Inference]	NS ^z [Episodic Memory Composite]		
				NS [Reaction Time Uncued]			
				NS [Reaction Time Cued]			
				NS [Word Fluency-Letter]			
				I>C ^z [Processing Speed Composite]			
			NS ^z [Executive Functioning Composite]				

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Physical Activity and Protein Supplementation Results Summary	NR	NR	NR	1 of 11 favors I	0 of 6 (no difference)	1 of 17 favor I	NR
Goal Setting and Mentoring							
Clare, 2015¹¹⁰ Goal Setting and Goal Setting with Mentoring vs. health information n=75 6 months			BCT I>C [MoCA]	I>C [TMT]	I>C [CVLT, Immediate Recall] C>I [CVLT, Delayed Recall]	3 of 4 favors I 1 of 4 favors C	NR
Goal Setting and Mentoring Results Summary	NR	NR	BCT 1 of 1 favors I	1 of 1 favors I	1 of 2 favors I 1 of 2 favors C	3 of 4 favors I 1 of 4 favors C	
Multimodal interventions vs. Inactive Control Results Summary	NR	NR	BCT 2 of 3 favors I (67%) MNP 1 of 1 favors I (50%)	5 of 26 favors I (19%)	2 of 21 favors I (10%) 1 of 21 favors C (5%)	10 of 51 favors I (21%) 1 of 51 favors C (2%)	NR

^a mean global composite z score composed of xxx; ^b composite z score of HVLT-R immediate and delayed word recall

3MS=Modified Mini-Mental State Examination; ACT=Auditory Consonant Trigram; BCT=Brief cognitive test performance; BVRT=Benton Visual Retention Test; C=Inactive control; CPT=Continuous Performance Test; CVLT=California Verbal Learning Test; DS=Digit Span; FAB=Frontal Assessment Battery; I=Intervention; MMSE=Mini-Mental State Examination; MOCA=Montreal Cognitive Assessment; MNP=Multidomain neuropsychological performance; NS=No statistically significant difference; NTB=Neuropsychological Test Battery; RAVLT=Rey Auditory Verbal Learning Test; Stroop=Modified Stroop; TMT=Trail Making Test

Comparative Effectiveness: Multimodal Interventions Versus Active Comparison

Multimodal interventions address several risk factors for CATD at once potentially creating a synergistic protective effect. Studies compare multimodal interventions with single component interventions to test this hypothesis. Different approaches to multimodal interventions may also affect their potential effectiveness. This is tested in studies comparing different multimodal interventions.

Three studies with low to medium risk of bias compared multimodal interventions with active controls in adults with normal cognition.^{53,64,97} All were RCTs. Total sample sizes ranged from 24 to 134. All of the interventions included physical activity as a component. Active comparisons were a single component intervention (diet or physical activity alone). Individual study results are summarized in Table 4E.4. No conclusion table is provided since evidence to draw conclusions was insufficient due to limited data (single study with n<500) or no data.

Physical Activity and Diet Versus Single-Component

Two trials (n=90) compared physical activity and diet changes with a single component (diet or physical activity).^{64,97} Napoli et al. reported brief cognitive test performance (3MS) and several measures of executive function/attention/processing speed outcomes using several instruments, and found no statistically significant improvement with physical activity and diet compared to either single component intervention.⁶⁴

Martin et al. compared physical activity and diet intervention with two diet interventions alone (calorie restriction alone and liquid calorie diet alone).⁹⁷ Across both comparisons, the trial reports 22 measures of memory and several measures of executive function/attention/processing speed outcomes using several instruments, none of which showed statistical differences between the physical activity and diet intervention compared with either diet alone. Evidence was inadequate to assess the strength of evidence for brief cognitive test performance or memory.

The trials reported no additional outcomes.

Multimodal Versus Multimodal

Eggenberger et al. (n=46) compared two interventions that each had a physical activity and cognitive training component.⁵³ Older adults were randomized to either virtual reality game dancing with cognitive training or treadmill walking with verbal memory exercise. The trial reported seven measures of executive function that showed no statistically significant differences between the intervention groups. The trial also reported two measures of memory that showed no statistically significant differences between the intervention groups. Evidence was insufficient to determine whether different multimodal interventions consisting of physical activity and cognitive training improves executive function/attention/processing speed due to limited data. The trial reported no additional outcomes.

Table 4E.4. Results Overview: Multimodal interventions versus active comparisons in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Physical Activity and Diet vs. Diet							
Napoli, 2014 Physical activity and diet vs. diet n=54 1 year			BCT I>C [3MS]	NS [TMT A]		1 of 3 favors I	NR
				NS [TMT B]			
Martin, 2007 Physical activity and diet vs. diet n=24 6 months				NS [CPT-II, Beta (response style)]	NS [RAVLT, Trial I-V]	0 of 19 (no difference)	
				NS [CPT-II, Omissions]	NS RAVLT, Trial B]		
				NS [CPT-II, Detectability]	NS [RAVLT, Trial VI]		
				NS [CPT-II, Reaction time]	NS [RAVLT, Delayed Recall]		
				NS [CPT-II, RT Std. Error]	NS [RAVLT, Recognition]		
				NS [CPT-II, Commissions]	NS [ACT, 9 sec]		
				NS [CPT-II, Perseverations]	NS [ACT, 18 sec]		
				NS [CPT-II, RT Block Changes]	NS [ACT, 36 sec]		
					NS [BVRT, Correct Deviation]		
					NS		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
					[BVRT, Error Deviation]		
					NS [BVRT, Correct Deviation]		
Martin, 2007⁹⁷ Physical activity and diet vs diet n=24 6 months				NS [CPT-II, Beta (response style)]	NS [RAVLT, Trial I-V]	0 of 19 (no difference)	
				NS [CPT-II, Omissions]	NS RAVLT, Trial B]		
				NS [CPT-II, Detectability]	NS [RAVLT, Trial VI]		
				NS [CPT-II, Reaction time]	NS [RAVLT, Delayed Recall]		
				NS [CPT-II, RT Std. Error]	NS [RAVLT, Recognition]		
				NS [CPT-II, Commissions]	NS [ACT, 18 sec]		
				NS [CPT-II, Perseverations]	NS [ACT, 36 sec]		
				NS [CPT-II, RT Block Changes]	NS [BVRT, Correct Deviation]		
					NS [BVRT, Error Deviation]		
					NS [BVRT, Correct Deviation]		
					NS [ACT, 18 sec]		
Physical Activity and Diet vs. Diet Results Summary	NR	NR	BCT 1 of 1 favors I	0 of 18 (no difference)	0 of 22 (no difference)	1 of 41 favors I	NR

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Physical Activity and Diet vs. Physical Activity							
Napoli, 2014⁶⁴ Physical activity and diet vs. physical activity n=54 1 year			BCT NS [3MS]	NS [TMT A] NS [TMT B]		0 of 3 (no difference)	
Physical Activity and Diet vs. Physical Activity Results Summary	NR	NR	BCT 0 of 1 (no difference)	0 of 2 (no difference)	NR	0 of 3 (no difference)	NR
Physical Activity and Cognitive Training vs. cognitive training							
Eggenberger, 2015⁵³ Physical activity and cognitive training vs. cognitive training n=46 6 months				NS [TMT A]	NS [Story Recall]	0 of 9 (no difference)	NR
				NS [TMT B]	NS [Paired Associates Learning]		
				NS [Executive Control]			
				NS [DS Forward]			
				NS [Age Concentration Test A]			
				NS [Age Concentration Test B]			
				NS [DSST]			
Physical Activity and Cognitive	NR	NR	NR	0 of 7 (no difference)	0 of 9 (no difference)	0 of 9 (no difference)	NR

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Training vs. Cognitive Training Results Summary							
Multimodal vs. Active Control Results Summary	NR	NR	BCT 1 of 2 (50%)	0 of 17 (no difference)	0 of 24 (no difference)	1 of 53 (favors I)	

3MS=Modified Mini-Mental State Examination; ACT=Auditory Consonant Trigram; BCT=Brief cognitive test performance; BVRT=Benton Visual Retention Test; C=Inactive control; CPT=Continuous Performance Test; DS=Digit Span; DSST= Digit Symbol Substitution; FAB=Frontal Assessment Battery; I=Intervention; MNP=Multidomain neuropsychological performance; NS=No statistically significant difference; NTB=Neuropsychological Test Battery; TMT=Trail Making Test

Adults with MCI

Only two unique studies compared multimodal interventions to inactive controls in older adults with MCI^{105,106} and two unique studies comparing multimodal interventions with active interventions in older adults with MCI.^{75,105} All were RCTs assessed as high risk of bias.

Interpreting the Findings

The available evidence is largely insufficient to draw conclusions about the effectiveness of an array of multimodal interventions for cognitive performance or progression to MCI or CATD, largely because the evidence base is weak with small trials of heterogeneous interventions. One important trial does provide sufficient evidence regarding multimodal interventions – the FINGER trial provided low-strength evidence that a combination of physical activity, diet changes, and cognitive training improved multidomain neuropsychological performance and executive function in adults at risk for MCI or CATD, although whether the improvement is clinically meaningful is unclear.¹¹¹ Results of other large well-designed ongoing trials (i.e. MAPT, PreDIVA) may provide additional clarity regarding the efficacy and effectiveness of multimodal interventions.¹²

The risk of bias and small sample sizes of identified studies were substantial barriers to our analysis. Of the 16 eligible studies, only six were of low to medium risk of bias. None of the trials examining multimodal interventions for individuals with MCI were analyzed due to high risk of bias. For adults with normal cognition, nearly all trials had sample sizes less than 100.

Chapter 4F. Results: Hormone Therapy Interventions

Key Messages

- Overall, low-strength evidence shows no significant differences in cognitive performance between hormone therapy and placebo groups.
- Low-strength evidence suggests that estrogen therapy may slightly increase the risk of probable MCI and clinical Alzheimer's-type dementia (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.

* Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified 30 eligible publications reporting 21 unique studies of hormone therapy interventions to prevent age-related cognitive decline, MCI, or CATD.^{85,113-141} The majority of studies were designed to examine cognition as a primary outcome. Exceptions included ancillary studies of the longitudinal Women's Health Initiative (WHI),^{115,118,135-138} two studies investigating the use of selective estrogen receptor modulators (SERMs) in preventing vertebral fractures,^{129,141} and a study on the effects of testosterone on bone and muscle.¹²⁶ Seven studies were assessed as high risk of bias and not used in our analysis.^{85,113,118,126,129,134,140}

We analyzed the efficacy and comparative effectiveness of hormone therapies separately for adults with normal cognition and those with MCI. Appendix K provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Hormone Therapy Interventions

Speculation is longstanding about the relationship between the pituitary endocrine axis and aging.¹⁴² While epidemiological studies have suggested that hormone replacement therapy may have a beneficial effect on cognition,¹⁴³ randomized trials have produced inconsistent results, even suggesting in some cases that some hormone therapies may have a detrimental effect on cognition.^{137,138}

Adults with Normal Cognition

Conclusions are summarized in Table 4F.1 and individual study results in Table 4F.2.

Table 4F.1. Conclusions: Hormone therapies versus inactive comparisons in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
HRT-estrogen vs. inactive control	Dementia	Increased risk of probable dementia/MCI associated with estrogen therapy (n=2947; 5-7 years) but no statistically significant difference in risk of probable dementia or MCI when diagnostic categories reported separately.	Low (medium study limitation, unknown consistency)
	MCI	No statistically significant difference between estrogen therapy and placebo groups in risk of MCI (n=2947; 5-7 years).	Low (medium study limitation, unknown consistency)
	Brief cognitive test performance	Estrogen therapy performed slightly worse than placebo on a brief test of cognitive performance on 3MS (n=2947; 5-7 years).	Low (medium study limitation, imprecise, unknown consistency)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	Limited data	Insufficient (limited data)
	Memory	Limited data	Insufficient (limited data)
HRT-estrogen + progestin vs. inactive control	Dementia	Increased risk of probable dementia associated with estrogen/progestin therapy (n=4532; 5-7 years) but no statistically significant difference in risk of probable dementia or MCI when the diagnostic categories were combined.	Low (medium study limitation, unknown consistency)
	MCI	No statistically significant differences between estrogen-progestin therapy and placebo in rates of MCI (n=4532; 5-7 years)	Low (medium study limitation, unknown consistency)
	Brief cognitive test performance	No benefit in brief cognitive test performance with estrogen/progestin versus placebo (n=4532; mean 5 years).	Low (medium study limitation, unknown consistency)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No benefit with estrogen/progestin versus placebo (n=1439; up to 7 years)	Low (medium study limitation, indirect, imprecise)
	Memory	No benefit with estrogen/progestin versus placebo (n=1581; up to 7 years)	Low (medium study limitation, indirect, imprecise)
DHEA vs. inactive control	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	Limited data available	Insufficient (limited data)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	Limited data available	Insufficient (limited data)
	Memory	Limited data available	Insufficient (limited data)
SERM vs. inactive control	Dementia	No statistically significant differences in risk of Alzheimer's disease, any type of dementia, or "dementia or MCI" between 2 doses of raloxifene (60 mg and 120 mg) and placebo (n=5386; 3 years)	Low (medium study limitation, unknown consistency)
	MCI	Slightly decreased risk of MCI in raloxifene compared (higher of 2 doses) to placebo	Low/insufficient (medium study limitations, unknown consistency)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
		(n=5386; 3 years), which may not be clinically meaningful.	
	Brief cognitive test performance	No data available	Insufficient (no data)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	Limited data available	Insufficient (limited data)
	Memory	Limited data available	Insufficient (limited data)
Soy vs. inactive control	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	Limited data available	Insufficient (limited data)
	Multidomain neuropsychological performance	Limited data available	Insufficient (limited data)
	Executive/Attention/Processing Speed	No benefit with soy versus placebo (n=631; up to 2.5 years)	Low (medium study limitation, imprecise)
	Memory	No benefit with soy versus placebo (n=631; up to 2.5 years)	Low (medium study limitation imprecise)

SERM= Selective estrogen receptor modulator

Efficacy: Hormone Therapy Versus Inactive Control

Twelve RCTs with low to medium risk of bias enrolling a total of 14,094 adults compared hormone therapy interventions to inactive controls in adults with normal cognition.^{115-117,119-124, 127,128,132,135-139,141} Interventions included hormone replacement therapies: estrogen only, estrogen and progestin combined, dehydroepiandrosterone (DHEA), and testosterone; SERM; and soy. Samples ranged from 23 to 5,386 participants, with followup duration of 6 months to over 7 years.

Hormone Replacement Therapies

Hormone replacement therapies included estrogen-only therapy estrogen plus progestin, DHEA, and testosterone. The two testosterone studies were assessed as high risk of bias due to attrition. Enrollment criteria differed among trials, with most studies focusing on older women. The estrogen-only and combined estrogen-progestin trials enrolled premenopausal and postmenopausal women aged 40 to 80 years with normal to “mildly impaired memory functioning”¹³⁹ at baseline. The study on DHEA included healthy men and women aged 55 to 85 years, and the studies of testosterone included men aged 65 to 87 years.

Estrogen Only

Two RCTs with low to medium risk of bias (including one small RCT and two ancillary studies of the large longitudinal WHI, the Women’s Health Initiative Memory Study [WHIMS] and Women’s Health Initiative Study of Cognitive Aging [WHISCA]) compared estrogen replacement therapy (0.625 mg/day of conjugated equine estrogen) to placebo in healthy postmenopausal women. Gorenstein et al. (n=59) randomized postmenopausal women aged 40 to 59 years to estrogen therapy or placebo for 6 months.¹²² WHIMS included 2947 community-dwelling postmenopausal women aged 65 to 79 years.¹³⁸ WHISCA¹³⁵ included a subset of women participating in WHIMS.

The WHIMS reported diagnostic outcomes.¹³⁸ After a mean followup of 7 years, women taking estrogen were significantly more likely to experience probable dementia or MCI when the two diagnostic categories were combined. Although an increase in probable dementia or MCI diagnosis was also observed for women taking estrogen when the diagnostic categories were examined separately, the results did not reach statistical significance. Evidence is low strength that estrogen-only therapy increases the combined risk of probable dementia/MCI given medium study limitations and unknown consistency.

WHIMS participants (520 women aged 71-89 years) were tested for total ischemic lesion volume¹¹⁵ and changes in brain volume.¹³⁶ No differences were found between estrogen and placebo groups in brain lesions. Of four measures of brain volume, women receiving estrogen therapy experienced statistically greater brain atrophy in frontal lobe volume.

The WHIMS used the 3MS as a brief test of cognitive performance.¹¹⁷ After a mean followup of 5.4 years, women taking estrogen performed slightly worse on the 3MS than women taking placebo (difference in mean change from baseline: -0.26, 95% CI: -0.52, 0). Evidence was rated low.

Both Gorenstein et al. (n=59)¹²² and the WHISCA (n=886)¹³⁵ examined changes in cognitive performance related to memory and executive function/attention/processing speed. Evidence was insufficient for the effects of estrogen-only therapy on cognitive performance in executive/attention/processing speed and memory domains.

WHIMS investigators conducted subgroup analyses to examine the effects of baseline risk factors on 3MS scores.¹¹⁷ Analyses examining the effects of age, education, race/ethnicity, annual household income, BMI, smoking status, alcohol consumption, prior cardiovascular disease, treatment for hypertension, diabetes mellitus, presence of moderate or severe vasomotor symptoms, prior hormone therapy use, age at hysterectomy, prior bilateral oophorectomy, prior use of HMG-CoA reductase inhibitors, baseline aspirin use, and baseline 3MS scores on changes in 3MS scores found statistically significant effects based on age, moderate or severe vasomotor symptoms, and baseline 3MS scores.¹¹⁷

Gorenstein et al. reported no serious adverse effects associated with estrogen therapy and noted that study withdrawals due to adverse effects were similar across estrogen and placebo groups.¹²² In the WHIMS, women taking estrogen experienced a higher risk of stroke in addition to a higher risk of probable CATD/MCI than women taking placebo.¹³⁸

Estrogen Plus Progestin

Three RCTs ranging in size from 23 to 4,532 participants (total n=4697) compared combination estrogen/progestin therapy with placebo in postmenopausal women. Studies included two small RCTs^{116,139} and the WHIMS and WHISCA substudies of the WHI.^{115,136,137} Specific estrogen/progestin combination therapies varied across studies and included conjugated equine estrogen plus medroxyprogesterone acetate,^{115,136,137} oral estradiol plus drospirenone,¹¹⁶ estradiol valerate plus norethisterone, and estradiol plus norethindrone.¹³⁹

The WHIMS was the only study to report diagnostic outcomes.¹³⁷ Of three diagnostic categories, including probable dementia, MCI, or probable dementia/MCI combined, only the probable dementia category showed statistically significant differences between estrogen/progestin and placebo groups, with women receiving estrogen/progestin experiencing higher rates of probable CATD. Evidence was rated low that estrogen-progestin increases the risk of probable CATD.

WHIMS participants (a subset of 883 women aged 71-89 years at the time of MRI scans) were tested for total ischemic lesion volume¹¹⁵ and changes in brain volume.¹³⁶ No differences in brain lesions or brain volume were found between estrogen/progestin and placebo groups.

Two studies (n=1,439) examined the effect of estrogen/progestin therapy versus placebo on cognition in the executive function/attention/processing speed domain.^{116,135} Three studies (n=1,581) examined differences in memory between estrogen/progestin and placebo groups.^{116,135,139} Test results in both the executive/attention/processing speed and memory categories favored placebo and evidence was low-strength that estrogen/progestin has no effect.

Several subgroup analyses were conducted. Tierney found that women in the estrogen/progestin group who scored at or above average at baseline on short-delay recall showed significantly less decline than the placebo group after 1 year, although this same result was not observed at year 2.¹³⁹ No treatment effects were found for women who scored below average on short-delay recall, nor for women in the estrogen-progestin group compared to placebo overall.

In the WHIMS, subgroup analyses examined the relationship between baseline risk factors and 3MS scores by treatment group.¹¹⁷ Of covariates including age, education, race/ethnicity, annual household income, BMI, smoking status, alcohol consumption, prior cardiovascular disease, treatment for hypertension, diabetes mellitus, presence of moderate or severe vasomotor symptoms, prior hormone therapy use, age at hysterectomy, prior bilateral oophorectomy, prior use of HMG-CoA reductase inhibitors, baseline aspirin use, and baseline 3MS scores statistically significant effects were found only for baseline 3MS scores.¹¹⁷ Also in the WHIMS,¹³⁷ no interaction was found between treatment assignment (estrogen/progestin or placebo) on rates of probable dementia diagnoses for 10 subgroups of women based on age, education, history of stroke, history of diabetes, prior hormone therapy, prior use of estrogen therapy, prior use of estrogen/progestin therapy, prior use of statins, prior use of aspirin, and baseline 3MS score.

Women taking estrogen/progestin in WHIMS experienced increased risk of probable CATD, as well as an increased risk of stroke.^{115,137} Tierney et al. reported death (two in hormone group and two in placebo group), deep vein thrombosis (DVT) (one participant in hormone group with a history of DVT), symptoms of heart failure (three women in hormone group, one of whom withdrew from study), colorectal cancer (one participant) and silent stroke (five participants in hormone group and four in placebo).¹³⁹ The reported deaths, silent strokes, and cancer were deemed by study physicians to be unrelated to hormone therapy. Other less serious adverse effects, which were experienced significantly more frequently by women taking hormones, included breast tenderness, vaginal bleeding and discharge, and gastrointestinal problems. In Davison et al., three women discontinued from the study due to vaginal bleeding, including one woman in the hormone group and two taking placebo.¹¹⁶

DHEA

One RCT (n=225) compared daily oral DHEA (50 mg) to placebo in women and men aged 55 to 85 years with a mean baseline 3MS score of 96.¹²⁸ Cognitive outcomes included three measures: a brief test of cognitive function (the 3MS), a test of executive function, and a test of verbal memory. After 1 year of treatment, no differences were found between DHEA and placebo groups in cognitive function. A total of 33 participants withdrew from the trial due to serious side effects, including 23 people receiving DHEA (67% of withdrawals) and 10 receiving placebo. Serious side effects included chest pain, heart palpitations, and an increase in prostate-

specific antigen (PSA) in men. No sub-analyses were reported. Strength of evidence was insufficient due to limited data (single study with n<500).

Testosterone

Two high risk of bias RCTs (n=136) with primary outcomes related to the effects of testosterone on bone density^{126,140} and muscle¹²⁶ in older men with low bioavailable testosterone levels examined the effect of testosterone on cognitive performance.

Selective Estrogen Receptor Modulators (SERM)

Two trials (n=5,529) compared the SERM raloxifene (60 mg or 120 mg daily in both trials) with placebo.^{132,141} Both studies enrolled women with osteoporosis aged 66 to 68 years.

Yaffe et al's 3-year study (n=5,386) reported diagnostic outcomes.¹⁴¹ Women assigned to 120 mg of raloxifene daily had a 33 percent lower risk of MCI than those taking placebo, although this same effect was not observed in women taking the lower dose (60 mg) of raloxifene. No statistically significant differences were found between treatment and placebo groups in three other diagnostic categories, including "Alzheimer's disease," "any type of dementia," and "dementia or MCI." As expected, women found to have MCI or CATD were likely to be older, less educated, more depressed, and further past menopause than women with normal cognition. Evidence was low/insufficient that raloxifene lowers the risk of MCI.

Nickelsen et al. (n=143) compared the effects of raloxifene and placebo on memory (using seven measures) and executive, attention, and processing speed (using three measures).¹³² After 1 year, the study found no difference in cognitive scores from baseline between raloxifene and placebo groups. Strength of evidence was insufficient due to limited data (single study with n<500).

No serious adverse effects related to raloxifene were described. In Nickelsen et al.'s study, the percentage of women withdrawing from the study due to adverse effects was similar across treatment and placebo groups.¹³²

Soy

Four RCTs ranging in size from 34 to 350 participants (total n=631) compared soy supplementation to placebo. Populations included men and women without dementia aged 62 to 89 years¹²¹ and generally healthy postmenopausal women.^{123,124,127} Mean baseline MMSE scores were not reported in Henderson et al.¹²³ but ranged from 28 to 29 in the other studies.^{121,124,127} Three of the studies took place over 6 months (n=281)^{121,124,127} and one lasted 2.5 years¹²³ (n=350).¹²³

None of the trials reported diagnostic outcomes. Ho (n=191) used the MMSE as a brief test of cognitive performance and found no pre/post differences between soy and placebo groups.¹²⁴ Strength of evidence was insufficient due to limited data (single study with n<500). Two studies (n=541) tested multi-domain neuropsychological performance and found no statistically significant differences between groups.^{123,124} Evidence was rated as insufficient.

All four studies measured cognitive performance in the executive function/attention/processing speed and memory categories (n=631). Placebo performed better than soy in two of 14 tests of executive function/attention/processing speed. Over the four studies, the soy group performed better on five of 27 memory tests, with the placebo group performing better on one memory test. Evidence is low-strength that soy has no effect on these cognitive domains.

Subanalyses conducted by Kritz-Silverstein et al. found that younger women taking placebo (those aged 50 to 59) improved in verbal memory scores whereas those aged 60 to 74 worsened in verbal memory over time.¹²⁷ Also in the Kritz-Silverstein study, women in both soy and placebo groups improved their performance on Trails B (a measure of executive function) between baseline and 6 month testing, but the soy group improved significantly more than placebo over time.¹²⁷ Neither Henderson nor Ho found differences in cognitive performance based on age.^{123,124}

Ho et al. reported no serious adverse effects and no significant differences in adverse effects experienced between treatment and placebo groups.¹²⁴ In the Henderson et al. study one person (in the soy group) experienced a stroke and five people (in the placebo group) reported cancer.¹²³ No other serious adverse effects were reported.

Table 4F.2. Results Overview: Hormone therapies in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
HRT-estrogen efficacy							
Gorenstein, 2011 ¹²² Estrogen (conjugated equine estrogen 0.625 mg/day) n=65 6 months				I>C [Digit Span Forward]	I>C [Paired Associate Learning Test, Easy]	2 of 10 favor I	No serious AEs reported
				NS [Digit Span Backward]	NS [Paired Associate Learning Test, Difficult]		
				NS [3-min Reasoning Test, Correct]	NS [Immediate Verbal Recall]		
				NS [3-min Reasoning Test, Time]	NS [Delayed Verbal Recall]		
				NS [DSST]	NS [Free Recall of Words]		
Women's Health Initiative (WHI) substudies ^{115, 117, 135, 136, 138} Estrogen (conjugated equine estrogen 0.625 mg) daily n=2947 ¹ n=520 ² n=520 ³ n=2947 ⁴ n=520 ⁵ Mean followup varies by outcome up to 8 years	NS [Probable Dementia] ¹	NS [MRI: Total Brain Volume] ²	BCT C>I [3MS] ⁴	NS [Letter Fluency] ⁵	NS [BVRT Errors] ⁵	2 of 16 favors C	Increased risk of probable dementia in women taking estrogen.
	NS [MCI] ¹	NS [MRI: Ventricle Volume] ²		NS [Digits Forward] ⁵	NS [CLVT Total List A Trials] ⁵		Increased risk of global cognitive decline in women taking estrogen.
	C>I [Probable Dementia or MCI] ¹	NS [MRI: Hippocampal Volume] ²		NS [Digits Backward] ⁵	NS [CVLT Total List B] ⁵		
		C>I [MRI: Frontal Lobe Volume] ²			NS [CVLT Short Delay Free] ⁵		
		NS			NS		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]	
		[White & Gray Matter] ³			[CVLT Long Delay Free] ⁵			
		NS [Basal Ganglia] ³						
		NS [Total Brain Lesion Volume] ³						
HRT-estrogen efficacy Results Summary	1 of 3 favors C	1 of 7 favors C	1 of 1 favors C	1 of 8 favors I	1 of 10 favors I	2 of 26 favor C 2 of 26 favor I		
HRT-estrogen + progesterin efficacy								
Women's Health Initiative (WHI) ^{138,115,117,135,136} Estrogen + progesterin daily n=4532 ¹ n=883 ² n=883 ³ n=4532 ⁴ n=1416 ⁵ Mean followup varies by outcome up to 8 years	C>I [Probable Dementia] ¹	NS [MRI: Total Brain Volume] ²	BCT NS [3MS] ⁴	NS [Letter Fluency] ⁵	C>I [BVRT Errors] ⁵	4 of 16 favor C	In addition to increased risk of probable dementia and	
	NS [MCI] ¹	NS [MRI: Ventricle Volume] ²		NS [Digits Forward] ⁵	C>I [CLVT Total List A Trials] ⁵		memory decline, women taking	
	NS [Probable Dementia or MCI] ¹	NS [MRI: Hippocampal Volume] ²		NS [Digits Backward] ⁵	NS [CVLT Total List B] ⁵		Estrogen + progesterin experienced more strokes	
		NS [MRI: Frontal Lobe Volume] ²			C>I [CVLT Short Delay Free] ⁵		than women taking placebo	
		NS [White and Gray Matter] ³			C>I [CVLT Long Delay Free] ⁵			
		NS [Basal Ganglia] ³						
		NS [Total Brain						

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
		Lesion Volume ³					
Davison, 2013 ¹¹⁶ Estrogen (oral estradiol + progesterin (drospirenone) n=23 (n=13 fMRI) 6 months				NS [CogState Identification]	NS [CogState International Shopping List, Learn]	1 of 8 favors C	3 women withdrew from study due to vaginal bleeding: 2 in estrogen + progesterin group and 1 in placebo.
				C>I [CogState, Detection Speed]	NS [CogState International Shopping List, Recall]		No serious AEs were reported.
				NS [Mental Rotation with functional MRI]	NS [Gorton Maze Learning Task]		
					NS [Gorton Maze Learning Task, Recall]		
					NS [CogState Continuous Paired Assoc Learning]		
Tierney, 2009 ¹³⁹ Estrogen (1 mg 17- B estradiol) daily + progesterin (0.35 mg norethindrone) 3 times weekly n=142 2 years					NS CVLT, Short Delay Recall]	0 of 1 (no differences)	Several serious AEs were reported, including deep vein thrombosis, episodes of heart failure, and stroke. Statistically significant differences between hormone and placebo group were less

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
							serious.
HRT-Estrogen + progestin efficacy Results Summary	1 of 3 favors C	0 of 7 (no differences)	BCT 0 of 1 (no differences)	1 of 6 favors C	4 of 11 favor C	5 of 25 favor C	
DHEA efficacy							
Kritz-Silverstein, 2008¹²⁸ Oral DHEA 50 mg daily n=225 1 year			BCT NS [MMSE]	NS [Trails B]	NS [Word List Memory]	0 of 4 (no differences)	23 participants experienced AEs, but no tests of significance are reported
DHEA efficacy Results Summary	NR	NR	BCT 0 of 1 (no differences)	0 of 1 (no differences)	0 of 2 (no differences)	0 of 4 (no differences)	
SERM efficacy							
Yaffe, 2005¹⁴¹ Raloxifene 60 mg or 120 mg daily vs. placebo n=5386 3 years	NS (60 mg group) [MCI] I>C (120 mg group) [MCI]					No intermediate outcomes reported	NR
	NS (60 mg						

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
	group) NS (120 mg group) [CATD]						
	NS (60 mg group) NS (120 mg group) [Any Type of Dementia]						
	NS (60 mg group) NS (120 mg group) [Dementia or MCI]						
Nickelsen, 1999 ¹³² Raloxifene 60 mg or 120 mg daily vs. placebo n=143 1 year				NS [WRPAB 2-Letter Search]	NS [MAC Battery: Name-Face Association, Total Acquisition]	0 of 10 (no differences)	No serious AEs reported and % of women with-
				NS [WRPAB 6-Letter Search]	NS [MAC Battery: Name-Face Association, Delayed Recall]		drawing from the study due to AEs was
				NS [WRPAB 4-Choice Serial Reaction Time]	NS [MAC Battery: First-Last Name Association, Delayed Recall]		similar across groups
					NS [MAC Battery: First-Last Name Association, Total Acquisition]		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
					NS [MAC Battery: Facial Recognition, Number Before 1st Error]		
					NS [MAC Battery: Telephone Number Recall, Before Interference]		
					NS [MAC Battery: Telephone Number Recall, After Interference]		
SERM efficacy Results Summary	1 of 8 favors I	NR	NR	0 of 3 (no differences)	0 of 7 (no differences)	0 of 10 (no differences)	NR
Soy efficacy							
Henderson, 2012¹²³ Soy isoflavone rich soy protein 25 g daily vs. matched placebo n=350 2.5 years			NS Composite: [Cognitive Composite, components not described]	NS [Symbol Digit Modalities Test]	NS [Verbal Episodic Memory, List Learning Factor: CVLT Immediate & Delayed Recall]	1 of 15 favors I	1 person (soy group) experienced a stroke and 5 people (placebo)
			NS [Executive/Expre ssive/Visuospatia l Factor Composite: Symbol Digit Modalities Test, TMT B, Shipley Abstraction, Letter-Number Sequencing, Block Design, Judgment of Line Orientation, Boston Naming	NS [TMT B]	NS [CVLT, Immediate Recall]		reported cancer. No other serious adverse effects were reported.

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
			Test]				
				NS [Shibley Abstraction]	NS [CVLT, Delayed Recall]		
				NS [Letter-Number Sequencing]	NS [Verbal Episodic Memory, Logical Memory Factor: EBMT, Immediate & Delayed Recall]		
					NS [EBMT, Immediate Recall]		
					NS [EBMT, Delayed Recall]		
					I>C [Visual Episodic Memory Factor: Faces I, Faces II]		
					NS [Faces I]		
					NS [Faces II]		
Gleason, 2009¹²¹ Soy isoflavonea 100 mg daily vs. placebo n=30 6 months				C>I [Stroop Color Word Test]	NS [Buschke Selective Reminding Test, Total of Learning Trials – Words]	4 of 14 favor I	NR
				C>I [Trail Making Test B]	NS [Buschke Selective Reminding Test, Learning Slope, Trial 5 vs. Trial 1]	3 of 14 favor C	
				NS [Mazes]	NS [Delayed Recall, Words]		
				NS [Language Fluency, Letter]	NS [Paragraph Recall Test, Total Immediate Recall]		
					NS		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
					[Paragraph Recall Test, Total Delayed Recall]		
					I>C [Rey Complex Figure Test, Immediate Recall]		
					I>C [Rey Complex Figure Test, Delayed Recall]		
					C>I [Visual Spatial Learning Test, Total Correct Position + Designs]		
					I>C [Visual Spatial Learning Test, Learning Slope Position + Design, Trial 5 vs. Trial 1]		
					I>C [Visual Spatial Learning Test, Learning Slope Incorrect Designs]		
Ho, 2007 ¹²⁴ Soy-derived isoflavones 80 mg vs. placebo n=191 6 months			BCT NS [MMSE]	NS [Color Trail I]	NS [HKLLT, Trials 1-5]	0 of 11 (no differences)	No significant differences
			MNP NS [Cognitive Score=z scores of all cognitive tests]	NS [Color Trail II]	NS [HKLLT, Short Delay Recall]		In AEs experienced or their severity were found between groups.
				NS [Digit Symbol – WAIS]	NS [HKLLT, Long Delay Recall]		No serious AEs were reported.
					NS [Visual Reproduction I]		
					NS		

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
					[Visual Reproduction II]		
					NS [Visual Reproduction, Copy]		
Kritz-Silverstein, 2003¹²⁷ Soy-extracted isoflavones 110 mg daily vs. placebo n=56; 6 months				NS [Trails A]	NS [Logical Memory I, Immediate]	0 of 4 (no differences)	NR
				NS [Trails B]	NS [Logical Memory II, Delayed]		
Soy efficacy Results Summary	NR	NR	BCT 0 of 1 (no differences) MNP 0 of 3 (no differences)	2 of 14 favor C	5 of 27 favor I 1 of 27 favors C	5 of 44 favor I (11%) 3 of 44 favor C (7%)	

Comparative Effectiveness: Hormone Therapies versus Active Comparison

Two studies (3 publications) with low to medium risk of bias compared hormone therapies with active interventions.^{130,131,133} Results are summarized in Table 4F.3. Both studies enrolled younger postmenopausal women (mean ages: 43 and 52 years) and assessed changes in cognition after a 6-month treatment period. Neither study reported diagnostic outcomes. Limited data prevented assessment of strength of evidence for other cognitive outcomes.

Table 4F.3. Results Overview: Hormone therapy versus active controls in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
HRT-estrogen + progestin vs. tibolone							
Pan, 2003 ¹³³ Estrogen + progestin (CEE 0.625 mg/day + methylprogesterone acetate 5 mg/day) vs. tibolone 2.5 mg/day n=50 6 months			BCT NS [MMSE]			0 of 2 (no differences)	AEs reported but differences
			BCT NS [CASl]				Not reported in terms of statistical significance.
HRT-estrogen + progestin vs. tibolone Results Summary	NR	NR	BCT 0 of 2 (no differences) MNP NR	NR	NR	0 of 2 (no differences)	
HRT-estrogen + testosterone vs. estrogen							
Moller 2013 ¹³¹ Moller 2010 ²¹³⁰ Estrogen + testosterone (I-1) versus estrogen + placebo (I-2) (estradiol valerate 2 mg/day + testosterone undecanoate 40 mg/day versus estradiol valerate 2				NS [Digit Symbol – WAIS, used to assess cognitive fatigue] ¹	I-1 < I-2 [Logical Story, Immediate Recall] ²	0 of 6 favors I-1	NR (other than 1 withdrawal due to migraine.
				NS [Digit Symbol, Free Recall of Symbols] ¹	NS [Logical Story, Delayed Recall] ²	1 of 6 favors I-2	
				NS [Digit Symbol, Paired Recall of Symbols] ¹			
				NS [Digit Symbol, %			

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
mg/day + placebo) n=50 6 months (crossover design; total trial period = 12 months)				Spatial Errors] ²			
HRT-estrogen + testosterone vs. estrogen Results Summary	NR	NR	NR	0 of 4 (no differences)	0 of 2 favor I1 (estrogen + testosterone) 1 of 2 favors I-2 (estrogen only)	0 of 6 favor I1 (estrogen + testosterone) 1 of 6 favors I2 (estrogen + placebo) (17%)	

*The difference between the # of digits produced during the first 30 seconds and last 30 seconds of a 90 second session]

Adults with MCI

Efficacy: Hormone Therapies versus Inactive Control

We identified two RCTs that compared hormone therapies with inactive controls in older adults with MCI.^{114,125} Results are summarized in Table 4F.4. Cherrier et al. compared the effects of testosterone gel (50-100 mg/day) versus placebo on cognitive performance in men diagnosed with MCI (according to Petersen's criteria) and low serum testosterone levels.¹¹⁴ The study was small (22 men) and conducted over a 6-month period. Of 14 cognitive tests involving memory and executive/attention/processing speed, only one showed a statically significant difference (in a test of verbal memory) between testosterone and placebo groups. Three serious adverse events were reported: one participant visited the emergency department (ED) for chest pains, upper arm pain, and dizziness; a second participant visited the ED for confusion and disorientation; a third participant had a rise in PSA levels and discontinued study medication per study protocol. Evidence was insufficient due to limited data (single study with n<500).

In another study, Kato-Kataoka et al. examined the use of soybean derived phosphatidylserine (soy-PS) at two doses, 100 mg and 300 mg daily, in 78 men and women with MCI and a mean age of 60 (SD: 1 year).¹²⁵ Treatment took place over a 6-month period, with an additional 3 months of followup. Two brief tests of cognitive performance (the MMSE and Hasegawa Dementia Scale) and a memory test were used to assess cognition. Although cognitive scores increased from baseline in all three treatment groups (soy-PS at 2 doses and placebo), no significant differences were observed between soy and placebo groups at any time point. No adverse effects were reported. Evidence was insufficient due to limited data (single study with n<500).

Table 4F.4. Results Overview: Hormone therapy versus inactive controls in adults with MCI

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
HRT-testosterone vs. placebo							
Cherrier, 2015¹¹⁴ Testosterone gel 50-100 mg/d with a target total T level of 500 to 900 ng/dL n=22 6 months				NS [Letter-Number Sequencing, Total Score]	NS [RAVLT, Immediate, Total Score, 4 Trials]	1 of 14 favors I	3 serious AEs reported (2 in treatment and 1 in placebo group), although no significance tests reported.
				NS [Letter-Number Sequencing, Span]	NS [RAVLT, Short Delay]		
				NS [Computerized Simple Reaction Time, 2-Second Interval]	I>C [RAVLT, Long Delay]		
				NS [Computerized Simple Reaction Time, 5-Second Interval]	NS [Story Recall, Immediate]		
				NS [Computerized Choice Reaction Time, 2-Second Interval]	NS [Story Recall, Delay]		
				NS [Computerized Choice Reaction Time, 5-Second Interval]	NS [Visual Spatial Learning Test, Immediate]		
				NS [Mental Rotation]	NS [Visual Spatial Learning Test, Delay]		
HRT-testosterone efficacy	NR	NR	Screening NR	0 of 7 (no differences)	1 of 7 favors I	1 of 14 favors I	

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
			Composites NR				
Soy vs. placebo							
Kato-Kataoka, 2010 ¹²⁵ Soybean derived phosphatidylserine (Soy-PS) 100 mg or 300 mg vs. placebo n=78 9 months			I>C (100 mg group) Screening: [MMSE] NS (300 mg group) Screening: [MMSE]		NS (100 mg group) [Rivermead Behavioral Memory Test] NS (300 mg group) [Rivermead Behavioral Memory Test]	1 of 6 favors I	NR
			NS (100 mg group) [Hawegawa Dementia Scale] NS (300 mg group) Screening: [Hawegawa Dementia Scale]				
HRT-testosterone efficacy	NR	NR	Screening 1 of 4 favors I Composites NR	NR	0 of 2 (no differences)	1 of 6 favors I (17%)	

Interpreting the Findings

Overall, evidence demonstrating the effect of hormone therapies on cognitive outcomes was deemed to be low or insufficient. While there was more evidence supporting the conclusion that the harms of hormone therapies on cognition may outweigh their benefits, differences between hormone therapy and inactive treatment groups tended to be small and lacking in clinical significance.

Some of the most compelling evidence against the use of hormone replacement therapy to prevent cognitive decline or dementia arose from the longitudinal WHI, a study well known for the early termination of its estrogen/progestin arm due to adverse events—cancer and cardiovascular disease in particular—associated with hormone therapy.¹⁴⁴ Particularly when data for women taking any hormone replacement therapy (estrogen-only or estrogen/progestin) were combined,¹³⁸ the detrimental effects of hormone therapy on cognition (both in terms of dementia-related diagnoses and cognitive performance) became more pronounced. Still, the differences remained small and lacking in clinical significance.

Studies of the effects of hormone therapies on cognition were generally relatively short, often one year or less, making it difficult to draw conclusions about the long-term effects of hormone therapies on cognition. Further, the considerable variation in cognitive measures across studies further complicates our ability to draw clear conclusions. Of 21 RCTs included in the review, only two included diagnostic outcomes. Both of the studies were ancillary/substudies of larger longitudinal clinical trials and cognitive outcomes were not the studies' primary outcomes. One of the studies found that hormone replacement therapy (estrogen-only or combined estrogen/progestin therapy) may *increase* the risk of probable dementia and/or MCI. The other study found that the selective estrogen receptor modulator raloxifene may *lower* the risk of MCI when compared to placebo. Both of these studies included older, postmenopausal women and less is known about the effects of hormone therapies on cognition in younger women, or on women who begin using hormone therapies at younger ages. Similarly, little is known about the effects of hormone therapies on cognition in men.

Chapter 4G. Results: Vitamin Interventions

Key Messages

- In adults with normal cognition, moderate-strength evidence shows no benefit in cognitive performance for vitamin E in women.
- Low-strength evidence shows benefit for vitamin B versus placebo for executive/attention/processing speed, brief cognitive test performance, and memory even after 2-4 years of use.
- Low-strength evidence shows no benefit in cognitive performance for multivitamins, vitamin B with omega-3, 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 clinical Alzheimer's-type dementia (CATD)* for multivitamins or vitamin D with calcium.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified 22 eligible publications reporting 17 unique studies of vitamin interventions to prevent age-related cognitive decline, MCI, or CATD.^{76, 77, 145-164} Five were assessed as high risk of bias and not used in our analysis. We analyzed the efficacy and comparative effectiveness of vitamin interventions separately for adults with normal cognition and those with MCI. Appendix L provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Vitamins Interventions

The logic underlying vitamin use varies with the vitamin. In the case of vitamin B the targeted pathway was through lowering homocysteine levels.

Adults with Normal Cognition

Efficacy: Vitamins Versus Inactive Control (Placebo)

Eleven RCTs with low or moderate risk of bias compared vitamins to inactive control (placebo) in adults with normal cognition.^{76,150-153,155,156,159,162-164} Total sample sizes ranged from 220 to 20,536. Conclusions are summarized in Table 4G.1 and individual study results in Table 4G.2.

Table 4G.1. Conclusions: Vitamins versus placebo in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Multivitamin vs. placebo	Dementia	No statistically significant difference in dementia diagnosis with multivitamins versus placebo in long term (n=20,536; 5 years).	Low (medium study limitations, imprecise, consistency unknown)
	MCI	No statistically significant difference in MCI diagnosis with multivitamins versus placebo in long term (n=20,536; 5 years).	Low (medium study limitations, imprecise, consistency unknown)
	Brief cognitive test performance	Data insufficient to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, consistency unknown)
	Multidomain neuropsychological performance	No benefit in multidomain neuropsychological performance with multivitamins versus placebo (n=5,947; followup time unclear).	Low (medium study limitations, indirect, precise, consistency unknown)
	Executive/Attention/Processing Speed	No benefit in executive/attention/processing speed with multivitamins versus placebo (n=1,130; up to 1 year).	Low (low-medium study limitations, indirect, precision unclear, consistent)
	Memory	No benefit in memory with multivitamins versus placebo (n=6,167; followup time unclear).	Low (low-medium study limitations, indirect, imprecise, consistent)
Vitamin B vs. placebo	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No benefit for brief cognitive test performance compared to placebo (n=4,904; up to 4 years).	Low (low-medium study limitations, indirect, imprecise, consistent)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No benefit for executive/attention/processing speed test performance compared to placebo (n=4,095; up to 2 years).	Low (low-medium study limitations, indirect, imprecise, consistent)
	Memory	Vitamin B improves memory with vitamin B versus placebo (n=2,148; up to 4 years).	Low (low-medium study limitations, indirect, imprecise, consistent)
Vitamin E vs. placebo	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No benefit for women in brief cognitive test performance with vitamin E versus placebo in long term (n=9,201; 4 years).	Moderate (low-medium study limitations, indirect, precise, consistent)
	Multidomain neuropsychological performance	No benefit for women in multidomain neuropsychological performance with vitamin E versus placebo in long term (n=9,201; 4 years).	Moderate (low-medium study limitations, indirect, precise, consistent)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)

Comparison	Outcome	Conclusion	Strength of Evidence (Justification)
	Memory	No benefit for women in memory with vitamin E versus placebo in long term (n=9,201; 4 years).	Moderate (low-medium study limitations, indirect, precise, consistent)
Vitamin C vs. placebo	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No benefit for women in brief cognitive test performance with vitamin C versus placebo in long term (n=2,824; 4 years).	Low (low-medium study limitations, indirect, imprecise, consistency unknown)
	Multidomain neuropsychological performance	No benefit for women in multidomain neuropsychological performance with vitamin C versus placebo in long term (n=2,824; 4 years).	Low (low-medium study limitations, indirect, imprecise, consistency unknown)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)
	Memory	No benefit for women in memory with vitamin C versus placebo in long term (n=2,824; 4 years).	Low (low-medium study limitations, indirect, imprecise, consistency unknown)
Vitamin D + Calcium vs. placebo	Dementia	No statistically significant difference in pooled dementia and MCI diagnosis with vitamin D and calcium versus placebo in long term (n=4,143; 7 years).	Low (low-medium study limitations, direct, precise, consistency unknown)
	MCI	See above.	
	Brief cognitive test performance	Data insufficient to draw conclusion.	Insufficient (low-medium study limitations, indirect, imprecise, consistency unknown)
	Multidomain neuropsychological performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No benefit for women in executive/attention/processing speed with vitamin D and calcium versus placebo in long term (n=4,143; 7 years).	Low (low-medium study limitations, indirect, precise, consistency unknown)
	Memory	No benefit for women in memory with vitamin D and calcium versus placebo in long term (n=4,143; 7 years).	Low (low-medium study limitations, indirect, imprecise, consistent)
Beta carotene vs. placebo	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No benefit for women in brief cognitive test performance with beta carotene versus placebo in long term (n=2,824; 4 years).	Low (low-medium study limitations, indirect, imprecise, consistency unknown)
	Multidomain neuropsychological performance	No benefit for women in multidomain neuropsychological performance with beta carotene versus placebo in long term (n=2,824; 4 years).	Low (low-medium study limitations, indirect, precise, consistency unknown)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)

Comparison	Outcome	Conclusion	Strength of Evidence (Justification)
	Memory	No benefit for women in memory with beta carotene versus placebo in long term (n=2,824; 4 years).	Low (low-medium study limitations, indirect, precise, consistency unknown)

Multivitamins

Four RCTs (n=27,613) with low or moderate risk of bias compared multivitamins with placebo. Multivitamin interventions included varying doses and combinations of vitamin A, vitamin B₁₂, vitamin C, vitamin D, vitamin E, beta carotene, biotin, cobalamin, copper, folic acid, iodine, iron, magnesium, manganese, niacin, panthothenic acid, pyridoxine, riboflavin, selenium, thiamine, and zinc.^{150,151,156,164} Participants varied; studies included physicians over 65,¹⁵⁰ women over 60,¹⁶⁴ adults at serious risk of death from heart disease aged 40 to 80,¹⁵¹ and adults over 65.¹⁵⁶ Study samples were large, ranging from 1,130 to 20,536, and duration ranged from 6 months to 8.5 years.

Low-strength evidence from one trial (n=20,536) shows no difference for diagnosis of either MCI or CATD over a 5-year time period.¹⁵¹

In general, low-strength evidence showed no statistical differences on cognitive performance tests, including multidomain neuropsychological performance,¹⁵⁰ executive/attention/processing speed,^{156,164} or memory.^{150,164} Evidence was insufficient for brief cognitive test performance.

None of the trials comparing multivitamins to placebo reported serious adverse effects.

Overall, no differences were found in subgroup analyses. Three trials assessed the effects of lifestyle factors on the effect of multivitamins.^{150,156,164} Cognitive results did not differ by the lifestyle factors of history of smoking, alcohol use, fruit and vegetable intake or nutritional deficiency.

Two trials assessed the effect of baseline cognition and education, prior supplement use, and comorbidities.^{150,164} Final cognitive or diagnostic results did not differ by cognitive performance at baseline, school graduation and job training. Final cognitive results also did not differ by status of BMI, diabetes, hypertension, hyperlipidemia or depression, or prior use of folates, hormone replacement therapy, or vitamin status.

Vitamin B

Four studies (n=4,904) compared vitamin B to placebo.^{76,155,162,163} Two used a combination of B₁₂ and folic acid; two added B₆ to this combination.^{162,163} None of the studies specifically addressed persons with evidence of vitamin deficiency. Participants took varying doses and combinations of B₆, B₁₂ and folate/folic acid or a matching placebo for 2 to 4 years. One trial also randomized participants to vitamin B with omega-3 versus placebo and vitamin B versus omega-3; these results are discussed below in comparative efficacy.⁷⁶ Studies recruited adults aged 65+ with elevated homocysteine levels,¹⁶² sedentary adults aged 60-74 with elevated psychological distress,¹⁶³ adults aged 45-70 with heart disease,⁷⁶ and adults aged 65+ with healthy cognition.¹⁵⁵

None of the trials reported diagnostic outcomes, multidomain neuropsychological performance, or adverse effects. All trials reported brief cognitive test performance (n=4,904). Two trials reported statistically significant improvement at 2 years, but of very small effect sizes:

between-groups change in MMSE scores from baseline of -0.4 points,¹⁶² and 0.17 on a time by intervention interaction.¹⁶³

Three studies (n=4,095) reported 13 tests assessing the effect of vitamin B on executive/attention/processing speed.^{155,162,163} Only one of 13 tests showed statistically significant improvement with placebo over vitamin B, and the results were below published neuropsychological test reliable change indices. McMahon et al. reported an adjusted between groups change from baseline of 1.08 on Trails B.¹⁵⁵

Two studies (n=2,148) reported 11 tests assessing the effect of vitamin B on memory.^{76, 163} Only two of 11 tests showed statistically significant improvement with vitamin B, and the effect sizes were small. Walker et al. reported a TICS time by intervention effect size of 0.15 for immediate recall and 0.18 for delayed recall, again.¹⁶³

Overall, subgroup analysis findings are mixed, finding no differences, or possible differences favoring either the placebo or vitamin B groups. In particular, Andreeva et al. reported participants with a history of myocardial infarction/unstable angina receiving vitamin B (with or without omega-3; see comparative effectiveness section) had lower semantic memory scores (TICS-m subscore) compared to participants of the same age taking placebo (odds ratio: 1.70; 90% CI 1.16 to 2.51), and participants aged 65+ and receiving vitamin B (with or without omega-3) had lower brief cognitive test performance scores (TICS-m) and recall memory scores (TICS-m subscore) compared to participants of the same age taking placebo (p<0.05).⁷⁶

Benefit on memory for vitamin B compared to placebo was reported for participants with low holotranscobalamin levels.¹⁶²

Vitamin E

Two trials (n=9,201) compared vitamin E with a placebo.^{152,153} Both studies randomized women aged 65+ to vitamin E or placebo every other day. However, one randomized women to 600 IU vitamin E for 10 years,¹⁵² while the other randomized women with cardiovascular disease or three or more coronary risk factors to 402 mg vitamin E for 9 years.¹⁵³ Due to high attrition at longer-term followup time points, results were extracted for both studies at 4-year followup. Kang et al. also included an additional two arms, vitamin C and beta carotene, reported separately below.

Neither trial reported diagnostic outcomes or executive/attention/processing speed. Both trials provide moderate-strength evidence showing no differences between vitamin E compared with placebo at 4-year followup were found in brief cognitive test performance (two tests), multidomain neuropsychological performances (two tests), or memory (two tests).

Kang et al. did not observe adverse effects in either vitamin E or placebo group.¹⁵³

Two trials assessed the effect of several participant characteristics on the effect of vitamin E.^{152, 153} Cognitive results did not differ by age, baseline cognition (baseline performance, highest attained education or perceived memory change), supplement use (antioxidants, multivitamins or hormone replacement therapy), comorbidities (BMI, cardiovascular disease, diabetes, hypertension, hyperlipidemia or depression), or lifestyle factors (smoking, alcohol use or exercise).

Vitamin C

Kang et al. (n=2,824) compared vitamin C with placebo.¹⁵³ The trial randomized women aged 65+ with or at risk for cardiovascular disease to 500 mg of vitamin C or placebo daily for 9

years. The longest followup with low or moderate risk of bias was approximately 4 years after baseline cognitive assessments.

The trial did not report diagnostic outcomes or executive/attention/processing speed and provided low-strength evidence showing no statistically significant improvements with vitamin C for brief cognitive test performance or multidomain neuropsychological performances.¹⁵³ One test assessing memory reported statistically significant improvement with vitamin C (author-created composite z-score between groups change from baseline: 0.07; 95% CI 0.0 to 0.13, $p=0.05$).¹⁵³ However, the study did not correct for multiple comparisons, and given the small effect size these results were not likely to be clinically meaningful. No serious adverse effects were observed in either vitamin C or placebo arm.

Kang et al. assessed the effect of several participant characteristics on the effect of vitamin C.¹⁵³ Only cognitive results differed by incident cardiovascular disease ($p<0.01$). Cognitive results did not differ by age, baseline cognition (baseline performance or highest attained education), supplement use (antioxidants or multivitamins), comorbidities (prior cardiovascular disease or associated risk factors), or lifestyle factors (smoking or alcohol use).

Vitamin D + Calcium

One trial ($n=4,143$) compared vitamin D with calcium to placebo.¹⁵⁹ Participants in the Women's Health Initiative Memory Study were previously randomized to 400 IU vitamin D₃ with 1000 mg calcium or a matching placebo for a mean of 7.8 years. People in the intervention group were also allowed to take an additional supplement containing 1000 mg calcium with 600 mg vitamin D. Followup assessment took place at approximately 7.8 years.

Rossom et al. did not report multidomain neuropsychological performances or adverse effects.¹⁵⁹ Low-strength evidence shows diagnosis of probable dementia or MCI, reported as one pooled outcome, did not differ statistically between vitamin and placebo groups. Evidence was insufficient to conclude differences between vitamin D and calcium versus placebo for brief cognitive test or multidomain neuropsychological performance. One test assessed executive/attention/processing speed and two tests assessed memory; all showed no statistically significant difference with vitamin D and calcium.

Beta carotene

Kang et al. ($n=2824$) compared beta carotene with placebo.¹⁵³ Women aged 65+ with or at risk for cardiovascular disease were randomized to 50 mg beta carotene or placebo every other day for 9 years. The longest followup with low or moderate risk of bias was approximately 4 years after baseline cognitive assessments.

Kang et al. did not report diagnostic outcomes or executive/attention/processing speed.¹⁵³ Low-strength evidence shows no statistically significant improvements with beta carotene for brief cognitive test performance (one test), multidomain neuropsychological performances (one test), or memory (one test). No serious adverse effects were observed in either vitamin C or placebo arm.

One trial assessed the effect of several participant characteristics on the effect of beta carotene.¹⁵³ Only one variable was significant; cognitive results differed by dietary antioxidant intake ($p=0.02$). Cognitive results did not differ by age, baseline cognition (baseline performance or highest attained education), multivitamin use, comorbidities (cardiovascular disease or associated risk factors), or lifestyle factors (smoking or alcohol use).

Table 4G.2. Results Overview: Vitamins versus inactive comparisons (placebo) in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Multivitamins Efficacy						
Grodstein, 2013 ¹⁵⁰ Multivitamin vs placebo n=5947 (men)		BCT NS [TICS]		NS [Composite ^b]	0 of 3 (no difference)	NR
		MNP NS [Composite ^a]				
McNeill, 2007 ¹⁵⁶ Micronutrient supplement vs placebo n=910 1 year			NS [Digit span forwards]		0 of 1 (no difference)	NR
Wolters, 2005 ¹⁶⁴ Multivitamin vs placebo n=220 (women) 6 months			NS [Kurztest fuer Allgemeine Intelligenz]	NS [Berliner Amnesit Test]	0 of 3 (no difference)	NR
			NS [WAIS-III symbol search]			
Heart Protection Study, 2002 ¹⁵¹ Vitamin C + vitamin B + beta carotene vs placebo n=20,536 5 years	NS [dementia]	BCT NS [TICS-m]			0 of 3 (no difference)	NR
	NS [MCI]					
Multivitamin Results Summary	0 of 2 (no difference)	0 of 2 (no difference)	0 of 3 (no difference)	0 of 2 (no difference)	0 of 10 (no difference)	
Vitamin B Efficacy						
van der Zwaluw,		BCT	NS	NS	1 of 14 favor I	NR

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
2014 ¹⁶² B vitamins (folic acid & B ₁₂) vs placebo n=2,919 (some domains = smaller n) 2 years		I>C [MMSE]	[Composite ^c]	[Composite ^f]		
			NS [Composite ^d]	NS [RAVLT-immediate recall]		
			NS [Composite ^e]	NS [RAVLT-delayed recall]		
			NS [Digit span forwards]	NS [RAVLT recognition]		
			NS [Trails A]			
			NS [Trails B]			
			NS [Stroop 1 & 2]			
			NS [Stroop Interference]			
Walker, 2012 ¹⁶³ B vitamins (folic acid & B ₁₂) vs placebo n=900 2 years		BCT I>C [TICS-m total]	NS [TICS-m orientation/calculation]	I>C [TICS-m immediate recall]	3 of 6 favor I	NR
			NS [TICS-m attention]	I>C [TICS-m delayed recall]		
				NS [TICS-m semantic memory]		
Andreeva, 2011 ⁷⁶ B vitamins (folate, B ₆ , B ₁₂) vs. placebo n=1,248 4 years		BCT NS [TICS-m]		NS [TICS-m memory]	0 of 3 (no difference)	NR
				NS [TICS-m recall]		
McMahon, 2006 ¹⁵⁵		BCT NS	NS [Raven's Progressive	NS [RAVLT]	1 of 5 favor C	NR

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
B vitamins (folate & vitamin B) vs placebo n=276 2 years		[MMSE]	Matrices]			
			C>I [Trails B]	NS [Paragraph recall]		
Vitamin B Results Summary		BCT 2 of 4 favor I	1 of 13 favor C	2 of 11 favor I	4 of 28 favor I 1 of 28 favor C	
Vitamin E Efficacy						
Kang, 2009 ¹⁵³ Vitamin E vs. placebo n=2,824 9 yrs Tx 5 yrs followup		BCT NS [TICS]		NS [Composite]	0 of 3 (no difference)	None
		MNP NS [Composite]				
Kang, 2006 ¹⁵² Vitamin E vs. placebo n=6,377 10 years Tx 4 years followup		BCT NS [TICS]		NS [Composite]	0 of 3 (no difference)	NR
		MNP NS [Composite]				
Vitamin E Results Summary		BCT 0 of 2 (no difference) MNP 0 of 2 (no difference)		0 of 2 (no difference)	0 of 6 (no difference)	
Vitamin C Efficacy						

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Kang, 2009¹⁵³ Vitamin C vs. placebo n=2,824 9 yrs Tx 5 yrs followup		BCT NS [TICS]		I>C [Composite]	1 of 3 favor I	None
		MNP NS [Composite]				
Vitamin C Results Summary		BCT 0 of 1 (no difference) MNP 0 of 1 (no difference)		1 of 1 favor I	1 of 3 favor I	
Vitamin D + Calcium Efficacy						
Rossum, 2012¹⁵⁹ Calcium & vitamin D vs placebo n=4,143 8 years	NS [probable dementia or MC]	BCT NS [MMSE-m]	NS [digit span forwards & backwards (pooled)]	NS [California Verbal Learning Test]	0 of 5 (no difference)	NR
				NS [Benton Visual Retention Test]		
Vitamin D Results Summary	0 of 1 (no difference)	BCT 0 of 1 (no difference)	0 of 1 (no difference)	0 of 2 (no difference)	0 of 5 (no difference)	
Beta carotene Efficacy						
Kang, 2009¹⁵³ Vitamin C vs.		BCT NS [TICS]		NS [Composite]	0 of 3 (no difference)	None

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
placebo n=2,824 9 yrs Tx 5 yrs followup		MNP NS [Composite]				
Beta carotene Results Summary		BCT 0 of 1 (no difference) MNP 0 of 1 (no difference)		0 of 1 (no difference)	0 of 3 (no difference)	

^a mean multidomain battery composite z score composed of TICS, EBMT, TICS 10-word list delayed recall, and category fluency; ^b composite z score of TICS and EBMT immediate and delayed word recall; ^c composite z score of Attention and working memory (Digit span forwards & backwards); ^d composite z score of Information Processing Speed (Trails A, Stroop I & II); ^e composite z score of Executive functioning (Trails B, Stroop Interference, Verbal fluency); ^f composite z score of Episodic memory (RAVLT immediate recall, decay, recognition)

3MS=Modified Mini-Mental State Examination; BCT=brief cognitive screening test; C=inactive control; DSST=Digit Symbol Substitution Test; DSy=Digit Symbol Coding; EMBT=East Boston Memory Test; HVLTR=Hopkins Verbal Learning Test; I=intervention; I=intervention; MNP=multidomain neuropsychological test; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; Stroop=Modified Stroop;

Comparative Effectiveness: Vitamins Versus Active Comparison

Two RCTs (n=1,916) reported three comparisons of vitamins with an active control group.^{76,147} Andreeva et al. analyzed the comparative effectiveness of vitamin B with and without omega-3 versus omega-3 alone.⁷⁶ They randomized adults aged 45-70 with heart disease to vitamin B (0.56 mg folate, 3 mg B6 and 0.02 mg B12) with or without omega-3 (600 mg EPA/DHA) daily for 4 years. Carlsson et al. analyzed vitamin E with pravastatin versus pravastatin alone.¹⁴⁷ They randomized adults aged 70+ with high cholesterol to vitamin E (400 IU) with pravastatin (20 mg) daily or vitamin E alone in a 1-year crossover trial. After 6 months both groups received vitamin E with pravastatin, so results are analyzed at 6 month followup. See Table 4G.3 for summary of conclusions and Table 4G.4 for results.

Table 4G.3. Conclusions: Vitamins versus active comparisons in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Vitamin B vs. omega-3	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No benefit in brief cognitive test performance with vitamin B versus omega-3 in long term (n=1,259; 4 years).	Low (low-medium study limitations, indirect, imprecise, consistency unknown)
	Multidomain neuropsychological performances	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)
	Memory	No benefit in memory with vitamin B versus omega-3 in long term (n=1,259; 4 years).	Low (low-medium study limitations, indirect, imprecise, consistent)
Vitamin B + omega-3 vs. vitamin B	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No benefit in brief cognitive test performance with vitamin B and omega-3 versus vitamin B alone in long term (n=1,246; 4 years).	Low (low-medium study limitations, indirect, imprecise, consistency unknown)
	Multidomain neuropsychological performances	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)
	Memory	No benefit in memory with vitamin B with omega-3 versus vitamin B alone in long term (n=1,236; 4 years).	Low (low-medium study limitations, indirect, imprecise, consistent)
Vitamin E + statin vs. vitamin E	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Brief cognitive test performance	No data available	Insufficient (no data)
	Multidomain neuropsychological performances	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	Limited data	Insufficient (limited data)
	Memory	No data available	Insufficient (no data)

MCI=mild cognitive impairment

The trial comparing vitamin B with omega-3 did not report diagnostic outcomes, multidomain neuropsychological performances, executive/attention/processing speed or adverse effects.⁷⁶ In the vitamin B and omega-3 arms (n=1,259), one screening test and two memory tests found low-strength evidence for no significant difference between vitamin B and omega-3 in preventing cognitive decline after 4 years of intervention. In the vitamin B with omega-3 versus omega-3 arms (n=1,246), one screening test and two memory tests found low-strength evidence for no significant difference between vitamin B with omega-3 versus omega-3 alone in preventing cognitive decline after 4 years of intervention.

The trial comparing vitamin E with and without pravastatin did not report diagnostic outcomes, brief cognitive test performance, multidomain neuropsychological performances, memory or adverse effects.¹⁴⁷ One test reported executive/attention/processing speed, but evidence was insufficient to analyze differences between groups at 6 month followup.

One trial assessed the effect of baseline homocysteine levels and cardiovascular disease history on the effect of vitamin B with and without omega-3.⁷⁶ Cognitive results did not differ by homocysteine levels. Participants with a history of myocardial infarction/unstable angina receiving vitamin B (with or without omega-3; see efficacy section) had lower semantic memory scores (TICS-m subscore) compared to participants of the same age taking placebo (odds ratio: 1.70; 90% CI 1.16 to 2.51).

Table 4G.4. Results Overview: Vitamins versus active comparisons in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Vitamin B ± omega-3						
Andreeva, 2011⁷⁶ Vitamin B vs. omega-3 n=1,259 4 years		BCT NS [TICS-m]		NS [TICS-m memory]	0 of 3 (no difference)	NR
				NS [TICS-m recall]		
Andreeva, 2011⁷⁶ Vitamin B + omega- 3 vs. vitamin B n=1,246 4 years		BCT NS [TICS-m]		NS [TICS-m memory]	0 of 3 (no difference)	NR
				NS [TICS-m recall]		
Vitamin B Results Summary		0 of 2 (no difference)		0 of 4 (no difference)	0 of 6 (no difference)	
Vitamin E + statin						
Carlsson, 2002¹⁴⁷ Vitamin E + statin vs. vitamin E n=41 6 months (12 months total with crossover)			NS [Digit Symbol Coding]			NR
Vitamin E Results Summary			0 of 1 (no difference)		0 of 1 (no difference)	

3MS=Modified Mini-Mental State Examination; BCT=brief cognitive screening test; C=inactive control; DSST=Digit Symbol Substitution Test; DSy=Digit Symbol Coding; EMBT=East Boston Memory Test; HVLt-R=Hopkins Verbal Learning Test; I=intervention; I=intervention; MNP=multidomain neuropsychological test; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; Stroop=Modified Stroop;t

Adults with MCI

Efficacy: Vitamins versus Inactive Control

Three trials reported in four publications (n=1,038) with low or moderate risk of bias compared vitamins with inactive control (placebo) in adults with MCI.^{145,148,149,157} Total sample sizes ranged from 256 to 516. Strength of evidence was only assessed for one study with a sufficiently large sample size.¹⁵⁷ Conclusions are summarized in Table 4G.5 and individual study results for all three trials are in Table 4G.6

One trial (n=516) compared vitamin E to placebo for preventing cognitive decline.¹⁵⁷ They randomized adults aged 55-90 with degenerative amnesic MCI to 2000 IU vitamin E or placebo daily for 3 years. They study also included a donepezil arm, the results of which are discussed in the Chapter 14.

Evidence was insufficient to determine improvement with vitamin E for brief cognitive test performance, multidomain neuropsychological performances, executive/attention/processing speed, or memory. Two tests assessed differences in diagnosis of CATD at 3 years and found low-strength evidence for no difference between groups. Serious adverse effects did not differ between groups.

Table 4G.5. Conclusions: Vitamins versus inactive comparisons in adults with MCI

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Multivitamin vs. placebo	Dementia	No data available	Insufficient (limited data)
	Brief cognitive test performance	No data available	Insufficient (limited data)
	Multidomain neuropsychological performances	No data available	Insufficient (limited data)
	Executive/Attention/Processing Speed	No data available	Insufficient (limited data)
	Memory	No data available	Insufficient (limited data)
Vitamin B vs. placebo	Dementia	No data available	Insufficient (limited data)
	Brief cognitive test performance	No data available	Insufficient (limited data)
	Multidomain neuropsychological performances	No data available	Insufficient (limited data)
	Executive/Attention/Processing Speed	No data available	Insufficient (limited data)
	Memory	No data available	Insufficient (limited data)
Vitamin E vs. placebo	Dementia	No statistically significant difference in CATD diagnosis with vitamin E versus placebo in long term (n=516; 3 years).	Low (medium study limitations, direct, imprecise, consistent)
	Brief cognitive test performance	Data insufficient to draw conclusions.	Insufficient (medium study limitations, indirect, imprecise, consistency unknown)
	Multidomain neuropsychological performances	Data insufficient to draw conclusions.	Insufficient (medium study limitations, indirect, precision unclear, consistency unknown)
	Executive/Attention/Processing Speed	Data insufficient to draw conclusions.	Insufficient (medium study limitations, indirect, imprecise, consistency unknown)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
	Memory	Data insufficient to draw conclusions.	Insufficient (medium study limitations, indirect, imprecise, consistency unknown)

Interpreting the Findings

Overall, little to no benefit was shown with vitamin use in preventing cognitive decline. The only benefits noted were for vitamin B for brief cognitive test performance, executive/attention/processing speed, and memory versus placebo in adults with normal cognition; however, the results were in a small proportion of cognitive performance tests and of small effect size. In several instances the cognitive effects of vitamins seem to have been an add-on to a broadly targeted test of vitamin effects. Additionally, many of the vitamins were examined in a few studies that enrolled only women.

Table 4G.6 Results Overview: Vitamins versus inactive comparisons for prevention of cognitive decline in adults with MCI

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Multivitamins Efficacy						
Alavi Naeini, 2014¹⁴⁵ Vitamin E + vitamin C vs. placebo n=256 1 year		BCT NS [MMSE]				NR
Multivitamin Results Summary		BCT 0 of 1 (no difference)			0 of 1 (no difference)	
Vitamin B Efficacy						
Smith, 2010¹⁶¹ deJager, 2012 Douaud, 2013¹⁴⁹ Vitamin B (folic acid + B ₁₂ + B ₆) vs. placebo N=217 2 years		BCT NS [MMSE]		NS [Hopkins Verbal Learning Test]		NR
Vitamin B Results Summary		BCT 0 of 1 (no difference)		0 of 1 (no difference)		
Vitamin E Efficacy						
Petersen, 2005¹⁵⁷ Vitamin E vs. placebo n=516 3 years	NS [CATD]	BCT NS [MMSE]	NS [Composite]	NS [Composite]		28% vs. 25%*; reasons NR
	NS [CDR sum of boxes]	MNP NS [ADAS-Cog]				
Vitamin E	0 of 2 (no	BCT	0 of 1 (no difference)	0 of 1 (no difference)	0 of 6 (no	

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsycholo gical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Results Summary	difference)	0 of 1 (no difference) MNP 0 of 1 (no difference)			difference)	

3MS=Modified Mini-Mental State Examination; BCT=brief cognitive screening test; C=inactive control; DSST=Digit Symbol Substitution Test; DSy=Digit Symbol Coding; EMBT=East Boston Memory Test; HVLT-R=Hopkins Verbal Learning Test; I=intervention; I=intervention; MNP=multidomain neuropsychological test; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; Stroop=Modified Stroop;

Chapter 4H. Results: Antihypertensive Treatment

Key Messages

- 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 ACE and thiazide versus placebo and ARBs versus placebo have no benefit on brief cognitive screening tests.
- Low-strength evidence shows that intensive versus standard antihypertensive medication appear to have no benefit on cognitive test performance.
- Low-strength evidence shows that antihypertensive medication versus antihypertensive medication appear to have no benefit on cognitive test performance.
- One trial found that a stepped multiple agent antihypertensive medication regimen reduced risk of dementia versus placebo at 2-year and 3.9-year median followup, but three other trials found no effect of antihypertensive treatment on clinical Alzheimer's-type dementia (CATD)* incidence.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified 20 eligible publications reporting 16 unique trials comparing antihypertensive medication treatment to placebo or active control to prevent age-related cognitive decline, MCI, or CATD.¹⁶⁵⁻¹⁸⁸ Three trials were assessed as high risk of bias and not used in our analysis.^{166,172,176} For our analyses, we evaluated the efficacy and comparative effectiveness of antihypertensive treatment regimens and the strength of evidence for these effects by drug class, but in the text below we present the results within the broader groups of antihypertensive medication treatment versus placebo, intensive versus standard antihypertensive treatment, and antihypertensive medication treatments versus each other. We also evaluated and report results separately for adults with normal cognition and those with MCI. Appendix M provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Antihypertensive Treatments

A meta-analysis of prospective cohort studies estimated that the presence of hypertension between the ages of 35 and 64 years but not in late life increased the risk of incident Alzheimer's disease by more than 50 percent.¹⁸⁹ Hypertension is thought to contribute to risk of both vascular and Alzheimer's dementia through unclear vascular mechanisms. Presumably hypertension is the cause or result of vascular changes in the blood supply to the brain that can adversely affect its function. It remains unclear whether this is a direct effect or the result of other factors that affect both the vasculature and the brain.

Adults with Normal Cognition

Conclusions are summarized in Table 4H.1 and individual study results in Table 4H.2.

Table 4H.1. Conclusions: Antihypertensives in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Antihypertensive vs Placebo			
ARBs vs. Placebo	Dementia	No statistically significant difference in dementia diagnoses with ARBs versus placebo (n = 4937; 44 months)	Low (medium study limitations, precise, unknown consistent, suspect reporting bias)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No statistically significant difference in brief cognitive test performance with ARBs versus placebo (n = 10,863; up to 56 months).	Moderate (medium study limitations, precise, consistent, suspect reporting bias)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	Data insufficient to draw conclusion.	Insufficient (medium study limitations, unknown, consistent, suspect reporting bias)
	Memory	Data insufficient to draw conclusion.	Insufficient (medium study limitations, unknown, inconsistent, suspect reporting bias)
Beta blocker vs. Placebo	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No data available	Insufficient (no data)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	Data insufficient to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspect reporting bias)
	Memory	Data insufficient to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspect reporting bias)
ACE and Thiazide vs. Placebo	Dementia	No statistically significant difference in dementia diagnoses with ACE and thiazide versus placebo (n = 14,985; up to 4.3 years)	Low (medium study limitations, imprecise precise, consistent, suspect reporting bias)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No statistically significant difference in brief cognitive test performance with ACE and thiazide versus placebo (n = 14,985; up to 4.3 years)	Moderate (medium study limitations, precise, consistent, suspect reporting bias)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)
	Memory	No data available	Insufficient (no data)
Combination therapy vs. Placebo	Dementia	Statistically significant difference in dementia diagnoses favoring combination therapy versus placebo (n = 3,228; up to	Low (medium study limitations, imprecise, unknown consistency, suspect reporting

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
		3.9 years)	bias)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No statistically significant difference in brief cognitive test performance with beta blocker versus placebo (n = 3,228; up to 3.9 years).	Low (medium study limitations, precise, consistent, suspect reporting bias)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	Data insufficient to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspect reporting bias)
	Memory	No data available	Insufficient (no data)
Intensive vs Standard			
Intensive blood pressure control (systolic blood pressure <120 mm Hg) vs. standard blood pressure control (standard therapy (systolic blood pressure <140 mm Hg))	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	Data insufficient to draw conclusion.	Insufficient (medium study limitations, precise, unknown consistency, suspect reporting bias)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No statistically significant difference in executive/attention/processing speed with intensive blood pressure control versus standard blood pressure control (n = 1,439; 40 months)	Low (medium study limitations, imprecise, consistent, suspect reporting bias)
	Memory	No statistically significant difference in memory with intensive blood pressure control versus standard blood pressure control (n = 1,439; 40 months)	Low (medium study limitations, precise, unknown consistency, suspect reporting bias).
Antihypertensive vs Antihypertensive			
Ramipril (I1) up to 10mg daily vs. (I2) combined ramipril up to 10mg daily plus telmisartan 80mg daily	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No statistically significant difference in brief cognitive test performance with ramipril versus ramipril combined with telmisartan (n = 17,078; 56 months)	Low (medium study limitations, precise, unknown consistency, suspect reporting bias)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No data available	Insufficient (no data)
	Memory	No data available	Insufficient (no data)
ARB vs. ACE	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No statistically significant difference in brief cognitive test performance with ARB versus ACE (n = 17,118; 56 months)	Low (medium study limitations, precise, unknown consistency, suspect reporting bias)
	Multidomain	No data available	Insufficient (no data)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
	Neuropsychological Performance		
	Executive/Attention/Processing Speed	Data insufficient to draw conclusion.	Insufficient (low study limitations, imprecise, unknown consistency, suspect reporting bias)
	Memory	Data insufficient to draw conclusion.	Insufficient (low study limitations, imprecise, inconsistent, suspect reporting bias)

Antihypertensive Medication Versus Placebo

Eight unique RCTs met eligibility criteria with low to medium risk of bias and randomized participants to an antihypertensive medication treatment versus placebo,^{165,167,170,171,173,175,178,179,184,186-188} Five of the eight studies had eligibility criteria related to cognition, including exclusion of participants with dementia;^{170,171,173,187} any mental disorder or clinically relevant chronic disease;¹⁸⁴ and either MMSE <24, severe brain disorders that may interfere with cognitive function, or treatment with antidementia drugs.¹⁷⁵ Four studies reported baseline MMSE, ranging from a median of 26 to 29.^{165,170,171,175,187}

Among the four unique trials that reported incident dementia outcomes,^{170,171,175,187,188} only the Syst-Eur trial reported a significantly reduced risk of dementia in the antihypertensive treatment group versus the placebo group,^{170,171} while the other three trials reported no difference in risk.^{175,187,188}

In the study showing decreased risk of CATD, which compared a stepped multiple agent antihypertensive regimen versus placebo, incident dementia diagnosis was based on DSM-3 criteria and was validated by a masked review board.^{170,171} Because the study was stopped early after planned interim analyses showed a significant reduction in stroke, the study primary endpoint, analyses for incident dementia only included 76 percent of randomized participants. Among these individuals, intervention reduced the rate of incident dementia from 7.7 to 3.8 cases per 1000 patient-years (RR 0.50 [0.24-1.00]).

In the three studies that showed no benefit on risk of CATD, incident dementia was defined as following DSM-4 criteria and a consensus committee in one study,¹⁸⁷ and using modified ICD-10 research criteria in another,¹⁷⁵ but was undefined in the third study.¹⁸⁶ Follow-up duration ranged between 2.2 and 4.3 years.

No study reported data on risk of incident MCI.

All eight trials reported at least one cognitive performance outcome.^{165,167,170,171,173,175,178,179,184,186,187} Four trials reported no difference in brief cognitive test performance between the antihypertensive medication treatment and placebo groups.

Three studies reported mixed results for a change in an executive/attention/processing speed test.^{167,173,175,178,179} All three trials reported results for attention; two trials found that individuals randomized to antihypertensive medication had significantly better attention than those assigned placebo,^{175,173} while the third study found no difference between treatment groups.¹⁶⁷

Two studies reported results for a change in memory tests and found mixed results.^{167,178} One study found no between-group difference in scores on the Paired Association Learning Test (PALS) after 9 months follow-up.¹⁶⁷ In another, the antihypertensive treatment group had a statistically significantly smaller decline between baseline and 3.7 years follow-up in the episodic

memory domain that was small in magnitude (Cohen D 0.28), but no difference in the change in working memory.¹⁷⁸

None of these studies reported data on biomarkers.

Three of these eight studies reported information on adverse effects.^{175,184,187} Participants assigned to methyl dopa, but not those assigned to calcium channel blocker, appeared significantly more likely than those assigned to a placebo to experience any adverse event, a sleep disorder, or a sexual disorder, while incidence of life-threatening events, and of headache, fatigue, and cardiovascular or gastrointestinal side effects were similar between each of these antihypertensive treatment groups and placebo.¹⁸⁴ In one trial, there were significantly fewer serious adverse events in the treatment group ($p < 0.01$).¹⁸⁷

Intensive versus Standard Antihypertensive Medication

Only one study with low to moderate risk of bias randomized participants to intensive versus standard blood pressure control.¹⁸³ This study reported no data on MCI or CATD outcomes. There was no significant difference between treatment groups at 40 months in brief cognitive screening tests, executive/attention/processing speed, or memory. The study reported results for the measure of change in MRI total brain volume between baseline and 40 months, but these results were not analyzed for this review because attrition exceeded 20 percent in one of the treatment groups. This study reported no data on adverse events.

Antihypertensive Medication Treatments versus Each Other

Eight RCTs met eligibility criteria, had low to medium risk of bias, compared different antihypertensive medication treatment regimens versus each other, and reported cognitive outcomes.^{165,167-169,174,177,182,184} Only four of the eight trials reported any entry criteria that could relate to cognition. Of these, one study required that participants have some executive dysfunction (CLOX1 clock draw < 10) but excluded those with dementia or an MMSE of < 20 ,¹⁷⁴ another excluded participants with either a mental disorder or any “clinically relevant chronic disease,”¹⁸⁴ another study excluded participants receiving any psychotropic drug that might interfere with cognition,¹⁶⁸ and a fourth study excluded individuals with a stroke in the last 6 months.¹⁶⁹ Baseline MMSE scores ranged from a mean of 23¹⁸² to a median of 29.¹⁶⁵

None of these studies reported data on MCI or CATD outcomes.

One trial reported incident cognitive impairment, which it defined as a composite of incident dementia, incident cognitive impairment, or MMSE < 24 in patients without baseline cognitive impairment.¹⁶⁵ During a mean follow-up of 4.7 years, incident cognitive impairment occurred in 8 percent, 7 percent and 8 percent of participants allocated to ACE inhibitor, ARB, and their combination, respectively. This corresponded to an odds ratio (OR) of 0.95 (95% CI, 0.85-1.07) for combination group versus the ACE inhibitor group and an OR of 0.90 (95% CI, 0.80-1.01) for the ARB group versus the ACE inhibitor group. Authors did not directly compare results between the ARB and combination groups.

All eight trials reported at least one cognitive performance outcome.^{165,167-169,174,177,182,184} Three reported results for a change in a brief cognitive screening test (MMSE).^{53,165,177,182} Two studies found no difference between their different antihypertensive medication treatment arms, in mean MMSE score at follow-up,¹⁷⁷ or incidence of > 3 point decline in MMSE.¹⁶⁵ In one study, while individuals randomized to thiazide had no significant improvement in MMSE between baseline and 26 months, those assigned to ARB had a significant improvement in this outcome during that time period.¹⁸² No direct between-group comparison was reported.

Two studies found no difference in executive/attention/processing speed tests between their different antihypertensive medication treatment arms.^{167,169} Three studies reported results for memory tests and found mixed results.¹⁶⁷⁻¹⁶⁹ One study found no difference on the Paired Association Learning Test (PALS) after 9 months follow-up between a group assigned a beta blocker and a group assigned a thiazide-potassium sparing diuretic combination.¹⁶⁷ In another trial, participants randomized to ARB performed significantly better at 6 months than those assigned to beta blocker on both immediate and delayed recall of a word list.¹⁶⁸ In a third trial, participants randomized to ARB plus thiazide performed no differently at 6 months than those assigned to ACE inhibitor plus thiazide group on immediate recall of a word list, but performed significantly better on delayed recall of the word list.¹⁶⁹

None of these studies reported data on biomarkers.

Four of these studies reported adverse events outcomes.^{168,169,174,184} In one study, participants assigned to methyldopa were significantly more likely than those assigned to a calcium channel blocker to experience any adverse event, a sleep disorder, or a sexual disorder, while incidence of life-threatening events, and of headache, fatigue, and cardiovascular or gastrointestinal side effects were similar between these two antihypertensive treatment groups.¹⁸⁴ In another, participants randomized to ARB were significantly less likely to have an adverse event than those assigned to beta blocker.¹⁶⁸ In another trial, there was no significant difference in risk of any adverse event (2.6 percent vs. 5.5 percent) between individuals randomized to ARB plus thiazide and those assigned to ACE inhibitor plus thiazide.¹⁶⁹ In the fourth trial, there was no significant difference in risk of nonelective hospitalizations or other selected adverse events (dizziness, weakness or fatigue, noninjurious fall, cough) between individuals randomized to ACE inhibitor, ARB, or thiazide treatment groups.¹⁷⁴

Table 4H.2. Results Overview: Antihypertensive treatments in adults with normal cognition

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
ARB vs placebo							
Anderson 2011 ¹⁶⁵ (TRANSCEND trial) telmisartan 80mg daily vs placebo n = 5926 56 months median follow up			BCT NS [drop of 3 or more MMSE points]			0 of 1 favored I	NR
Saxby 2008 ¹⁷⁸ (single center in SCOPE trial) candesartan (8mg – 16mg) daily vs placebo n = 257 44 months mean follow up			BCT NS [MMSE]	NS [executive function composite] ^a I>C [attention composite] ^a NS [speed of cognition composite] ^a	I>C [episodic memory composite] ^a NS [working memory composite] ^a	2 of 6 favored I	NR
Lithell 2003 ¹⁷⁵ Skoog 2005 ¹⁷⁹ (SCOPE trial) Candesartan (8mg – 16mg) daily with hydrochlorothiazide 12.5mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed vs Placebo daily and hydrochlorothiazide 12.5mg added as needed. When	NS [Dementia]		BCT NS [MMSE] NS [significant cognitive decline]			0 of 2 favored I	NS [serious adverse events]

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
target blood pressure not achieved (<160/90 mmHg) other drugs added as needed n = 4937 44 months mean follow up							
ARB vs placebo Results Summary	0 of 1 favored I		BCT 0 of 3 favored I	1 of 3 favored I	1 of 2 favored I	1 of 8 favored I	0 of 1 favored I
Beta blocker vs placebo							
Bird 1990 ¹⁶⁷ atenolol 50mg daily vs. placebo n = 2401 9 months				NS [Trails A]	NS [Paired Associated Learning Test]	0 of 2 favored I	NR
Beta blocker Results Summary				0 of 1 favored I	0 of 1 favored I	0 of 1 favored I	
Combination Therapy vs placebo							
Forette 2002 ¹⁷⁰ (Syst-Eur trial) Antihypertensive stepwise therapy with titration with goal of lowering systolic blood pressure below 150 mm Hg (step 1: nitrendipine 10 -40 mg daily; step 2: enalapril 5 – 20 mg daily; step 3: hydrochlorothiazide 12.5 – 25 mg daily)	I>C [Dementia]		BCT NS [MMSE]			0 of 1 favored I	NR

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
vs placebo n = 3228 3.9 years median follow up							
Forette 1998 ¹⁷¹ (Syst-Eur trial) Antihypertensive stepwise therapy with titration with goal of lowering systolic blood pressure below 150 mm Hg (step 1: nitrendipine 10 -40 mg daily; step 2: enalapril 5 – 20 mg daily; step 3: hydrochlorothiazide 12.5 – 25 mg daily) vs placebo n = 3162 2 year median follow up	I>C [Dementia]		BCT NS [MMSE]			0 of 1 favored I	NR
Gurland 1988 ¹⁷³ (SHEP trial) Step therapy: step 1: chlorthalidone; step 2: reserpine, metoprolol, or hydralazine) vs placebo n = 551 1 year				NS [DSST] I>C [Trails A] NS [composite] ^b		1 of 2 favored I	NR
Combination therapy Results Summary	1 of 1 favored I		BCT 0 of 2 favored I	1 of 2 favored I	0 of 2 favored I	1 of 6 favored I	
ACE and Thiazide							

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
vs placebo							
Peters 2008¹⁸⁷ (HYVET-COG) Indapamide 1.5 mg with optional perindopril (2mg up to 4 mg) vs. matching placebo n = 3,845 26.4 months mean follow up	NS		BCT NS [MMSE] NS [MMSE <24 or a decline of >3 MMSE points in a year]			0 of 2 favored I	I>C [number of adverse events]
ADVANCE Collaborative Group 2007¹⁸⁶ Combined perindopril (2 mg up to 4 mg) and indapamide (0.625 mg up to 1.25 mg) and open label perindopril up to 4 mg vs. matching-placebo and open label perindopril up to 4 mg. n = 11140 51 months mean follow up	NS		BCT NS [MMSE]			0 of 1 favored I	NS [number with serious drug reactions]
ACE and Thiazide Results Summary	0 of 2 favored I		BCT 0 of 3 favored I			0 of 3 favored I	
Comparative Effectives: ARB versus ACE							
Hajjar 2013 ¹⁷⁴ Lisinopril (10mg - 40mg) vs candesartan (8mg –							

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
32mg) vs hydrochlorothiazide (12.5mg – 25mg) n = 53 6 months							
Andrerson 2011 ¹⁶⁵ (ONTARGET trial) ramipril (I ₁) 5mg (increased to 10mg after 2wks) daily vs telmisartan (I ₂) 80mg daily n = 17118 56 months median follow up			BCT NS [drop of 3 or more MMSE points]			0 of 1 favored ARB 0 of 1 favored ACE	NR
Forgari 2006 ¹⁶⁹ telmisartan 80mg and hydrochlorothiazide 12.5mg daily (I ₁) vs lisinopril 20mg and hydrochlorothiazide 12.5mg daily (I ₂) n = 160 6 months				NS [Trails B]	NS [word-list memory] I ₁ >I ₂ [word-list recall] NS [word-list recognition]	0 of 3 favored ARB 1 of 3 favored ACE	NS [Adverse events]
Combination therapy Results Summary	0 of 2 favored ARB 0 of 2 favored ACE		BCT 0 of 1 favored ARB 0 of 1 favored ACE	0 of 1 favored ARB 0 of 1 favored ACE	0 of 3 favored ARB 1 of 3 favored ACE	0 of 5 favored ARB 1 of 5 favored ACE	0 of 1 favored ARB
Comparative Effectives: ARB versus Thiazide							
Hajjar 2013 ¹⁷⁴ Lisinopril (10mg - 40mg) vs							NS

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
candesartan (8mg – 32mg) vs hydrochlorothiazide (12.5mg – 25mg) n = 53 6 months							
Tedesco 1999 ¹⁸² Losartan (I ₁) 50mg daily vs hydrochlorothiazide (I ₂) 25mg daily n = 69 26 months							NS
ARB versus Thiazide therapy Results Summary							0 of 1 favored ARB
Comparative Effectives: Intensive vs standard							
Willamson 2014 ¹⁸³ (ACCORD BP trial) intensive intervention (systolic blood pressure <120 mm Hg) vs standard therapy (systolic blood pressure <140 mm Hg) n = 1439 40 months			BCT NS [MMSE]	NS [modified Stroop Color-Word Test] NS [DSST]	NS [Rey Auditory Verbal Learning]	0 of 4	NR
Comparative Effectives: Intensive vs standard							
Comparative			BCT	0 of 2	0 of 1	0 of 4	

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Effectives: Antihypertensives versus Active Comparison Results Summary			0 of 1				
Hajjar 2013 ¹⁷⁴ Lisinopril (10mg - 40mg) vs candesartan (8mg – 32mg) vs hydrochlorothiazid e (12.5mg – 25mg) n = 53 6 months							
Sato 2013 ¹⁷⁷ (CAMUI trial) combined losartan 50mg and hydrochlorothiazide 12.5mg daily vs combined amlodipine 5mg and typical dosage of a angiotensin receptor blocker daily n = 142 12 months			BCT NS [MMSE]			0 of 1	NS
Anderson 2011 ¹⁶⁵ (ONTARGET trial) (I ₁) ramipril up to 10mg daily vs (I ₂) combined ramipril up to 10mg daily plus telmisartan 80mg daily n = 17078			BCT NS [drop of 3 or more MMSE points]			0 of 1	NR

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
56 months median follow up							
Fogari 2003 ¹⁶⁸ atenolo (I ₁ ;50mg with titration to 100mg) vs losartan (I ₂ ;50mg with titration to 100mg) n = 120 6 months					I ₂ >I ₁ [word-list memory] I ₂ >I ₁ [word-list recall]	2 of 2 favors I ₂	NS
Yodfat 1996 ¹⁸⁴ Isradipine (I ₁) 1.25mg twice a day vs methyldopa (I ₂)250mg twice a day vs placebo (I ₃) n = 368 12 months							NS [Life threatening events] I ₂ < I ₁ , I ₃ [adverse reaction]
Bird 1990 ¹⁶⁷ atenolol 50mg daily vs. Moduretic (hydrochlorothiazide 25mg and amiloride 2.5mg) daily n = 2401 9 months				NS [Trails A]	NS [Paired Associated Learning Test]	0 of 2	NR
Antihypertensives versus Active Comparison Results Summary			0 of 2	0 of 1	2 of 3 favors I ₂	2 of 6	

^a Saxby 2008¹⁷⁸ evaluated composite measures of episodic memory (composed of immediate word recall, immediate word recognition, delayed word recall, delayed word recognition, picture recognition), attention (composed of simple reaction time, number vigilance, choice reaction time), working memory (composed of spatial memory, numeric working memory), speed of cognition (composed of reaction time scores from episodic memory recognition tasks, attention, and working memory tasks), and executive function (composed of trail making A & B, verbal fluency for letters F, A, and S, verbal fluency for category animals).

^b Gurland 1988¹⁷³ evaluated a composite executive/attention/processing speed measure composed of SHORT-CARE dementia, Trail Making, and Digit Symbol test.

Adults with MCI

Just one antihypertensive treatment trial, the HOPE study, met eligibility criteria, had low to medium risk of bias and evaluated cognitive outcomes in participants categorized at baseline as having mild cognitive impairment.^{180, 181} This study randomized 81 older hypertensive adults to ACE inhibitor versus thiazide treatment and followed them for 6 months. Participants were hypertensive, yet had never received prior antihypertensive treatment. They were defined as having a “mild degree of cognitive impairment” based on a baseline MMSE of 20-28 (mean baseline MMSE was 26.1). No information was provided about participant education. Mean age was 76 years. This study reported no data on MCI or CATD outcomes. The treatment showed no effect in a model of all cognitive tests at all time-points, including two measures of executive/attention/processing speed and four measures of memory. This study reported no data on biomarker outcomes or adverse events. Evidence was insufficient to draw conclusions due to limited data (single study n<500).

Interpreting the Findings

Though one trial of stepped multiple agent antihypertensive regimen found a statistically significant reduction in incident CATD, the Syst-Eur trial,^{170, 171} it was a large study in which incident dementia was a relatively rare secondary outcome, and the three other trials that reported an incident dementia outcome found no difference between antihypertensive treatment and placebo. We also found low-strength evidence that antihypertensive treatment regimens appear to have little to no benefit on cognitive performance. However, these results should be interpreted in light of the fact that many trials were probably too short in duration to observe a clinically meaningful change in cognitive function in the middle-aged and older, and largely cognitively normal participants.

Chapter 4I. Results: Lipid Lowering Treatment

Key Messages

- Due to limited data, evidence was insufficient to assess the effect of 5 years of statin treatment on the risk of incident clinical Alzheimer's-type dementia (CATD)* or for preventing MCI.
- Low-strength evidence shows no benefit in brief cognitive test performance, executive/attention/processing speed, or memory for statin plus fenofibrate versus statin plus placebo in adults with normal cognition.
- Low-strength evidence shows benefit in executive/attention/processing speed for statin versus placebo for the control group.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified nine unique studies of low to medium risk of bias that compared treatment with lipid lowering medications versus control treatment to prevent age-related cognitive decline, MCI, or CATD.^{147,183,190-196} Two were rated high risk of bias and excluded from our analyses.^{193,196} The remaining seven studies were RCTs that enrolled a total of 23,286 adults.^{147,183,190-192,194,195} Appendix N provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Lipid Lowering Treatments

A systematic review of prospective cohort studies found mixed results regarding whether saturated fat intake was positively associated with CATD, MCI, or cognitive decline.¹⁹⁷ Authors cited studies suggesting that intracellular cholesterol may impact brain beta amyloid production and deposition. In 2012, based largely on post-marketing adverse event reporting, the Federal Drug Administration revised labeling for statins to warn of a possible associated increase in risk of memory loss, forgetfulness and confusion. These effects were characterized as mild and reversed by stopping use of the statin.¹⁹⁸ However, subsequent systematic reviews of RCTs in both individuals who were cognitively normal and those with CATD showed no difference between statins and placebo in cognitive test performance,¹⁹⁹ including no protective effect with late-life statin use.²⁰⁰

Adults with Normal Cognition

Only two studies excluded participants based on any cognitive criteria; one excluded individuals with a diagnosis of clinical dementia¹⁸³ and another excluded individuals with a score on the MMSE of <24.¹⁹⁴ No studies reported information on the proportion of participants with any cognitive impairment or diagnosis at baseline. Given that, and the largely normal baseline cognitive test performance in the studies that reported results of baseline cognitive testing, participants in all eligible lipid lowering medication versus control trials were presumed to have normal cognition. A summary of conclusions is provided in Table 4I.1 and individual study results are in Table 4I.2.

Table 4I.1. Conclusions: Lipid lowering interventions in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Statins vs. Placebo	Dementia	Data insufficient to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspect reporting bias)
	MCI	No data available	Insufficient (no data)
	Biomarkers	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	Data insufficient to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspect reporting bias)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	Statistically significant improvement in 2 of 3 executive/attention/process speed outcomes for placebo versus statins (n = 948; 6 months)	Low (medium study limitations, imprecise, inconsistent)
	Memory	Data insufficient to draw conclusion.	Insufficient (medium study limitations, imprecise, inconsistent, suspect reporting bias)
Statin plus fenofibrate vs. Statin plus placebo	Dementia	No data available	Insufficient (no data)
	MCI	No data available	Insufficient (no data)
	Biomarkers ^a	No data available	Insufficient (no data)
	Brief Cognitive Test Performance	No statistically significant difference in brief cognitive test performance with statins plus fenofibrate versus statins plus placebo (n = 1,538; 40 months)	Low (low study limitations, precise, unknown consistency, suspect reporting bias)
	Multidomain Neuropsychological Performance	No data available	Insufficient (no data)
	Executive/Attention/Processing Speed	No statistically significant difference in executive/attention/processing speed with statins plus fenofibrate versus statins plus placebo (n = 1,538; 40 months)	Low (low study limitations, precise, consistent, suspect reporting bias)
	Memory	No statistically significant difference in memory with statins plus fenofibrate versus statins plus placebo (n = 1,538; 40 months).	Low (low study limitations, precise, unknown consistency, suspect reporting bias)

Statin Versus Placebo

Four RCTs met eligibility criteria with low to medium risk of bias and randomized participants to statin versus placebo (n = 21,484).^{190-192,194} One large study randomized 20,536 participants to simvastatin (40 mg/day) versus placebo and followed them for 5 years. One trial randomized 209 participants to lovastatin (20 mg/day) versus placebo,¹⁹¹ and another randomized 308 participants to simvastatin (10 or 40 mg/day) versus placebo and followed them for 6 months. A fourth study randomized 431 participants to lovastatin (20 or 40 mg/day) versus placebo, respectively, and followed them for 6 months.¹⁹⁴ Three studies assessed baseline cognition and found at least normal functioning.^{191,192,194} One study reported no information about baseline cognitive function.¹⁹⁰

Only one study, which was not originally designed to evaluate cognitive outcomes, reported data on incident MCI or CATD. It reported no difference in the risk of incident dementia during 5

years of followup between participants assigned to statin versus placebo.¹⁹⁰ The same study found no difference in brief cognitive screening test performance at 5 years. However, the evidence was found to be insufficient.

One trial, which compared 40 mg/day lovastatin, 20 mg/day lovastatin, and placebo groups, found no between-treatment difference in change from baseline in one test of executive/attention/processing speed.¹⁹⁴ Two other trials reported between-group differences favoring the placebo group for executive/attention/processing speed, but not for memory. Low-strength evidence from these three studies suggested that statins are associated with less improvement at 6 months than placebo in the domains of executive/attention/processing speed.^{191, 192} Evidence was insufficient for no difference between treatment groups in memory at 6 months. None of these studies reported biomarker results.

One study reported no difference between treatment groups in either the number of participants hospitalized (no data provided) or in the percentage of participants who discontinued treatment due to adverse events.¹⁹⁰ Another reported more abdominal complaints in the two lovastatin groups compared to placebo, but no between-group differences in the proportion of participants with other adverse events.¹⁹⁴ None of the other eligible studies reported adverse events data.

Statin Plus Ezetimibe Versus Placebo

One RCT randomized 34 participants to atorvastatin 40 mg/day plus ezetimibe 10mg/day versus placebo and followed them for one year.¹⁹⁵ Participants were excluded for a history of stroke or other severe neurologic condition. Mean baseline MMSE was 27.4 and mean NART IQ was 101.

No data on MCI or CATD outcomes were reported. All between-group differences in executive/attention/processing speed and memory were small and unlikely to be clinically meaningful. Compared with the placebo group, participants randomized to atorvastatin plus ezetimibe had statistically significantly less decline in both left amygdala volume, but not in decline in right amygdala volume, in decline in right or left hippocampal volume, or in change in white matter lesion volume.¹⁹⁵ This study reported no data on adverse events outcomes.

Statin Plus Fenofibrate Versus Statin Plus Placebo

One study met eligibility criteria with low risk of bias and randomized a subset of participants in the ACCORD trial (n = 10,251 with diabetes and high risk for cardiovascular events).¹⁸³ Individuals were excluded from participation if they had preexisting clinical evidence of dementia. Other than reporting a median baseline MMSE of 28, baseline cognitive status was not further defined.

This study reported no data on MCI or CATD outcomes. The study provided low-strength evidence that treatment with statin plus fenofibrate is similar to treatment with statin plus placebo for brief cognitive test performance (MMSE), two measures of executive/attention/ processing speed, and memory at 40-month followup. The study reported no data on adverse events.

Statin Versus Alpha Tocopherol

One trial met eligibility criteria with medium risk of bias and randomized 41 older adults with high LDL levels to pravastatin 20 mg/day versus tocopherol 400 IU/day for 6 months.¹⁴⁷ The study used no cognitive-related eligibility criteria.

The study reported no data on MCI or dementia outcomes. Although no significant change was observed in executive function within either treatment group between baseline and 6 months,

results of direct between-group comparisons were not reported. The study reported no data on biomarkers relevant to cognitive function. The study reported that there was no between treatment group difference in any of an extensive list of physical adverse events (e.g. rash, diarrhea, dizziness).

Table 4I.2. Results Overview: Lipid lowering interventions in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Efficacy							
Statins versus placebo							
Muldoon, 2004 ¹⁹² Simvastatin 10 mg daily or Simvastatin 40 mg daily vs. placebo n = 308 6 month followup				C>I [composite executive/attention/pr ocessing speed 1] ^a	C>I [memory composite 1] NS [memory composite 2]	0 of 3 favored I 2 of 3 favored C	1 person with drew in active therapy due to stroke
Heart Protection Study, 2002 ¹⁹⁰ Simvastatin 40 mg daily vs. matching placebo n = 20,536 5 years mean followup	NS [reported number who developed dementia]		BCT NS [Telephone Interview for Cognitive Status] NS [Telephone Interview for Cognitive Status <22]			0 of 2 favored I	NS [hospitalizations]
Muldoon, 2000 ¹⁹¹ Lovastatin 20 mg daily vs. matching- placebo n = 209 6 months followup				C>I [composite measure of attention] ^b C>I [composite measure psychomotor speed]	NS [working memory composite] NS [memory recall composite]	0 of 4 favored I 2 of 4 favored C	NR
Santanello, 1997 ¹⁹⁴ lovastatin 20 mg daily vs. lovastatin 40 mg daily vs. placebo n = 431 6 months follow up				NS [Digit Symbol Substitution Test]		0 of 1 favored I	NS [number of events reported]
Statin vs Placebo Results Summary	0 of 1 favored I		BCT 0 of 2 favored I	0 of 4 favored I 3 of 4 favored C	0 of 4 favored I 1 of 4 favored C	0 of 10 favored I 4 of 10 favored C	
Statin Plus							

Ezetimibe Versus Placebo							
Tendolkar, 2012 ¹⁹⁵ Atorvastatin 20mg for 2 weeks then increased to 40mg, after 4 weeks ezetimibe 10mg was added. Standard anticoagulant therapy vs matching-placebo and standard anticoagulant therapy n = 34 1 year follow up		I>C [Left amygdala volume] NS [Right amygdala volume] NS [Left hippocampal volume] NS [Right hippocampal volume] NS [White matter lesion volume]	BCT [MMSE] ^c	I>C [Digit Symbol Substation]	NS [Dutch Modified version of the Rey Auditory Verbal Learning Immediate word recall] I>C [Dutch Modified version of the Rey Auditory Verbal Learning Delayed word recall]	2 of 9 favored I	NR
Statin Plus Ezetimibe Versus Placebo Results Summary		1 of 5 favored I	BCT 0 of 1 favored I	1 of 1 favored I	1 of 2 favored I	3 of 9 favored I	
Statin Plus Fenofibrate versus Statin plus placebo							
Willamson, 2014 ¹⁸³ (ACCORD-MIND Lipid trial) Statin plus Fenofibrate vs statin n = 1,538 40 months follow up			BCT NS [MMSE]	NS [Stroop Color-Word Test] NS [Digit Symbol Substitution Test]	NS [Rey Auditory Verbal Learning]	0 of 4 favored I	NR
Statin Plus Fenofibrate versus Statin Plus Placebo Results Summary			BCT 0 of 1 favored I	0 of 2 favored I	0 of 1 favored I	0 of 4 favored I	
Comparative Effectiveness							
Muldoon, 2004 ^{192d} Simvastatin 10 mg daily vs. Simvastatin 40 mg daily							1 person with drew in active therapy due to stroke

n = 189 6 month followup							
Carlsson, 2002¹⁴⁷ Pravastatin 20 mg daily vs. tocopherol 440 IU daily n = 41 6 month followup				NS [Digit Symbol Substitution Test]			NS [physical adverse events and hospitalizations]
Statin versus Statin Results Summary			BCT				

aMuldoon 2004¹⁹² evaluated composite measures. If the composite measure was significant then individual measures within the composite were tests. The test of the composite measures within the composite executive/attention/processing speed 1: NS [Digit Vigilance], C>I [Recurrent words], C>I [Elithorn Mazes]. The test of the composite measures within memory composite: NS[Mirror Tracking], C>I[4-word Memory]

b Muldoon 2000¹⁹¹ evaluated composite measures. If the composite measure was significant then individual measures within the composite were tests. The test of the composite measures within the attention composite: C>I [Digit Vigilance], C>I [Recurrent words], C>I [Elithorn Maze]

cTendolkar 2012¹⁹⁵ did not report between-group difference at follow up.

d Muldoon 2004¹⁹² compared simvastatin 10 mg versus simvastatin 40 mg. Not enough information was reported in the text to extract data. The authors comment on the comparison: “when the two active treatment groups (10 mg and 40mg) were compared to test for the presence of a dose response relation, we found that the 40-mg dose of simvastatin did not have greater effects on cognitive performance than the 10-mg dose (P >0.15)”

Adults with MCI

None of the studies were restricted to participants with MCI and none reported results for individuals with MCI.

Interpreting the Findings

Statins do not show evidence of improving or maintaining cognitive function. Results for cognitive performance were inconsistent across studies. The one instance of a positive effect was offset by other studies showing no effect in cognitive performance in statins versus placebo. Moreover, in another study the control group outperformed the intervention group in cognitive performance. Further, study followup was likely too short to observe clinically meaningful changes in cognition in the middle-aged and older and largely cognitively normal participants. Hence, statins do not appear to be a fruitful area for further study in the area of CATD prevention.

Chapter 4J. Results: Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Key Messages

- No evidence was available for the effect of low-dose aspirin on MCI or clinical Alzheimer’s-type dementia (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 nonsteroidal anti-inflammatory drugs (NSAIDs), including both selective and nonselective cyclooxygenase-2 (COX-2) inhibitors, to reduce CATD incidence, and multidomain neuropsychological performance, or memory, with 8 years of use.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified seven eligible publications reporting four unique studies of NSAIDs to prevent age-related cognitive decline, MCI, or CATD.²⁰¹⁻²⁰⁷ Two were assessed as high risk of bias and were not used in our analysis.^{206,207} We separately analyzed the efficacy of NSAID interventions for adults with normal cognition and those with MCI. Appendix O provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of NSAIDs

Numerous epidemiological studies have shown an association between NSAID use and a reduced prevalence of dementia, specifically Alzheimer’s disease.²⁰⁸ The brains of those with Alzheimer’s disease have abundant amyloid plaque, which is associated with an inflammatory reaction and related neurodegeneration. In vitro and animal models of Alzheimer’s disease pathology show that NSAIDs reduce plaque-related inflammation and improve function, both at a cellular and behavioral level.

Adults With Normal Cognition

NSAIDs Versus Placebo

Two RCTs in five publications with low to medium risk of bias enrolling a total of 8,905 adults compared NSAIDs to placebo in adults with normal cognition.²⁰¹⁻²⁰⁵ Total sample sizes ranged from 2,528 to 6,377. The results of these studies are summarized in Tables 4J.1 and 4J.2.

Table 4J.1. Conclusions: NSAIDs in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Aspirin vs. placebo	Dementia	No data	Insufficient (no data)
	MCI	No data	Insufficient (no data)
	Brief Cognitive Test	No benefit in brief cognitive test performance	Low (medium study limitations,

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
	Performance	with aspirin versus placebo in long term (n=6,377; 10 years).	indirect, precise, unknown consistency)
	Multidomain Neuropsychological Performance	No benefit in multidomain neuropsychological performance with aspirin versus placebo in long term (n=6,377; 10 years).	Low (medium study limitations, indirect, precise, unknown consistency)
	Executive/Attention/Processing Speed	No data	Insufficient (no data)
	Memory	No benefit in memory with aspirin versus placebo in long term (n=6,377; 10 years).	Low (medium study limitations, indirect, precise, unknown consistency)
Non-aspirin NSAIDs vs. placebo	Dementia	No significant difference in dementia diagnosis with celecoxib/naproxen versus placebo in long term (n=2,117; 8 years).	Low (medium study limitations, direct, precise, unknown consistency)
	MCI	No data	Insufficient (no data)
	Brief Cognitive Test Performance	No benefit in brief cognitive test performance with celecoxib/naproxen versus placebo in long term (n=2,117; 8 years).	Low (medium study limitations, indirect, precise, unknown consistency)
	Multidomain Neuropsychological Performance	No benefit in multidomain neuropsychological performance with celecoxib/naproxen versus placebo in long term (n=2,117; 8 years).	Low (medium study limitations, indirect, precise, unknown consistency)
	Executive/Attention/Processing Speed	No benefit in executive/attention/processing speed with celecoxib/naproxen versus placebo in long term (n=2,117; 8 years).	Low (medium study limitations, indirect, imprecise, consistent)
	Memory	No benefit in memory with celecoxib/naproxen versus placebo in long term (n=2,117; 8 years).	Low (medium study limitations, indirect, imprecise, consistent)

One trial (n=6,377) compared aspirin (100 mg every other day) to placebo.²⁰⁵ Subjects were drawn from a pool of 39,876 participants in the Women’s Health Study, which enrolled healthy women age 45 and over from 1992 to 1995. Participants completed an initial cognitive assessment by telephone at an average of 5.6 years after randomization; but there was no baseline assessment. The primary outcome was a global score averaging performance across a battery of cognitive tests, and the key secondary outcome was a score averaging four measures of verbal memory. The sample provided at least 80 percent power to detect a modest relative risk of 0.76 in aspirin compared with placebo. The trial reported brief cognitive test performance, multidomain neuropsychological performance, and memory at 10-year followup. No benefit was found for any outcome.

The ADAPT trial (n=2,528) was specifically designed to test the hypothesis that NSAIDs, either selective (celecoxib) or nonselective (naproxen) cyclooxygenase-2 inhibitors, would work for the primary prevention of CATD.²⁰¹⁻²⁰⁴ The trial had three arms comparing celecoxib (200 mg twice daily) or naproxen (220 mg twice daily) with placebo.

The ADAPT trial reported CATD diagnosis at 8-year followup, and brief cognitive test performance, multidomain neuropsychological performance, executive/attention/ processing speed, and memory at 4-year followup. No benefit was found for any outcome.

Adults with MCI

The only eligible study had a high risk of bias.²⁰⁶

Interpreting the Findings

Despite the compelling epidemiological data and strong pathophysiological rationale, no evidence shows that NSAIDs prevent CATD adults with normal cognition.

Table 4J.2. Results Overview: NSAIDs versus placebo in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/ Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Aspirin Efficacy						
Kang 2007 ²⁰⁵ Aspirin vs placebo n=6,377 10 years		BCT NS [TICS] MNP NS [Composite ¹]		NS [Composite ²]	0 of 3 (no difference)	NR
Aspirin Results Summary		BCT 0 of 1 (no difference) MNP 0 of 1 (no difference)		0 of 1 (no difference)	0 of 3 (no difference)	
Non-aspirin NSAIDs Efficacy						
ADAPT ²⁰¹⁻²⁰⁴ Celecoxib or naproxen vs placebo n=2,117 8 years (diagnosis) 4 years (brief cognitive test performance, multidomain neuropsychological performance, executive/ attention/processing speed, memory)	Celecoxib: NS Naproxen: NS [CATD]	BCT Celecoxib: NS Naproxen: NS [3MS] MNP Celecoxib: NS Naproxen: NS [Composite ³]	Celecoxib: NS Naproxen: NS [Digit Span Forward] Celecoxib: NS Naproxen: NS [Digit Span Backward]	Celecoxib: NS Naproxen: NS [Hopkins Verbal Learning Test] Celecoxib: NS Naproxen: NS [Rivermead Behavioral Memory Test] Celecoxib: NS Naproxen: NS [Brief Visuospatial Memory Test- Revised]	0 of 16 (no difference)	Study discontinued due to increased cardiovascular risk from celecoxib
NSAIDs Results Summary	0 of 2 (no difference)	BCT 0 of 2 (no difference)	0 of 4 (no difference)	0 of 6 (no difference)	0 of 16 (no difference)	

		MNP 0 of 2 (no difference)				
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¹TICS, category fluency, 10 words list (immediate and delayed recall), East Boston Memory Test; ²10 words list (immediate and delayed recall), East Boston Memory Test;

³Hopkins Verbal Learning Test-Revised, informant-rated Dementia Severity Rating Scale, Digit Span, Naming supermarkets, Rivermead Behavioral Memory Test

3MS=Modified Mini-Mental State Examination; C=inactive control; DSST=Digit Symbol Substitution Test; DSy=Digit Symbol Coding; HVLt-R=Hopkins Verbal Learning Test;

I=intervention; I=intervention; NS=no statistically significant difference; QAD=every other day; RAVLT=Rey Auditory Verbal Learning Test; Stroop=Modified Stroop

Chapter 4K. Results: Antidementia Drugs

Key Messages

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

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified 12 eligible publications involving 10 unique studies of antidementia drugs to prevent age-related cognitive decline, MCI, or CATD.^{157,209-219} All but two were assessed as high risk of bias and not used in our analysis. Interventions used in the studies included in the analysis were all AChEIs. We analyzed the efficacy of these drugs for adults with normal cognition and those with MCI separately. Appendix P provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Antidementia Drugs

The AChEIs (donepezil, galantamine, and rivastigmine) have consistently demonstrated a modest but positive benefit to cognition in persons with CATD from mild through severe stages. They may likewise provide benefit to persons with age-related cognitive decline or MCI through the same mechanisms of action by increasing the duration of action of acetylcholine in the synapse through inhibition of its breakdown by acetylcholinesterase. The drugs have been approved by the Federal Drug Administration for people with mild to moderate Alzheimer's Disease but not for people with age-related cognitive decline or MCI.

Adults with Normal Cognition

We identified one study evaluating the use of antidementia medications versus placebo. The individual study results are in Table 4K.1. In this small RCT of middle-aged menopausal women with subjective complaints of cognitive loss, donepezil had no effect on a variety of objective cognitive outcomes, at 26 weeks.²⁰⁹ The study did not show cognitive benefits in persons with normal cognition compared with placebo. No conclusion table is provided given evidence was insufficient due to limited data (single study with n<500).

Table 4K.1. Results Overview: Antidementia medication in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Antidementia medication vs. placebo							
Devi 2007²⁰⁹ Donepezil 5mg/d (6 weeks), then 10mg/d vs. Placebo n=28 26 weeks				NS [COWA]	NS [WMS-III, Logical Memory]	0 of 4 (no difference)	NR
				NS [WMS-III, Working Memory]	NS [Buschke, list learning]		
Donepezil vs. Placebo Results Summary				0 of 2 (no difference)	0 of 2 (no difference)	0 of 4 (no differences)	

C=placebo/control; COWA=Controlled Oral Word Association; I=intervention; NS=no statistically significant difference; WMS=Wechsler Memory Scale

Adults with MCI

We identified 10 eligible publications reporting eight unique studies of antedementia drug interventions versus placebo to prevent cognitive decline in adults with MCI.^{157,210,211,213-219} All but one were assessed as high risk of bias and not used in our analysis. Appendix P provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes. Conclusions are summarized in Table 4K.2 and individual study results in Table 4K.3.

Table 4K.2. Conclusions: Antedementia medications in adults with MCI

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Antedementia medication vs. placebo	Dementia	No statistically significant difference in dementia diagnoses with donepezil versus placebo (n=769, 3 years)	Low (medium study limitations, imprecise, unknown consistency)
	MCI	NR	
	Biomarkers	No data	Insufficient (no data)
	Brief cognitive test performance	No statistically significant difference in brief cognitive test performance with donepezil versus placebo (n=769, 3 years)	Low (medium study limitations, imprecise, unknown consistency)
	Multidomain neuropsychological performance	No statistically significant difference in multidomain neuropsychological performance with donepezil versus placebo (n=769, 3 years)	Low (medium study limitations, imprecise, unknown consistency)
	Executive/Attention/Processing Speed	No statistically significant difference in executive function/attention/processing speed with donepezil versus placebo (n=769, 3 years)	Low (medium study limitations, imprecise, unknown consistency)
	Memory	No statistically significant difference in memory with donepezil versus placebo (n=769, 3 years)	Low (medium study limitations, imprecise, unknown consistency)

One RCT (n=769) with moderate risk of bias compared donepezil to placebo in adults with MCI.¹⁵⁷ Petersen et al. found low-strength evidence that donepezil reduced the likelihood of progression to dementia at 1 year but not at 3 years.¹⁵⁷

Petersen et al. also assessed cognition with a brief test of cognitive performance (MMSE), 2 tests of multidomain neuropsychological performance, 1 test of executive function/attention/processing speed and a memory composite.¹⁵⁷ Donepezil performed better than placebo on the MMSE for the first 2 years and on 2 cognitive test composites (1 related to executive/attention/processing speed and the other related to memory) until 18 months, after which there were no differences between groups. No other differences between groups were observed. ApoE4 carriers on donepezil had a reduced likelihood of progression to dementia throughout the 3-year study.

Interpreting the Findings

The slim set of included studies with low to medium risk of bias provides no suggestion of a significant benefit of AChEIs in preventing cognitive decline in persons with MCI. At most, there may be a modest delay in decline. There are even fewer data available to assess the effects of AChEIs in persons with normal cognition; the strength of evidence was insufficient to conclude whether these drugs offer any benefits.

Several large RCTs with high risk of bias were not used in analysis, but came to the same conclusion: there was no significant benefit of antedementia drugs on the progression of MCI to

CATD, biomarkers, or on overall cognitive function. Apparently since an earlier, 3-year trial of donepezil (which showed no effects after 3 years) had shown a positive effect at 1 year,¹⁵⁷ donepezil was studied again in a 1-year RCT.²¹⁰ Instead of conversion to CATD, the primary outcomes were the modified ADAS-Cog and CDR-sum of the boxes (CDR-SB). This dual primary efficacy endpoint was not reached, though a small but significant decrease (improvement) in the modified ADAS-Cog was seen. A 2-year RCT employing galantamine to prevent dementia^{215,219} concluded that galantamine failed to significantly influence conversion to dementia. Similarly, a 2-year RCT examining the use of rivastigmine in people with MCI found no significant benefit on rate of progression to AD or on cognitive function over 4 years.²¹¹

Several high risk of bias studies examined biomarkers in people with MCI. A 2-year study of galantamine (n=364) found lower rates of brain atrophy in those taking galantamine, but no difference between galantamine and placebo groups in rate of hippocampal atrophy.^{215,219} Similarly, data collected as part of the 1 year trial of donepezil in MCI revealed no significant difference in the primary outcome of annualized percentage change (APC) in hippocampal volumes²¹⁰ but a significant differences favoring drug (less volume loss) in the secondary outcome of APC in whole brain volumes.²¹⁸ While hippocampal volume loss/atrophy is associated with MCI and progression to CATD, the significance of whole brain changes are less obvious, particularly given the negative clinical results of both trials. Whole brain atrophy is seen in Alzheimer's disease, particularly in the later stages. However, inflammation associated with amyloid plaque is felt by many to be important to the pathophysiology of dementia, and plaque is widely distributed, even in pre-clinical dementia. Were treatment aimed at reducing inflammation, a decrease in whole brain volume might be an expected positive biomarker.

Table 4K.3. Results Overview: antideementia medications in adults with MCI

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance & Multidomain neuropsychological performance	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Antideementia Medication vs. Placebo							
Petersen 2005 ¹⁵⁷ Donepezil 5mg/d (6 weeks), then 10mg/d vs. Placebo n=769 3 years	I>C at 6 & 12 mo, then NS [Clinical Criteria]		BCT I>C until 2 years, then NS [MMSE]	NS [Composite]	I>C at 6 and 18 mo, then NS [Composite]	0 of 5 (no difference at 3 years)	NS [mortality]
			MNP NS [ADAS-Cog-original]				
			MNP I>C until 18 mo, then NS [ADAS-Cog modified]				
Donepezil Efficacy Results Summary	0 of 1 (no difference)	NR	BCT 0 of 1 (no difference at 3 years) MNP 0 of 2 (no difference at 3 years)	0 of 1 (no difference)	0 of 1 (no difference)	0 of 5 (no difference at 3 years)	
Galantamine Efficacy							
Prins 2014 ²¹⁵ Galantamine vs. Placebo n=364 2 years		I>C [whole brain atrophy]				1 of 2 favors I	NR
		NS [hippocampal atrophy]					
Galantamine Efficacy Results Summary		1 of 2 favors I				1 of 2 favors I	

3MS=Modified Mini-Mental State Examination; C=inactive control; DSST=Digit Symbol Substitution Test; DSy=Digit Symbol Coding; HVLt-R=Hopkins Verbal Learning Test; I=intervention; I=intervention; NS=no statistically significant difference; QAD=every other day; RAVLT=Rey Auditory Verbal Learning Test; Stroop=Modified Stroop

Chapter 4L. Results: Diabetes Medication Treatment

Key Messages

- No studies reported on the effect of diabetes treatment on the risk of incident clinical diagnoses of MCI or clinical Alzheimer's-type dementia (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.

*Note that the literature currently does not use the term CATD; we specified whenever the diagnosis of dementia was defined.

Eligible Studies

We identified seven eligible studies that compared diabetes medication treatment versus control treatment to prevent age-related cognitive decline, MCI, or CATD.^{56,95,220-224} We rated three of these studies as having high risk of bias and excluded them from our analyses.^{220,221,223} The remaining four studies (three unique trials) enrolled a total of 15,592 adults.^{56,95,222,224} Appendix Q provides evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Logic of Diabetes Medication Treatment

A recent meta-analysis of prospective cohort studies estimated that the presence of a diabetes diagnosis between the ages of 20 to 79 years increased the risk of incident CATD by nearly 50 percent.²²⁵ Diabetes may increase risk of Alzheimer's disease through vascular mechanisms, direct effects of elevated blood glucose, insulin resistance associated inflammation, and/or a pathway in which peripheral hyperinsulinemia inhibits brain insulin production, which then results in impaired brain amyloid clearance.¹⁸⁹

Adults with Normal Cognition

Two trials addressed persons with presumed normal cognition but only the ACCORD-MIND study specifically reported excluding subjects with preexisting clinical evidence of dementia.²²⁶ Both trials addressed persons at high risk for cardiovascular events; both compared intensive and standard glucose control for diabetics. Both were large substudies. The ACCORD-MIND trial enrolled 2977 older adults.^{222,224} The ORIGIN study randomized 12,537 older adults.²²⁷ It provided no information about how normal cognition was defined and did not report any cognition-related exclusion criteria. Conclusions are reported in Table 4L.1 and individual study results in Table 4L.2.

Table 4L.1. Conclusions: Antidiabetic intervention in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Glycemic control vs. placebo	Dementia	No statistically significant difference in dementia diagnoses with glycemic control versus placebo (n=12,537, 6 years)	Low (due to study limitation of composite outcome with component of unequal importance, one of which is not clinical diagnosis and may be achieved due to chance)
	MCI	No data	Insufficient (no data)
	Biomarkers	Data not sufficient to draw conclusion.	Insufficient (indirect, inconsistent)
	Brief cognitive test performance	A 40 month trial and a six year trial found no statistically significant differences in brief cognitive test performance in glycemic control versus placebo (n=15,514, up to 6 years)	Low (indirect, imprecise)
	Multidomain neuropsychological performance	No data	Insufficient (no data)
	Executive/Attention/Processing Speed	A 40 month trial and a six year trial found no statistically significant difference in executive function, attention, and processing speed with glycemic control versus placebo (n=15,514, up to 6 years)	Low (indirect, imprecise)
Memory	A 40 month trial found no statistically significant difference in memory with glycemic control versus placebo (n=2,977, 3.3 years)	Low (indirect, imprecise)	

No study reported the outcomes of incident clinically diagnosed MCI or dementia. The ORIGIN trial found no difference after a mean followup of 6.2 years in the risk of probable incident cognitive impairment as defined by either a diagnosis of dementia on the study case report forms or a decline in followup MMSE.⁹⁵ However, the overall ORIGIN trial reported little difference in mean HbA1C at 6 years between the intensive and standard control groups.²²⁷

Low-strength evidence from both trials shows no difference in change in cognitive performance between those assigned to intensive versus standard glycemic control. In the ACCORD-MIND trial, over a 40-month followup there was no difference between the groups in the mean decline in MMSE, a global measure of cognition.^{222,224} Similarly, in the ORIGIN trial, over a mean followup of 6.2 years, there was no between-group difference in the mean annualized MMSE decline.⁹⁵ Within specific cognitive domains, these trials reported no statistically significant difference between treatment groups for change in verbal memory,²²² executive function,^{95,224} attention,²²² or processing speed.^{95,222,224}

The ACCORD-MIND trial enrolled participants with normal cognition and measured brain MRI in a subset of participants.²²² Among the 503 participants with followup MRIs at 40 months, those randomized to intensive glycemic control had significantly smaller declines in total brain volume, but significantly more abnormal white matter tissue volume.

The ACCORD-MIND trial reported no difference between the intensive and standard glycemic control groups in risk of mortality.²²²

Table 4L.2. Results Overview: Antidiabetic interventions in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological test performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Glycemic control vs. placebo							
ACCORD-MIND Trial Seaquist 2013 ²²⁴ Laurer 2011 ²²² Intensive glycemic control targeting HbA1c to less than 6.0% vs. standard glycemic control targeting HbA1c to 7-7.9% n=2977 40 months		I>C [total brain volume]	BCT NS [MMSE]	NS [DSST]	NS [RAVLT]	1 of 6 favor I	NS [mortality] ¹
		C>I [abnormal white matter]		NS [Stroop Test]		1 of 6 favor C	
Cukierman-Yaffe 2014⁹⁵ Titrated basal insulin glargine targeting a fasting plasma glucose concentration vs. standard of care n=12537 72 months	NS [MMSE<24, or diagnosed on report forms]		BCT NS [MMSE]	NS [DSST]		0 of 3 (no difference)	NR
Glycemic control vs. placebo Results Summary	0 of 1 favor I	1 of 2 favor I 1 of 2 favor C	BCT 0 of 2 (no difference)	0 of 3 (no difference)	0 of 1 (no difference)		

¹In February, 2008, raised mortality risk in the main ACCORD study led to the end of the intensive treatment and a transition of those participants to standard treatment

C=placebo/control; DSST=Digit Symbol Substitution Test; I=intervention; MMSE=Mini-Mental State Examination; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test

Adults with MCI

Hildreth et al. randomized 78 older adults with MCI, central obesity (presumed to confer insulin resistance), and no diabetes to pioglitazone versus endurance exercise training or control (placebo, no exercise).⁵⁶ The trial was rated as having low risk of bias, but was likely too small to detect the small changes in cognitive outcomes that might realistically be expected in its MCI population over its 6 month duration, let alone differences in these outcomes between pioglitazone and control groups.

The trial reported no information on the outcome of the clinical diagnosis of dementia.⁵⁶ There was no difference in intervention and control groups in change between baseline and 6 months in a single global measure of cognition—the ADAS-Cog, nor in change in the cognitive domains of memory, language, visuospatial or executive function, or in change in the Stroop Color-Word Interference test, Digits Backward component of the Wechsler Adult Intelligence Scale-Revised Digit Span test, or Clock Drawing test. The trial did not report information on biomarker outcomes or adverse events. Individual study results are provided in Table 4L.3. No conclusion table is provided given evidence was insufficient due to limited data (single study with $n < 500$).

Interpreting the Findings

Because there was minimal or no change in cognitive performance tests from baseline among control group participants in the included studies, it was not possible for these studies to demonstrate whether intensive glycemic control prevents cognitive decline, though they more strongly suggested that it does not lead to clinically meaningful improvements in cognition from baseline. To the extent that the level of glycemic control is a mechanism affecting cognitive function, the small difference in glycemic control between treatment groups in the ORIGIN trial may have limited the ability of that study to observe a difference in cognitive outcomes. However, cognitive results also were not meaningfully different between treatment groups in the ACCORD-MIND trial despite the markedly improved glycemic control in their intervention group versus placebo group.

Table 4L.3. Results Overview: Antidiabetic medication in adults with MCI

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief Cognitive Test Performance/ Multidomain Neuropsychological Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Antidiabetic medication vs. placebo							
Hildreth 2015⁵⁶ Pioglitazone 30mg daily for 1 month, then 45mg daily as tolerated for 5 months vs. Placebo n=78 6 months			MNP NS [ADAS-cog]	NS [Stroop Test]	NS [RAVLT]	1 of 10 (no difference)	NR (there were no cases of new or worsening heart failure in the treatment group)
				NS [Trail Making Test B]	NS [Logical Memory II]		
				NS [Digit Span Backwards]	NS [Composite]		
				NS [Digit Symbol Test]	I>C [Visual Reproduction]		
				NS [Composite]			
Antidementia medication vs. placebo Results Summary			MNP 0 of 1 (no difference)	0 of 5 (no difference)	1 of 4 (no difference)		

C=placebo/control; I=intervention; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test

Chapter 4M. Results: Other Interventions

Key Messages

- Other interventions that have been explored include lithium, a nicotine patch, individual piano instruction, multitask exercise to music, sleep interventions, and social engagement.
- Evidence on each of these interventions is insufficient.
- We found no relevant studies for depression treatments, smoking cessation, or community-level interventions.

Eligible Studies

We identified eight eligible studies of other varied interventions to prevent age-related cognitive decline, MCI, or CATD.^{61, 75, 112, 228-232} Four studies four adults with normal cognition^{61, 228-230} and one for adults with MCI⁷⁵ were assessed as high risk of bias and thus are discussed only briefly. Appendix R provides evidence tables and summary risk of bias assessments.

Adults with Normal Cognition

Hars et al. (n=134) examined the effects of a weekly 1 hour supervised group class in which participants performed multitask exercises to rhythmic music versus inactive control in adults ≥ 65 years who were at increased risk of falling. After 6 months, no significant differences in MMSE scores or executive function were observed.¹¹² Adverse events were not reported. Table 4M.1 summaries results. A conclusion table is not provided since evidence was insufficient due to limited data (single study n<500).

The remaining four studies with adults with normal cognition were high risk of bias. Interventions examined in these studies included: individualized piano instruction for musically naïve older adults (n=31, 9 month followup);²³⁰ personalized sleep plans to extend sleep for obese adults who sleep for shorter periods (n=121, 14 month followup);²²⁸ guided progressive muscle relaxation tapes to improve sleep in older adults with reduced sleep quality (n=80, 12 months);²²⁹ and group social interaction for 1 hour three times per week at a neighborhood community center for older adults (n=276, 40 weeks).⁶¹

Adults with MCI

Table 4M.2 summarizes results for two medium risk of bias studies of adults with MCI. A conclusion table is not provided since evidence was insufficient due to limited data (single study n<500).

Forlenza et al. (n=45) examined the effects of lithium versus placebo in adults at least 60 years old with amnesic MCI as assessed by the Mayo criteria.²³¹ Dosage was titrated to a level below that used for affective disorders to avoid problems of tolerability. No difference in conversion to AD was found after 12 months. The lithium group showed improvement in amyloid-beta and phosphorylated tau but not total tau when compared to placebo. The study found no severe adverse events deemed related to the treatment.

Newhouse et al. (n=74) examined the effects of transdermal nicotine patches in non-smoking adults at least 55 years old with probable MCI.²³² Numerous cognitive performance tests were assessed as secondary outcomes at 6 months, however not all outcomes were reported as tests of

differences between groups, so the possibility of selective outcome reporting was high.²³² The study found no severe adverse events deemed related to the treatment.

One other study with high risk of bias examined cognitive group social interaction (board games, reading/discussing newspapers) at least three times per week for 1 hour in adults with MCI (n=276, 12 months).⁷⁵

Table 4M.1. Results Overview: Other intervention in adults with normal cognition

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsychological performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Music intervention vs. inactive control							
Hars 2014¹¹² Weekly 1 hour supervised group class; multitask exercises to rhythm n=134 6 months			BCT NS [MMSE]	NS [Clock drawing test] NS [Frontal assessment battery]			NR
Music intervention vs. inactive control Results Summary			BCT 0 of 1 (no difference)	0 of 2 (no difference)			

BCT=brief cognitive test performance; C=placebo/control; I=intervention; NS=no statistically significant difference;

Table 4M.2. Results Overview: Other intervention in adults with MCI

Author Year Comparison N= Followup	Diagnosis	Biomarkers [specific biomarker]	Brief cognitive test performance/ Multidomain neuropsycholog ical performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Other medications vs. inactive control							
Newhouse 2012 ²³² Ncotine patch 15 mg/day vs placebo n=67 6 months				Selective outcome reporting			NS [no severe AEs classified as related to drug treatment]
Forlenza 2011 ²³¹ Lithium titrated to serum levels 0.25- 0.5 mmol/l vs placebo n=41 12 months	NS [Convert to probable AD]	I>C [Amyloid-beta] NS [Total tau] I>C [Phosphorylated tau]					NS [ischemic stroke, death due to sepsis; neither deemed due to treatment]
Other medications vs. inactive control Results Summary	0 of 1 (no difference)	2 of 3 favors I		Unclear			

C=placebo/control; COWA=Controlled Oral Word Association; I=intervention; NS=no statistically significant difference; WMS=Wechsler Memory Scale

Chapter 4N. Results: Agreement of Biomarkers and Measures of Cognitive Performance

Key Messages

- Only a few studies used biomarkers; most of those used some form of brain scan.
- The overall rate of agreement between biomarkers and cognitive testing was 61 percent but 80 percent of that agreement resulted from both approaches showing no effect. In eight out of 33 instances (24 percent) when the biomarker showed a significant result, there was agreement with a cognitive test.

Association Between Biomarkers and Cognitive Tests

Substantial work has gone into searching for biomarkers in living persons that indicate the level of dementia activity.²³³ In most cases, the biomarkers are validated by comparing them with a systematic clinical evaluation, but in some cases the biomarkers may predict subsequent development of cognitive decline.

KQ3 compares the biomarkers results with cognitive testing results in the studies used for KQs 1 and 2. No study with biomarkers also included incidence of MCI or clinical Alzheimer's-type dementia. Table 4N.1 summarizes those comparisons. We used a simple calculation of agreement rates between each biomarker and the tests used in a domain to distinguish differences between experimental and control subjects. Only a small number of studies used both biomarkers and cognitive testing. A few studies used only biomarkers (and are omitted from this comparison). Few studies used the same biomarker. The biomarkers used here were all based on brain scans (MRI or PET).

The overall rate of agreement was 61 percent (40/65) but much of that agreement (32/40) occurred when both the biomarker and the cognitive tests showed no significant effect. In the 33 instances when the biomarker showed a significant difference, there was agreement with a cognitive test eight times (24 percent). However, there were no instances where all measures (biomarkers and cognitive tests) from a given study were not significant. The ability to detect a difference somewhere in the study suggests that lack of statistically significant findings was not solely attributable to small sample sizes. Nonetheless, interpreting the implications of agreement when both approaches failed to detect a difference is challenging.

Table 4N.1 shows the rate of agreement between a given biomarker and the cognitive domains that were simultaneously tested. For example, in three studies of omega-3 fatty acids grey matter volume was found to be decreased in those receiving the intervention compared to the controls. In one instance (executive attention) the cognitive test showed a similar pattern. In another (memory) it did not. Hence the rate of agreement for a finding of biomarker difference in this case was 1/2. When the grey matter volume showed no difference in one study of in adults receiving resveratrol, cognitive performance showed a difference. Hence the agreement rate was 0/1.

Table 4N.1. Summary of agreement between biomarkers and cognitive tests

Biomarker	Overall Results					Agreement Rate	Intervention
	Biomarkers	Diagnosis	Dementia screens	Executive/Attention/ Processing Speed	Memory		
MRI-grey matter volume	I>C			I>C	NS	1/2	Omega 3 ⁹²
	NS				I>C	0/1	Resveratrol ⁹³
MRI- white matter integrity	NS			I>C	NS	1/2	Omega 3 ⁹²
MRI-HC microstructure	NS				I>C	0/1	Resveratrol ⁹³
MRI-HC frontal	I>C				I>C	1/1	
MRI-HC parietal	I>C				I>C	1/1	
MRI-HC occipital	I>C				I>C	1/1	
MRI-total brain volume	NS	C>I	C>I	NS	NS	2/4	Estrogen ^{135, 136, 138, 234}
	NS	C>I	NS	NS	C>I	2/4	Estrogen+ progestin ^{117, 135-137}
	I>C		NS	NS	NS	0/3	Glycemic control ^{222, 224}
MRI-ventricular volume	NS	C>I	C>I	NS	NS	2/4	Estrogen ^{135, 136, 138, 234}
	NS	C>I	NS	NS	C>I	2/4	Estrogen + progestin ^{117, 135-137}
MRI-HC volume	NS	C>I	C>I	NS	NS	2/4	Estrogen ^{117, 135-137}
	NS	C>I	NS	NS	C>I	2/4	Estrogen+ progestin ^{117, 135-137}
Left HC volume	NS			I>C	NS, I>C	1/3	Statins ¹⁹⁵
Right HC volume	NS			I>C	NS, I>C	1/3	
MRI-frontal lobe volume	C>I	C>I	C>I	NS	NS	2/4	Estrogen ^{117, 135-137}
	NS	C>I	NS	NS	C>I	2/4	Estrogen+ progestin ^{117, 135-137}
White and grey matter	NS	C>I	C>I	NS	NS	2/4	Estrogen ^{222, 224}
	NS	C>I	NS	NS	C>I	2/4	Estrogen+ progestin ^{117, 135-137}
Basal ganglia	NS	C>I	C>I	NS	NS	2/4	Estrogen ^{117, 135-137}
	NS	C>I	NS	NS	C>I	2/4	Estrogen+ progestin ^{117, 135-137}
Total brain	NS	C>I	C>I	NS	NS	2/4	Estrogen ^{117, 135-137}

Biomarker	Overall Results					Agreement Rate	Intervention
	Biomarkers	Diagnosis	Dementia screens	Executive/Attention/ Processing Speed	Memory		
lesion volume	NS	C>I	NS	NS	C>I	2/4	Estrogen+ progestin ^{117, 135-137}
Posterior atrophy	I>C		NS		NS	0/2	Vitamin B ^{149 148, 161}
Left amygdala volume	I>C			I>C	NS, I>C	2/3	Statins ¹⁹⁵
Right amygdala volume	NS			I>C	NS, I>C	1/3	
White matter lesion volume	NS			I>C	NS, I>C	1/3	
Dorsolateral prefrontal activation	I>C		NS	NS	NS	0/3	Antidementia ²¹⁴
Ventrolateral prefrontal cortex activation	I>C		NS	NS	NS	0/3	
Glucose uptake (PET scan)	I>C		NS, I>C	NS	NS	1/3	Cognitive training Forster 2011 ⁴²
Amyloid-beta	I>C	NS				0/1	Lithium ²³¹
Phosphorylated tau at threonine	I>C	NS				0/1	
Total tau	NS	NS				1/1	
Overall agreement rate						40/65 (61%)	61%
Agreement based on both showing no significant pattern of effect (NS)						32/65 (49%)	
Agreement based on both showing the same pattern of effect						8/65 (12%)	

	Overall Results						
Biomarker	Biomarkers	Diagnosis	Dementia screens	Executive/Attention/Processing Speed	Memory	Agreement Rate	Intervention
Agreement rate when the biomarker showed a significant difference						8/33 (24%)	

C=control; HC = hippocampus; I=intervention; NS=not significant

Chapter 5. Discussion

Research on interventions to prevent or slow age-related cognitive decline, MCI, or clinical Alzheimer's-type dementia (CATD) has focused largely 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, and 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 slow 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 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 show no benefit to those receiving interventions compared to control groups. Three intervention classes show some positive results and seem the most promising for further study: cognitive training, physical activity, and vitamins.

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.

Dementia Incidence

Cognitive decline can be 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 on multiple cognitive domains, the more likely the intervention may 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 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 slow the onset of CATD.

Unfortunately for our review, the largest and longest study of prevention of cognitive decline, the ACTIVE trial, was designed to enhance and monitor changes in specific areas of cognitive performance, but not the incidence of CATD. Efforts to adapt the ACTIVE trial to this important outcome were challenging; there was substantial attrition and the CATD diagnosis measures were weak. The measures related to diagnosis of CATD were developed late in the study and relied on either simple clinical measures or reports from family about cognitive problems or institutionalization. The analyses used did not overcome these problems.

Other interventions do show some benefit in slowing dementia, although the results are mixed at best. What explains the variation in results? To help explore possible answers to this question,

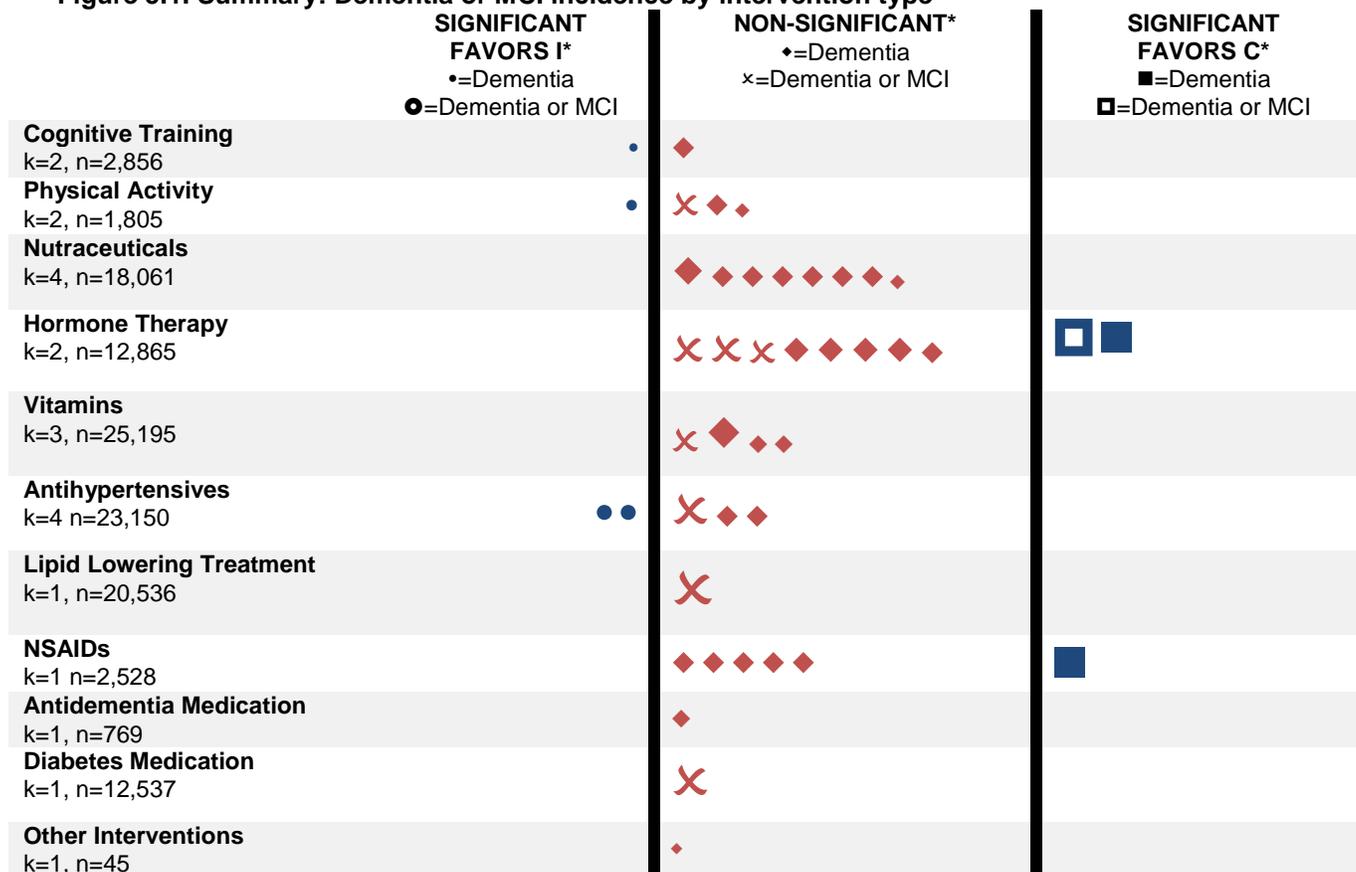
and later issues regarding the results for cognitive performance, we provide some summary figures that are intended to provide a bird's-eye view of the results detailed in the previous chapters. The figures do not provide detailed information on the specifics of the findings or the assessed strength of evidence. Instead, they show patterns of nonsignificant findings and significant findings that benefit either the intervention or the control groups. Table 5.1 provides a key to interpret the sample size from the symbol size. Different symbols are used to represent different outcomes in the figures. One symbol is assigned for every reported outcome; if a single study reported multiple outcome measures or tests for a give outcome, multiple symbols will be assigned. For example, if 3 different tests for memory were used by a single study, 3 symbols will be assigned to the memory category.

Table 5.1. Symbol sizes and related sample size information.

Symbol Sizes Used	Sample Sizes Represented
	N<100
	N=100-500
	N=501-1,000
	N=1,001-5,000
	N=5,001-10,000
	N=10,001-15,000
	N=15,000+

Figure 5.1 summarizes the findings on the range of interventions aimed at reducing the incidence of dementia or MCI. The preponderance of studies shows no effect. In some cases the controls did better than the experimental groups, especially in a few trials of antihypertensive treatment; but the positive results were outweighed by null findings.

Figure 5.1. Summary: Dementia or MCI incidence by intervention type



*Categorized by whether results showed statistically significant differences between groups. Each symbol represents a reported test result; as described in Table 5.1, size of symbol indicates the relative sample size for test. More than one test per domain was frequently used in any given trial.

I = intervention; C = control k = number of studies; n =sample size

Maintaining a long followup cohort is difficult, but important in any future research examining potential interventions that could slow or prevent dementia. In addition to long followup periods, studying the incidence of dementia requires that attrition be minimized. Attrition bias presents challenges similar to those associated with selection bias. However, with attrition, investigators have more information about the dropouts, and those data could permit better modelling to assess its potential impact. Subjects who drop out because of functional reasons should be evaluated for cognitive status. Death will play a censoring role, but analyses can explore its role in attrition bias because a larger pool of variables is available for modeling. The rate of dementia incidence will increase with age. Starting with an older cohort will facilitate accumulating cases with less attrition, but it will make it more difficult to ascertain the relationship between the intervention and subject age.

Cognitive Performance

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 subjects. For the most part, the training had sustained effects on cognitive performance in the domain trained but there was little evidence of diffusion into other cognitive domains. There was an effort to assess the effects of booster training, but assignment to receive a booster was not random; subjects with high initial compliance received most of the boosters.

As shown in Figure 5.2, the ACTIVE study showed mixed effects. The positive results were in the training domain and one instance of spillover. The nonsignificant results were for domains not trained, showing generally a lack of diffusion across domains.

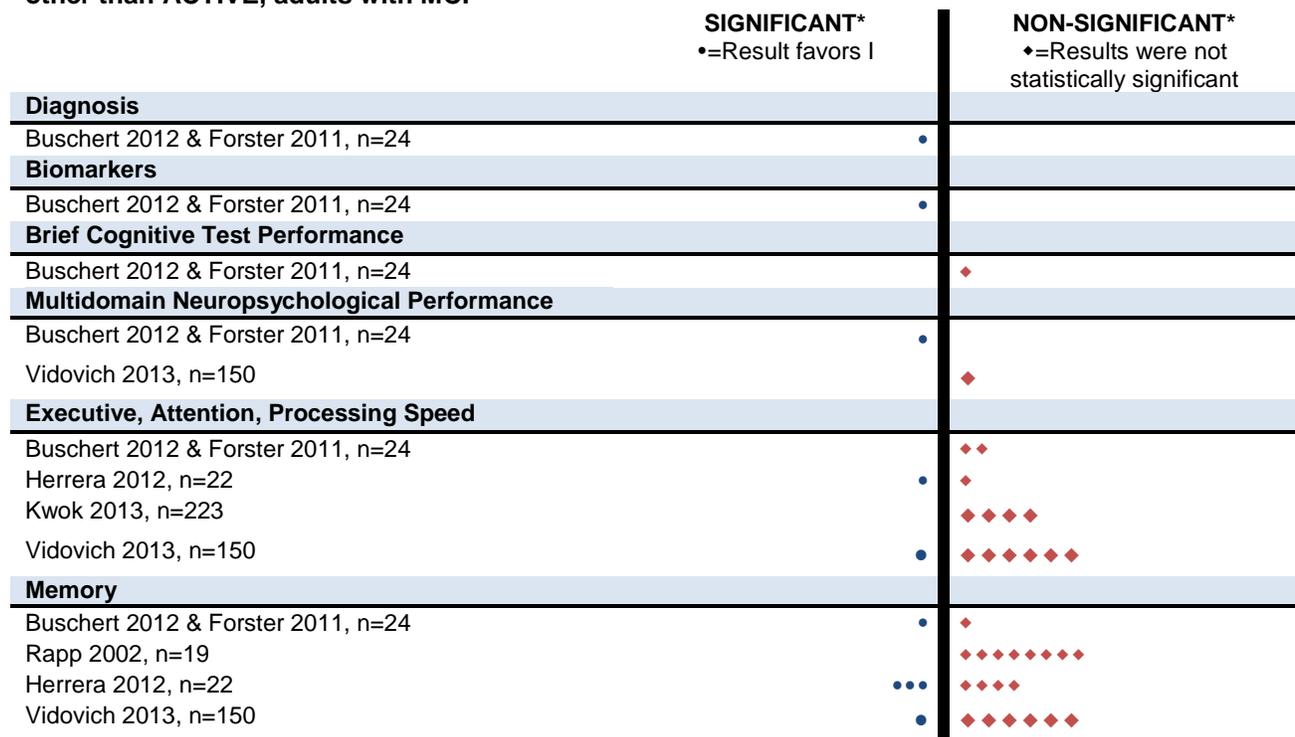
Figure 5.2. Summary of the tests of cognitive performance: results of ACTIVE trial

	SIGNIFICANT* •=Result favors I	NON-SIGNIFICANT* ◆=Results were not statistically significant
2-year Outcomes		
Ball 2002, n=2,832		
Memory Training	•	◆ ◆
Reasoning Training	•	◆ ◆
Speed of Processing Training	•	◆ ◆
5-year Outcomes		
Willis 2006, n=2,832		
Memory Training	•	◆ ◆
Reasoning Training	• •	◆
Speed of Processing Training	•	◆ ◆
10-year Outcomes		
Rebok 2014, n=2,832		
Memory Training		◆ ◆ ◆
Reasoning Training	•	◆ ◆
Speed of Processing Training	•	◆ ◆
Dementia Diagnosis (5-year)		
Unverzagt 2012, n=2,832		
		◆

*Categorized by whether results showed statistically significant differences between groups. Each symbol represents a reported test result; as described in Table 5.1, size of symbol indicates the relative sample size for test. More than one test per domain was frequently used in any given trial. The nonsignificant results were for domains not trained, showing generally a lack of diffusion across domains.

I = intervention; C = control k = number of studies; n =sample size

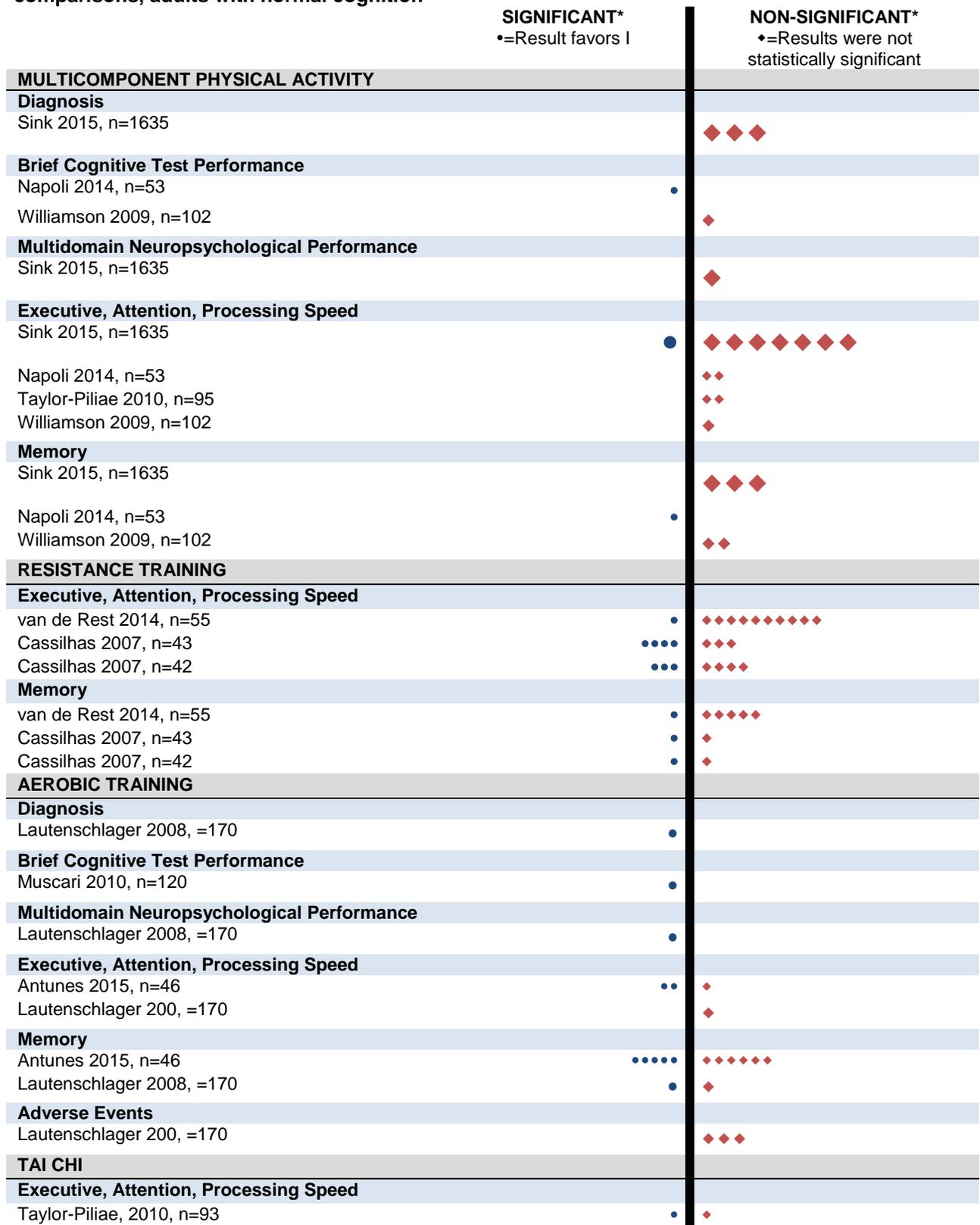
Figure 5.4. Summary of the tests of cognitive performance from additional cognitive training trials other than ACTIVE, adults with MCI



*Categorized by whether results showed statistically significant differences between groups. Each symbol represents a reported test result; as described in Table 5.1, size of symbol indicates the relative sample size for test. More than one test per domain was frequently used in any given trial. I = intervention; n =sample size

Aerobic training provided the highest proportion of significant positive results among physical activity interventions. As seen in Figure 5.5, 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 and raises questions about whether the effect is due to physical activity *per se*. Resistance training appears to have little in common with aerobic exercise, but studies of both have produced some positive results. The underlying logic linking exercise to cognitive function presumed some sort of physiological effect on blood supply or stimulation of naturally occurring chemicals. But the different types of exercise showing some effect causes us to reconsider the underlying mechanisms. For example, could the effect lie in some form of socialization associated with the exercise, which could also explain positive effects of group-based cognitive training, but not similar training done alone? None of the interventions shows an overwhelming or consistent effect, but one cannot ignore the positive results. Aerobic training appears to offer the greatest promise for further research of the effects of physical activity.

Figure 5.5. Summary of the tests of cognitive performance for physical activity versus inactive comparisons, adults with normal cognition



*Categorized by whether results showed statistically significant differences between groups. As described in Table 5.1, each symbol represents a reported test result; size of symbol indicates the relative sample size for test. I = intervention; n =sample size

While the overall findings for the remaining interventions described in Chapters 4C through 4N showed little benefit, several studies of the treatment of hypertension showed improved cognitive functioning. Given that hypertension control is already an actively espoused goal for the treatment of cardiovascular disease, these positive outcomes can be viewed as a potential additional benefit from efforts to control blood pressure. However, it is not clear that the pathway to less cognitive decline is directly linked to blood pressure control. Ironically, if the hypertensive treatment lowered mortality, its benefits for dementia might be underestimated because of selective attrition.

Vitamin B also showed benefit in brief cognitive test performance, executive/attention/processing speed and memory; however, vitamin B₁₂ with omega-3 showed no effect. With this exception, vitamins had no 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 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 but none seemed to have been chosen on the basis of underlying vitamin deficiencies. In the case of B₁₂, oral treatment would likely not have worked on such participants because they typically suffer from malabsorption of this vitamin.

Methods Issues

For the vast majority of studies showing no significant effect, we need to separate the potential of small sample sizes from a true lack of effect. Ideally meta-analysis would make use of many small studies to show an overall pattern, but the populations, interventions, and outcomes assessed were heterogeneous. At best, the categories of cognitive performance were composed of different types of tests and aggregating across domains is not likely appropriate methodologically.

Although we cannot say with certainty that many interventions definitely have no effect, it seems unwise to prioritize future research in areas that show little promise, such as hormone replacement therapy, NSAIDs, statins, and antidiabetic treatment. The argument around antihypertensive treatment is different. Some studies showed benefit, but given the extant commitment to blood pressure reduction further studies of its role in preventing dementia should have lower priority than areas less endorsed currently. Applying strength of evidence criteria to largely negative studies poses challenges. The goal of rating strength of evidence is to assess the level of confidence in the findings. How comfortable can we be that the negative results would not be overturned with further research? Some of the core elements of strength of evidence are not as helpful for studies that show no effect. Effect size is obviously zero. We can look at risk of bias and consistency. Precision can be examined to some degree, but the crux of the problem is estimating the uncertainty of the Type 2 error. Studies that show no effect differ from non-inferiority studies, which compare effects of two interventions. Both require looking for Type 2 errors, which necessitates larger sample sizes than Type 1 errors.

A separate issue concerns the interpretation of small effect sizes. All but a few of the results showed small changes in scores expressed as a proportion of the score range. In some cases clinicians have determined what constitutes a clinically important difference, but these are typically cast in terms of a given patient's progress as opposed to the differences in means of study groups.

In deciding what studies warranted strength of evidence rating, we determined not to rate single studies that tested a specific intervention/outcome pair if the total sample was less than 500.

As shown in Table 5.2, these eliminations would have little potential effect on the pattern of findings.

Table 5.2. Findings from smaller single studies for which strength of evidence was not assessed, by intervention type

Interventions	Number of Findings without Strength of Evidence Rating; Finding Not Reported
Antidementia	0
Antidiabetic	0
Antihypertensive	0
Statins	0
NSAIDs	0
Hormone Therapies	3: 1 for healthy subjects NS; 2 for MCI—testosterone 1 of 14 tests favor I; soy 1 of 6 tests favors I
Vitamins	2 (both MCI)—vitamins E+C NS; vitamin B 2 of 6 tests favor I
Nutraceuticals	6: for healthy subjects Omega 3 (biomarkers) 1 of 2 favors I; resveratrol 5 of 15 tests favor I; plant sterols/stanols NS. For MCI Omega 3 4 of 9 favor I; ginkgo biloba diagnosis NS, executive function 2 of 2 favor I
Diet	3: for global cognition 1/1 favors I; for memory 2 studies NS
Physical Activity	Multicomponent Physical Activity multidomain composite 2 of 2 favor I; executive function 1 of 2 favor I; memory 1 of 2 favor I

In the text we comment on the studies with risk of bias that were not analyzed. Again, including them would not change the pattern of our findings.

Many limitations arose from the available literature on this topic. A large number of the eligible studies evaluating the effectiveness of interventions in preventing incidence of MCI or Alzheimer’s disease had relatively short durations and followups, although the expected latency period to reach clinical MCI and Alzheimer’s disease and even intermediate cognitive outcomes may be quite long in younger adult populations. Consequently, short-term studies may be inadequate to test effectiveness of interventions to prevent these outcomes. Studies with longer durations and followup may experience different rates of mortality and loss to followup between intervention and comparison subjects that result in biases in missing data and confound interpretation about the effectiveness of the interventions.

Cognitive outcomes were assessed with a wide array of neuropsychologic tests. Some studies tested effects using several different tests over several time periods without any correction for multiple comparisons. Additionally, many studies tested participants at intervals not considered adequate for repeated applications of those tests. Although the specific length of the re-test gap may vary with the test, many opportunities for practice effects occurred.

Types of Studies

This review was open to three types of studies:

1) Purposefully developed trials: trials designed to address slowing or preventing age-related cognitive decline, MCI, or CATD

2) Add-on trials: trials of an intervention originally targeted at another outcome (e.g., hypertension) to which a cognitive outcome was appended, and

3) Prospective cohort studies: studies that categorized but do not assign an intervention; these frequently relied on self-reported outcomes of the intervention’s impact if the studies used analytic tools to simulate quasi-experimental design and address selection bias.

In general, one might expect that the more stringent the design, the less often positive results were seen. The add-on studies (Type 2 above) frequently used less sophisticated measures and had

no baseline values. The cohort studies typically had vague measures of exposure to the intervention which was not randomly assigned and hence subject to confounding. The quality of the outcome measures varied.

Baseline cognitive status was not carefully ascertained. While some studies collected baseline cognitive function as part of their design, others paid much less attention. They typically described participants in vague terms such as “normal” or “presumed healthy.” In some cases subjects were described as having cognitive complaints but no diagnosis.

Value of Biomarkers

The evidence synthesis of biomarkers and measures of cognitive function introduces two important, related challenges. One is understanding the relationship between these outcomes and MCI or dementia incidence. Without a clear understanding this relationship, it is difficult to interpret findings from short-term studies reporting only biomarkers or cognitive performance.

Biomarkers may have two levels of correlation with more clinical outcomes.

- 1) They may simultaneously reflect the outcome of interest.
- 2) They may predict a subsequent change in the outcome interest.

The biomarkers we encountered were either used alone or in parallel with other outcomes. We limited our analysis of the agreement of biomarkers (primarily MRI and PET scans) to their ability to distinguish outcomes in experimental and control groups.

The role of biomarkers as intermediate outcomes is unclear. Our results show a low level of agreement between the biomarkers (which were primarily some form of brain scan) and various cognitive tests. The field of biomarkers is expanding rapidly. There has been growing concern about the analytic methodology in one of the more common types of biomarkers, functional MRI, related to frequent lack of adjustment for large numbers of comparisons.²³⁵ More needs to be known about their ability to predict the clinical course of persons with various levels of cognitive function.

Limitations

This review encountered several limitations. Certain limitations stemmed from the topic and our approach to address it. The outcomes of interest are inconsistently defined, while there are 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 (even forest plots) proved unwieldy to conduct. Instead we opted to simply show the proportion of tests. While it would be possible to create a standardized score for each cognitive performance test and ultimately for each domain, we would be concatenating summary measures; such a level of abstraction would likely diminish the value potentially gained from artificially increasing the sample sizes.

As noted earlier, assessing 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.

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.

Chapter 6. Conclusion

Table 6.1 provides a summary of the key messages from the chapters detailing intervention results. Of the 13 classes of interventions we examined, we found no high-strength evidence for any intervention to delay or prevent age-related cognitive decline, MCI, and/or clinical Alzheimer's-type dementia (CATD). A few specific interventions reached moderate-strength evidence for *no* benefit in cognitive performance: vitamin E in women; and ACE and thiazide versus placebo and ARBs versus placebo on specifically brief cognitive screening tests. A few intervention types show more potential than others at benefiting cognitive performance. These include cognitive training, physical activity, and vitamins B₁₂. Cognitive training reached moderate-strength evidence; i.e., that cognitive training can improve cognitive function in the domain trained at 2 years, but diffusion to other domains was rare.

It is important to note that not all risk factors of interest were addressed by sufficient literature 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.

Table 6.1 Summary of result chapter key messages

Intervention	Key Message
Cognitive Training	<ul style="list-style-type: none"> • 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 diffusion to other domains was rare. • Other than the ACTIVE trial, the few studies that examined CATD incidence (one study for adults with MCI) or patient-reported memory function (three for adults with MCI) showed mixed results.
Physical Activity Interventions	<ul style="list-style-type: none"> • Studies of physical activity interventions examined a wide variety of activities potentially targeting different pathways to affect cognition. • Low-strength evidence shows that neither multicomponent physical activity nor resistance training offers clear benefit in cognitive outcomes over attention control in adults with normal cognition. • While the majority of the results showed little to no effect for resistance training, there were several instances of improvement in cognitive outcomes for resistance training compared with attention control. • Low-strength evidence shows benefits in some cognitive domains with aerobic training interventions when compared to attention control in adults with normal cognition. • Evidence is insufficient to conclude whether physical activity prevents MCI or CATD incidence.
Nutraceutical Interventions	<ul style="list-style-type: none"> • Low-strength evidence suggests omega-3 fatty acids and ginkgo biloba did not improve CATD incidence or cognitive performance in adults with normal cognition. • Evidence is insufficient to conclude whether resveratrol or plant

	<p>sterol/stanol esters improved CATD incidence or cognitive performance in adults with normal cognition.</p> <ul style="list-style-type: none"> • Few studies examined the effects of nutraceuticals on adults with MCI.
Diet Interventions	<ul style="list-style-type: none"> • Evidence is insufficient to conclude whether protein supplementation or energy-deficit diets have an effect on cognitive performance or incidence of MCI or CATD.
Multimodal Interventions	<ul style="list-style-type: none"> • Evidence is insufficient to conclude whether most multimodal interventions offer benefit 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 certain cognitive performance outcomes (executive function, attention, and processing speed).
Hormone Therapy Interventions	<ul style="list-style-type: none"> • Overall, there were few statistically significant differences in cognitive outcomes between hormone therapy and placebo groups. • Low-strength evidence suggests that estrogen therapy may slightly increase the risk of probable dementia and MCI when the two diagnostic categories are examined together. • Low-strength evidence suggests that estrogen plus progestin therapy may slightly increase the risk of probable dementia.
Vitamin Interventions	<ul style="list-style-type: none"> • In adults with normal cognition, moderate-strength evidence shows no benefit in cognitive performance for vitamin E in women. • Low-strength evidence shows benefit for vitamin B versus placebo for executive/attention/processing speed, brief cognitive test performance, and memory even after 2-4 years of use. • Low-strength evidence shows no benefit in cognitive performance for multivitamins, vitamin B with omega-3, vitamin C (in women), vitamin D with calcium (in women), vitamin E(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.
Antihypertensive Treatment	<ul style="list-style-type: none"> • 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 ACE and thiazide versus placebo and ARBs versus placebo have no benefit on brief cognitive screening tests. • Low-strength evidence shows that intensive versus standard antihypertensive medication, appear to have no benefit on cognitive test performance. • Low-strength evidence shows that antihypertensive medication versus antihypertensive medication appear to have no benefit on cognitive test performance. • One trial found that a stepped multiple agent antihypertensive medication regimen reduced risk of dementia versus placebo 2-year and 3.9-year median followup, but three other trials found no effect of antihypertensive treatment on CATD incidence.
Lipid Lowering Treatment	<ul style="list-style-type: none"> • Due to limited data, 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 no benefit in brief cognitive test performance, executive/attention/processing speed, or memory for statin plus fenofibrate versus statin plus placebo in adults with normal cognition. • Low-strength evidence shows benefit in executive/attention/processing speed for statin versus placebo for the control group.
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	<ul style="list-style-type: none"> • 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,

	<p>or memory, even with 10 years of use.</p> <ul style="list-style-type: none"> • Low-strength evidence shows no benefit for NSAIDs, including both selective and nonselective cyclooxygenase-2 (COX-2) inhibitors, to reduce CATD incidence, and multidomain neuropsychological performance, or memory, with 8 years of use.
Antidementia Treatments	<ul style="list-style-type: none"> • Low-strength evidence shows acetylcholinesterase inhibitor (AChEI) antidementia drugs did not reduce the incidence of CATD in persons with MCI; evidence is insufficient for persons with normal cognition. • Low-strength evidence shows AChEI provide no significant effect on cognitive performance in adults with MCI.
Diabetes Medication Treatment	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Other interventions that have been explored include lithium, nicotine patch, individual piano instruction, multitask rhythmic exercise to music, sleep interventions, or social engagement. • Evidence on these interventions is insufficient. • We found no relevant studies for depression treatments, smoking cessation, or community-level interventions.
Agreement of Biomarkers and Measures of Cognitive Performance	<ul style="list-style-type: none"> • Only a few studies used biomarkers; most of those used some form of brain scan. • The overall rate of agreement between biomarkers and cognitive testing was 61 percent but 80 percent of that agreement resulted from both approaches showing no effect. In eight out of 33 instances (24 percent) when the biomarker showed a significant result, there was agreement with a cognitive test.

CATD=clinical Alzheimer's-type dementia; MCI=mild cognitive impairment

Chapter 7. Suggestions for Future Research

The ability to draw meaningful conclusions regarding interventions that can delay or slow age-related cognitive decline and prevent onset of MCI or clinical Alzheimer's-type dementia (CATD) is hampered by limitations in existing research. The bulk of the studies examined raise more questions than answers. Low-strength evidence in some areas may provide guidance as to the types of interventions that should be prioritized for further study. However, common problems with study design/methodology and measurement need to be rectified in future research if effective methods of preventing cognitive deterioration in older age are to be identified.

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. Priority should be given to interventions that already show some promise, most notably cognitive training and physical activity. Although it cannot be said with complete certainty that other types of interventions have no effect, work examining hormone replacement therapy, 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.

Study Design / Methodology

Trials should be designed *intentionally* to study methods of slowing and preventing age-related cognitive decline and MCI and CATD incidence. Many studies originally designed for other purposes have added cognitive measures post-hoc. These “add-on” trials frequently use less sophisticated measures, do not adequately evaluate baseline characteristics, and do not randomly assign subjects, all of which confounds data and limits 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, etc.) and whether outcomes are intended to detect a delay in cognitive decline or a reduction in dementia incidence. Focusing on longitudinal investigations with follow-up 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.

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. Knowing

that a specific intervention, such as cognitive training or a particular form of physical activity, could meaningfully impact dementia incidence is only helpful to the extent that various intensities of the intervention have been studied and reported. Equally important is more clearly elucidating the specific mechanisms associated with positive effects. For example, the underlying logic linking physical activity to improved cognitive performance has historically been physiological effects on blood or oxygen supply or stimulation of neurochemicals. However, the fact that remarkably different forms of physical activity, such as resistance training and aerobic exercise, show possible effects on cognition suggests that the mechanism of action may need to be reconsidered. Perhaps the effect lies in socialization which could help explain positive effects associated with group-based cognitive training, but not similar training done alone.

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. Thus far, only the FINGER trial has published results that we identified. Results from that trial were promising.¹¹¹ More studies assessing a combination of interventions would benefit the field.

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. This practice is problematic because the ability to detect change in cognitive performance over time is greatly influenced by the sensitivity, specificity, and reliability of the test. Although there are no perfect tests, the psychometric properties of neuropsychological measures vary considerably. For this reason, some are probably preferred over others. In addition, 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. Moreover, it is not uncommon for studies to use many tests over several time periods without any correction for multiple comparisons. Practice effects are also a concern when participants are evaluated at timeframes designed to complement the duration of the study but not at intervals acceptable for repeated applications of the tests. Research in the field could be enhanced greatly through development of consensus guidelines that encourage investigators to use a standardized battery or batteries of tests in these trials. Such a model has precedence in the pharmaceutical industry, and in Alzheimer's disease clinical trial research specifically, which unified methodology many years ago using the ADAS-Cog and by defining appropriate test/re-test timeframes.

The baseline status of subjects 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). Complicating matters, some trials describe participants with terms like "normal" or "presumed

healthy” while in other cases subjects are described as having cognitive complaints but no diagnosis. Self-reported cognitive status is not an acceptable proxy for objective measurement. Studies examining the impact of physical activity on cognitive performance report enrolling “sedentary” adults yet fail to define exactly what this means or how this classification was determined. There does not seem to be any standardization or common understanding of such terms.

Finally, future research trials that include incident CATD as a study outcome requires evaluation of subjects using formal diagnostic guidelines for dementia such as those from the National Institute of Neurological and Communicative Disorders and Stroke, or the Alzheimer’s Disease and Related Disorders Association. Including both measures of cognitive performance and CATD incidence as study outcomes would allow researchers to better understand how these two constructs are related. Important questions that need to be addressed include 1) what patterns of cognitive change predict dementia? 2) do some domains predict better than others and therefore become more important targets of intervention? 3) does the difference lie in the number of cognitive domains affected? 4) is the rate of change important? and 5) in what specific populations are particular interventions most effective – in healthy adults or those with mild cognitive impairment or other risk factors? 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. Some work has been done on this, but consensus is not yet clear and a range of values may be needed to establish what is considered clinically meaningful to whom. Consistently including objective measures of everyday function (IADLs) in future trials may prove valuable in addressing this question.

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Abbreviations

3MS	Modified Mini-Mental State Examination
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADL	Activities of Daily Living
ADRDA	Alzheimer's Disease and Related Disorders Association
APC	Annualized percentage change
AVLT	Auditory Verbal Learning Test
BID	Twice daily
BNT	Boston Naming Test
BOLD	Blood oxygen level-dependent
BVRT	Benton Visual Retention Test
CANTAB PAL	Cambridge Neuropsychological Test Automated Battery Paired Associated Learning Test
CANTAB	Cambridge Neuropsychological Test Automated Battery Paired Associated Learning Test
CATD	Clinical Alzheimer's-type Disease
CDR	Change in Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CFS	Cerebrospinal fluid
CHD	Coronary heart disease
COWA	Controlled Oral Word Association
COWAT	Controlled Oral Word Association Test
CPT	Continuous Performance Task
CT	Computerized tomography
CVLT	California Verbal Learning Test
DKEFS	Delis-Kaplan Executive Function System
DSM	Diagnostic and Statistical Manual of Mental Disorders (DSM)
DSM	Diagnostic Statistical Manual of Mental Disorders
DSS	Digit Symbol Substitution
DSST	Digit Symbol Substitution Test
DSy	Digit Symbol Coding
DVT	Digit Vigilance Test
ES	Effect size
fMRI	Functional magnetic resonance imaging
FSIQ	Full Scale IQ
F-TICS	French version, Telephone Interview Cognitive Status
HC	Hippocampus
HVLT-R	Hopkins Verbal Learning Test-Revised
IADL	Instrumental Activities of Daily Living
IHAMS	Iowa Health and Active Minds Study
IOM	Institute of Medicine
KQ	Key Question
MCI	Mild cognitive impairment
MFQ	Memory Functioning Questionnaire

MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NINCDS	Neurological and Communicative Disorders and Stroke
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NS	Not significant
NSAIDS	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PALS	Paired Association Learning Test
PET	positron emission tomography
PICOTS	Populations, Interventions, Comparisons, Outcomes, Timing, and Setting
PIQ	Performance IQ
POI	Perceptual Organization Index
PRM	Pattern Recognition Memory
PSI	Processing Speed Index
QAD	Every other day
RAVLT	Rey's Auditory Verbal Learning Test
RCI	Reliable Change Index
RCT	Randomized Controlled Trial
RT	Reaction time
RVLT	Rey Verbal Learning Test
SDMT	Symbol Digit Modalities Test
SDMT	Symbol Digit Modalities Test
SOE	Strength of Evidence
SoE	Strength of Evidence
SPECT	Single photon emission computed tomography
SWM	Spatial Working Memory
TIA	Transient Ischemic Attack
TICS	Telephone Interview Cognitive Status
TICS	Telephone Interview for Cognitive Status
TICS-M	Modified Telephone Interview for Cognitive Status
TMT	Trail Making Trial
UFOV	Useful Field of View
VCI	Verbal Comprehension Index
VIQ	Verbal IQ
VR	Visual reproduction
VRM	Verbal Recognition Memory
WAIS	Wechsler Adult Intelligence Scale
WMI	Working Memory Index
WMS	Wechsler Memory Scale