Comparative Effectiveness Review
Number 188

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

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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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 AHRQ Evidence-based Practice Center (EPC) Program. The report was presented October 25, 2016, at the National Academies of Sciences, Engineering, and Medicine public meeting 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 Officers 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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Key Informants and Technical Expert Panel

The role of the Key Informants was filled by the National Academies of Sciences, Engineering, and Medicine Committee on Preventing Dementia and Cognitive Impairment, which 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 prevent or delay the onset of age-related cognitive decline, mild cognitive impairment, or clinical Alzheimer's-type dementia for the National Academies and the National Institute on Aging. (An overview of the National Academies' 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 National Academies Committee would not see the draft Key Questions, PICOTS (populations, interventions, comparators, outcomes, timing, and settings), and analytic framework until the Key Questions were posted for public comment, a panel of content experts from Federal agencies acted as proxy Key Informants prior to posting. The proxy Key Informants disclosed any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. The role of the Technical Expert Panel (TEP) was filled by the National Academies Committee.

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Prior to publication of the final evidence report, the EPC 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.

Peer Reviewers 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 nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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

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

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

Results. We identified 263 eligible studies addressing 13 classes of interventions: cognitive training, physical activity, nutraceuticals, diet, multimodal interventions, hormone therapy, vitamins, antihypertensive treatment, lipid lowering treatment, nonsteroidal anti-inflammatory drugs (NSAIDs), antidementia drugs, diabetes treatment, and "other interventions." We found no high-strength evidence for the effectiveness of any intervention to delay or prevent age-related cognitive decline, MCI, and/or CATD. Moderate-strength evidence shows cognitive training in adults with presumed normal cognition improves performance in the cognitive domain trained (memory, reasoning, or processing speed), but not transfer of benefits to other cognitive areas and little evidence for benefit beyond 2 years; evidence for effect on CATD is weak. Interventions with moderate-strength evidence for having *no* benefit in cognitive performance included: vitamin E in women; B_{12} plus folic acid for executive/attention/processing speed; and angiotensin-converting enzyme plus thiazide versus placebo and angiotensin receptor blockers versus placebo on brief cognitive screening tests. We found low-strength evidence that the selective estrogen receptor modulator raloxifene reduced risk of probable MCI, but also that estrogen replacement with or without progesterone therapy increased risk of MCI and CATD. Physical activity interventions show no consistent benefit in preventing cognitive decline, but the percent of results showing benefit was unlikely to be explained solely by chance, providing a signal of a possible relationship. A few other interventions (vitamin B_{12} plus folic acid; nutraceuticals; one multimodal intervention using diet, physical activity, and cognitive training; antihypertensives; and NSAIDs) showed at least one positive finding for a specific outcome, some reaching low strength of evidence, but these were more than offset by findings of no effect for other outcomes. Many interventions (e.g., nutraceuticals; one multimodal intervention using lifestyle advice and drug treatment; hormone therapy; antihypertensives; NSAIDs; acetylcholinesterase inhibitors; diabetes management) showed low-strength evidence for no

benefit for some cognitive performance tests. We found no eligible studies for the following interventions: depression treatment, smoking cessation, and community-level interventions.

Conclusions. We found mostly low-strength evidence that a wide variety of interventions had little to no benefit for preventing or delaying age-related cognitive decline, MCI, or CATD. There was moderate-strength evidence that cognitive training improved performance in the trained cognitive domains, but not in domains not trained. Evidence of an effect on CATD incidence was weak. There was a mix of positive and negative findings for different outcomes, all of low strength, for physical activity, antihypertensives, NSAIDs, B vitamins, nutraceuticals, and multimodal interventions. Signals seem more promising for physical activity and vitamin B_{12} plus folic acid. Testing interventions that address modifiable risk factors can help to establish their causative role in MCI and CATD. Methodological problems in the available literature were widespread and should be addressed in future studies, including use of consistent cognitive outcome measures, longer followups, and recognizing that attrition is a major problem in longer studies. More work is needed to understand the relationship between intermediate outcomes such as cognitive test results and the onset of mild cognitive impairment and dementia.

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Background

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

The terminology used to describe dementia and cognitive impairment is inconsistent and changing, although the National Institute on Aging (NIA) and the Alzheimer's Association have jointly issued criteria and guidelines.[6] Diagnosis of a neurocognitive disorder due to Alzheimer's disease requires steadily progressive cognitive decline from a previous level, generally with predominant early impairment in learning and memory that occurs outside the context of delirium and is not better explained by other mental disorders. If the decline interferes with independence in everyday activities, it is classified as major; if not, as mild. For this report, the term clinical Alzheimer's-type dementia (CATD) is used to recognize the clinical reality that a certain diagnosis of Alzheimer's disease is rarely possible in clinical settings and patients often have dementia from some unknown mix of etiologies. This term (CATD) is designed to be inclusive but does exclude several other forms of dementia (such as Lewy body disease, infectious disease, frontotemporal, traumatic brain injury, or isolated post-stroke dementia), including some that can otherwise be well-identified. Because the literature currently does not use the term CATD, we specified whenever the diagnosis of dementia was defined.

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

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

Edition (DSM-5).[10] Roughly half of people with MCI will progress to a more severe form of cognitive decline over about 3 years.[11]

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

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

A number of reviews have assessed the evidence of relationships between risk and protective factors and/or cognitive decline, MCI, and CATD, including the 2015 Institute of Medicine report on cognitive aging cited above[7] and a 2010 Agency for Healthcare Research and Quality (AHRQ) systematic review.[12] Nonmodifiable risk factors for CATD include age, sex, race/ethnicity, and family history. Certain medical conditions are associated with an increased risk of developing MCI and CATD, including depression, cancer, cardiovascular disease, diabetes, delirium, thyroid disorders, chronic kidney disease, and loss of hearing and/or vision. Modifiable risk or protective factors may include diet, physical activity, education and intellectual engagement, social engagement, alcohol, smoking, and substance abuse, medications, and vitamins. Interventions represent one way to establish the veracity of risk factors. If changing a putative risk factor changes the cognitive course, it will be seen as more salient. Interventions have been developed to prevent or treat chronic diseases and to modify risk factors and protective factors. Multidomain interventions address multiple risk factors simultaneously, including nutrition, physical activity, cognitive training, social activity, and/or vascular risk factor management.[13]

Theories justifying various interventions to slow or prevent cognitive decline are diverse. If cognitive decline is due to natural age-related degeneration of the brain, the theory of neuroplasticity suggests that cognitive training could be useful to stimulate the brain to build additional neural pathways and to retain existing ones to build brain reserve against future decline. If brain degeneration and cognitive decline are due to toxins or lack of specific nutrients, changes in diet or nutritional supplements could be effective. If adequate blood flow to the brain is important in preventing cognitive decline, then medications and exercise that stimulate and maintain the health of the vascular system may be helpful. If inflammation is part of the disease process, anti-inflammatory drugs may be effective. These theories support prevention trials testing cognitive training, physical exercise, cardiovascular and other medications, diets, and

nutraceuticals (products derived from food sources that are purported to provide extra health benefits). Preventive efforts can target people with any level of cognitive function, from normal, to age-related cognitive decline, to MCI, and finally, to dementia.

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

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

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

Scope and Key Questions

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

is focused on prevention, studies must be at least 6 months in duration to demonstrate some sustainability of the intervention effects. It is important to note that this duration requirement by necessity eliminates many short-term studies in this field.

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

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

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

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

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

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

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

Methods

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

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

Literature Search Strategy

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

Eligibility

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

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

Data Extraction

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

Quality (Risk of Bias) Assessment of Individual Studies

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

Data Synthesis

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

We reported summary results for primary and intermediate outcomes and harms. Intermediate cognitive outcomes were assessed using neuropsychological tests or biomarkers. Because studies used a highly varied set of tests, we opted to group them into categories to facilitate analysis. We categorized neuropsychological tests for extraction and analysis by their purpose and/or what they attempt to measure, such as specific cognitive domains (e.g., executive function, memory) (Appendix C of the full report). Since cognitive interventions often targeted

individual cognitive functions, we reported on these domains in greater detail than was necessary for other sections of the report. The wide variety and inconsistency of tests used made it difficult to summarize the findings and prevented meta-analysis. For the cognitive training interventions we did use Cohen's D to estimate effect size where possible.

Strength of the Body of Evidence

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

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

Applicability

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

Results

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

A few intervention types show more potential than others at benefiting cognitive performance. We found moderate-strength evidence that cognitive training can improve cognitive function in the domain trained up to 2 years (low strength of evidence at 5 and 10 years), but generalization/transfer to other domains was rare. Although there was some evidence

for improvement in instrumental activities of daily living (IADLs), these studies had design problems and short-term studies may not predict long-term outcomes. Moreover, IADLs may be a benefit *per se*, but are not directly linked to dementia.

Although the evidence is less compelling, physical activity and perhaps vitamin B_{12} plus folic acid may also show potential benefit. While the majority of the results for physical activity showed little to no effect, the percent of results showing benefit in cognitive performance, particularly in resistance training and aerobic exercise, were unlikely to be explained solely by chance. Results for B_{12} plus folic acid are more spotty and so less persuasive; vitamin B_{12} and folic acid showed benefit in brief cognitive test performance and memory, but not for executive/attention/processing speed. There were also conflicting findings for B_{12} when used in combination with other B vitamins.

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

Table A. Summary of key messages by intervention class

Intervention	Key Message
Cognitive Training	• Most studies addressed intermediate outcomes of cognitive training in terms of cognitive performance and a few measures of brain activity. • The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial provided the strongest and most comprehensive design to assess the effect of cognitive training on cognitive performance for older adults with normal cognition. Its results provide moderate-strength evidence at 2 years (but low-strength at 5 and 10 years) that cognitive training can improve cognitive function in the domain trained, but transfer to other domains was rare. There is some suggestion that processing speed training is associated with improved IADL performance, but longer term studies were rated as low strength of evidence. • Other than the ACTIVE trial, the few studies that examined CATD incidence or cognitive performance showed mixed results.
Physical Activity Interventions	• Studies of physical activity interventions examined a wide variety of activities potentially targeting different pathways to affect cognition. • Evidence is insufficient to conclude whether physical activity interventions prevent MCI or CATD incidence. • Low-strength evidence shows that multicomponent physical activity interventions offer no clear benefit in cognitive performance over attention control in adults with normal cognition. • Evidence was insufficient to conclude whether other types of physical activity interventions had benefits for cognitive outcomes in adults with normal cognition. • While the majority of results showed no significant difference, the pattern of results across very different types of physical activity interventions provides an *indication* of effectiveness of physical activity.

Nutraceutical Interventions	• Low-strength evidence suggests omega-3 fatty acids and ginkgo biloba did not reduce CATD incidence or improve cognitive performance in adults with normal cognition. • Evidence is insufficient to conclude whether resveratrol or plant sterol/stanol esters reduced CATD incidence or improved cognitive performance in adults with normal cognition. • Few studies examined the effects of nutraceuticals on adults with MCI.
Diet Interventions	• Evidence is insufficient to conclude whether protein supplementation or energy-deficit diets have an effect on cognitive performance or incidence of MCI or CATD.
Multimodal Interventions	• Evidence is insufficient to conclude whether most multimodal interventions offer benefits for cognitive performance or incidence of MCI or CATD, largely because few studies have examined interventions with similar components. • Low-strength evidence shows that a multimodal intervention composed of diet, physical activity, and cognitive training provides benefits in executive function/attention/processing speed. • Low-strength evidence shows that a multimodal intervention composed of lifestyle advice and drug treatment is not effective in reducing incidence of CATD or benefiting brief cognitive test performance or memory.
Hormone Therapy Interventions	• Hormone therapy shows mixed results of harm and benefit. • Low-strength evidence suggests that estrogen therapy may slightly increase the risk of probable MCI and CATD when the two diagnostic categories are examined together. • Low-strength evidence suggests that estrogen plus progestin therapy may slightly increase the risk of probable CATD. • Low-strength evidence suggests that raloxifene may decrease the risk of MCI but not the risk of CATD or of a combined outcome of MCI or CATD compared to placebo. • In addition to these outcomes, hormone therapy has been associated with serious adverse events, including increased risk of certain cancers and cardiovascular disease
Vitamin Interventions	• Moderate-strength evidence shows no benefit in cognitive performance for vitamin E in women. • There was some signal that B_{12} plus folic acid may benefit brief cognitive test performance and memory but not executive function/attention/ processing speed. • Low-strength evidence for folic acid (0.4 mg) plus vitamin B_{12} (0.1-0.5 mg) shows benefit in brief cognitive test performance and memory. • Moderate-strength evidence shows no benefit for folic acid (0.4 mg) plus B_{12} (0.1-0.5 mg) versus placebo for executive/attention/processing speed. • Low-strength evidence for vitamin B_{12} (0.02=0.5 mg), B_6 (3-10 mg), and folate (0.56-1 mg) shows no benefit for executive/attention/processing speed. • Low-strength evidence shows no benefit in cognitive performance for multivitamins, vitamin C (in women), vitamin D with calcium (in women), or beta carotene (in women). • Low-strength evidence shows no benefit in incident MCI or CATD for multivitamins or vitamin D with calcium. • In adults with MCI, low-strength evidence shows no benefit for vitamin E in incident CATD.
Antihypertensive Treatment	• Generally, low-strength evidence shows that 3 to 4.7 years of antihypertensive treatment regimens versus placebo appear to have no benefit on cognitive test performance in adults with normal cognition. • Moderate-strength evidence shows that angiotensin converting enzyme (ACE) plus thiazide versus placebo and angiotensin receptor blockers (ARBs) versus placebo have no benefit on brief cognitive screening tests. • Low-strength evidence shows that intensive versus standard antihypertensive control shows no benefit on cognitive test performance. • Low-strength evidence shows no benefit on cognitive test performance of

	any fixed antihypertensive treatment regimen versus another among those directly compared. • Effects of stepped multiple agent antihypertensive medication regimens to reduce risk of dementia are inconsistent; one trial showed a positive effect but three other trials found no effect of antihypertensive treatment on CATD incidence. • The only two trials that reported subgroup data found no differential effect of treatment group on cognition by participant age or other baseline characteristics.
Lipid Lowering Treatment	• Evidence was insufficient to assess the effect of 5 years of statin treatment on the risk of incident CATD or for preventing MCI. • Low-strength evidence shows a small, 6-month improvement in executive/attention/ processing speed with placebo treatment that was not found with statin treatment, presumed to be due to practice effects and of uncertain clinical significance. • Low-strength evidence shows no benefit on brief cognitive test performance, executive/attention/processing speed, or memory for statin plus fenofibrate versus statin plus placebo in adults with normal cognition. • Evidence was insufficient to assess whether effects of statins on any cognitive outcomes differ by patient age, baseline lipid level, or other characteristics.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	• No evidence was available for the effect of low-dose aspirin on MCI or CATD incidence. • Low-strength evidence shows no benefit for low-dose aspirin on brief cognitive screening tests, multidomain neuropsychological performance, or memory, even with 10 years of use. • Low-strength evidence shows no benefit for NSAIDs, including both selective and nonselective cyclooxygenase-2 (COX-2) inhibitors, to reduce CATD incidence, or to benefit multidomain neuropsychological performance or memory, with 8 years of followup after 1 to 3 years of use.
Antidementia Treatments	• Low-strength evidence shows AChEI antidementia drugs did not reduce the incidence of CATD in persons with MCI over 3 years; evidence is insufficient for persons with normal cognition. • Low-strength evidence shows AChEIs for 3 years provide no significant effect on cognitive performance in adults with MCI.
Diabetes Medication Treatment	• No studies reported on the effect of diabetes treatment on the risk of incident clinical diagnoses of MCI or CATD. • In middle-aged older adults with diabetes and presumed normal cognition, low-strength evidence shows intensive versus standard glycemic control had no significant effect on cognitive performance.
Other Interventions	• Evidence was insufficient for lithium, a nicotine patch, individual piano instruction, multitask rhythmic exercise to music, sleep interventions, and social engagement. • We found no relevant studies for depression treatments, smoking cessation, or community-level interventions.
Agreement of Biomarkers and Measures of Cognitive Performance	• Only a few (9) low or medium risk of bias studies for cognitive performance also used biomarkers; most of those used some form of brain scan. • The overall rate of agreement between biomarkers and cognitive testing was 57%, but 90% of that agreement resulted from both approaches showing no effect. When the biomarker showed a significant result, there was agreement in 25% of cognitive tests conducted.

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

Discussion

Research on interventions to prevent or slow age-related cognitive decline, MCI, or CATD has focused largely on their effect on decline in measures of cognition. The reasons for this are many, including: 1) Meaningful investigation of dementia-onset requires either a long followup

period or a large cohort of older individuals. 2) Long followups in the target population face serious attrition problems due to death or comorbidities. 3) The risk of selective attrition whereby the intervention might also affect mortality risk and hence create attrition bias if survivors have more health problems.

Interventions to slow or prevent age-related cognitive decline, MCI, or CATD are often chosen because of evidence from epidemiological studies that examine actions of individuals at higher or lower than expected risk for these conditions. In other cases, theories of brain function (e.g., neuroplasticity) justify the development and testing of experimental interventions. Not all such interventions would be expected to be found to be effective in controlled experiments. This systematic review cast a wide net and only a few interventions showed any evidence of an effect, all of which raise many questions. Most of the studies showed no benefit to those receiving interventions compared to control groups. Four intervention classes show some positive results and seem the most promising for further study: cognitive training, physical activity, raloxifene, and vitamin B_{12} although the evidence for vitamin B_{12} and raloxifene is lower than the others. Problems with study designs make strong conclusions difficult. Assessing the strength of evidence for negative findings is a special challenge. There is a persistent concern about Type II errors.

Dementia Incidence

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

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

Cognitive Performance

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

Cognitive training studies were dominated by the ACTIVE trial, which investigated the effects of different types of group-based cognitive training on various cognitive performance outcomes for presumably cognitively healthy participants. For the most part, the training had sustained effects (up to 2 years) on cognitive performance in the domain trained but there was little evidence of generalization to other cognitive domains. There was an effort to assess the

effects of booster training, but assignment to receive a booster was not random; participants with high initial compliance received most of the boosters. More work on cognitive training with longer followup is needed.

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

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

Vitamin B_{12} and folic acid also showed benefit in brief cognitive test performance and memory, but not for executive/attention/processing speed. There were also conflicting findings for B_{12} when in combinations with other B vitamins. The other vitamins had no substantial benefit on cognition. Little or no benefit for cognitive performance was shown for multivitamins, vitamin C, vitamin D with calcium, or beta carotene (all low strength of evidence). Vitamins may work differently if given to a person to address an insufficiency compared to a megadose for a person with otherwise adequate basic vitamin intake. The participants varied widely in this and other respects.

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

Limitations of the Review Process

This review encountered several limitations, including but limited to those stemming from the topic and our approach to address it. For example, (as requested) we deliberately excluded dementias with specific and clear etiologies, including stroke. By doing so, we may underestimate the importance of hypertension treatment. The outcomes of interest were inconsistently defined in the literature, and there were numerous and widely varied interventions to address those outcomes. Other limitations arose from conceptual and methodologic issues with eligible studies. These included sample size, length of followup, measurement issues, and attrition. Our search strategy was challenging to design given the wide range of interventions and types of studies measuring cognitive outcomes as secondary outcomes. We designed a strategy to capture a wide variety of intervention types and outcomes with a degree of precision making the review process feasible and efficient. The scale and scope of the topic made identifying all relevant studies extremely difficult. We addressed this by supplementing our bibliographic database searches with citation searches.

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

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

evidence of an effect and strong evidence of no effect. We have tried to make that distinction whenever feasible.

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

Prioritizing Future Research

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

Recommendations for Design and Methodology of Future Studies

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

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

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

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

Measurement

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

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

Conclusion

At present, there is not sufficient strength of evidence to justify large-scale investing in public health activities aimed at preventing dementia; some results may be viewed as potential added benefits to already identified public health interventions. There was moderate-strength evidence that cognitive training improved performance in the trained cognitive domains, but not in domains not trained, and the evidence of an effect of cognitive training on reducing CATD incidence was weak. There was a mix of positive and negative findings, all of low strength, for physical activity, antihypertensives, NSAIDs, vitamin B_{12}, nutraceuticals, and multimodal interventions. Signals seem more promising for resistance training and aerobic exercise, and vitamin B_{12}.

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

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Chapter 1. Introduction

Background

Dementia severely erodes individuals' functioning and quality of life, creates burden and stress on the entire family, and is a major predictor of institutionalization. Although the age and sex standardized prevalence of dementia and the rates of incident dementia have fallen over the last several decades,[1, 2] the number of U.S. adults over 70 with dementia and mild cognitive impairment is rising.[3, 4]

Additionally, dementia-related costs are high, exceeding even those of heart disease and cancer, and are often paid directly by families.[5] Given such enormous family and societal burdens, identifying interventions with potential to prevent or delay the onset of dementia is an urgent public health priority. Although many putative risk factors have been identified, the challenge is to identify any interventions that can lead to reductions in dementia incidence and make them more widespread.

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 have been used to diagnose dementia (typically dementia-causing diseases), 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.[6] More recently, the National Institute on Aging (NIA) and the Alzheimer's Association jointly issued criteria and guidelines.[7] 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.).[8] Diagnosis of a neurocognitive disorder due to Alzheimer's disease requires steadily progressive cognitive decline, generally with early 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 (CATD) is designed to be inclusive but does exclude several other forms of dementia (such as Lewy body disease or infectious disease; see Table 1.1), including some that can otherwise be well-identified). 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 for people past the age of 60 years. For example, reaction time and speed of processing are known to decline slowly throughout adulthood Therefore, greater difficulty learning new information by 70 or 80 years old may not necessarily be a warning sign of neurocognitive disease in the absence of other signs or symptoms of cognitive difficulty.

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 decline 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 which compares an individual's cognitive performance against same-aged normative samples.[9] Roughly half of people with MCI will progress to a more severe form of cognitive decline over about 3 years.[10] 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.[11] 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.[12]

Distinguishing Between Mild Cognitive Impairment and Dementia

A separate Institute of Medicine (IOM) committee (not connected with this study) has recently recognized potential problems with using cognitive and functional decline elements of the definition for dementia and MCI.[12] 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 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, but persons with dementia may experience several types simultaneously. Individuals who meet the clinical criteria for Alzheimer's disease are more likely than others to have certain genetic markers, patterns on brain imaging (e.g. atrophy), specific types of protein accumulation 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 the biological changes underlying laboratory or imaging findings are causes of or caused by Alzheimer's disease. This type of uncertainty greatly complicates efforts to prevent or slow impairments in cognition that are a prelude to Alzheimer's disease. 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
Frontotemporal lobar degeneration
Lewy body disease
Traumatic brain injury
Substance/medication use
HIV infection
Prion disease
Parkinson's disease
Huntington's disease
Another medical condition
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.
Italicized causes are outside the scope of this review.

Interventions To Prevent or Slow Cognitive Decline

Interventions and Underlying Theories

A number of reviews have assessed the evidence of the relationships between risk and protective factors and/or cognitive decline, MCI, and CATD, including the 2015 Institute of Medicine report on cognitive aging cited above[12] and a 2010 Agency for Healthcare Research and Quality (AHRQ) systematic review.[13] 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.[14]

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)

MCI=Mild Cognitive Impairment; CATD=Clinical Alzheimer's-Type Dementia

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.[12]

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, antiinflammatory 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 dementia.

Research participants seeking to slow or prevent age-related cognitive decline, MCI, and CATD may have more than one risk factor. CATD may result from cumulative and possibly synergistic effects. Interventions may address one or multiple possible mechanisms with complex or multiple prevention strategies. Differential effects of interventions on subgroups defined on the basis of cumulative risk factors (both modifiable and nonmodifiable) may be of concern. Many studies testing the association of preventive factors or effectiveness of interventions for preventing dementia have looked at only the one-to-one relationship with a single risk factor or intervention. 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 participants at any point along the cognitive continuum. Various proposed strategies target young and middle-aged adults with no evidence of cognitive decline, older adults worried about age-related changes, people with documented MCI, and those with major neurocognitive disorders. Common diseases that cause cognitive decline, especially CATD, progress slowly. Lengthy time periods are required between an intervention and the expectation of measurable cognitive decline or function in those not receiving an effective preventive intervention; the younger the participant, the longer the latency period. Short-term benefits on cognitive tests or biomarker measures are uncertain predictors of long-term effects on cognition.

Proof that an intervention prevents or delays MCI or dementia ideally includes evidence that the intervention led to fewer individuals with a subsequent diagnosis of MCI or CATD. Such measures are rarely possible, due to the extended study length required (i.e., >10 years) or the extremely large number of participants (i.e., thousands) required plus the complexity of measuring both cognition and functional abilities. Over shorter terms and in smaller studies, changes in cognitive function are assessed using validated neurocognitive tests addressing various domains of cognition. 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 measuring multiple domains of cognition.[15]

To assess changes in brain functional abnormalities earlier or with greater sensitivity than is possible with behavior-based testing or interviews, a variety of laboratory and brain imaging tests are used to look for changes in specific biologic substances, structures, or processes; collectively these are called biomarkers. Examples include total brain and hippocampal volumes; white matter hyperintensity volume;[16] 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 a slower deterioration from baseline of specific biomarker measures could indicate a slowing of age- or disease-related decline as a result of an intervention, to the extent that the biomarker is an accurate reflection of brain capacity and activity. As noted before, there is a good deal of inconsistency regarding the relationships between biomarkers. However, many studies have included or focused on measures of biomarkers and cognitive function.

Scope and Key Questions

This systematic review is focused on intervention studies that target populations who are cognitively normal or may have age-related changes or MCI but do not yet have dementia. With the focus on CATD, the review does not include forms of dementia with multiple other causes, e.g., Lewy body, infectious diseases, frontotemporal, and traumatic brain injury (see the italicized conditions in Table 1.1). The review does include studies addressing vascular components of mixed dementia, but clear post-stroke dementia is out of scope. Intermediate outcomes such as measures of biomarkers and cognitive performance are included. However, since the review is focused on prevention, studies must be of at least 6 months duration to demonstrate some level of sustainability of the intervention effects. It is important to note that this duration requirement by necessity leaves out many short-term studies in this field.

Key Questions

The review addresses two Key Questions (KQs) and the PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) framework that address the effects of interventions for delaying or slowing age-related cognitive decline and preventing, delaying, or slowing MCI and clinical Alzheimer's-type dementia (Table 1.3). The third KQ addresses the strength of association between various intermediate outcomes (e.g. biomarkers) with MCI and CATD.

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

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

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

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

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

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

Table 1.3. Populations, interventions, comparators, outcomes, timing, and settings (PICOTS)

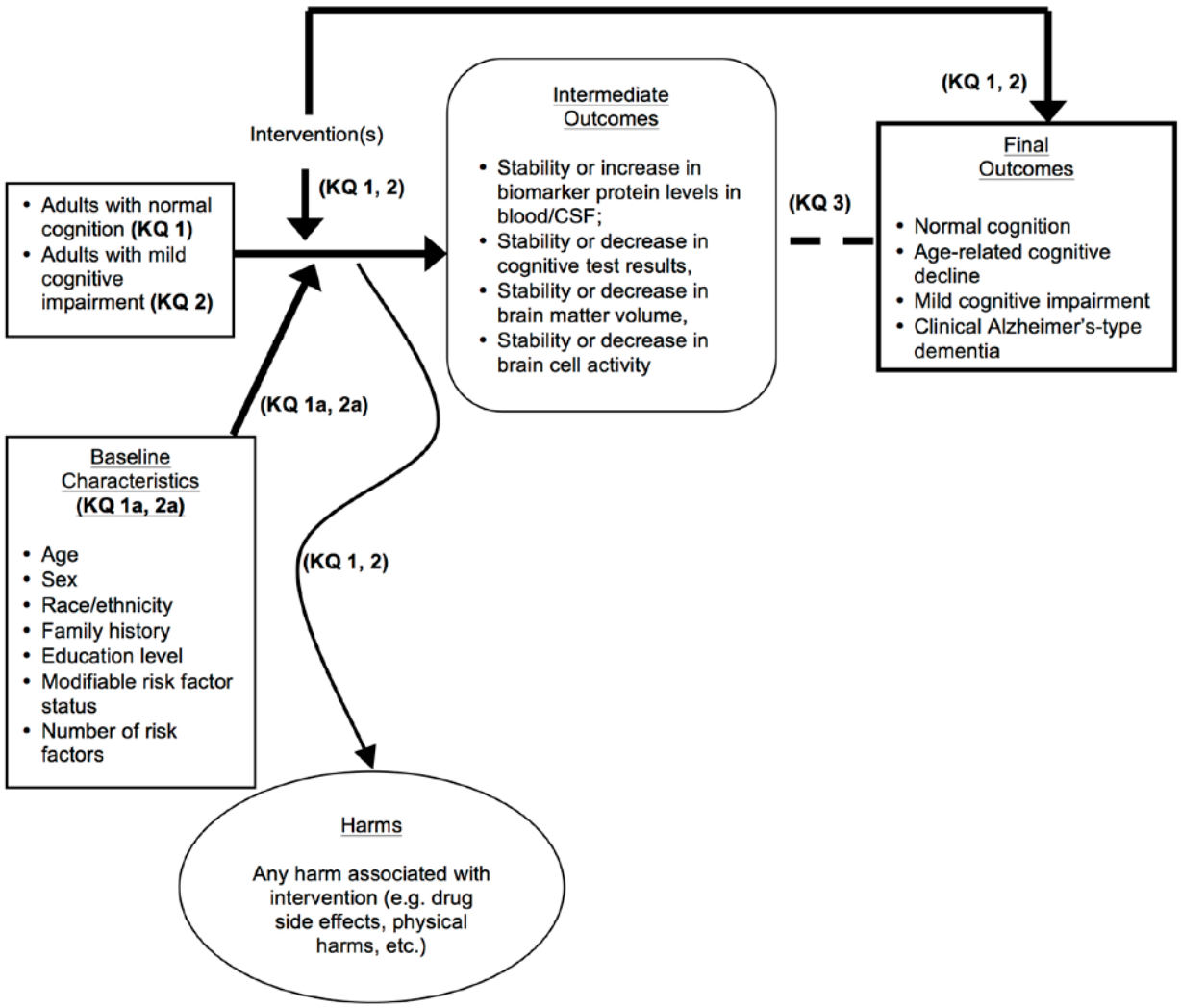
PICOTS	KQ 1	KQ 2	KQ 3
Population	Adults with normal cognition	Adults with MCI	Adults with normal cognition or MCI
Intervention	Interventions aimed at preventing, delaying, or slowing the development of age-related cognitive decline, incident MCI or CATD	Interventions aimed at preventing, delaying, or slowing the development 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	Final health or patient-centered outcomes: normal cognition, age-related cognitive decline, incident MCI or CATD (includes vascular or mixed dementia incidence but not post-stroke dementia incidence) Intermediate outcomes: Biomarker protein level(s) Cognitive test results Brain matter volume Brain cell activity level <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 Adverse effects of intervention(s): Pharmacologic side effects, Psychological, Financial, Physical	Final health or patient-centered outcomes: Incident CATD (includes vascular or mixed dementia incidence but not post-stroke dementia incidence) Intermediate outcomes: Biomarker protein level(s) Cognitive test results Brain matter volume Brain cell activity level <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 Adverse effects of intervention(s): Pharmacologic side effects, Psychological, Financial, Physical	Final health or patient-centered outcomes: Incident MCI or CATD (includes vascular or mixed dementia incidence but not post-stroke dementia incidence)
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=clinical Alzheimer's-type dementia; CSF=cerebrospinal fluid; CT=computerized tomography; fMRI=functional magnetic resonance imaging; KQ=Key Question; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; NA=not applicable; 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



CSF=cerebrospinal fluid; KQ=Key Question

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 finishes 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 plan for the use of this review given by the National Institute on Aging (NIA) sponsor, this project follows a unique model. The role of the Key Informants was filled by the Committee on Preventing Dementia and Cognitive Impairment of the National Academies of Sciences, Engineering, and Medicine (The National Academies), which will use the report to help develop its own report to the NIA on the state of knowledge on the efficacy, comparative effectiveness, and harms of interventions to prevent or delay the onset of age-related cognitive decline, MCI, or CATD. (An overview of the National Academies' 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 National Academies Committee did 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 National Academies 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 outcomes and incidence of MCI of clinical Alzheimer's-type dementia.
Study Design	For KQ1-2: RCTs of any size and large prospective quasi-experimental cohort studies with comparator arms ($n \geq 250$ per arm). For KQ3: Studies identified in KQs 1 and 2
Outcomes	Cognitive performance measured with validated instruments, biomarker measures associated with clinical Alzheimer's-type dementia, and incident MCI or clinical Alzheimer's-type dementia (pure vascular dementia including strokes is excluded)
Timing	For KQ1-2: Minimum 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; KQ=Key Question; MCI=mild cognitive impairment; n=sample size; 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 September 2016. We identified eligible studies published prior to 2009 using the previous AHRQ review, including the excluded study bibliography.[13] 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 National Academies 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. Two independent investigators reviewed titles and abstracts to identify publications of studies potentially relevant to our inclusion criteria. Two investigators independently screened the 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 for citations that underwent full-text screening were documented.

We searched grey literature sources to identify relevant completed and ongoing studies using ClinicalTrials.gov. These results were used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and inform future research needs.

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.

Assessing 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).[17] 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 study limitations.

Data Synthesis

We summarized results in summary tables, excluding studies with high risk of bias and synthesized the evidence for each unique population, intervention, comparison, and outcome and harm. We organized evidence tables and results by intervention type and the 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 biomarker measurements in the literature. Because studies used a highly varied set of tests, we grouped 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 (e.g., 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. The wide variety on inconsistency of tests used made it difficult to summarize the findings and prevented meta-analysis. For the cognitive training component we did use Cohen's D where possible.

Changes in neuropsychological test scores can vary in clinical significance. While cognitive function declines as we age, it can be challenging to identify a level of change that is concerning. Reliable change indices have been suggested for many commonly used instruments assessing cognitive function. These serve to provide a benchmark of meaningful change in the test scores for individuals.[18] 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.[18] 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. Effect sizes were calculated using STATA 14/SE (Stata).[19] We

assessed clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[20] Clinical and methodological heterogeneity precluded quantitative pooling of results.

Assessing the Strength of Evidence for Major Comparisons and Outcomes

When sufficient data were available (more than one study or one large study [n ≥500]), the overall strength of evidence for select outcomes within each comparison were 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.[21] Study limitations were rated as low, medium, or high based on study design and the risk of bias of eligible studies in a particular evidence base (comparison). 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 between the intervention and the outcome of interest was needed to reach the conclusion. For instance, a medication that lowers blood pressure might affect dementia risk by first lowering blood pressure. The reduced blood pressure may then lower the risk of dementia. This relationship is indirect. However, if a medication directly lowers dementia risk without acting through altering a risk factor such as blood pressure, the relationship would be direct. Indirectness can also occur when the study uses a shorter followup time to test a relationship. Such evidence may help formulate a potential linkage, but it does not test it directly. 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. Publication bias is more easily addressed for RCTs than observational studies by searching for registered trials using sources like ClinicalTrials.gov. (However, we did not identify any observational studies to include.) Other factors we considered in assessing strength of evidence include the presence of a dose-response relationship, the presence of confounders, and the strength of the association.

Assessing strength of evidence for studies with null findings is especially challenging because several strength of evidence are designed to address differences. Although it is important to assess the strength of evidence for negative (no effect) findings, it is hard to assess effect size when there is no effect. 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 from a given intervention 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.[22] Here again data were frequently missing or implied. For example, baseline cognitive status was not consistently or precisely assessed in many instances. Applicability issues are addressed in Chapter 5.

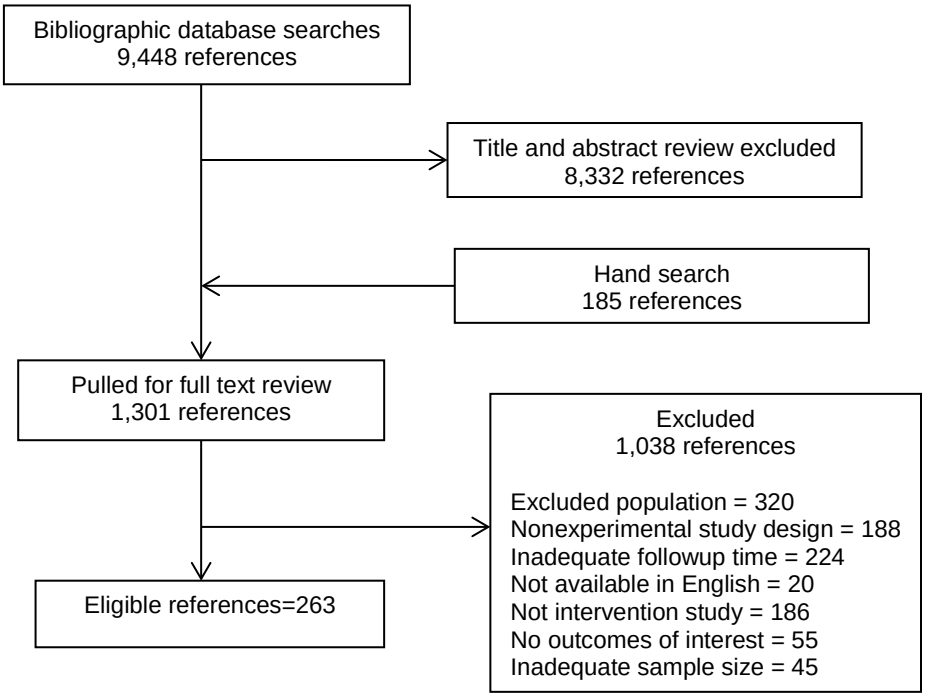
Peer Review and Public Commentary

Experts in dementia and systematic reviews were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a disposition of comments report that will be made available after AHRQ posts the final systematic review on the Effective Health Care Web site.

Chapter 3. Search Results

Bibliographic database searches identified 9,448 unique references (Figure 3.1). Title and abstract screening of these yielded 1,116 references for full text review. Hand searching identified an additional 185 references yielding a total of 1,301 references for full text review. Full text review yielded 263 references eligible for our review. Common exclusion reasons included ineligible populations (n=320; e.g., individuals with dementia), ineligible study designs (n=188; i.e., nonexperimental designs), ineligible interventions (n=186; interventions not intended to prevent dementia), and inadequate followup time (n=224; 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 prompted 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 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	46
Physical activity/exercise	Physical activity	48
Nutraceuticals	Nutraceuticals	25
Diet types	Diet types	9
Multimodal interventions	(No direct match to groups listed in original protocol)	21
Hormone therapy	Hormone therapies	44
Vitamins	Vitamin supplements	29
Antihypertensive treatment	Cardiovascular and cerebrovascular disease treatments	24
Lipid lowering treatment	Cardiovascular and cerebrovascular disease treatments	10
Nonsteroidal anti-inflammatory drugs	Aspirin/NSAIDS	8
Acetylcholinesterase inhibitors	Pharmacologic	13
Diabetes medication treatment	Diabetes treatments	8
Other interventions		
Other drugs	Pharmacologic	2
Social engagement	Social engagement	2
Sleep disorder treatments	Sleep disorder treatments	2
Music-based interventions	Music-based interventions	2
Depression treatments	Depression treatments	0
Obesity treatments	Obesity treatments	0
Smoking cessation	Smoking cessation	0
Community-level interventions	Community-level interventions	0
	Brain stimulation	1
TOTAL INTERVENTIONS		294
	Minus duplicates (publications in more than 1 intervention type)	-31
TOTAL PUBLICATIONS		263

NSAIDS=Nonsteroidal anti-inflammatory drugs

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 transfer to other domains was rare. There is some suggestion that processing speed training is associated with improved instrumental activities of daily living (IADL) performance, but longer term studies were rated as low strength of evidence.
- Other than the ACTIVE trial, the few studies that examined clinical Alzheimer's-type dementia (CATD)* incidence or cognitive performance 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.

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. The overarching goal of the study was to test whether different types of cognitive training could improve daily life (as captured in IADLs, problem solving, and speed of performance); but also improved cognitive performance, which as an intermediate outcome is a focus of interest for this review. Its findings have been interpreted differently by various groups of investigators.[16, 23, 24]

Among the large number of publications from the ACTIVE trial, we actively discuss four, three of which reported the results for proximal and primary outcomes, as described in the ACTIVE protocol, at 2 years,[25] 5 years,[26] and 10 years.[27] We include the latter two publications although they have high risk of bias because of the salience of the topic. The fourth study looked at incident dementia at 5 years.[28] 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. 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 and Effect Size (ES)	Strength of Evidence (justification)
Cognitive training k=1	Dementia	Unable to draw conclusion.	Insufficient (high study limitations, imprecise)
	MCI	Unable 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=2,832; 2 years). Improvement remained at 5 (ES=0.26) and 10 years (ES=0.23)	Moderate (medium study limitations, indirect) 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=2,832; 2 years). Improvement remained at 5 (ES=0.76) and 10 years (ES=0.66).	Moderate (medium study limitations, indirect) 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=2,832; 2 years). Improvement remained at 5 (ES=0.23) but not 10 years.	Moderate (medium study limitations, indirect) Low (high study limitation, indirect)

ES=effect size; k=number of studies included; MCI=mild cognitive impairment; n=sample size

Between March 1998 and October 1999, 2,832 adults aged 65 years or older whose Mini-Mental State Examination (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 on the extent of spillover, or transfer, into other domains as well as to explore the impact of each arm on more generalizable effects like IADLs. (The ACTIVE trial included other outcomes, such as depression and specific performance of tasks like driving, which were not judged salient to the Key Questions in this review.)

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. The first set of sessions emphasized cognitive performance, whereas the last five sessions emphasized adaptation to daily life. Initial training was conducted between May 1998 and December 1999. The reasoning and speed of processing arms, but not the memory arm, were tailored to participant baseline performance.[29] Booster training at 1 and 3 years (1 month before testing) was given to a random sample of participants in each arm who completed the initial ten sessions.

Memory was evaluated using the Hopkins Verbal Learning Test, Rey Auditory-Verbal Learning Test, and the Rivermead Behavioral Memory Test. Reasoning was evaluated using the word series, letter series, and letter sets tests. Speed was evaluated using Digit Symbols Substitution, Digit Symbols Copy, and the Useful Field of View (UFOV) test. All measures were traditional examiner-administered tests with the exception of the computer-based UFOV. Timed IADL was assessed for five tasks: using a phone book, reading food and medication labels, finding an item on a crowded pantry shelf, and counting change.

Findings from the four studies are summarized in Table 4A.2. Only the 2-year outcome study had a medium risk of bias.[25] 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 based on enrollment numbers (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 18 percent 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 25 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 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, the 5- and 10-year outcomes were rated low.

The ACTIVE trial was not designed to study the incidence of dementia, and 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 standard deviations (SD), or a report from a proxy or the subject that the subject had dementia).[28] 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 participants 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. Baseline impairment was associated with a higher rate of dementia as classified by the study. So, too, was

the drop-out rate. We rated the strength of evidence for this aspect of the ACTIVE portfolio as insufficient.

Table 4A.2. Key ACTIVE studies

Characteristics	Ball, 2002[25]	Willis, 2006[26]	Unverzagt, 2012[28]	Rebok, 2014[27]
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 (estimated)	Everyday Problem Solving, Everyday Speed, IADL/ADL,	Everyday Problem Solving, Everyday Speed, IADL/ADL,
Key Findings	• 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	• 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	• 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	• 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 testing 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	**0.15***	**0.76***
10-year Outcomes	Memory	0.06	0.11	0.05
	Reasoning	0.02	**0.23***	0.06
	Speed of Processing	0.07	0.01	**0.66***

*p<.01 (also noted by bold font)
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

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

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 participants showed significant benefits in IADLs. Reasoning and speed training

were associated with fewer motor vehicle collisions.[30, 31] Depression was assessed but was deemed outside of this review's scope.[32, 33] Again, the high attrition rates need to be considered.

In an effort to establish generalizability, Prindle and McArdle[34] compared the demographic characteristics of the ACTIVE sample to the sample in the Health and Retirement Study,[35] a representative sample of about 20,000 Americans. They found similar patterns of measurable demographic variables, but cannot correct for unmeasured differences in cognition or other factors associated with volunteering for the study. Likewise, additional analyses focused on participants with algorithmic classification of cognitive impairment and found no difference between participants with low cognition versus those who were not low.[36, 37]

Table 4A.5. Effect sizes for various activity outcomes

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 (also noted by bold font) Effect sizes = (group mean-control-mean at time point) – (group mean – control mean at baseline) divided by intrasubject standard deviation. ADL=activities of daily living; IADL=instrumental activities of daily living; NR=not reported

In a study with only a 6-week followup Edwards and her colleagues showed an improvement in timed IADLs after speed of processing training.[38] A second 6-week study, where outcomes were assessed upon completion of training, addressing only those with initial deficits also showed short-term improvement in timed IADL performance.[39]

Other Studies

We were unable to standardize scores for the cognitive tests. Reliable change indices (RCIs) for most of the tests were not available. We were uncertain about the applicability of the RCIs, as they may not account for differences across populations.[40] It was unclear whether a RCI calculated from a population with normal cognition accurately would capture clinically meaningful change in a population with mild cognitive impairment. In addition, several of the

included studies were conducted in international settings. Previous research shows that a RCI may differ across racial and ethnic groups.[41]

We were able to calculate effect size (Cohen's D) for five studies. Three studies had participants with normal cognition (Miller 2013,[42] Klusmann 2010,[43] and Carretti 2012[44]) and two studies had participants with mild cognitive impairment (MCI) (Rapp 2002,[45] Herrera 2012[46]). We were also able to extract effect sizes and 95% confidence intervals reported in Wolinksy, et al. 2013, which had participants with normal cognition.[47] Four studies reported insufficient data to calculate effect size (Buschert 2012[48] & Forster 2011,[49] Kwok 2012,[50] Vidovich 2015,[51] Stine-Morrow 2014[52]).

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.[42-44, 47, 52] Three of the five trials for older adults with presumed normal cognition used computer-based interventions;[42, 43, 47] two of which used computer programs directly targeting specific cognitive domains and administered the training individually;[42, 47] 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.[43] Two trials used a noncomputer-based intervention.[44, 52]

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[47] 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	• Used one of the ACTIVE tools, speed of processing arm • Found significant changes on domain trained using UFOV test • Mixed results on 9 other secondary testing outcomes
Miller, 2013[42] 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	• 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[43] 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	• 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[44] 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	• 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, 2014[52] Medium	395/461 14% 8 months	Reasoning (cognitive training arm), divergent thinking (engage-ment 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	• 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.

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.[47] 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). Similar to the ACTIVE design, a booster was provided, but here to a pre-randomized group at 11 months. (Unlike ACTIVE, the booster assignment was made at the outset.) The authors used a university-based attention control activity (computerized crosswords) compared with one of three active intervention arms (visual speed of processing training at the university, visual speed of processing training at the university with a booster, or the same visual speed of processing training at home on the participant's personal computer). Ten hours of training were provided over 5 weeks (similar to ACTIVE). Outcomes were assessed at baseline and at 6 months and 1 year post-training. The primary outcome was determined using the 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, favoring the intervention). Nine additional cognitive tests were administered: Trail Making Tests (TMT) A and B, Symbol Digit Modalities Test (SDMT), Stroop Color and Word Tests (3 tests), Controlled Oral Word Association Test (COWAT), and the Digit Vigilance Test (DVT). Many of these additional tests can evaluate higher-order cognitive domains (e.g., executive functioning) than the training specifically targeted. For the onsite training interventions, significant effects of training on these secondary outcomes were found on TMT A, SDMT, and Stroop-Word, but not TMT B, Stroop-Color, Stroop Color-Word, COWAT, or DVT. For the onsite training intervention with boosters, significant effects of training on these secondary outcomes were found on TMT B, SDMT, and Stroop-Word, but not TMT A, Stroop-Color, Stroop Color-Word, COWAT, or DVT. For the at home training, significant effects of training on these secondary outcomes were found on TMT A and B, SDMT, and Stroop-Word, but not Stroop-Color, Stroop Color-Word, COWAT, or DVT. Across all of the secondary outcomes, effects sizes were smaller than in the trained domain and few exceed 0.5. This may suggest more potential for cognitive transfer than that seen in the ACTIVE study, although one cannot rule out that the timed nature of the tests may be driving improvement. Also, the large number of analyses needs to be kept in mind. Of the 30 analyses that were done, six had a positive Cohen's D. Effect sizes were generally small; few exceeded 0.5. The UFOV results were meant to reflect skills useful in daily life (e.g., driving) but were not necessarily evidence of overall cognitive performance.

The study by Miller was much smaller, enrolling just 84 participants.[42] 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 immediate memory, delayed 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. None of the six memory tests reported in the study had a positive Cohen's D in our analysis.

The Klusmann trial was conducted in Berlin, Germany, and enrolled 259 nondepressed women with over the age of 70.[43] Participants were randomized to a computer-based cognitive 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 traditional examiner administered 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 tasks (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 (TMT B/A), compared with a no intervention control. Computer training did not improve free recall (short delay), verbal fluency, or the other executive measure (Stroop). This Cognitive Training Chapter of our report is restricted to 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 same tests at followup, compared with no-contact controls. Of the four memory tests included in the study, two (RBMT immediate and delayed recall) showed positive Cohen's D. The effect sizes for both were 0.33. Neither of the two tests of executive/ attention/processing speed domains showed positive Cohen's D. Klusmann et al. argue that this outcome may be due to improved "management of new complex situations," and 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.[44] 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 sessions. The control group also attended three sessions with experimenters where they filled out paper-pencil questionnaires. Outcomes were evaluated at baseline, after completing training, and at 6 months. Outcomes measures included 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 outcomes compared with those in the control group. No significant differences were observed between groups for reading comprehension or fluid intelligence outcomes. The Cohen's D values for the memory tests were quite high, ranging between 1.4 to 1.9.

Another pathway through which group activities may affect cognitive outcomes is through social engagement. The Stine-Morrow et al. study aimed to test the differential effects of domain-specific cognitive training and engagement activities that may broadly stimulate the mind.[52] 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 (including 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, delayed recall score, and immediate sentence free-recall). 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 outcome (also the skill they practiced) than the training and waitlist arms. However, generalizations of training to other cognitive abilities 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[53] **Forster, 2011**[49] 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), TMT A & B	Conversion to CATD; Glucose uptake (PET scans)	• Intervention improved 1 of 2 global cognitive measures (ADAS-cog) • 1 of 4 domain-specific tests was significantly improved (RBANs immediate memory); • Forster study reports FDG-PET results: intervention group showed no decline in uptake during the 6-months, while control showed widespread decline in uptake. • 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[45] 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)	• 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[51] 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 (DS Forward, Symbol Search, TMT A), executive (COWAT, TMT B)	Perception of memory (Memory Functioning Questionnaire)	• 1 of 9 cognitive assessments (DS 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, 2012[50] Medium	197/223 12% 12 months	Attention/ processing 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	• 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, 2012[46] Medium	22/22 No attrition reported 6 months	Recognition, working memory, recall	Individual, computer-based	24 hours over 12 weeks	Recognition (Doors Recognition Sets A and B, DMS48), Working memory (DS Forward and Backward), Recall (BEM-144 12-word-list, 16-Item free and cued, MMSE 3 words, Rey Complex Figure)	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

ACTIVE= Advanced Cognitive Training for Independent and Vital Elderly; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BEM-144= Batterie d'Efficience Mnesique 144; CATD=clinical Alzheimer's-type dementia; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CAMCOG-R=Cambridge Cognitive Examination-Revised; COWAT=Controlled Oral Word Association Test; CVLT-II=California Verbal Learning Test-Second Edition; DS=Digit Span (Forward & Backward); DMS48=delayed matching-to-sample task; FDG-PET=fluorodeoxyglucose positron emission tomography; MMSE=Mini Mental State Examination; PET=positron emission tomography; RBANS=Repeatable Battery for Neuropsychological Status; TMT A/B=Trail Making Test A & B

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.[48, 49] 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) memory subscores and 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 TMT 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. FDG-PET was used to measure declines in brain glucose uptake as a marker of disease progression. People with MCI who received the intervention showed no decline in glucose 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 group (n=10).[45] 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 memory measures included immediate and delayed word list, shopping list, names and faces, and paragraph. The nine subjective measures of memory originated from one tool, the Memory Functioning Questionnaire, and included self-reported present memory 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). For all eight reported test results, none of the analyses showed a positive Cohen's D.

The Promoting Healthy Ageing with Cognitive Exercise (PACE) trial randomized 160 adults with MCI to a cognitive activity intervention or an educational control.[51] 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] cognitive battery; MMSE; Cambridge Cognitive Examination-Revised), three measures of attention or processing speed (Digit Span, Symbol Search, TMT A), two measures of executive functioning (TMT B, 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 identified dementia (>19 on the Chinese MMSE).[50] 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 (Chinese versions of the MMSE and the Mattis Dementia Rating Scale battery). 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.[46] Twenty-two people with MCI were randomized to cognitive training or cognitive activity (control) 60 minutes, twice a week, for 12 weeks. 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 outcomes were assessed using the Digit Span, 12-word list recall (BEM-144), 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. The authors conceptualize these outcomes as 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 Complex Figure). Results were mixed. One of three recognition tests improved at 6 months compared to control condition (Doors, Set A); one of two working memory tests improved (Digit Span Forward); and two of four recall tests improved (BEM-144 and MMSE). This small study showed remarkable results when analyzed with Cohen's D. For six of the seven reported memory tests showed a positive Cohen's D result. Effect sizes ranged between 1.9 and 3.1. Both of the tests in the executive, attention, processing speed category showed positive Cohen's D results, with effect sizes up to 4.5.

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 generalization to other cognitive 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*. Processing speed training was associated with IADL improvement (or less decline) but that benefit is not linked to dementia per se.

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[25]	Memory, reasoning, speed of processing	Group	Computer	10-12 hours over 6 weeks, booster at 11 months	• Speed (only for Attn/ Speed Arm, ES=.87) • Memory (only for Attn/ Speed arm, ES=.17) • Reasoning (only for Reasoning Arm, ES=.26)	• NS Everyday problem solving • NS IADL • NS Everyday Speed Habits	• Memory (HVLT, RAVLT, and RBMT) • Reasoning (word series, letter series, letter sets) • Speed (DSST, Digit Symbol Copy, UFOV)
Wolinsky, 2013[47]	Speed of processing	Individual	Computer	10 hours over 5 weeks, booster at 11 months	• Speed (ES=.32-.58 depending on booster) • NS Executive (+ TMT A and B, SDMT, and Stroop-Word, • NS Stroop-Color, COWAT or DVT)	None	• Speed (UVOF) • Executive (TMT A and B, SDMT, SCWT, COWAT, and the DVT)
Miller, 2013[42]	Short- and long-term memory, language, visual spatial processing, reasoning, and calculation	Individual	Computer	13 hours over 8 weeks	• Delayed memory • NS Immediate memory • NS language • (Other domains not reported)	None	• Delayed (Delayed Buschke-Fuld, Delayed Rey-Osterrieth, VP) • Immediate (Buschke-Fuld Total, Rey-Osterrieth Copy, VP Total) • Language (FAS, Animal Naming, BNT)
Carretti, 2013[44]	Working memory	Individual	Computer	2.5-3.5 hours over 2 weeks (50-70 minutes per session, 3 sessions total)	• Delayed memory • NS Immediate memory • NS language • (Other domains not reported)	• Listening comprehension (True/False, Map Drawing) • NS Reading Comprehension • NS Fluid Intelligence	• 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[43]	None, general computer instruction	Group	Computer	112.5 hours over 6 months of in-class instruction	• Delayed Memory • NS Immediate Memory • NS Executive Attention • NS Verbal Fluency	None	• Immediate and delayed story recall (RBMT) • Short and long delay free word recall (FCSRT) • Semantic verbal fluency • Executive functioning (SCWT, TMT B/A)

Attn=attention; BNT=Boston Naming Test; COWAT=Controlled Oral Word Association Test; DSST=Digit Symbol Substitution 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; HVLT=Hopkings Verbal Learning Test; IADL=instrumental activities of daily living; NS=no statistically significant difference; RAVLT= Rey Auditory Verbal Learning Test; RBMT=Rivermead Behavioral Memory Test; SCWT=Stroop Color Word Test; SDMT=Symbol Digit Modalities Test; TMT=Trail Making Test (Parts A & B); UFOV=Useful Field of View; 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[48] **Forster, 2011**[49]	Mnemonic memory training	Group	No Computer	12 hours over 6 weeks	• NS Global Cognition (+ ADAS-Cog, NS MMSE, ES=.26) • NS Immediate & Delayed Memory (+ immediate, NS delayed) • NS Executive/Attention	• Conversion to CATD • Glucose uptake	• Brief cognitive test performance/ Multidomain neuropsychological test performance (ADAS-Cog & MMSE) • Immediate & Delayed Memory (RBANS) • Executive/Attention (TMT A & B)
Kwok, 2012[50]	Memory, reasoning, speed of processing	Group	No Computer	18 hours over 12 weeks	• NS Attention • NS Initiation/ preservation • NS Construction • NS Conceptualization • NS Memory	Subjective Memory Complaints (results not reported)	• Attention, initiation/ preservation, construction, conceptualization, and memory (Domains from Chinese Mattis Dementia Rating Scale) • Subjective memory complaints (Chinese Memory Symptom Scale)
Rapp, 2002[45]	Memory	Group	No Computer	12 hours over 6 weeks	• 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, 2015[51]	Attention, memory, executive processes	Group	No Computer	15 hours over 5 weeks	• NS Global Cognition • NS Memory • NS Executive • Attention or Processing (+ DS Forward, NS DS Backward, symbol search, and TMT 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 (DS, Symbol Search, TMT B), executive (COWAT, TMT A)
Herrera, 2012[46]	Memory, executive, attention, processing speed Note: authors classify as recognition, working memory and recall	Individual	Computer	24 hours over 12 weeks	•Recognition (+ Doors Set A, NS Doors B and DSM48) •Working memory (+ DS Forward, NS DS Backward) •Working memory (+BEM-144 12-word list and MMSE 3 words, NS 16-Item free and cued and Rey Complex Figure)	NR	Recognition (Doors Recognition Sets A and B, DMS48), Working memory (DS Forward and Backward), Recall (BEM-144 12-word-list, 16-Item free and cued, MMSE-3 words, Rey Complex Figure)

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BEM-44= Batterie d'Efficience Mnesique 144; CAMCOG-R=Cambridge Cognition Examination-Revised; CATD=clinical Alzheimer's-type dementia; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; COWAT=Controlled Oral Word Association Test; CVLT-II=California Verbal Learning Test, Second Edition; DMS48=Delayed Matching-to-Sample Task; DS=Digit Span; ES=effect size; MMSE=Mini-Mental State Examination; NR=not reported; NS=no statistically significant difference; RBANS=Repeat Battery for the Assessment of Neuropsychological Status; TMT=Trail Making Test (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 interventions prevent mild cognitive impairment (MCI) or clinical Alzheimer's-type dementia (CATD)* incidence.
- Low-strength evidence shows that multicomponent physical activity interventions offer no clear benefit in cognitive performance over attention control in adults with normal cognition.
- Evidence was insufficient to conclude whether other types of physical activity interventions had benefits for cognitive outcomes in adults with normal cognition.
- While the majority of results showed no significant difference, the pattern of results across very different types of physical activity interventions provides an *indication* of effectiveness of physical activity.

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

Eligible Studies

We identified 48 eligible publications reporting 43 unique studies of physical activity interventions to prevent age-related cognitive decline, MCI, or CATD.[43, 54-100] Twenty-four were assessed as high risk of bias and not used in our analysis, leaving 19 publications for 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. Many justify the relationship by citing previous research. Authors only sometimes proposed mechanisms of action, which included enhanced blood flow and neuronal connectivity,[80, 91] increased brain volume,[80, 91, 100] potential reductions in β-amyloid deposition,[91] reductions in chronic disease risk,[54, 95] anxiety and depression (which are associated with cognitive function), and lowered blood viscosity (which improves aerobic capacity and cognition).[54]

Adults With Normal Cognition

Efficacy: Physical Activity Versus Inactive Control

Twelve randomized controlled trials (RCTs) reported in eight publications with low to medium risk of bias compared physical activity interventions to inactive controls in adults with normal cognition.[54, 60, 71, 80, 83, 85, 86, 89, 91, 95, 97, 100] Total sample sizes ranged from 42 to 1,635. Four studies examined multicomponent physical activity interventions.[83, 91, 95, 100] Single component physical activity interventions consisted of resistance training,[60, 71, 97] aerobic exercise/endurance,[54, 74, 80, 85, 86, 89] and Tai Chi.[95] 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.1 and individual study results in Table 4B.2.

Table 4B.1. Conclusions: Physical activity versus inactive comparisons in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Multicomponent physical activity vs. attention control k=4	Dementia	Unable to draw conclusion.	Insufficient (medium study limitations, imprecise, unknown consistency)
	MCI	Unable to draw conclusion.	Insufficient (medium study limitations, imprecise, unknown consistency)
	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).	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
	Multidomain neuropsychological performance	No benefit in multidomain neuropsychological performance with multicomponent physical activity versus attention control (n=1,635; 2 years).	Low (medium study limitations, indirect, unknown consistency)
	Executive/Attention/ Processing speed	No benefit in executive/attention/processing speed with multicomponent physical activity versus attention control (n=1,885; 6 months to 1 year).	Low (medium study limitations, indirect, imprecise)
	Memory	No benefit in memory with multicomponent physical activity versus attention control (n=1,836; 6 months to 1 year).	Low (medium study limitations, indirect, imprecise)
Resistance training vs. attention control k=3	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/Attention/ Processing speed	No benefit in executive/attention/processing speed with resistance training versus attention control (n=120; 6 months).	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
	Memory	No benefit in brief cognitive test performance with resistance training versus attention control (n=172; 6 months).	Insufficient (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)
k=6	Brief cognitive test performance	No benefit in brief cognitive test performance with aerobic training interventions (n=162; 6 months to 1 year).	Insufficient (medium study limitations, indirect, imprecise)
	Multidomain neuropsychological performance	Limited data.	Insufficient (limited data)
	Executive/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
	Memory	Unable to draw conclusion	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
Tai Chi vs. attention control k=1	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/Attention/ Processing speed	Limited data.	Insufficient (limited data)
	Memory	No data available.	Insufficient (no data)

k=number of studies included; MCI=mild cognitive impairment; n=sample size; vs.=versus

Multicomponent Physical Activity

Multicomponent physical activity interventions included flexibility, strength, balance, endurance, and/or aerobic components.[83, 91, 95, 100] Enrollment criteria varied by trial. One trial enrolled sedentary adults over 70;[91, 100] another enrolled adults over 60,[95] and the last enrolled frail obese older adults.[83]

Only the large 2-year trial (n=1,635) reported diagnostic outcomes, finding no difference between multicomponent physical activity and attention control in diagnosis of MCI or CATD.[91] 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=155) assessed cognition with brief cognitive tests.[83, 100] 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. Evidence was insufficient to conclude whether multicomponent physical activity interventions with durations of 6 months to 1 year have an effect on brief cognitive test performance when compared to attention control in older sedentary adults.

The large 2-year trial (n=1,635) showed no statistical difference with multicomponent physical activity versus attention control in multidomain neuropsychological performance assessed using an investigator-created composite score.[91] Low-strength evidence shows that a multicomponent physical activity intervention with duration of 2 years has 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.[83, 91, 95, 100] Only one of the 13 tests showed a statistically significant improvement with multicomponent physical activity compared with attention control. Low-strength evidence shows 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.

Three trials (n=1,890) reported results of six memory tests; only one test result showed a statistical difference favoring the intervention.[83, 91, 100] Napoli et al. showed greater improvements from baseline with multicomponent physical activity than attention control.[83] 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. Low-strength evidence shows 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, biomarker measures, or adverse effects.

Sink et al. report subgroup effects by sex, age, baseline MMSE and baseline Short Physical Performance Battery scores.[91] 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

Three studies compared resistance training to attention control or placebo.[60, 71, 97] Van de Rest, et al. enrolled adults over 65;[97] Cassilhas et al. enrolled sedentary men between 65 and 75;[60] and Lachman et al. enrolled sedentary older adults with at least one disability.[71] Cassilhas et al. randomized participants to one of three groups (attention control, high-resistance training, and low-resistance training). Lachman et al. randomized participants to the Strong for Life program or waitlist control.

Neither trial reported diagnoses or overall cognitive performance outcomes. Van de Rest reported 11 tests of executive function, attention, and processing speed and Cassilhas et al. reported seven (making comparison for each of the intervention groups to attention control).[60] Evidence was insufficient to draw conclusions about the effects of resistance training on executive function/attention/processing speed or memory. Results were inconsistent. 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 significant

improvement with resistance training compared to placebo control.[97] 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; Corsi's block-tapping, backward; and similarities improved with high resistance training compared with attention control.[60] Scores on digit span, forward; Corsi's block-tapping, backward; and similarities improved with moderate resistance training compared with attention control.[60]

Van de Rest reported six measures of memory;[97] Cassilhas et al. reported two;[60] and Lachman et al. reported one.[71] Van de Rest et al. showed no statistical differences between resistance training and attention control in any memory score.[97] 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.[60] Lachman et al. showed no statistical difference on memory with resistance training versus waitlist control.[71] Evidence was insufficient to draw conclusions about the effects of resistance training on memory.

None of the resistance training intervention studies reported adverse effects.

Van de Rest et al. examined the effect of frailty on the effect of resistance training on reaction time.[97] Treatment-time interaction was not significant for any of the five reaction time measures compared.

Aerobic Activity

Six trials with low to medium risk of bias compared aerobic or endurance programs to an attention control.[54, 74, 80, 85, 86, 89] Antunes et al. enrolled sedentary older men;[54] Ruscheweyh et al. enrolled healthy older adults;[89] Muscari et al. enrolled healthy older adults;[80] Lautenschlager et al. enrolled adults having difficulty with memory and MMSE scores of 24 or greater;[74] Oken et al. enrolled healthy older adults;[85] Okumiya enrolled healthy older adults.[86]

Only Lautenschlager et al. reported dementia diagnosis outcomes and found that aerobic training was less likely to lead to a diagnosis than attention control.[74] Evidence was insufficient to conclude whether aerobic training offers benefits related to preventing dementia.

Three trials reported either brief cognitive or multidomain neuropsychological test performance. Muscari et al. showed that brief cognitive test performance was better with aerobic training[80] Oken et al. showed no statistical difference with aerobic exercise with two tests of brief cognitive test performance.[85] Antunes et al. found that multidomain neuropsychological test performance was better with aerobic training.[54] 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 two of four tests and memory was better in six 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.[95] 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.2. 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Multicomponent Physical Activity Results Summary k=4; n=1,885	**0 of 3 (no difference) k=1**	**NR**	**BCT 1 of 2 favors I k=2 MNP 0 of 1 (no difference) k=1**	**1 of 13 favor I k=4**	**1 of 6 favor I k=3**	**3 of 25 favor I**	**NR**
Sink, 2015[91] Multicomponent physical activity vs. attention control n=1,635 2 years	NS [Dementia]			NS [DSST]	NS [HVLT, Immediate Recall]	1 of 15 favor I	NR
	NS [MCI]		**MNP** NS [Global Composite[a]]	NS [N-Back, 1 back]	NS [HVLT, Delayed Recall]		
	NS [Dementia or MCI]			NS [N-Back, 2 back]	NS [HVLT, Composite[b]]		
				NS [RT on Task Switching, No]			
				NS [RT on task switching, Yes]			
				I>C [RT on Flanker Test, Congruent]			
				NS [RT on Flanker Test, Incongruent]			
				NS [Composite of Flanker test scores[c]]			

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]
Napoli, 2014[83] Multicomponent physical activity vs. attention control n=53 1 year			**BCT** I>C [3MS]	NS [TMT A]	I>C [Word List Fluency]	2 of 4 favor I	NR
				NS [TMT B]			
Taylor-Piliae, 2010[95] I_1 Multicomponent physical activity vs. attention control n=95 6 months				NS [DS Forward]		0 of 2 (no difference)	NR
				NS [DS Backward]			
Williamson, 2009[100] Multicomponent physical activity vs. attention control n=102 1 year			**BCT** NS [3MS]	NS [SCWT]	NS [RAVLT]	0 of 4 (no difference)	NR
					NS [DSST]		
Resistance Training Results Summary k=3; n=170	**NR**	**NR**	**NR**	**8 of 25 favor I k=3**	**3 of 11 favor I k=1**	**11 of 36 favor I**	**NR**
van de Rest, 2014[97] 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	NS		

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]
				[Stroop 1]	[Word Learning Test, Recognition, 30 Words]		
				NS [Stroop 2]	I>C[z] [Attention and Working Memory Composite]		
				NS [Stroop Inference]	NS[z] [Episodic Memory Composite]		
				NS [RT Uncued]			
				NS [RT Cued]			
				NS [Word Fluency-Letter]			
				NS[z] [Processing Speed Composite]			
				NS[z] [Executive Functioning Composite]			
Cassilhas, 2007[60] High resistance training (I_1) 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 Neuropsychological 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[60] Moderate resistance training (I_2) 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]			
Lachman, 2006[71] Resistance training vs. waitlist n=52					NS [DS Backward]		
Aerobic Training Results Summary k=6; n=531	**1 of 1 favors I k=1**	**NR**	**BCT 1 of 3 favor I k=2** **MNP**	**3 of 14 favor I k=3**	**6 of 18 favor I k=5**	**10 of 21 favor I**	**0 of 3 (no difference) (k=1)**

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]
			1 of 1 favor I k=1				
Antunes, 2015[54] Multicomponent physical activity vs. usual care n=46 older males 6 months				I>C [Picture Arrangement, WAIS-III]	NS [Verbal Paired Associates, Trial 1, Easy Pair]	7 of 16 favor I	
				I>C [Corsi Block-tapping, Forward]	I>C [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-		

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]
					Semantic)]		
					I>C [Free Word Recall, Total Words Recalled (Semantic)]		
					NS [Free Word Recall, Intrusions]		
					Unclear [Free Word Recall, Repetitions]		
					Unclear [Free Word Recall, Preservations]		
Ruscheweyh 2011[89] Gymnastics vs.no intervention n=42 6 months					NS [RAVLT-German]	0 of 1 (no difference)	
Ruscheweyh 2011[89] Nordic walking vs. no intervention n=41 6 months					NS [RAVLT-German]	0 of 1 (no difference)	
Muscari, 2010[80] Endurance training vs. information control n=120 1 year			**BCT** I>C [MMSE]			1 of 1 favor I	NR
Lautenschlager, 2008[74] Home-based physical activity vs.			**MNP** I>C [ADAS-Cog]	NS [DSST]	NS [Word List, Immediate Recall]	3 of 5 favor I	NS [Cardiovascular problem]
	I>C				I>C		

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]
information control n=170 6 months	[Clinical Dementia Rating, Sum of Boxes (diagnosis estimate)]				[Word List, Delayed Recall]		NS [Stroke] NS [Shoulder operation]
Oken 2006[85] Aerobic exercise vs. waitlist control n=91 6 months				NS [SCWT Inference]	NS [Word List, Delayed Recall]	0 of 9 (no difference)	
				NS [Covert Orienting (Invalid-Valid)]	NS [Letter-Number Sequencing]		
				NS [Divided Attention]			
				NS [% Errors Above Threshold]			
				NS [Set Shifting: Highest Shift]			
				NS [Simple RT]			
				NS [Choice RT]			
Okumiya 1996[86] Aerobic exercise program vs. no program n=42 6 months			**BCT** NS [MMSE]			0 of 2 (no difference)	
			BCT NS [Hasegawa Dementia Scale]				
Tai Chi Results Summary k=1; n=93	**NR**	**NR**	**NR**	**1 of 2 favor I (k=1)**	**NR**	**NR**	**NR**
Taylor-Piliae,				I_2>C		1 of 2 favor I_2	NR

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]
2010[95] I_2 Tai Chi vs. attention control n=93 6 months				[DS Backward]			
				NS [DS Forward]			

[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. Shading indicates summary rows and columns.

3MS=Modified Mini-Mental State Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BCT=brief cognitive test performance; C=inactive control; DS=Digit Span (Forward or Backward); DSST=Digit Symbol Substitution Test; HVLT-R=Hopkins Verbal Learning Test-Revised; I=intervention; I_1=first intervention; I_2=second intervention; k=number of studies; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological performance; n=sample size; NR=not reported; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; RCFT=Rey-Osterrieth Complex Figure Test; RT=reaction time; SCWT=Stroop Color Word Test; TMT=Trail-Making Test (Parts A and/or B); vs.=versus; WAIS=Wechsler Adult Intelligence Scale

Comparative Effectiveness: Physical Activity Versus Active Comparison

Seven studies compared physical activity interventions to active interventions.[56, 60, 62, 83, 85, 89, 95] Individual study results are provided in Table 4B.3. 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.[62] Napoli et al. (n=54) compared exercise with an exercise and diet program.[83] Baker et al. (n=34) compared 6-months of an aerobic exercise program with stretching.[56] Taylor-Piliae et al. (n=132) compared multicomponent physical activity with Tai Chi.[95] Cassilhas et al. (n=39) compared a high intensity resistance training with a lower intensity resistance training.[60] Oken et al. (n=91) compared yoga to aerobic exercise.[85] Ruscheweyh et al. (n=41) compared two types of aerobic activity, an aerobic exercise class with Nordic walking.[89]

None of the eligible studies reported diagnostic outcomes. Five comparative effectiveness trials showed no statistical differences in any cognitive category, despite examining many comparisons.[60, 62, 83, 85, 89] 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.[56] 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.[95]

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.3. 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Aerobic vs. Stretching/Toning/ Yoga Results Summary k=2; n=125	**NR**	**NR**	**NR**	**3 of 12 favor I_1 k=2**	**0 of 3 favor I_1 k=2**	**3 of 15 favor I_1**	**NR**
Baker, 2010 [56] Aerobic exercise (I_1) vs. stretching (I_2) n=34 6 months				$I_1>I_2$ [TMT B]	NR [Story Recall]	3 of 7 favor I_1	NR
				$I_1>I_2$ [Task Switching]			
				$I_1>I_2$ [SCWT Inference			
				NS [Self-Ordered Point Test]			
				NS [Verbal Fluency]			
Oken 2006[85] Yoga vs. aerobic exercise n=91 6 months				NS [SCWT Inference]	NS [Word List, Delayed Recall]	0 of 9 (no difference)	
				NS [Covert Orienting (Invalid-Valid)]	NS [Letter-number sequencing, WAIS-III]		
				NS [Divided Attention Threshold]			
				NS [% Errors Above Threshold]			
				NS [Set Shifting: Highest Shift]			
				NS [Simple RT]			
				NS			

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]
				[Choice RT]			
Unique Comparisons	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Eggenberger, 2015[62] Dance/treadmill memory training vs. treadmill n=89 6 months				NS [TMT A]	NS [Story Recall]	0 of 9 (no difference)	NR
				NS [TMT B]	NS [Paired Associates Learning]		
				NS [Executive Control Task]			
				NS [DS Forward]			
				NS [Age Concentration Test A]			
				NS [Age Concentration Test B]			
				NS [DSST]			
Napoli, 2014[83] I_1 Exercise vs. I_2 diet + exercise n=54 1 year			**BCT** NS [3MS]	NS [TMT A]	NS [Word List Fluency]	0 of 4 favor (no difference)	NR
				NS [TMT B]			
Ruscheweyh 2011[89] Nordic walking vs. gymnastics n=41 6 months					NS [AVLT]	0 of 1 (no difference)	
Taylor-Piliae, 2010[95] I_1 Multicomponent physical activity vs.				I_2>I_1 [DS Backward]		1 of 2 favor I_2	
				NS [DS Forward]			

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]
I_2 Tai Chi n=70							
Cassilhas, 2007[60] High resistance training (I_1) vs. Moderate resistance training (I_2) n=39 6 months				NS [DS Forward]	NS [RCFT, Copy]	0 of 9 (no difference)	NR
				NS [DS Backward]	NS [RCFT, Immediate Recall]		
				NS [Corsi Block, Forward]			
				NS [Corsi Block, Backward]			
				NS [Corsi Block, Similarites]			
				NS [Toulouse-Pieron, Cancellations Numbers]			
				NS [Toulouse-Pieron, Errors]			

AVLT=Auditory Verbal Learning Test; C=inactive control; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution Test; I=intervention; I_1=first intervention; I_2=second intervention; k=number of studies; n=sample size; NR=not reported; NS=no statistically significant difference; RCFT=Rey-Osterrieth Complex Figure Test; RT=reaction time; SCWT=Stroop Color Word Test; TMT=Trail Making Test (A and/or B) vs.=versus; WAIS=Wechsler Adult Intelligence Scale
Shading indicates summary rows and columns.

Adults With MCI

Conclusions are provided in Table 4B.4 and individual study results in Table 4B.5.

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

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Multicomponent physical activity vs. attention control k=1	Dementia	No data available.	Insufficient (no data)
	MCI	No data available.	Insufficient (no data)
	Brief cognitive test performance	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise)
	Multidomain neuropsychological performance	Limited data.	Insufficient (limited data)
	Memory	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise)
Aerobic training vs. attention control k=2	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	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
	Executive Function	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise)
	Memory	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise)

k=number of studies included; MCI=mild cognitive impairment; vs.=versus

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.[67, 74, 93, 94] Lautenschlager et al. (n=170) compared a 24-week home-based exercise program with usual care.[74] Hildreth et al. (n=78) compared a 6-month endurance exercise program with placebo in obese older adults with MCI.[67] Suzuki et al. compared a 6-month multicomponent physical activity program to attention control in older adults with MCI or amnestic MCI.[93]

All three trials reported multidomain neuropsychological test performance measured with the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Lautenschlager et al. showed improvements with the home-based physical activity program versus usual care.[74] Hildreth et al. showed no statistical difference with endurance exercise versus placebo (for control for a pioglitazone arm) and no exercise.[67] Suzuki et al. showed no statistical difference with a 6-month multicomponent physical activity program versus attention control.[93] Lautenschlager et al. showed no difference in executive function/ attention/processing speed with home exercise versus usual care compared using two different measures.[74] 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.[93]

We identified six reports of five unique studies comparing physical activity interventions to active interventions in older adults with MCI.[56, 72, 73, 75, 81] All were assessed high risk of bias.

Interpreting the Findings

These results show no 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. If physical activity lowers risk for cognitive decline and CATD and interventions can be effectively implemented to change behaviors, these interventions likely involve long-term investment and may need to begin earlier in the aging process. Long-term studies enrolling younger adults would greatly benefit the field and provide important insight on prevention.

Table 4B.5. 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Multicomponent Physical Activity Results Summary k=1; n=100	**NR**	**0 of 2 (no difference) k=1**	**BCT 1 of 3 favor I k=1 MNP 0 of 1 (no difference) k=1**	**0 of 4 (no difference) k=1**	**1 of 5 favors I k=1**	**2 of 15 favor I**	**0 of 1 (no difference) k=1**
Suzuki, 2013[93] Multicomponent physical activity vs. attention control n=100 6 months		NS [MTA-ERC]	**BCT** NS [MMSE]		NS [WMS-LM I]	0 of 6 (no difference)	NS [Falls and hospitalization for illness]
		NS [WBC]	**MNP** NS [ADAS-Cog]		NS [WMS-LM II]		
Suzuki, 2012[94] Multicomponent physical activity vs. attention control (aMCI subgroup of Suzuki 2013) n=50 6 months 12 months			**BCT** I>C [MMSE, 6 months]	NS [SCWT-I]	I>C [WMS-LM I, 6 months]	2 of 9 favor I	
			BCT NS [MMSE, 12 months]	NS [SCWT-II]	NS [WMS-LM I, 12 months]		
				NS [DSST]	NS [WMS-LM II]		
				NS [LVFT]			
Aerobic Training Results Summary k=2; n=153	**0 of 1 (no difference) k=1**	**NR**	**MNP 1 of 2 favors I k=2**	**0 of 8 (no difference) k=2**	**0 of 5 (no difference) k=2**	**1 of 16 favor I**	**0 of 4 (no difference) k=2**
Hildreth, 2015[67] Endurance training vs. usual care +			**MNP** NS [ADAS-Cog]	NS [WMS-R VR II]	NS[a] [Memory Composite]	0 of 11 (no difference)	Unclear [Musculo-skeletal Complaints]

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]
placebo (for control for pioglitazone arm) n=53 6 months				NS [Picture Completion, WAIS-R]	NS [WMS-R, LM II]		
				NS[b] [Executive Function Composite]	NS [RAVLT]		
				NS [TMT B]			
				NS [DSST]			
				NS [SCWT]			
				NS [DSST]			
Lautenschlager, 2008[74] Home-based physical activity vs. information control n=100 6 months	NS [CDR, Sum of Boxes (diagnosis estimate)]		**MNP** I>C [ADAS-Cog]	NS [DSST]	NS [Word List, Immediate Recall]	1 of 5 favor I	NS [Cardiovascular Problem] NS [Stroke] NS [Shoulder Operation]
					NS [Word List, Delayed Recall]		

[a]=Scaled score for domain: visual reproduction II, logical memory II, RAVLT; [b]= Domain scaled score: TMT B, DSST
Shading indicates summary rows and columns.

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BCT=brief cognitive test performance; C=inactive control; CDR=Clinical Dementia Rating; DSST=Digit Symbol Substitution Test; I=intervention; k=number of studies included; LM=logical memory; LVFT= letter verbal fluency test; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological test performance; MTA-ERC=medial temporal areas including the entorhinal cortex; n=sample size; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; SCWT=Stroop Color and Word Test; TMT=Trail-Making Test (A and/or B); VR=Visual Reproduction; vs.=versus; WAIS-R=Wechsler Adult Intelligence Scale-Revised; WMS=Wechsler Memory Scale; WBC= whole brain cortices

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 reduced CATD incidence or improved cognitive performance in adults with normal cognition.
- Few studies examined the effects of nutraceuticals on adults with mild cognitive impairment (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 25 eligible publications reporting 23 unique studies of nutraceutical interventions to prevent age-related cognitive decline, MCI, or CATD.[59, 101-124] Eight were assessed as high risk of bias and not used in our analysis, leaving 15 studies to use 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 Nutraceutical 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 k=7	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 limitations 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)
	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 limitations, indirect, imprecise)
	Multidomain neuropsychological	No benefit in multidomain neuropsychological performance with omega-3 fatty acids versus	Low (medium study limitations, indirect, imprecise, unknown

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
	performance	placebo in long term (n=744; 2 years).	consistency)
	Executive/Attention/ Processing speed	No benefit in executive/attention/processing speed with omega-3 fatty acids versus placebo in long term (n=5,079; up to 6 years).	Low (medium study limitations, indirect, imprecise)
	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 limitations, indirect, imprecise)
Omega -3 fatty acids vs. B vitamins (folate, B_6, B_{12}) k=1	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 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 + B vitamins (folate, B_6, B_{12}) vs. B vitamins (folate, B_6, B_{12}) k=1	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 B vitamins and omega-3 versus B vitamins alone in long term (n=884; 4 years).	Low (low 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 B vitamins with omega-3 versus B vitamins alone in long term (n=884; 4 years).	Low (low study limitations, indirect, imprecise, consistent)
Ginkgo biloba vs. inactive control k=3	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)
	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=3,069; 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=5,079; 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)

k=number of studies included; MCI=mild cognitive impairment; n=sample size; vs.=versus

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.[101, 103, 107, 115, 117, 119, 120] Total sample sizes ranged from 65 to 11,685. Yurko-Mauro et al. used only docosahexaenoic acid (DHA),[119]

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.[107] Only the ORIGIN study (n=15,077) allowed adults already using omega-3 supplementation to participate in the study.[120] All studies assessed baseline cognition; six reported baseline Mini-Mental State Examination (MMSE) score of at least 28[103, 107, 115, 117, 119, 120] while one study used the Isaacs Set Test (35.8).[101] However, only three studies specified a baseline cognition inclusion criterion.[103, 115, 119] Populations studied included adults with diabetes or impaired glucose tolerance,[120] a history or ischemic heart disease,[101] coronary patients,[107] or healthy adults.[103, 115, 117, 119]

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]).[120]

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. None of four studies (n=16,431) found a statistical improvement in brief cognitive test performance, such as the MMSE;[101, 107, 119, 120] likewise, one study that assessed multidomain neuropsychological performance using a global composite also found no statistical difference between groups.[103] Of 32 tests to assess executive function in five studies (n=5,079), 29 tests did not find a significant difference between groups, with a maximum followup of 6 years.[103, 115, 117, 119, 120] 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.[117, 119] Similarly, of 25 tests to assess memory in five studies (n=3,428),[101, 103, 115, 117, 119] 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 six memory tests (n=483).[119]

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 subgoups. No significant differences in effect were found for age,[101, 107, 115, 120] sex,[107, 115, 120] or inclusion criteria disease condition.[107, 120]

Andreeva et al. used a 2X2 factorial design, assigning adults with a history of ischemic heart disease to four groups: placebo, omega-3, B vitamins (folate, B_6, B_{12}), or omega-3 plus B vitamins.[101] 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 B vitamins alone group also found no significant differences between groups for any outcome. Likewise, the omega-3 plus B vitamins versus B vitamins alone did not result in significant differences between groups.

Ginkgo Biloba Extract

Three randomized controlled trials (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.[104, 105, 113, 116] Total sample sizes ranged from 118 to 3,069. All studies assessed baseline cognition, two reporting baseline MMSE scores of at least 27.6[105, 116] while one reported baseline Modified Mini-Mental State Examination (3MS) of 93 and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) of 6.5.[104, 113]

All studies specified a baseline cognition inclusion criterion.[103, 115, 119] Age inclusion criterion were ≥70,[116] ≥75,[104, 113] and ≥85.[105]

Two studies provide low-strength evidence suggesting that ginkgo biloba does not affect incidence of probable CATD compared to placebo.[104, 113, 116] Both studies assessed probable CATD according to Diagnostic Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria by adjudication panels of clinical experts.

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.[113] Likewise, no differences between groups were found in either executive function[113] or memory.[105, 113]

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).[104, 113, 116] Dodge et al., who recruited 122 adults 85 years and older with normal cognition, reported a larger number of strokes and transient ischemic attacks (TIA) in the gingko biloba group over 3.5 years (7 vs. 0, p=.01).[105] However, the larger study by Vellas et al. (n=2,820) found no significant differences between groups in stroke, hemorrhagic events, and cardiac disorders over 5 years.

Two studies explored the effects of the ginkgo biloba interventions versus placebo on several subgoups. 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.[116] The authors also advised caution in interpreting the results since they assessed 13 planned subgroups (including age, APOE-4, MMSE ≤27 at baseline, hypertension, diabetes, hypercholesterolemia, 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).[116] 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

Three 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.[118] 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 after 85 weeks no differences between groups.[111]

Strike et al. (n=27) examined a commercial supplement containing 1 g DHA, 160 mg EPA, 240 mg ginkgo biloba, 60 mg phosphatidylserine, 20 mg vitamin E, 1 mg folic acid, and 20 mcg vitamin B_{12} per day versus placebo.[121] The authors hypothesized the combination would provide a synergistic effect. After 6 months, the intervention group improved compared to the control

group in one out of three executive function/attention/processing speed outcomes and one out of three memory tests.

No adverse effects were reported in any study. Due to the evidence base of single studies with small sample sizes (n<500), strength of evidence was not assessed for these three interventions.

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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Omega-3 Results Summary k=7; n=21,027	**0 of 1 (no difference) k=1**	**1 of 2 favor I k=2**	**BCT 0 of 9 (no difference) k=4 MNP 0 of 1 (no difference) k=1**	**2 of 31 favor I k=5**	**3 of 25 favor I k=1**	**6 of 68 favor I**	**0 of 4 (no difference) k=2**
Cukierman-Yaffe, 2014[120] Omega-3 (EPA 465 mg + DHA 375 mg daily) n=15,077 Median 6.2 years	NS [Incident probable cognitive impairment = reported dementia or an MMSE score of < 24] (n=12,536)		**BCT** NS [MMSE] (n=11,685)	NS [DSST] (n=3,392)		0 of 2 favor I	NR
Witte, 2014[117] 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, SCWT Parts 1-3]	Ns [Memory Composite: AVLT Learning, Delayed Recall, Recognition, DS Backward]	2 of 6 favor I	NR
		NS [MRI - White Matter Integrity]		NS [Sensorimotor Speed Composite: TMT A, SCWT A & B]			
				NS [DS Forward]			

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]
Geleijnse, Geleijnse 2012[107] Omega-3 (EPA-DHA 400mg/d) vs. placebo n=2,522 40 months			**BCT** NS [MMSE]			0 of 3 (no difference)	
			BCT NS [Risk of Moderate/Severe Cog Decline, MMSE][a]				
			BCT NS [Risk of Severe Cog Decline, MMSE][b]				
Geleijnse, 2012[107] Omega-3 (ALA 200mg/d) vs. placebo n=2,522 40 months			**BCT** NS [MMSE]			0 of 3 (no difference)	NR
			BCT NS [Risk of Moderate/Severe Cog Decline, MMSE][a]				
			BCT NS [Risk of Severe Cog Decline, MMSE][b]				
Andreeva, 2011 [101] Omega-3 (EPA-DHA 600 mg/d in a 2:1 ratio) vs. placebo n=1,741 4 years			**BCT** NS [F-TICS Overall Score]		NS [F-TICS Attention & Semantic Memory Subscore]	0 of 3 (no difference)	NR
					NS [F-TICS Recall/Repetition Subscore]		

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]
Dangour, 2010 [103] 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 difference)	NS [hospitalization for stroke or MI]
				NS [Processing Speed Composite: Letter Cancellation, Simple RT, Choice RT, DSST]	NS [CVLT - Delayed Recall]		
				NS [Letter Search/ Cancellation]	NS [Memory Composite: CVLT Sum of Words, CVLT Delayed Recall, Location Memory & Delayed, Story Recall & Delayed]		
				NS [SDMT]	NS [Global Delay Composite: CVLT Delayed Recall, Location Memory Delayed Recall, Story Recall delayed]		
				NS [RT, Simple]	NS [Story Recall - Immediate]		
				NS [RT, Choice]	NS [Story Recall - Delayed]		
				NS [DS Forward]	NS [Spatial Memory - Immediate]		
				NS [DS Backward]	NS [Spatial Memory -		

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]
					Delayed]		
Yurko-Mauro, 2010[119] 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 [Musculoskeletal]
					I>C [CANTAB VRM - Immediate Recall]		NS [Gastrointestinal]
					I>C [CANTAB VRM - Delayed Recall]		NS [Nervous System]
					NS [CANTAB SWM]		
					NS [CANTAB PRM - Delayed]		
Van de Rest, 2008[115] Omega-3 (EPA-DHA 400 mg/d) vs. placebo n=196 6 months				NS [Executive Composite: TMT A & B, SCWT Part 3: (part 1 + part 2/2), Word Fluency Animals & Letter]	NS [Memory Composite: Word Learning Immediate, Delayed, & Recognition, DS Backward]	0 of 13 (no difference)	
				NS [Attention Composite]	NS [Word Learning - Immediate Recall]		
				NS [DS Forward]	NS [Word Learning - Delayed Recall]		
				NS [DS Backward]	NS [Word Learning - Recognition]		
				NS [TMT A]			

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]
				NS [TMT B]			
				NS [SCWT Part 1]			
				NS [SCWT Part 2]			
				NS [SCWT Part 3: (part 1 + part 2/2)]			
Van de Rest, 2008[115] 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 difference)	
				NS [Attention Composite]	NS [Word Learning, Immediate Recall]		
				NS [DS Forward]	NS [Word Learning, Delayed Recall]		
				NS [DS Backward]	NS [Word Learning, Recognition]		
				NS [TMT A]			
				NS [TMT B]			
				NS [SCWT Part 1]			
				NS [SCWT Part 2]			
				NS [SCWT Part 3: (part 1 + part 2/2)]			
B vitamins (folate/B_6/B_{12}) vs. omega-3	**NR**	**NR**	**0 of 1 (no difference) k=1**	**NR**	**0 of 2 (no difference) k=1**	**0 of 3 (no difference)**	**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]
Results Summary k=1; n=885							
Andreeva, 2011[101] B vitamins (folate, B_6, B_{12}) vs. Omega-3 n=885 4 years			**BCT** NS [TICS]		NS [TICS Memory]	0 of 3 (no difference)	NR
					NS [TICS Recall]		
B vitamins (folate/B_6/B_{12}) + omega-3 vs. B vitamins Results Summary k=1; n=884	**NR**	**NR**	**0 of 1 (no difference) k=1**	**NR**	**0 of 2 (no difference) k=1**	**0 of 3 (no difference)**	**NR**
Andreeva, 2011[101] B vitamins (folate, B_6, B_{12}) + omega-3 vs. B vitamins (folate, B_6, B_{12}) n=884 4 years			**BCT** NS [TICS]		NS [TICS Memory]	0 of 3 (no difference)	NR
					NS [TICS Recall]		
Ginkgo biloba Results Summary k=3; n=6,041	**0 of 11 (no difference) k=3**	**NR**	**MNP 0 of 1 (no difference) k=1**	**0 of 5 (no difference) k=1**	**0 of 4 (no difference) k=2**	**0 of 10 (no difference)**	**All serious AEs NS except C>1 [Stroke/ TIA]**
Vellas, 2012[116] Ginkgo biloba extract (EGb761) 120 mg twice daily vs. placebo n=2,820 5 years	NS [Incidence of Probable CATD, Each Year For 5 Years]					No intermediate outcomes reported	NS [stroke, haemorrhagic events, cardiac disorders]

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]
Snitz, 2009[113] **DeKosky 2008**[104] Ginkgo biloba extract 120 mg twice daily n=3,069 (normal cog & MCI, cognitive test results) n=2,587 (incident AD/dementia) Median 6.1 years	NS [All Dementia]		**MNP** NS [Composite: 3MS & ADAS-Cog]	NS [Executive Composite: TMT B & SCWT]	NS [Memory Composite: CVLT & Recall Conditions - Modified RCFT]	0 of 9 (no difference)	NS [mortality, CHD, stroke, major bleeding]
	NS [CATD Without Vascular Dementia]			NS [Attention & Psychomotor Speed Composite: WAIS-R DS & TMT A]	NS [CVLT]		
	NS [CATD With Vascular Dementia]			NS [TMT B]	NS [Recall Conditions - Modified RCFT]		
	NS [total CATD]			NS [TMT A]			
				NS [WAIS-R DS]			
Dodge, 2008[105] 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 1 (no difference)	C>I [Stroke/ TIA] [AEs in treatment group]
							NS [Cardiac, renal, falls, other]
Resveratrol	**NR**	**3 of 5 favor I**	**NR**	**NR**	**2 of 6 favor I**	**5 of 11 favor**	**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]
Results Summary k=1; n=46		**k=1**			**k=1**	**I**	
Witte, 2014[118] 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]		
Plant Sterols/Stanols Results Summary	**NR**	**NR**	**NR**	**0 of 3 (no difference) k=1**	**0 of 1 (no difference) k=1**	**0 of 4 (no difference)**	**NR**
Schiepers, 2009[111] Margarines enriched with plant sterol esters (2.5 g/d) or plant stanol				NS [Simple Information Processing Speed Composite: SCWT 1 & 2, Concept Shifting Tests A & B]	NS [Composite: Visual Verbal Word Learning Task Total Free Recall, Delayed Recall, Recognition]	0 of 4 (no difference)	No adverse effects reported

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]
esters (2.5 g/d) n=57 1.6 years (85 weeks)				NS [Complex Speed Composite: SCWT 3, Complex Shifting Test]			
				NS [DSST]			
Omega 3 Multinutrient Results Summary k=1; n=27	**NR**	**NR**	**NR**	**1 of 3 favor I k=1**	**1 of 3 favor I k=1**	**2 of 6 favor I**	**NR**
Strike, 2016 [121] Efalex Active 50+ per day vs. placebo n=27 6 months				I>C [CANTAB Motor Screening Task]	I>C [CANTAB VRM Immediate]	2 of 6 favor I	
				NS [CANTAB Motor Screening Touch Accuracy]	NS [CANTAB VRM Delayed]		
				NS [Stockings of Cambridge]	NS [CANTAB PAL]		
Omega-3 versus B Vitamins Results Summary k=1; n=884	**NR**	**NR**	**BCT 0 of 1 (no difference) k=1 MNP NR k=1**	**NR**	**0 of 2 (no difference) k=1**	**0 of 3 (no difference)**	**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]
Andreeva, 2011[101] Omega-3 + B vitamins (folate, B_6, B_{12}) vs. B vitamins (folate, B_6, B_{12}) n=884 4 years			**BCT** NS [TICS-m]		NS [TICS-m Memory]	0 of 3 (no difference)	NR
					NS [TICS-m Recall]		

[a]Decrease of 3 or more MMSE points or, if missing, incidence of cognitive decline or dementia.
[b]Decrease of 5 or more MMSE points or, if missing, incidence of cognitive decline or dementia.
[c]Composite: 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]

Shading indicates summary rows and columns.

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; Ads=adverse effects; AVLT=Auditory Verbal Learning Test; B_6=vitamin B_6; B_{12}=vitamin B_{12}; BCT=brief cognitive test performance; C=control; CANTAB=Cambridge Nueropsychological Test Automated Battery; CANTAB PAL=Cambridge Nueropsychological Test Automated Battery Paired Associated Learning Test; CATD=clinical Alzheimer's-type dementia; CDR=Clinical Dementia Rating; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CHD=coronary heart disease; CVLT=California Verbal Learning Test; DHA=docosahexaenoic acid; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution; EPA=eicosapentaenoic acid; F-TICS=French version, Telephone Interview Cognitive Status; g/d=grams per day; HC=hippocampus; I=intervention; k=number of studies included; MCI=mild cognitive impairment; mg/d=milligrams per day; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological test performance; MRI=magnetic resonance imaging; n=sample size; NR=not reported; NS=no statistically significant difference; PRM=Pattern Recognition Memory; RCFT=Rey-Osterrieth Complex Figure Test; RT=reaction time; SCWT=Stroop Color Word Test; SDMT=symbol digit modalities test; SWM=Spatial Working Memory; TIA=transient ischemic attack; TICS=Telephone Interview Cognitive Status; VRM=Verbal Recognition Memory; WAIS=Wechsler Adult Intelligence Scale;

Adults With MCI

Nutraceuticals Versus Inactive Control

Three RCTs compared nutraceuticals to inactive controls in older adults with MCI.[104, 106, 108] 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.[108] After 1 year, no significant change in MMSE scores was observed. However, people taking omega-3 performed better than those on placebo on one of three tests of executive function/attention/processing speed, and better on three of five 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.[104, 106] Follow-up periods in the studies varied, with Gavrilova's study lasting 6 months[81] and median follow-up in DeKosky et al. lasting 6.1 years.[79]

DeKosky et al. examined diagnostic outcomes.[104] Of five categories of dementia, no significant differences were found between ginkgo and placebo groups. Gavrilova et al. included two 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.[106]

Gavrilova et al. reported no serious adverse effects.[106] 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.[104] Evidence to draw conclusions was insufficient due to limited data (single study with n<500) or no data.

Interpreting the Findings

The results show no benefit for the nutraceuticals that have been examined. Some nutraceuticals, such as resveratrol, have not been studied enough 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 Results Summary k=1; n=36	**NR**	**NR**	**0 of 1 (no difference) k=1**	**1 of 3 favor I k=1**	**3 of 5 favor I k=1**		**No serious AEs reported**
Lee, 2013[108] Omega-3 fatty acids (DHA 430 mg and EPA 150 mg) daily n=36 1 year			**BCT** NS [MMSE]	NS [Composite: CLOX-1, DS Forward]	I>C [Composite: VR I, VR II, RAVLT – Immediate & Delayed Recall, DS Backward]	4 of 9 favor I	No serious AEs reported
				NS [DSST]	I>C [VR I]		
				I>C [DS Forward & Backward]	NS [VR II]		
					NS [RAVLT, Immediate Recall]		
					I>C [RAVLT, Delayed Recall]		
Ginkgo Biloba Results Summary k=2; n=642	**0 of 5 (no difference) k=1**	**NR**	**NR**	**2 of 2 favor I**	**NR k=1**	**2 of 2 favor I**	**NS k=1**
Gavrilova, 2014 [106] 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]			
DeKosky, 2008 [104] Ginkgo biloba extract 120 mg twice daily n=482 (MCI sub-	NS [All Dementia]						Serious AEs reported (NS):
	NS						death,

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]
sample) Median 6.1 years	[CATD Without Vascular Dementia]						bleeding, CHD, stroke.
	NS [CATD With Vascular Dementia]						
	NS [Total AD]						
	NS [Vascular Dementia Without CATD]						

AD=Alzheimer's disease; AE=adverse event; BCT=brief cognitive test performance; C=control; CATD: clinical Alzheimer's-type dementia; CHD=coronary heart disease; CLOX-1=Clock Drawing Test; DHA=docosahexaenoic acid; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution Test; EPA=eicosapentaenoic acid; I=intervention; k=number of studies included; MMSE=Mini-Mental State Examination; n=sample size; MCI=mild cognitive impairment; mg=milligrams; MMSE=Mini-Mental State Examination; NR=not reported; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; RCT: randomized controlled trial; TMT=Trails Making Test (A & B); VR=visual reproduction

Shading indicates summary rows and columns.

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 mild cognitive impairment (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 nine eligible publications reporting six unique studies evaluating the effect of diet interventions to prevent age-related cognitive decline, MCI, or CATD.[69, 83, 125-131] Six studies were high risk of bias (including studies of the Mediterranean diet) 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.[83, 125] Another proposed mechanism involves the effect of antioxidants (diets rich in these foods) on oxidative stress and vascular impairment, decreasing risk.[129]

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.[130] Sixty-five older adults were randomized to receive either 15mg of protein twice daily or a placebo drink for 24 weeks. No diagnostic 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 randomized controlled trial (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.[83] 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 $\pm$ 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/ Multidomain Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Protein Supplement vs. Placebo Results Summary k=1; n=65	**NR**	**NR**	**NR**	**0 of 13 (no difference) k=1**	**0 of 3 (no difference) k=1**	**0 of 16 (no difference)**	**NR**
van der Zwaluw, 2014[130] Protein drink (15 mg of protein) twice daily vs. placebo n=65 24 weeks				NS [DS Forward]	NS [WLT, Immediate]	0 of 16 (no difference)	NR
				NS [DS Backward]	NS [WLT, Delayed]		
				NS [TMT A]	NS [WLT, Recognition]		
				NS [SCWT 1]			
				NS [SCWT 2]			
				NS [SCWT 3]			
				NS [RT Test]			
				NS [TMT B/A]			
				NS [Word Fluency, Animals]			
				NS [Word Fluency, Letter P]			
				NS [Composite]			
				NS [Composite]			
				NS [Composite]			

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]
Energy Restriction Results Summary k=1; n=53	**NR**	**NR**	**1 of 1 favors I**	**0 of 2 (no difference)**	**NR**	**1 of 3 favors I**	**NR**
Napoli, 2014[83] Energy deficit of 500–750 kcal/d from daily requirements vs. control n=53 1 year			**BCT** I>C [3MS]			1 of 3 favors I	NR
				NS [TMT A]			
				NS [TMT B]			

3MS=Modified Mini-Mental State Examination; BCT=brief cognitive test performance; C=control; DS=Digit Span (Forward and/or Backward); k=number of studies included; kcal/d=calories per day; I=intervention; n=sample size; MNP=multidomain neuropsychological test performance; NR=not reported; NS=no statistically significant difference; RT=reaction time; SCWT=Stroop Color/Word Test; TMT=Trail Making Test (Part A and/or B); vs.=versus; WLT=Word Learning Test.
Shading indicates summary rows and columns.

Chapter 4E. Results: Multimodal Interventions

Key Messages

- Evidence is insufficient to conclude whether most multimodal interventions offer benefits for cognitive performance or incidence of mild cognitive impairment (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.
- Low-strength evidence shows that a multimodal intervention composed of lifestyle advice and drug treatment is not effective in reducing incidence of CATD or benefiting brief cognitive test performance or memory.

*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 that reported unique studies of multimodal interventions to prevent age-related cognitive decline, MCI, or CATD.[62, 66, 69, 72, 83, 87, 97, 126, 132-144] Thirteen were assessed as high risk of bias and not used in our analysis.[66, 69, 72, 87, 132, 134, 136-140, 143, 144] 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.[62, 133, 142] 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[54, 80, 91] or cognitive training[25] and reduced dementia risk. Because an almost infinite number of interventions can be combined, creating categories for review and analysis is a daunting task.

Table 4E.1 lists the components included in the seven studies that had low to medium risk of bias. Six of the eight studies included physical activity as part of the multimodal intervention. The two most frequent combinations across the eight 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 Supplements	Goal Setting	Lifestyle Advice	Drug Treatment
Clare, 2015[133]					•		
Eggenberger, 2015[62]	•		•				
Ngandu, 2015[142]	•	•	•				
Hars, 2014[135]	•		•				
Napoli, 2014[83]	•	•					
van de Rest, 2014[97]	•			•			
Martin, 2007[126]	•	•					
Moll van Charante, 2016						•	•

Adults With Normal Cognition

Efficacy: Multimodal Interventions Versus Inactive Control

Seven studies with low to medium risk of bias enrolling a total of 5,132 adults compared multimodal interventions with inactive controls in adults with normal cognition.[83, 97, 126, 133, 135, 141, 142] All were randomized controlled trials (RCTs). Total sample sizes ranged from 24 to 3,526. 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 k=2	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/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, inconsistent)
	Memory	Limited data.	Insufficient (limited data)
Physical Activity and Cognitive Training k=1	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/Attention/ Processing speed	No data available.	Insufficient (no data)
	Executive/Attention /Processing speed	No data available.	Insufficient (no data)
Physical Activity, Diet, and Cognitive Training k=1	Dementia	No data available.	Insufficient (no data)
	MCI	No data available.	Insufficient (no data)
	Brief cognitive test	No data available.	Insufficient (no data)

Intervention Components	Outcome	Conclusion	Strength of Evidence (justification)
	performance		
	Multidomain neuropsychological performance	Intervention composed of diet, physical activity, and cognitive training improves multidomain neuropsychological test performance; unclear if improvement is clinically meaningful (n=1,260; 2 years).	Low (indirect, unknown consistency)
	Executive/Attention/Processing speed	Intervention composed of diet, physical activity, and cognitive training improves executive/attention/processing speed; unclear if improvement is clinically meaningful (n=1,260; 2 years).	Low (indirect, unknown consistency)
	Memory	Unable to draw conclusion (n=1,260; 2 years).	Insufficient (indirect, imprecise, inconsistent)
Physical Activity and Protein Supplementation k=1	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/Attention/ Processing speed	Limited data.	Insufficient (limited data)
	Memory	Limited data.	Insufficient (limited data)
Goal Setting and Mentoring k=1	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/Attention/ Processing speed	Limited data.	Insufficient (limited data)
	Memory	Limited data.	Insufficient (limited data)
Individualized Lifestyle Advice and Medical Management k=1	Dementia	No benefit to dementia risk from individualized intervention composed of lifestyle advice and medical management (n=526; 6 years).	Low (medium study limitations, direct, imprecise, unknown consistency)
	MCI	No data available.	Insufficient (no data)
	Brief cognitive test performance	No benefit in brief cognitive test performance from individualized intervention composed of lifestyle advice and medical management (n=526; 6 years).	Low (medium study limitations, indirect, unknown consistency)
	Multidomain neuropsychological performance	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	No data available.	Insufficient (no data)
	Memory	No benefit to memory from individualized intervention composed of lifestyle advice and medical management (n=526; 6	Low (medium study limitations, indirect, unknown consistency)

Intervention Components	Outcome	Conclusion	Strength of Evidence (justification)
		years).	

K=number of studies included; MCI=mild cognitive impairment; n=sample size

Physical Activity and Diet

Two trials (n=79) compared physical activity and diet with inactive controls.[83, 126] 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, three times per week for 1 year.[83] Martin et al. randomized overweight young to middle aged adults to a calorie restriction diet and structured exercise for 6 months.[126]

Neither trial reported diagnostic outcomes or multidomain neuropsychological test performance. Napoli et al. reported brief cognitive test performance for one measure (Modified Mini-Mental State Examination, 3MS) and found a statistically significant improvement with the physical activity and diet intervention compared with attention control.[83] Martin et al. reports 11 measures of memory, none of which differed between physical activity with diet and attention control.[126] 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,[83] and Martin et al. reported eight.[126] 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.[83] The remaining nine measures from Napoli et al. and Martin et al. showed no statistically significant difference with multimodal intervention compared with attention control.[83, 126] 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.[135] Adults who were frail or had an increased risk of falling were randomized to a structured, music-based exercise or their usual lifestyle habits.[135] The intervention involved weekly 60-minute structured music-based multitasking exercise classes for 6 months.

One measure of brief cognitive test performance (Mini-Mental State Examination, MMSE) showed no statistically significant improvements with the intervention compared with the control. Hars et al. also reported two measures of executive function.[135] 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, biomarker measures, 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.[142] 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 one to three aerobic exercise sessions per week; two to five 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, biomarker measures, or harms.[142]

Physical Activity and Protein Supplementation

Van de Rest et al. (n=58) compared physical activity and protein supplementation with usual care.[97] 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, biomarker measures, or harms.[97]

Multimodal Goal Setting

Clare et al. (n=75) compared goal setting (with and without mentoring) with attention control.[133] 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 California Verbal Learning Test (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, biomarker measures, or harms.

Lifestyle Advice and Drug Treatment

Moll van Charante et al. (n=3,526) reports on the Prevention of Dementia by Intensive

Vascular care (PreDIVA) trial which compared a multimodal intervention that aimed to identify risks and provide individualized lifestyle advice and medical management with inactive control.[141] Community-dwelling adults without dementia were randomized to a multimodal intervention (individualized lifestyle advice and, if indicated, medical management of chronic disease) or usual care (based on standards for cardiovascular risk management). The intervention consisted of visits for a general practice nurse every 4 months over 6 years. Nurses assessed cardiovascular risk factors (smoking habits, diet, physical activity, weight, and blood pressure), blood sugar, and cholesterol and provided individualized lifestyle advice based on these assessments. Subjects were prescribed drugs to manage identified cardiovascular risk factors, blood sugar, and cholesterol as needed. Antithrombotic drugs were also prescribed if needed.

At 6 years, there was no statistically significant difference between the intervention and control group in cases of all-cause dementia, Alzheimer's disease, or unspecified types of dementia.[141] Low strength evidence shows individualized multimodal intervention does not decrease dementia incidence.

There were statistically significant differences in cases of dementia in two subgroups: participants with untreated hypertension that were adherent to the intervention and participants without a history of cardiovascular disease who were adherent to the intervention. For both of these subgroups, there were fewer cases of dementia with the intervention.

One measure of brief cognitive test performance was reported. There was no statistically significant difference between intervention and control groups in MMSE scores at 6 years.[141] In addition, one measure of memory was reported. There was no statistically significant difference between intervention and control groups in Visual Association Test A scores at 6 years. Low strength evidence shows individualized multimodal intervention does not benefit brief cognitive test performance or memory.

Moll van Charante et al. reported no difference in serious adverse effects between the intervention and control groups.[141] The study reported no other diagnoses, cognitive outcomes, or biomarker measures.

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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Physical Activity and Diet Results Summary k=2; n=79	**NR**	**NR**	**BCT 1 of 1 favors I k=1**	**1 of 10 favors I k=2**	**0 of 11 (no difference) k=1**	**2 of 22 favor I**	**NR**
Napoli, 2014[83] 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, 2007[126] 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, RT]	NS [RAVLT, Delayed Recall]		
				NS [CPT-II, RT SE]	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 [BVRT, Error Deviation]		

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]
					NS [BVRT, Correct Deviation]		
Physical Activity and Cognitive Training Results Summary k=1; n=134	**NR**	**NR**	**BCT 0 fo1 (no difference) k=1**	**1 of 2 favors I k=1**	**NR**	**1 of 3 favors I**	**NR**
Hars, 2014[135] Physical activity and cognitive training vs. usual lifestyle n=134 6 months			**BCT** NS [MMSE]	NS [FAB]		1 of 2 favors I	NR
				I>C [Sensitivity to Inference Sub-test, FAB]			
Physical Activity, Diet, and Cognitive Training Results Summary k=1; n=1,260	**NR**	**NR**	**MNP 1 of 1 favors I**	**2 of 2 favors I k=1**	**1 of 2 favors I k=1**	**4 of 5 favors I**	
Ngandu, 2015[142] Physical activity, diet, and cognitive training vs. health information n=1,260 2 years			**MNP** I>C [NTB, Total Score]	I>C NTB, Executive Functioning]	NS [NTB, Memory]	4 of 5 favor I	Unclear [Musculoskeletal pain]
				I>C NTB, Processing Speed]	I>C [NTB, Abbreviated Memory]		
Physical Activity and Protein Supplementation Results Summary k=1; n=58	**NR**	**NR**	**NR**	**1 of 11 favors I k=1**	**0 of 6 (no difference) k=1**	**1 of 17 favor I**	**NR**
van de Rest, 2014[97]				NS [DS Forward]	NS [Word Learning Test, Immediate Recall-75	1 of 17 favor I	NR

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]
Resistance-type exercise program vs. usual care n=58 6 months					Words]		
				NS [DS Backward]	NS [Word Learning Test, Delayed Recall-15 Words]		
				NS [TMT A]	NS Word Learning Test, Decay]		
				NS [SCWT 1]	NS [Word Learning Test, Recognition, 30 Words]		
				NS [SCWT 2]	NS [Attention and Working Memory Composite]		
				NS [SCWT Inference]	NS[z] [Episodic Memory Composite]		
				NS [RT Uncued]			
				NS [RT Cued]			
				NS [Word Fluency-Letter]			
				I>C[z] [Processing Speed Composite]			
				NS[z] [Executive Functioning Composite]			
Goal Setting and Mentoring Results Summary k=1; n=75	**NR**	**NR**	**BCT 1 of 1 favors I k=1**	**1 of 1 favors I k=1**	**1 of 2 favors I 1 of 2 favors C k=1**	**3 of 4 favors I 1 of 4 favors C**	

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]
Clare, 2015[133] 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]	3 of 4 favors I 1 of 4 favors C	NR
					C>I [CVLT, Delayed Recall]		
Lifestyle Advice and Drug Treatment Summary **k=1; n=3,526**	**1 of 4 favors I** **k=1**	**NR**	**0 of 1 (no difference)** **k=1**	**NR**	**0 of 1 (no difference)** **k=1**	**1 of 6 favors I**	
Moll van Charante, 2016[141] Lifestyle advice and drug treatment vs. usual care n=3,526 6 years	NS [All-Cause Dementia]	NR	**BCT** NS [MMSE]		NS [Visual Association Test A]	1 of 6 favors I	NS [Severe Adverse Events]
	NS [AD]						
	NS [Unspecified Dementia]						
	I>C [Non-Alzheimer's Dementia]						

[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; AD=Alzheimer's disease; 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 (Forward and/or Backward); FAB=Frontal Assessment Battery; I=Intervention; k=number of studies included; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MNP=multidomain

neuropsychological test performance; n=sample size; NR=not reported; NS=not significant; NTB=Neuropsychological Test Battery; RAVLT=Rey Auditory Verbal Learning Test; RT=reaction time; SE=standard error; SCWT=Stroop Color Word Test; TMT=Trail Making Test (Part A and/or B); vs.=versus.

Shading indicates summary rows and columns.

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.[62, 83, 126] 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).[83, 126] Napoli et al. reported brief cognitive test performance (3MS) and several measured 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.[83]

Martin et al. compared physical activity and diet intervention with two diet interventions alone (calorie restriction alone and liquid calorie diet alone).[126] Across both comparisons, the trial reports 22 measures of memory and several measured 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.[62] Older adults were randomized to either virtual reality game dancing with cognitive training or to 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Physical Activity and Diet vs. Diet Results Summary k=2; n=102	**NR**	**NR**	**BCT 1 of 1 favors I k=1**	**0 of 18 (no difference) k=2**	**0 of 22 (no difference) k=1**	**1 of 41 favors I**	**NR**
Napoli, 2014 [83] 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[126] 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, RT]	NS [RAVLT, Delayed Recall]		
				NS [CPT-II, RT SE]	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 Neuropsychological 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, 2007[126] 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. Physical Activity	**NR**	**NR**	**BCT 0 of 1 (no difference)**	**0 of 2 (no difference) k=1**	**NR**	**0 of 3 (no difference)**	**NR**

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]
Results Summary k=1; n=54			**k=1**				
Napoli, 2014[83] Physical activity and diet vs. physical activity n=54 1 year			**BCT** NS [3MS]	NS [TMT A]		0 of 3 (no difference)	
				NS [TMT B]			
Physical Activity and Cognitive Training vs. Cognitive Training Results Summary k=1; n=46	**NR**	**NR**	**NR**	**0 of 7 (no difference) k=1**	**0 of 9 (no difference) k=1**	**0 of 9 (no difference)**	**NR**
Eggenberger, 2015[62] 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 [PAL]		
				NS [Executive Control]			
				NS [DS Forward]			
				NS [Age Concentration Test A]			
				NS [Age Concentration Test B]			
				NS [DSST]			

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 (Forward and/or Backward); I=intervention; k=number of studies included; MNP=Multidomain neuropsychological test performance; n=sample size; NR=not reported; NS=not significant; NTB=Neuropsychological Test Battery; PAL=Paired Associations Learning Test; RAVLT=Rey Auditory Verbal Learning Test; RT=reaction time; SE=standard error; TMT=Trail Making Test (Part A and/or B); vs.=versus.

Shading indicates summary rows and columns.

Adults With MCI

Only two unique studies compared multimodal interventions to inactive controls in older adults with MCI[66, 136] and two unique studies comparing multimodal interventions with active interventions in older adults with MCI.[66, 72] 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.[142]

The results of PreDiva study showed no difference between the multimodal and usual care for most outcomes; however, the intervention had no specific cognitive training, physical activity, or diet component.[141] Subjects were counseled to make lifestyle changes, but no specific regimen was implemented. In addition, a large number of participants discontinued the intervention over the 6-year period (final outcomes were obtained through medical records). Results of the ongoing MAPT trial, another large well-designed trial, may provide additional clarity regarding the efficacy and effectiveness of multimodal interventions.[14]

The risk of bias and small sample sizes of identified studies were substantial barriers to our analysis. Of the 20 eligible studies, only eight 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. Multimodal studies make sense to test two concepts: 1) additive effects of strong interventions and 2) overall effects of combinations. The first strategy uses a control of one of the components. The second compares the combination to a control group. The second strategy may facilitate the search for interventions. If a combination does not work, then either component alone likely will not. If it does work, one can compare the marginal benefit of adding the second component.

Chapter 4F. Results: Hormone Therapy Interventions

Key Messages

- Hormone therapy shows mixed results of harms and benefits.
- Low-strength evidence suggests that estrogen therapy may slightly increase the risk of probable mild cognitive impairment (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.
- Low-strength evidence suggests that raloxifene may decrease the risk of MCI but not the risk of CATD or of a combined outcome of MCI or CATD compared to placebo.
- In addition to these outcomes, hormone therapy has been associated with serious adverse events, including increased risk of certain cancers and cardiovascular disease.

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

Eligible Studies

We identified 44 eligible publications reporting 31 unique studies of hormone therapy interventions to prevent age-related cognitive decline, MCI, or CATD.[110, 145-186] Eight studies were assessed as high risk of bias, resulting in 23 low or medium risk of bias studies used in our analysis.[110, 145-147, 152, 165, 169, 182]

Soy and red clover interventions are included in this section due to their phytoestrogenic properties. Not only do the soy and red clover interventions vary considerably from the hormone therapies included in this section, but also the hormone therapies differ from each other.

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),[149, 152, 177-180] two studies investigating the use of selective estrogen receptor modulators (SERMs) in preventing vertebral fractures,[169, 184] two studies (three articles) on the use of hormones to prevent cardiovascular disease,[156, 158, 163] and one study on the effects of testosterone on bone and muscle.[165]

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.[187] While epidemiological studies have suggested that hormone replacement therapy may have a beneficial effect on cognition,[188] randomized trials have produced inconsistent results, even suggesting in some cases that some hormone therapies may have a detrimental effect on cognition.[179, 180]Although it is not precisely a hormone, we included soy in this section because it is often used by people in lieu of hormone replacement therapy.

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 k=6	Dementia	Increased risk of probable dementia/MCI associated with estrogen therapy (n=2,947; 5-7 years) but no statistically significant difference in risk of probable dementia or MCI when diagnostic categories reported separately.	Low (medium study limitations, unknown consistency)
	MCI	No statistically significant difference between estrogen therapy and placebo groups in risk of MCI (n=2,947; 5-7 years).	Low (medium study limitations, unknown consistency)
	Brief cognitive test performance	Decreased performance in brief cognitive test performance with higher dose estrogen compared to placebo (n=3,364; 5-7 years).	Low (medium study limitations, indirect, imprecise)
	Multidomain neuropsychological performance	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, unknown consistency, imprecise)
	Executive/Attention/ Processing speed	No benefit with estrogen compared to placebo (n=2,056; 5-7 years)	Low (medium study limitations, indirect, imprecise)
	Memory	No benefit with estrogen compared to placebo (n=2,056; 5-7 years)	Low (medium study limitations, indirect, imprecise)
HRT-estrogen + progestin vs. inactive control k=5	Dementia	Increased risk of probable dementia associated with estrogen/progestin therapy (n=4,532; 5-7 years) but no statistically significant difference in risk of probable dementia or MCI when the diagnostic categories were combined.	Low (medium study limitations, unknown consistency)
	MCI	No statistically significant difference between estrogen-progestin therapy and placebo in rates of MCI (n=4,532; 5-7 years)	Low (medium study limitations, unknown consistency)
	Brief cognitive test performance	No benefit in brief cognitive test performance with estrogen/progestin versus placebo (n=6,100; up to 7 years).	Low (medium study limitations, indirect)
	Multidomain neuropsychological performance	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	No benefit in executive/attention/ processing speed with estrogen/progestin versus placebo (n=3,007; up to 7 years)	Low (medium study limitations, indirect, imprecise)
	Memory	Decreased memory performance with estrogen/progestin versus placebo (n=3,149; up to 7 years)	Low (medium study limitations, indirect, imprecise)
DHEA vs. inactive control k=1	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/Attention/ Processing speed	Limited data.	Insufficient (limited data)
	Memory	Limited data.	Insufficient (limited data)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
SERM vs. inactive control k=2	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=5,386; 3 years)	Low (medium study limitations, unknown consistency)
	MCI	Slightly decreased risk of MCI in raloxifene compared to placebo (120mg but not 60 mg of raloxifene) (n=5,386; 3 years).	Low (medium study limitations, unknown consistency)
	Brief cognitive test performance	No data available.	Insufficient (no data)
	Multidomain neuropsychological performance	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	No benefit in executive/attention/ processing speed with SERM versus placebo (n=5,877; 3 years)	Low (medium study limitations, indirect)
	Memory	No benefit in memory with SERM versus placebo (n=5,739; 3 years)	Low (medium study limitations, indirect)
Soy vs. inactive control k=5	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 soy versus placebo (n=393; 1 year).	Insufficient (medium study limitations, indirect, imprecise)
	Multidomain neuropsychological performance	No benefit in multidomain neuropsychological performance with soy versus placebo (n=393; 2.5 years)	Insufficient (medium study limitations, indirect, imprecise)
	Executive/Attention/ Processing speed	No benefit with soy versus placebo (n=829; up to 2.5 years)	Low (medium study limitations, imprecise)
	Memory	No benefit with soy versus placebo (n=829; up to 2.5 years).	Low (medium study limitations imprecise)
Red clover vs. inactive control k=1	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/Attention/ Processing speed	Limited data.	Insufficient (limited data)
	Memory	Limited data.	Insufficient (limited data)

DHEA=dehydroepiandrosterone; k=number of studies included; MCI=mild cognitive impairment; n=sample size; SERM= selective estrogen receptor modulator; vs.=versus

Efficacy: Hormone Therapy Versus Inactive Control

Nineteen randomized controlled trials (RCTs) with low to medium risk of bias enrolling a total of 19,154 adults compared hormone therapy interventions to inactive controls in adults with normal cognition.[150, 151, 153-163, 166-168, 172, 174, 175, 177-181, 183-186, 189] Interventions included hormone replacement therapies: estrogen only, combined estrogen and progestin, dehydroepiandrosterone (DHEA), and testosterone; SERM; soy; and red clover. Samples ranged from 23 to 7,478 participants, with followup duration of 6 months to over 5 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 91 years with normal to "mildly impaired memory functioning"[181] 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

Six RCTs (n=4,117) with low to medium risk of bias compared estrogen replacement therapy to placebo in healthy postmenopausal women.[149, 151-153, 157, 160, 174, 175, 177, 178, 180, 183, 186] Studies included several small to moderately-sized RCTs (n=57-567 participants) and two ancillary studies of the large longitudinal WHI (n=2,947, estrogen-only arm), the Women's Health Initiative Memory Study (WHIMS) and Women's Health Initiative Study of Cognitive Aging (WHISCA). Study durations ranged from 6 months to over 5 years.

The WHIMS reported diagnostic outcomes (n=2,947).[180] 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 volume[149] and changes in brain volume.[178] 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.

Two studies (n=3,364), the WHIMS and Yaffe et al., used the 3MS as a brief test of cognitive performance.[151, 186] The dose of estrogen used in Yaffe et al.'s study was very low, only 0.014 mg daily (compared to 0.625 mg daily in WHIMS). Yaffe et al. found no statistically significant differences between estrogen and placebo groups after two years. After a mean followup of 5.4 years in the WHIMS, however, women taking estrogen performed slightly worse on the Modified Mini-Mental State Examination (3MS) than women taking placebo (difference in mean change from baseline: -0.26, 95% CI: -0.52, 0). Evidence was rated low that higher dose estrogen is associated with decreased performance on the 3MS compared to placebo.

Henderson et al.[160] (n=567) assessed cognition using a multi-domain composite. No difference was found between estrogen and placebo groups. Evidence was rated insufficient.

All six studies (n=2,056) examined changes in cognitive performance related to executive function/attention/processing speed and memory. (A sub-set of 886 WHISCA participants contributed to these outcomes.)[177] Two of 19 tests of executive function, attention, and processing speed favored estrogen, with none of the tests favoring placebo. Similarly, of 35 tests of memory across the studies, two favored estrogen and none favored placebo. Evidence was rated low that estrogen provides no benefit to executive function/ attention/processing speed or memory over placebo.

Henderson et al. found no difference in outcomes between women nearer to and further from menopause.[160] WHIMS investigators conducted subgroup analyses to examine the effects of

baseline risk factors on 3MS scores.[151] Analyses examining the effects of age, education, race/ethnicity, annual household income, Body Mass Index (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.[151]

Henderson et al.[160] (n=567) reported similar rates of serious adverse effects across estrogen and placebo groups. 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.[157] 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.[180]

Estrogen Plus Progestin

Five RCTs with low to medium risk of bias ranging in size from 23 to 4,532 participants (total n=6,332) compared combination estrogen/progestin therapy with placebo in postmenopausal women. Studies included three small RCTs[150, 158, 181], the Kronos Early Estrogen Prevention Study-Cognitive and Affective Study (KEEPS-Cog) (n=505)[156] and the WHIMS and WHISCA substudies of the WHI.[149, 175, 178, 179, 189] Specific estrogen/progestin combination therapies varied across studies.

The WHIMS was the only study to report diagnostic outcomes (n=4,532).[179] 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 volume[149] and changes in brain volume.[178] No differences in brain lesions or brain volume were found between estrogen/progestin and placebo groups.

Three studies (n=6,100) used the 3MS as a brief cognitive test.[156, 158, 175] Only the WHIMS found a statistically significant difference between estrogen/progestin and placebo groups, favoring the controls. Although performance on the 3MS improved over time for both WHIMS groups, the improvement was more marked for women taking placebo.[175] Evidence was rated low.

Four studies (n=3,007) examined the effect of estrogen/progestin therapy versus placebo on cognition in the executive function/attention/processing speed domain.[150, 177] One of nine tests of executive/attention/processing speed favored placebo. Evidence was low-strength that combined estrogen/progestin therapy has no effect on this domain.

All five studies (n=3,149) tested the effects of estrogen/progestin on memory.[156, 158, 175, 181] Four of 16 memory tests favored placebo and no tests favored estrogen/progestin. Evidence was rated low that combined estrogen/progestin therapy negatively affects memory compared to placebo.

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.[181] 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.[151] 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.[151] Also in the WHIMS,[179] 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.[149, 179] 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).[181] 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 women in the hormone group and two taking placebo.[150]

DHEA

One RCT (n=225) compared daily oral DHEA (50mg) to placebo in women and men aged 55 to 85 years with a mean baseline 3MS score of 96.[168] Cognitive outcomes included three measures: a brief cognitive test (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[165, 182] and muscle[165] in older men with low bioavailable testosterone levels examined the effect of testosterone on cognitive performance.

Selective Estrogen Receptor Modulators (SERM)

Two trials (n=7,621) compared the SERM raloxifene (60 mg or 120 mg daily in both trials) with placebo.[172, 184] Both studies enrolled women with osteoporosis aged 66 to 68 years.

Yaffe et al.'s 3-year study (n=7,478) reported diagnostic outcomes.[184] At year 3, women who scored in the bottom 10 percent of cognitive scores or who had symptoms of cognitive impairment were referred for further evaluation. Evaluation for MCI or CATD involved interview, physical, and neurological examination by a clinician who was blinded to treatment, as well as administration of several cognitive tests. Participants suspected of having CATD based on clinical assessment and a Mini-Mental State Examination (MMSE) score of < 24 underwent magnetic resonance imaging (MRI) scans, which were subsequently assessed by a blinded reader to determine whether scans were clinically relevant. Women assigned to 120 mg of raloxifene daily had a 33 percent lower risk of MCI than those taking placebo, although the 95 percent confidence interval was 0.46 to 0.98. The 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 that raloxifene lowers the risk of MCI.

Both Nickelsen et al. and Yaffe et al. (n=5,877) compared the effects of raloxifene and placebo on executive/attention/processing speed and memory.[172, 184, 185] A total of six cognitive tests related to executive, attention, and processing speed were conducted between the two studies, and a total of nine memory tests. No significant differences were found between raloxifene and placebo groups after 3 years. Strength of evidence was rated low.

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.[172]

Soy

Five low to medium risk of bias RCTs ranging in size from 34 to 350 participants (total n=829) compared soy supplementation to placebo. Populations included men and women without dementia aged 62 to 89 years[155] and generally healthy postmenopausal women.[159, 161, 167] Mean baseline MMSE scores were not reported in Henderson et al.[159] and Kreijkamp-Kaspers et al.,[166] but ranged from 28 to 29 in the other studies.[155, 161, 167] Three of the studies took place over 6 months (n=281),[155, 161, 167]one lasted 1 year (n=202), and one lasted 2.5 years (n=350).[159]

None of the trials reported diagnostic outcomes. Ho[161] (n=191) and Kreijkamp-Kaspers et al.,[166] (n=202) used the MMSE as a brief cognitive test and found no pre/post differences between soy and placebo groups.[161] Strength of evidence was insufficient. Two studies (n=541) tested multi-domain neuropsychological performance and found no statistically significant differences between groups.[159, 161] Evidence was rated as insufficient.

All five studies measured cognitive performance in the executive function/attention/ processing speed and memory categories (n=829). Placebo performed better than soy in two of 21 tests of executive function/attention/processing speed. Over the five studies, the soy group performed better on five of 31 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.[167] Neither Henderson nor Ho found differences in cognitive performance based on age.[159, 161]

Ho et al. and Kreijkamp-Kaspers et al. reported no serious adverse effects and no significant differences in adverse effects experienced between treatment and placebo groups.[161, 166] In Henderson et al.'s study, one person in the soy group experienced a stroke and five people in the placebo group reported cancer.[159] No other serious adverse effects were reported.

Red Clover

A single study (n=30)[162] with medium risk of bias compared isoflavone supplementation with red cover to placebo. Red clover performed better than placebo on one of five tests of executive function/attention/processing speed and placebo performed better on two of seven memory tests. However, the study authors note that none of the results remained significant after correcting for multiple comparisons. Strength of evidence was insufficient due to a single study of less than 500 participants.

Table 4F.2. Results overview: Hormone therapies versus inactive controls 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]
HRT-Estrogen Results Summary k=6; n=4,117	**1 of 3 favors C k=1**	**1 of 7 favors C k=1**	**BCT 1 of 2 favors C k=2** **MNP 0 of 1 (no difference) k=1**	**2 of 19 favors I k=6**	**2 of 35 favors I k=6**	**4 of 64 favors I** **2 of 64 favors C**	
Henderson, 2016[160] Oral estrogen therapy (17-beta estradiol 1 mg) daily n=567 2.5 years (5 year outcomes = High ROB)			**MNP** NS [Global Cognition Composite]	NS [Executive Function Composite]	NS [Verbal Episodic Memory Composite]	0 of 3 (no difference)	1 death in estradiol group; other serious AEs equal between groups but not included in article
Wroolie, 2015[183] Continued estrogen-based hormone therapy n=64 2 years				I>C [Attention/Working Memory/Processing Speed Composite]	I>C [Verbal Memory Composite]	2 of 5 favor I	NR
				NS [Executive Function Composite]	NS [Visual Memory Composite]		
					NS [Subjective Memory Composite]		
Women's Health Initiative (WHI) substudies **Coker, 2009** **Resnick, 2009a** **Resnick, 2009b** **Espeland, 2004**	NS [Probable Dementia] n=2,947	NS [MRI: Total Brain Volume] n=520	**BCT** C>I [3MS] N=2,947	NS [Letter Fluency] n=886	NS [BVRT Errors] n=886	2 of 16 favors C	Increased risk of probable dementia in women taking estrogen.
	NS [MCI] n=2,947	NS [MRI: Ventricle Volume]		NS [DS Forward] n=886	NS [CLVT Total List A Trials] n=886		Increased risk of global cognitive

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]
Shumaker, 2004 **Rapp, 2003**[149, 151, 175, 177, 178, 180] Estrogen (conjugated equine estrogen 0.625 mg) daily n=2,947 Mean followup varies by outcome up to 8 years		n=520					
	C>I [Probable Dementia or MCI] n=2,947	NS [MRI: Hippocampal Volume] n=520		NS [DS Backward] n=886	NS [CVLT Total List B] n=886		decline in women taking estrogen.
		C>I [MRI: Frontal Lobe Volume] n=520			NS [CVLT Short Delay Free] n=886		
		NS [White & Gray Matter] n=520			NS [CVLT Long Delay Free] n=886		
		NS [Basal Ganglia] n=520					
		NS [Total Brain Lesion Volume] n=520					
Gorenstein, 2011[157] Estrogen (conjugated equine estrogen 0.625 mg) daily n=65 6 months				I>C [DS Forward]	I>C [PAL, Easy]	2 of 10 favor I	No serious AEs reported
				NS [DS Backward]	NS [PAL, 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]		
Pefanco 2007[174] Estrogen (micronized 17-beta				NS [COWAT]	NS [Immediate Recall]	0 of 22 (no difference)	NR
				NS	NS		

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]
estradiol 0.25 mg) daily n=57 3 years				[Animal Naming]	[Delayed Recall]		
				NS [TMT A]	NS [Fuld Object Memory Evaluation]		
				NS [TMT B]	NS [Total Recall Trial 5]		
				NS [Wisconsin Test]	NS [Total Recall, 5-Minute Delay]		
				NS [Total Perservative Error]	NS [Total Recognized 5-Delay]		
				NS [Digital Written Score]	NS [Wechsler Logical Memory 1]		
					NS [Verbal Paired Association 1]		
					NS [Visual Representation 1]		
					NS [Logical Memory 2]		
					NS [Verbal Paired Association 2]		
					NS [Visual Representation]		
					NS [Recognition Total Score 1]		
					NS [Recognition Total Score 2]		
					NS [Recognition Total Score 3]		

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]
Yaffe, 2006[186] Estrogen (transdermal patch delivering 0.014 mg estradiol) daily n=417 2 years			**BCT** NS [3MS]	NS [TMT B]	NS [Logical Memory, Immediate]	0 of 8 (no difference)	NR
					NS [Logical Memory, Delayed]		
					NS [BVMT, Immediate]		
					NS [BVMTt, Delayed]		
					NS [Word List, Memory]		
					NS [Word List, Recall]		
HRT-Estrogen + Progestin Results Summary k=5, n=6,332	**1 of 3 favors C k=1**	**0 of 7 (no differences) k=1**	**BCT 1 of 4 favors C k=3**	**1 of 9 favors C k=4**	**4 of 16 favor C k=5**	**6 of 36 favors C**	
Gleason, 2015[156] Estrogen + (conjugated equine estrogen 0.45 mg) + progestin (cyclical micronized progesterone 200mg) daily n=482 (o-CEE + placebo) Mean 3.2 years			**BCT** NS [3MS]	NS [Visual Attention & Executive Function Composite]	NS [Verbal Learning & Memory Composite]	0 of 4 (no difference)	4 cases of breast cancer 3 in CEE group, 1 in placebo; 2 cardiac or cerebrovascular events – 1 placebo, 1 CEE, 2 cases
					NS [Auditory Attention & Working memory Composite]		of major depression, CEE group
Gleason, 2015[156] Estrogen (transdermal estradiol 200 mg)			**BCT** NS [3MS]	NS [Visual Attention & Executive Function Composite]	NS [Verbal Learning & Memory Composite]	0 of 4 (no difference)	3 cases of breast cancer (2 estradiol, 1 placebo), 1 stroke, 2

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]
daily + progestin (cyclical micronized progesterone 200 mg) daily n=431 (t-E2 + placebo) Mean 3.2 years							cases
					NS [Auditory Attention & Working Memory Composite]		of venous thrombotic disease (1 estradiol, 1 placebo)
Women's Health Initiative (WHI) **Coker, 2009** **Resnick, 2009a** **Resnick, 2009b** **Espeland, 2004** **Shumaker, 2004** **Rapp, 2003**[180,149, 151, 175, 177, 178, 189] Estrogen + progestin daily n=4,532 Mean followup varies by outcome up to 8 years	C>I [Probable Dementia] n=4,532	NS [MRI: Total Brain Volume] n=883	**BCT** C>I [3MS] n=4,532	NS [Letter Fluency] n=1,416	C>I [BVRT Errors] n=1,416	5 of 16 favor C	In addition to increased risk of probable dementia and
	NS [MCI] n=4,532	NS [MRI: Ventricle Volume] n=883		NS [DS Forward] n=1,416	C>I [CLVT Total List A Trials] n=1,416		memory decline, women taking
	NS [Probable Dementia or MCI] n=4,532	NS [MRI: Hippocampal Volume] n=883		NS [DS Backward] n=1,416	NS [CVLT Total List B] n=1,416		estrogen + progestin experienced more strokes
		NS [MRI: Frontal Lobe Volume] n=883			C>I [CVLT Short Delay Free] n=1,416		than women taking placebo
		NS [White and Gray Matter] n=883			C>I [CVLT Long Delay Free] n=1,416		
		NS [Basal Ganglia] n=883					
		NS [Total Brain Lesion Volume] n=883					

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]
Davison, 2013[150] Estrogen (oral estradiol + progestin (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
				C>I [CogState, Detection Speed]	NS [CogState International Shopping List, Recall]		estrogen + progestin group and 1 in placebo.
				NS [Mental Rotation with functional MRI]	NS [Gorton Maze Learning Task]		No serious AEs were reported.
					NS [Gorton Maze Learning Task, Recall]		
					NS [CogState Continuous Paired Assoc Learning]		
Tierney, 2009[181] Estrogen (1 mg 17-B estradiol) daily + progestin (0.35 mg norethindrone) 3 times weekly n=142 2 years					NS CVLT, Short Delay Recall]	0 of 1 (no difference)	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 serious.
Grady, 2002[158] Conjugated			**BCT** NS [MMSE]	NS [TMT B]	NS [Word List Recall]	0 of 3 (no difference)	

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]
estrogen 0.625 mg) plus medroxyprogerstone acetate (2.5 mg) daily n=1,063 Mean 4.2 years							
DHEA Results Summary k=1, n=225	**NR**	**NR**	**BCT 0 of 1 (no difference) k=1**	**0 of 1 (no difference) k=1**	**0 of 2 (no difference) k=1**	**0 of 4 (no difference)**	
Kritz-Silverstein, 2008[168] Oral DHEA 50 mg daily n=225 1 year			**BCT** NS [MMSE]	NS [TMT B]	NS [Word List Memory]	0 of 4 (no difference)	23 participants experienced AEs,
					NS [Word List Recall]		but no tests of significance are reported
SERM Results Summary k=2, n=7,621	**1 of 8 favors I k=1**	**NR**	**NR**	**0 of 6 (no difference) k=2**	**0 of 9 (no difference) k=2**	**0 of 15 (no difference)**	**NR**
Yaffe, 2005[184] **Yaffe, 2001**[185] Raloxifene 60 mg or 120 mg daily vs. placebo n=7,478 years	NS (60 mg group) [MCI] I>C (120 mg group) [MCI]			NS [Short Blessed] n=5,734	NS [Word List Recall] n=5,596	0 of 5 (no difference)	NR
	NS (60 mg group) NS (120 mg group) [CATD]			NS [TMT A] n=5,685	NS [Word List Memory] n=3,607		

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]
	NS (60 mg group) NS (120 mg group) [Any Type of Dementia]			NS [TMT B] n=5,538			
	NS (60 mg group) NS (120 mg group) [Dementia or MCI]						
Nickelsen, 1999[172] 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 difference)	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 RT]	NS [MAC Battery: First-Last Name Association, Delayed Recall]		similar across groups
					NS [MAC Battery: First-Last Name Association, Total Acquisition]		
					NS [MAC Battery: Facial Recognition, Number Before 1st Error]		
					NS		

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]
					[MAC Battery: Telephone Number Recall, Before Interference]		
					NS [MAC Battery: Telephone Number Recall, After Interference]		
Soy Results Summary k=5; n=829	**NR**	**NR**	**BCT 0 of 2 (no difference) k=2 MNP 0 of 3 (no difference) k=2**	**2 of 21 favor C k=5**	**5 of 31 favor I 1 of 31 favors C k=5**	**5 of 57 favor I 3 of 57 favor C**	
Henderson, 2012[159] Soy isoflavone rich soy protein 25 g daily vs. matched placebo n=350 2.5 years			**MNP** NS [Composite, components not described]	NS [SDMT]	NS [Verbal Episodic Memory, List Learning Factor: CVLT Immediate & Delayed Recall]	1 of 15 favors I	1 person (soy group) had a stroke and 5 people (placebo) reported cancer.
			MNP NS [Executive/Expressive/Visuospatial Factor Composite: SDMT, TMT B, Shipley Abstraction, Letter-Number Sequencing, Block Design, Judgment of Line Orientation, BNT]	NS [TMT B]	NS [CVLT, Immediate Recall]		No other serious adverse effects were reported.
				NS	NS		

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]
				[Shipley Abstraction]	[CVLT, Delayed Recall]		
				NS [Letter-Number Sequencing]	NS [Verbal Episodic 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, 2009[155] Soy isoflavonea 100 mg daily vs. placebo n=30 6 months				C>I [SCWT]	NS [Buschke Selective Reminding Test, Total of Learning Trials – Words]	4 of 14 favor I	NR
				C>I [TMT 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 [Paragraph Recall Test,		

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]
					Total Delayed Recall]		
					I>C [RCFT, Immediate Recall]		
					I>C [RCFT, 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[161] 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 difference)	No significant differences in AEs experienced
			MNP NS [Cognitive Score=z scores of all cognitive tests]	NS [Color Trail II]	NS [HKLLT, Short Delay Recall]		or their severity were found between groups.
				NS [DSST – WAIS]	NS [HKLLT, Long Delay Recall]		No serious AEs were reported.
					NS [VR I]		
					NS [VR II]		

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]
					NS [VR, Copy]		
Kreijkamp-Kaspers, 2004{Kreijkamp-Kaspers, 2004) Soy-derived isoflavones 99 mg vs. placebo n=202 1 year			**BCT** NS [MMSE]	NS [DS Forward]	NS [RAVLT, Immediate Recall]	0 of 13 (no difference)	No serious AEs reported and no significant
				NS [DS Backward]	NS [RAVLT, Delayed Recall]		differences between groups were
				NS [TMT A1]	NS [RAVLT, Recognition]		found.
				NS [TMT A2]	NS [Doors Test]		
				NS [TMT B]			
				NS [DSST]			
				NS [Verbal Fluency, N]			
				NS [Verbal Fluency, A]			
Kritz-Silverstein, 2003[167] Soy-extracted isoflavones 110 mg daily vs. placebo n=56 6 months				NS [TMT A]	NS [Logical Memory I, Immediate]	0 of 4 (no difference)	NR
				NS [TMT B]	NS [Logical Memory II, Delayed]		
Red Clover Results Summary k=1; n=30	**NR**	**NR**	**NR**	**1 of 5 favors I k=1**	**2 of 7 favor C k=1**	**1 of 12 favors I** **2 of 12 favor C**	
Howes, 2004[162] Isoflavones from red clover				NS [Arithmetic Test]	C>I [Digit Recall Test]	1 of 12 favors I 2 of 12 favor C	1 person receiving placebo died. No other

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]
n=30 6 months							serious
				NS [TMT A]	NS [Memory 1 Test]		AEs were reported.
				NS [TMT B]	NS [Memory 2 Test]		
				I>C [Block Design Test]	NS [Verbal Memory 1 Test]		
				NS [DSST]	C>I [Verbal Memory 2 Test]		
					NS [Visual Memory 1 Test]		
					NS [Visual Memory 2 Test]		

3MS=Modified Mini-Mental State Examination; AE=adverse effect; BCT=brief cognitive test performance; BNT=Boston Naming Test; BVMT=Brief Visuospatial Memory Test; BVRT=Benton Visual Retention Test; C=control; CATD=clinical Alzheimer's-type dementia; COWAT=Controlled Oral Word Association Test; CVLT=California Verbal Learning Test; DHEA=dehydroepiandrosterone; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution Test; EBMT=East Boston Memory Test; fMRI=functional magnetic resonance imaging; HKLLT=Hong Kong List Learning Test; HRT=hormone replacement therapy; I=intervention; k=number of studies included; mg=milligrams; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological test performance; MRI=magnetic resonance imaging; n=sample size; NS=no statistically significant difference; NR=not reported; PAL=Paired Associated Learning Test; RAVLT=Rey Auditory Verbal Learning Test; RCFT=Rey-Osterrieth Complex Figure Test; SCWT=Stroop Color Word Test; SERM=selective estrogen receptor modulator; TMT=Trail Making Test (Part A and/or B)

Shading indicates summary rows and columns.

Comparative Effectiveness: Hormone Therapies Versus Active Comparison

Two studies (three publications) with low to medium risk of bias compared hormone therapies with active interventions.[170, 171, 173] 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
HRT-Estrogen plus Progestin vs. Tibolone Results Summary k=1; n=50	**NR**	**NR**	**BCT 0 of 2 (no difference) k=1**	**NR**	**NR**	**0 of 2 (no difference)**	
Pan, 2003[173] Estrogen + progestin (CEE 0.625 mg/day + methylprogresterone acetate 5 mg/day) vs. tibolone 2.5 mg/day n=50 6 months			**BCT** NS [MMSE]			0 of 2 (no difference)	AEs reported but differences
			BCT NS [CASI]				Not reported in terms of statistical significance.
HRT-Estrogen plus Testosterone vs. Estrogen Results Summary k=1; n=50	**NR**	**NR**	**NR**	**0 of 4 (no difference) k=1**	**0 of 2 favor I1 (estrogen + testosterone k=1** **1 of 2 favors I-2 (estrogen only) k=1**	**0 of 6 favor I_1 (estrogen + testosterone)** **1 of 6 favors I_2 (estrogen + placebo)**	
Moller, 2013[171] **Moller, 2010**[170] Estrogen + testosterone (I_1) versus estrogen + placebo (I_2) (estradiol valerate 2 mg/day + testosterone undecanoate 40 mg/day versus estradiol valerate 2 mg/day + placebo) n=50				NS [DSST – 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 [DSST, Free Recall of Symbols] [1]	NS [Logical Story, Delayed Recall][2]	1 of 6 favors I_2	
				NS [DSST, Paired Recall of Symbols] [1]			
				NS [DSST, % Spatial Errors][2]			

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]
6 months (crossover design; total trial period = 12 months)							

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

AE=adverse effect; BCT=brief cognitive test performance; C=control; CASI=Cognitive Abilities Screening Instrument; DSST=Digit Symbol Substitution Test; HRT=hormone replacement therapy; I=intervention; I_1=first intervention; I_2=second intervention; k=number of studies included; mg=milligrams; MMSE=Mini-Mental State Examination; n=sample size; NS=no statistically significant difference; NR=not reported

Shading indicates summary rows and columns.

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.[148, 164] 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.[148] 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).[164] 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 two 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
HRT-Testosterone Results Summary k=1; n=22	**NR**	**NR**	**NR**	**0 of 7 (no difference) k=1**	**1 of 7 favors I k=1**	**1 of 14 favors I**	
Cherrier, 2015[148] 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
				NS [Letter-Number Sequencing, Span]	NS [RAVLT, Short Delay]		group), although no significance tests reported
				NS [Computerized Simple RT, 2-Second Interval]	I>C [RAVLT, Long Delay]		
				NS [Computerized Simple RT, 5-Second Interval]	NS [Story Recall, Immediate]		
				NS [Computerized Choice RT, 2-Second Interval]	NS [Story Recall, Delay]		
				NS [Computerized Choice R, 5-Second Interval]	NS [Visual Spatial Learning Test, Immediate]		
				NS [Mental Rotation]	NS [Visual Spatial Learning Test, Delay]		
Soy Results Summary k=1; n=78	**NR**	**NR**	**BCT 1 of 2 favors C (100 mg group) k=1** **0 of 2 (no difference) (300**	**NR**	**0 of 1 (no difference) (100 & 300 mg groups) k=1**	**1 of 6 favors I (3 tests, 2 doses)**	**NR**

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]
			mg group) k=1				
Kato-Kataoka, 2010[164] Soybean derived phosphatidylserine (Soy-PS) 100 mg or 300 mg vs. placebo n=78 9 months			**BCT** I>C (100 mg group) [MMSE] **BCT** NS (300 mg group) [MMSE]		NS (100 mg group) [RBMT] NS (300 mg group) [RBMT]	1 of 6 favors I	NR
			BCT NS (100 mg group) [Hawegawa Dementia Scale] **BCT** NS (300 mg group) [Hawegawa Dementia Scale]				

AE=adverse effect; BCT=brief cognitive test performance; C=control; HRT=hormone replacement therapy; I=intervention; k=number of studies included; mg=milligrants; mg/d=milligrams per day; MMSE=Mini-Mental Status Examination; n=sample size; ng/dL=nanograms per deciliter; NR=not reported; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; RBMT= Rivermead Behavioral Memory Test; RT=reaction time;

Shading indicates summary rows and columns.

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 associated with hormone replacement therapies (estrogen and combined estrogen/progestin therapy in particular) may outweigh their benefits, less is known about the effects of other hormone therapies, such as SERM and plant-based estrogens, on cognition. In most cases, differences in cognitive performance between hormone therapy and control groups tended to be relatively 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 associated adverse events—cancer and cardiovascular disease in particular.[190] Particularly when data for women taking either hormone replacement therapy (estrogen-only or estrogen/progestin) were combined,[180] the detrimental effects of hormone therapy on cognition (both in terms of dementia-related diagnoses and cognitive performance) became more pronounced. Importantly, the trial found a 76 percent increased hazard for dementia associated with hormone therapy.[180]

Many studies of the effects of hormone therapies on cognition were relatively short, 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 31 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 these studies, the WHI, 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.

Finally, although a number of studies examined the effects of phytoestrogens (soy in particular) on cognition, none of these studies looked at diagnostic outcomes. Low-strength evidence suggests that soy offers no benefit to cognition related to executive/attention/processing speed or memory, yet evidence was deemed insufficient for other cognitive outcomes.

Chapter 4G. Results: Vitamin Interventions

Key Messages

- Moderate-strength evidence shows no benefit in cognitive performance for vitamin E in women.
- There was some signal that B_{12} plus folic acid may benefit brief cognitive test performance and memory but not executive function/attention/ processing speed.
- Low-strength evidence for folic acid (0.4 mg) plus vitamin B_{12} (0.1-0.5 mg) shows benefit in brief cognitive test performance and memory.
- Moderate-strength evidence shows no benefit for folic acid (0.4 mg) and B_{12} (0.1-0.5 mg) versus placebo for executive/attention/processing speed.
- Low-strength evidence for vitamin B_{12} (0.02-0.5 mg), B_6 (3-10 mg), and folate (0.56-1 mg) shows no benefit for executive/attention/processing speed.
- Low-strength evidence shows no benefit in cognitive performance for multivitamins, vitamin 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.
- In adults with mild cognitive impairment (MCI), low-strength evidence shows no benefit for vitamin E in incident 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 29 eligible publications reporting 24 unique studies of vitamin interventions to prevent age-related cognitive decline, MCI, or CATD.[98, 101, 102, 191-217] Ten were assessed as high risk of bias and not used in our analysis. Of the remaining 19 publications of 16 unique studies, 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 Vitamin Interventions

The logic underlying vitamin use varies with the vitamin. In the case of B vitamins the targeted pathway may involve lowering of homocysteine levels.

Adults With Normal Cognition

Efficacy: Vitamins Versus Inactive Control (Placebo)

Twelve randomized controlled trials (RCTs) with low or moderate risk of bias compared vitamins to inactive control (placebo) in adults with normal cognition.[101, 196-199, 201, 202, 205, 208-210, 212] Total sample sizes ranged from 220 to 20,536. Conclusions are summarized in Table 4G.1 and individual study results are shown 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 k=4	Dementia	No statistically significant difference in dementia diagnosis with multivitamins versus placebo long-term (n=20,469; 5 years).	Low (medium study limitations, imprecise, unknown consistency)
	MCI	No statistically significant difference in MCI diagnosis with multivitamins versus placebo long-term (n=20,469; 5 years).	Low (medium study limitations, imprecise, unknown consistency)
	Brief cognitive test performance	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, unknown consistency)
	Multidomain neuropsychological performance	No benefit in multidomain neuropsychological performance with multivitamins versus placebo (n=5,296; followup time unclear).	Low (medium study limitations, indirect, precise, unknown consistency)
	Executive/Attention/ Processing speed	No benefit in executive/attention/processing speed with multivitamins versus placebo (n=992; up to 1 year).	Low (low-medium study limitations, indirect, precision unclear)
	Memory	No benefit in memory with multivitamins versus placebo (n=5,516; followup time unclear).	Low (low-medium study limitations, indirect, imprecise)
Folic acid vs. placebo k=1	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	Unable to draw conclusion.	Insufficient (low study limitations, indirect, precise, unknown consistency)
	Executive/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (low study limitations, indirect, imprecise, inconsistent)
	Memory	Unable to draw conclusion.	Insufficient (low study limitations, indirect, unknown consistency)
Folic acid + B_{12} vs. placebo k=2	Dementia	No data available.	Insufficient (no data)
	MCI	No data available.	Insufficient (no data)
	Brief cognitive test performance	Unable to draw conclusion.	Insufficient (low study limitations, indirect, inconsistent)
	Multidomain neuropsychological performance	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	No benefit for executive/attention/processing speed test performance with folic acid (0.4 mg) and B_{12} (0.1-0.5 mg) compared to placebo (n=3,456; up to 2 years).	Medium (low study limitations, indirect, precision unclear)
	Memory	Folic acid (0.4 mg) and B_{12} (0.1-0.5 mg) improved memory versus placebo (n=3,456; up to 2 years).	Low (low study limitations, indirect, imprecise)
Folate + B_6 +	Dementia	No data available.	Insufficient (no data)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
B_{12} vs. placebo k=2	MCI	No data available.	Insufficient (no data)
	Brief cognitive test performance	No benefit for brief cognitive test performance with folate (0.56-1.0mg), B_6 (3-10mg) and B_{12} (0.2-0.5mg) compared to placebo (n=1,124; up to 4 years).	Low (low study limitations, indirect)
	Multidomain neuropsychological performance	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (low study limitations, indirect, imprecise, inconsistent)
	Memory	No benefit for memory with folate (0.56-1.0mg), B_6 (3-10mg) and B_{12} (0.2-0.5mg) compared to placebo (n=1,124; up to 4 years).	Low (low study limitations, indirect, imprecise)
Vitamin E vs. placebo k=2	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 (400-600mg) versus placebo long term (n=7,497; 4 years).	Moderate (low-medium study limitations, indirect)
	Multidomain neuropsychological performance	No benefit for women in multidomain neuropsychological performance with vitamin E versus placebo long term (n=7,497; 4 years).	Moderate (low-medium study limitations, indirect)
	Executive/Attention/ Processing speed	No data available.	Insufficient (no data)
	Memory	No benefit for women in memory with vitamin E versus placebo long term (n=7,497; 4 years).	Moderate (low-medium study limitations, indirect t)
Vitamin C vs. placebo k=1	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=2,271; 4 years).	Low (low-medium study limitations, indirect, imprecise, unknown consistency)
	Multidomain neuropsychological performance	No benefit for women in multidomain neuropsychological performance with vitamin C versus placebo long term (n=2,271; 4 years).	Low (low-medium study limitations, indirect, imprecise, unknown consistency)
	Executive/Attention/ Processing speed	No data available.	Insufficient (no data)
	Memory	No benefit for women in memory with vitamin C versus placebo long term (n=2,471; 4 years).	Low (low-medium study limitations, indirect, imprecise, unknown consistency)
Vitamin D + calcium vs. placebo k=1	Dementia	No statistically significant difference in pooled dementia and MCI diagnosis with vitamin D and calcium versus placebo long term (n=4,122; 7 years).	Low (low-medium study limitations, unknown consistency)
	MCI	See above.	
	Brief cognitive test performance	Unable to draw conclusion.	Insufficient (low-medium study limitations, indirect, imprecise, unknown

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
			consistency)
	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 long term (n=4,122; 7 years).	Low (low-medium study limitations, indirect, unknown consistency)
	Memory	No benefit for women in memory with vitamin D and calcium versus placebo long-term (n=4,122; 7 years).	Low (low-medium study limitations, indirect, imprecise)
Beta carotene vs. placebo k=1	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 long term (n=2,271; 4 years).	Low (low-medium study limitations, indirect, imprecise, unknown consistency)
	Multidomain neuropsychological performance	No benefit for women in multidomain neuropsychological performance with beta carotene versus placebo long term (n=2,271; 4 years).	Low (low-medium study limitations, indirect, , unknown consistency)
	Executive/Attention/ Processing speed	No data available.	Insufficient (no data)
	Memory	No benefit for women in memory with beta carotene versus placebo long term (n=2,271; 4 years).	Low (low-medium study limitations, indirect, unknown consistency)

B_6=vitamin B_6; B_{12}=vitamin B_{12}; k=number of studies included; MCI=mild cognitive impairment; mg=milligrams; n=sample size; vs.=versus

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, B vitamins, 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.[196, 197, 202, 210] Participants varied; studies included physicians over 65,[196] women over 60,[210] adults at serious risk of death from heart disease aged 40 to 80,[197] and adults over 65.[202] 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 period.[197]

In general, low-strength evidence showed no statistical differences on cognitive performance tests, including multidomain neuropsychological performance,[196] executive/attention/processing speed,[202, 210] or memory.[196, 210] 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.[196, 202, 210] 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.[196, 210] 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.

B Vitamins: Folic Acid

One study (n=818) compared folic acid to placebo.[212] Participants took folic acid (0.8mg) or matching placebo for 3 years. People aged 50-70 with high homocysteine levels likely caused by suboptimal folate concentrations were recruited.

Durga et al. did not report diagnostic outcomes, brief cognitive test performance, or adverse effects. Evidence was insufficient to determine improvement with folic acid for multidomain neuropsychological performance, executive/attention/processing speed, or memory.

B Vitamins: Folic Acid and B_{12}

Two studies (n=3,819) compared folic acid and B_{12} to placebo.[208, 209] Participants took folic acid (0.4mg) and B_{12} (0.1-0.5mg) or a matching placebo for 2 years. One study specifically addressed persons with elevated homocysteine levels of at least 12 micromoles/liter (presumed vitamin deficiency status).[208] Studies recruited adults aged 65+ [208] and sedentary adults aged 60-74 with elevated psychological distress.[209]

Neither trial reported diagnostic outcomes, multidomain neuropsychological performance, or adverse effects. Both trials reported brief cognitive test performance (n=3,819). Evidence was insufficient to conclude possible effects.

Both studies reported 11 tests assessing the effect of folic acid/B_{12} on executive/attention/ processing speed.[208, 209] None showed statistically significant improvement with folic acid/B_{12} over placebo (medium-strength of evidence).

Both studies reported seven tests assessing the effect of folic acid/B_{12} on memory.[208, 209] Only two of seven tests showed statistically significant improvement with folic acid/$B_{12,}$ and the effect sizes were small. Walker et al. reported a Telephone Interview for Cognitive Status (TICS) time by intervention effect size of 0.15 for immediate recall and 0.18 for delayed recall, again (low-strength evidence).[209]

Regarding subgroup analyses, benefit on memory for folic acid/B_{12} compared to placebo was reported for participants with low holotranscobalamin levels.[208]

B Vitamins: Folate, B_6, and B_{12}

Two studies (n=1,524) compared folate, B_6 and B_{12} to placebo.[101, 201] Participants took folate (0.56-1.0 mg), B_6 (3-10 mg) and B_{12} (0.2-0.5 mg) or matching placebo for 2 to 4 years. One trial also randomized participants to folate/B_6/B_{12} with omega-3 versus placebo and folate/B_6/B_{12} versus omega-3; these results are discussed below in comparative efficacy.[101] Studies recruited adults aged 45-70 with heart disease,[101] and adults aged 65+ with healthy cognition and homocysteine levels at least 13 micromoles/liter. [201]

Neither trial reported diagnostic outcomes, multidomain neuropsychological performance, or adverse effects. The studies reported two tests assessing the effect of folate/B_6/B_{12} on brief cognitive test performance; neither were statistically significant with intervention (low-strength evidence).

One study reported two tests assessing the effect of folate/B_6/B_{12} on executive/attention/processing speed, but evidence was insufficient to conclude possible effects.[201]

Both studies reported four tests assessing the effect of folate/B_6/B_{12} on memory.[101, 201] None showed statistically significant improvement with folate/B_6/B_{12} (low-strength evidence).

Subgroup analysis findings were mixed, finding no differences, or possible differences favoring either the placebo or folate/B_6/B_{12}. In particular, Andreeva et al. reported participants with a history of myocardial infarction/unstable angina receiving folate/B_6/B_{12} 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). Also, participants aged 65+ and receiving folate/B_6/B_{12} 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 ($p<0.05$).[101]

Vitamin E

Two trials (n=9,201) compared vitamin E with a placebo.[198, 199] Both studies randomized women aged 65+ to vitamin E or placebo every other day. However, one randomized women to 600 IU (equivalent of about 400 mg) vitamin E for 10 years,[198] while the other randomized women with cardiovascular disease or three or more coronary risk factors to 402 mg vitamin E for 9 years.[199] 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.[199]

Two trials assessed the effect of several participant characteristics on the effect of vitamin E.[198, 199] 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 (body mass index (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.[199] 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.[199] 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, $p=0.05$).[199] 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.[199] 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 Plus Calcium

One trial (n=4,143) compared vitamin D with calcium to placebo.[205] Participants in the Women's Health Initiative Memory Study were previously randomized to 400 IU vitamin D_3 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.[205] 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=2,824) compared beta carotene with placebo.[199] 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.[199] 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 beta carotene or placebo arm.

One trial assessed the effect of several participant characteristics on the effect of beta carotene.[199] 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Multivitamin Results Summary k=4; n=20,536	**0 of 2 (no difference) k=1**	**0 of 3 (no difference) k=2**	**0 of 3 (no difference) k=2**	**0 of 2 (no difference) k=2**	**0 of 8 (no difference)**	
Grodstein, 2013[196] Multivitamin vs. placebo n=5,947 (men)		**BCT** NS [TICS]		NS [Composite[b]]	0 of 3 (no difference)	NR
		MNP NS [Composite[a]]				
McNeill, 2007[202] Micronutrient supplement vs. placebo n=910 1 year			NS [DS Forward]		0 of 1 (no difference)	NR
Wolters, 2005[210] 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[197] Vitamin C + B vitamins + beta carotene vs. placebo n=20,536 5 years	NS [Dementia]	**BCT** NS [TICS]			0 of 3 (no difference)	NR
	NS [MCI]					
B Vitamins: Folic Acid		**MNP** **1 of 1 favor I**	**1 of 3 favor I** **k=1**	**1 of 1 favor I** **k=1**	**2 of 4 favor I**	

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]
Results Summary k=1; n=818		**k=1**				
Durga, 2007[212] B vitamins: folic acid vs. placebo n=818 3 years		**MNP** I>C [Composite]	I>C [DSST]	I>C [RAVLT]	3 of 5 favor I	NR
			NS [SCWT]			
			NS [Concept Shifting Test]			
B Vitamins: Folic Acid + B_{12} Results Summary k=2; n=3,819		**BCT** **2 of 2 favor I** **k=2**	**0 of 11 (no difference)** **k=2**	**2 of 7 favor I** **k=2**	**2 of 18 favor I**	
van der Zwaluw, 2014[208] B vitamins: folic acid + B_{12} vs. placebo n=2,919 2 years		**BCT** I>C [MMSE]	NS [Composite[c]]	NS [Composite[f]]	1 of 14 favor I	NR
			NS [Composite[d]]	NS [RAVLT Immediate Recall]		
			NS [Composite[e]]	NS [RAVLT Delayed Recall]		
			NS [DS Forward]	NS [RAVLT Recognition]		
			NS [TMT A]			
			NS [TMT B]			
			NS [SCWT 1 & 2]			
			NS [SCWT Interference]			

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]
			NS [SDMT]			
Walker, 2012[209] B vitamins: folic acid + B_{12} vs. placebo n=900 2 years		**BCT** I>C [TICS Total]	NS [TICS Orientation/ Calculation]	I>C [TICS Immediate Recall]	3 of 6 favor I	NR
			NS [TICS Attention]	I>C [TICS Delayed Recall]		
				NS [TICS Semantic Memory]		
B Vitamins: Folate + B_6 + B_{12} Results Summary k=2; n=1,524		**BCT 0 of 2 (no difference) k=2**	**1 of 2 favor C k=2**	**0 of 4 (no difference) k=2**	**1 of 8 favor C**	
Andreeva, 2011[101] B vitamins: folate + B_6 + B_{12} vs. placebo n=1,248 4 years		**BCT** NS [TICS]		NS [TICS Memory]	0 of 3 (no difference)	NR
				NS [TICS Recall]		
McMahon, 2006[201] B vitamins: folate + B_6 + B_{12} vs. placebo n=276 2 years		**BCT** NS [MMSE]	NS [RCPM]	NS [RAVLT]	1 of 5 favor C	NR
			C>I [TMT B]	NS [Paragraph Recall]		
Vitamin E Results Summary k=2; n=9,201		**BCT 0 of 2 (no difference) k=2 MNP 0 of 2 (no difference) k=2**		**0 of 2 (no difference) k=2**	**0 of 6 (no difference)**	**None k=1**
Kang, 2009[199]		**BCT**		NS	0 of 3 (no	None

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]
Vitamin E vs. placebo n=2,824 9 years treatment 5 years followup		NS [TICS]		[Composite]	difference)	
		MNP NS [Composite]				
Kang, 2006[198] Vitamin E vs. placebo n=6,377 10 years treatment 4 years followup		**BCT** NS [TICS]		NS [Composite]	0 of 3 (no difference)	NR
		MNP NS [Composite]				
Vitamin C Results Summary k=1; n=2,824		**BCT** **0 of 1 (no difference)** **k=1** **MNP** **0 of 1 (no difference)** **k=1**		**1 of 1 favor I** **k=1**	**1 of 3 favor I**	**None** **k=1**
Kang, 2009[199] Vitamin C vs. placebo n=2,824 9 years treatment 5 years followup		**BCT** NS [TICS]		I>C [Composite]	1 of 3 favor I	None
		MNP NS [Composite]				
Vitamin D + Calcium Results Summary k=1; n=4,143	**0 of 1 (no difference)** **k=1**	**BCT** **k=1** **0 of 1 (no difference)**	**0 of 1 (no difference)** **k=1**	**0 of 2 (no difference)** **k=1**	**0 of 4 (no difference)**	
Rossom, 2012[205]	NS [Probable	**BCT** NS	NS [DS Forward &	NS [CVLT]	0 of 5 (no difference)	NR

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]
Vitamin D + calcium vs. placebo n=4,143 8 years	Dementia or MCI]	[MMSE]	Backward (pooled)]			
				NS [BVRT]		
Beta carotene Results Summary k=1; n=2,824		**BCT 0 of 1 (no difference) k=1 MNP 0 of 1 (no difference) k=1**		**0 of 1 (no difference) k=1**	**0 of 3 (no difference)**	**None k=1**
Kang, 2009[199] Vitamin C vs. placebo n=2,824 9 years treatment 5 years followup		**BCT** NS [TICS]		NS [Composite]	0 of 3 (no difference)	None
		MNP NS [Composite]				

[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 Forward & Backward); [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)

B_6=vitamin B_6; B_{12}=vitamin B_{12}; BCT=brief cognitive screening test; BVRT=Benton Visual Retention Test; C=inactive control; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution Test; I=intervention; k=number of studies included; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological test performance; n=sample size; NR=not reported; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; RCPM= Raven's Colored Progressive Matrices; SCWT=Stroop Color Word Test; SDMT=Symbol Digit Modalities Test; TICS=Telephone Interview for Cognitive Status; TMT=Trail Making Test (Part A and/or B); vs.=versus; WAIS=Wechsler Adult Intelligence Scale

Shading indicates summary rows and columns.

Comparative Effectiveness: Vitamins Versus Active Comparison

One RCT (n=167) compared vitamins with an active control group.[216] Stott et al. analyzed the comparative effectiveness of varying combinations of B vitamins (folic acid/B_{12} vs. B_2 vs. B_6 vs. folic acid/B_{12}/B_2 vs. folic acid/B_{12}/B_6 vs. B_2/B_6 vs. folic acid/B_{12}/B_2/B_6). They randomized people aged 65+ with a history of ischemic vascular disease to the above combinations of 2.5 mg folic acid, 25 mg B_2, 25 mg B_6, and/or 0.4 mg B_{12} daily for 3 months. Cognitive outcomes were assessed at 6 and 12 months. The sample size for this unique comparison was too small to assess strength of evidence. See Table 4G.3 for summary of results.

Other studies that used B vitamins as components of active controls can be found in Chapter 4C.

Table 4G.3. Results overview: Vitamins versus active comparisons 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]
B vitamins Combinations* Results Summary k=1; n=167		**BCT 0 of 1 (no difference) k=1**	**0 of 1 (no difference) k=1**		**0 of 2 (no difference)**	
Stott, 2005[216] B vitamins combinations (folic acid, B_2, B_6, B_{12}) n=167 **1 year**		**BCT** NS [TICS-M]	NS [SDMT]		0 of 2 (no difference)	NR

*Participants randomized to one of 7 combinations: 1) folic acid/B_{12} 2) B_2 3) B_6 4) folic acid/B_{12}/B_2 5) folic acid/B_{12}/B_6 6) B_2/B_6 7) folic acid/B_{12}/B_2/B_6. None were significantly different for any outcome.

B_2=vitamin B_2; B_6=vitamin B_6; B_{12}=vitamin B_{12}; BCT=brief cognitive test performance; k=number of studies included; n=sample size; NR=not reported; NS=no statistically significant difference; SDMT=Symbol Digit Modalities Test; TICS-M=Telephone Interview for Cognitive Status-Modified

Shading indicates summary rows and columns.

Adults With MCI

Efficacy: Vitamins Versus Inactive Control

Three trials reported in six publications (n=1,038) with low or moderate risk of bias compared vitamins with inactive control (placebo) in adults with MCI.[191, 194, 195, 203, 213, 215] Total sample sizes ranged from 256 to 516. Strength of evidence was only assessed for one study with a sufficiently large sample size.[203] Conclusions are summarized in Table 4G.4 and individual study results for all three trials are in Table 4G.5

One trial (n=516) compared vitamin E to placebo for preventing cognitive decline.[203] They randomized adults aged 55-90 with degenerative amnestic 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 4K.

Evidence was insufficient to determine improvement with vitamin E for brief cognitive test performance, multidomain neuropsychological performance, 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.4. Conclusions: Vitamins versus inactive comparisons in adults with MCI

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Multivitamin vs. placebo k=1	Dementia	No data available.	Insufficient (no data)
	Brief cognitive test performance	Limited data.	Insufficient (limited data)
	Multidomain neuropsychological performances	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	No data available.	Insufficient (no data)
	Memory	No data available.	Insufficient (no data)
B Vitamins (folic acid/ B_6/B_{12}) vs. placebo k=1	Dementia	No data available.	Insufficient (no data)
	Brief cognitive test performance	Limited data.	Insufficient (limited data)
	Multidomain neuropsychological performances	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	No data available.	Insufficient (no data)
	Memory	Limited data.	Insufficient (limited data)
Vitamin E vs. placebo k=1	Dementia	No statistically significant difference in CATD diagnosis with vitamin E versus placebo long term (n=516; 3 years).	Low (medium study limitations, imprecise)
	Brief cognitive test performance	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, unknown consistency)
	Multidomain neuropsychological performances	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, precision unclear, unknown consistency)
	Executive/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (medium study limitations, indirect, imprecise, unknown consistency)

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

B_6=vitamin B_6; B_{12}=vitamin B_{12}; k=number of studies included; MCI=mild cognitive impairment; n=sample size;

Interpreting the Findings

Overall, little to no benefit was shown with vitamin use in preventing cognitive decline. The only benefits noted were for folic acid plus B_{12} for memory versus placebo in adults with normal cognition; one of these studies administered high doses of folic acid and B_{12} in adults with elevated homocysteine levels. However, no benefit was found for folate, B_6, B_{12} versus placebo for brief cognitive test performance or memory. The differences between studies could not be explained by dosage or deficiency state. Further, the positive results were in a small proportion of cognitive performance tests and of small effect size. Additionally, many of the vitamins were examined in a few studies that enrolled only women.

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

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]
Multivitamin Results Summary k=1; n=256		**BCT 0 of 1 (no difference) k=1**			**0 of 1 (no difference)**	
Naeini, 2014[191] Vitamin E + vitamin C vs. placebo n=256 1 year		**BCT** NS [MMSE]				NR
B vitamins: Folic acid + B_6 + B_{12} Results Summary k=1; n=217		**BCT 0 of 1 (no difference) k=1**		**0 of 1 (no difference) k=1**	**0 of 2 (no difference)**	
Smith, 2010[207] deJager, 2012(de Jager, 2012 #372} Douaud, 2013[195] Oulhaj 2016[215] B vitamins (folic acid + B_{12} + B_6) vs. placebo n=217 2 years		**BCT** NS [MMSE]		NS [HVLT]		NR
Vitamin E Results Summary k=1; n=516	**0 of 2 (no difference) k=1**	**BCT 0 of 1 (no difference) k=1** **MNP 0 of 1 (no difference) k=1**	**0 of 1 (no difference) k=1**	**0 of 1 (no difference) k=1**	**0 of 4 (no difference)**	28% vs. 25%*; reasons NR
Petersen, 2005[203] Vitamin E vs. placebo	NS [CATD]	**BCT** NS [MMSE]	NS [Composite]	NS [Composite]		

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]
n=516 3 years	NS [CDR Sum of Boxes]	**MNP** NS [ADAS-Cog]				

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; B_6=vitamin B_6; B_{12}=vitamin B_{12}; BCT=brief cognitive test performance; C=inactive control; CATD=clinical Alzheimer's-type Dementia; CDR=Clinical Dementia Rating; HVLT=Hopkins Verbal Learning Test; k-number of studies included; I=intervention; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological test performance; n=sample size; NR=not reported; NS=no statistically significant difference; vs.=versus

Shading indicates summary rows and columns.

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

  *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, mild cognitive decline (MCI), or CATD.[218-241] Three trials were assessed as high risk of bias and not used in our analysis.[219, 225, 229]We did not include studies specifically designed to address clear post-stroke dementia, however, studies addressing mixed dementias including a vascular component *were* included. 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 (single or multiple agents) versus placebo, intensive versus standard antihypertensive treatment (with respect to blood pressure treatment targets), and antihypertensive medication treatments versus each other (either or both treatment groups may be single or multiple agents). 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.[242] 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(s) vs. placebo			
ARBs vs. placebo k=3	Dementia	No statistically significant difference in dementia diagnoses with ARBs versus placebo (n=4,937; 44 months).	Low (medium study limitations, unknown consistency, suspected reporting bias)
	MCI	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, suspected reporting bias
	Multidomain neuropsychological performance	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (medium study limitations, unknown consistency, suspected reporting bias)
	Memory	Unable to draw conclusion.	Insufficient (medium study limitations, inconsistent, suspect reporting bias)
Beta blocker vs. placebo k=1	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/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspected reporting bias)
	Memory	Unable to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspected reporting bias)
ACE and Thiazide vs. placebo k=2	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 suspected reporting bias)
	MCI	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, suspected reporting bias)
	Multidomain	No data available.	Insufficient (no data)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
	neuropsychological performance		
	Executive/Attention/ Processing speed	No data available.	Insufficient (no data)
	Memory	No data available.	Insufficient (no data)
Combination therapy vs. placebo k=3	Dementia	Statistically significant difference in dementia diagnoses favoring combination therapy versus placebo (n=3,228; up to 3.9 years).	Low (medium study limitations, imprecise, unknown consistency, suspected reporting bias)
	MCI	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, suspected reporting bias)
	Multidomain neuropsychological performance	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspected reporting bias)
	Memory	No data available.	Insufficient (no data)
Intensive vs. Standard			
Intensive blood pressure control (systolic blood pressure <120 mmHg) vs. standard blood pressure control (standard therapy (systolic blood pressure <140 mmHg) k=1	Dementia	No data available.	Insufficient (no data)
	Brief cognitive test performance	Unable to draw conclusion.	Insufficient (medium study limitations, unknown consistency, suspected 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, suspected 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, unknown consistency, suspected reporting bias).
Antihypertensive vs. Antihypertensive			
Ramipril (I1) up to 10 mg daily vs. (I2) combined ramipril up to 10 mg daily plus telmisartan 80mg daily k=1	Dementia	No data available.	Insufficient (no data)
	MCI	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, unknown consistency, suspected 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 k=3	Dementia	No data available.	Insufficient (no data)
	MCI	No data available.	Insufficient (no data)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
	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, unknown consistency, suspected reporting bias)
	Multidomain neuropsychological performance	No data available.	Insufficient (no data)
	Executive/Attention/ Processing speed	Unable to draw conclusion.	Insufficient (low study limitations, imprecise, unknown consistency, suspected reporting bias)
	Memory	Unable to draw conclusion.	Insufficient (low study limitations, imprecise, inconsistent, suspected reporting bias)

ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blocker; I1=intervention 1; I2=intervention 2; k=number of studies included; MCI=mild cognitive impairment; mg=milligram; mmHg=millimeter of mercury;

Antihypertensive Medication(s) Versus Placebo

Eight unique RCTs met eligibility criteria with low to medium risk of bias and randomized participants to an antihypertensive medication treatment (single or multiple agent) versus placebo,[218, 220, 223, 224, 226, 228, 231, 232, 237, 239-241] Five of the eight studies had eligibility criteria related to cognition, including exclusion of participants with dementia;[223, 224, 226, 240] any mental disorder or clinically relevant chronic disease;[237] and either Mini-Mental State Examination (MMSE) <24, severe brain disorders that may interfere with cognitive function, or treatment with antidementia drugs.[228] Four studies reported baseline MMSE, ranging from a median of 26 to 29.[218, 223, 224, 228, 240]

Among the four unique trials that reported incident dementia outcomes,[223, 224, 228, 239, 240] only the Syst-Eur trial reported a significantly reduced risk of dementia in the antihypertensive treatment group versus the placebo group,[223, 224] while the other three trials reported no difference in risk.[228, 239, 240] During the double-blinded portion of the Syst-Eur trial, which was stopped early after planned interim analyses showed a significant reduction in stroke, 11 cases of incident dementia occurred in the antihypertensive treatment group (none with vascular dementia) and 21 in placebo group (two with vascular dementia). Intervention reduced the rate of incident dementia from 7.7 to 3.8 cases per 1000 patient-years (relative risk (RR) 0.50 [0.24-1.00]).

The Syst-Eur trial compared a stepped multiple agent antihypertensive regimen versus placebo, and defined incident dementia diagnosis based on Diagnostic Statistical Manual of Mental Disorders Third Edition (DSM-3) criteria and was validated by a masked review board.[170,171] By comparison, among the three studies that showed no benefit on risk of CATD, one compared a stepped multiple agent antihypertensive regimen versus placebo,[240] one compared a fixed antihypertensive agent combination versus placebo,[239] and one compared monotherapy versus placebo.[228] Among these three studies, a committee defined participants with incident dementia by consensus using DSM-4 criteria in one study,[240] incident dementia was defined using modified ICD-10 research criteria in another,[228] and no definitions were reported in the third study.[239] Followup 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.[218, 220, 223, 224, 226, 228, 231, 232, 237, 239, 240] 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.[220, 226, 228, 231, 232] All three trials reported results for attention; two trials found that individuals randomized to antihypertensive medication had significantly better attention than those assigned placebo,[228,226] while the third study found no difference between treatment groups.[220]

Two studies reported results for a change in memory tests with mixed findings.[220, 231] One study found no between-group difference in scores on the Paired Association Learning Test (PALS) after 9 months follow-up.[220] 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.[231]

None of these studies reported data on biomarkers.

Three of these eight studies reported information on adverse effects.[228, 237, 240] Participants assigned to methyldopa, 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.[237] In one trial, significantly fewer serious adverse events occurred in the treatment group ($p<0.01$).[240]

The TRANSCEND study (ARB vs. placebo) was the only one of the eight eligible RCTs comparing antihypertensive medication treatment versus placebo that reported subgroup analyses.[218] Authors reported no significant differential effects of treatment on cognitive outcomes in patient subgroups defined by age, history of hypertension, or previous stroke or transient ischemic attack (TIA), though they presented no data for these analyses.

Intensive Versus Standard Antihypertensive Medication

Only one study with low to moderate risk of bias randomized 2,977 participants to intensive versus standard blood pressure control (goal systolic blood pressure <120 vs. <140 mm Hg).[236] This study reported no data on MCI or CATD outcomes. Despite achieving substantial separation between the groups in systolic blood pressure at 40 months (119.0 vs. 133.2 mm Hg), 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. There were no consistent between treatment group differences in change in cognitive performance from baseline as a function of baseline age, gender, executive/attention/processing speed, history of cardiovascular disease, or diabetes duration.

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.[218, 220-222, 227, 230, 235, 237] 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,[227] another excluded participants with either a mental disorder or any "clinically relevant chronic disease,"[237] another excluded participants receiving any psychotropic drug that might interfere with

cognition,[221] and a fourth study excluded individuals with a stroke in the last 6 months.[222] Baseline MMSE scores ranged from a mean of 23[235] to a median of 29.[218]

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.[218] 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.[218, 220-222, 227, 230, 235, 237] Three reported results for a change in a brief cognitive screening test (MMSE).[62, 218, 230, 235] Two studies found no difference between their different antihypertensive medication treatment arms, in mean MMSE score at follow-up,[230] or incidence of >3 point decline in MMSE.[218] 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.[235] 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.[220, 222] Three studies reported results for memory tests and found mixed results.[220-222] 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.[220] 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.[221] 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.[222]

None of these studies reported data on biomarkers.

Four of these studies reported adverse events outcomes.[221, 222, 227, 237] 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.[237] In another, participants randomized to ARB were significantly less likely to have an adverse event than those assigned to beta blocker.[221] 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.[222] 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.[227]

The ONTARGET study (ACE inhibitor vs. ARB vs. combination) was the only one of the eight eligible RCTs comparing one antihypertensive medication treatment versus another that reported subgroup analyses.[218] Authors stated that they found no significant differential effects of treatment on cognitive outcomes in patient subgroups defined by age, history of hypertension, or previous stroke or TIA, although they presented no data for these analyses.

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 Results Summary k=3; n=11,120	**0 of 1 (no difference) k=1**		**BCT 0 of 4 (no difference) k=3**	**1 of 3 favored I k=1**	**1 of 2 favored I k=1**	**1 of 9 favored I**	**0 of 1 (no difference) k=1**
Anderson, 2011[218] (TRANSCEND trial) telmisartan 80 mg daily vs. placebo n=5,926 56 months median followup			**BCT** NS [Drop of 3 or more MMSE points]			0 of 1 (no difference)	NR
Saxby, 2008[231] (single center in SCOPE trial) candesartan (8 mg – 16mg) daily vs. placebo n=257 44 months mean followup			**BCT** NS [MMSE]	NS [Executive Function Composite][a]	I>C [Episodic Memory Composite][a]	2 of 6 favored I	NR
				I>C [Attention Composite][a]	NS [Working Memory Composite][a]		
				NS [Speed of Cognition Composite][a]			
Lithell, 2003[228] **Skoog 2005** [232] (SCOPE trial) Candesartan (8 mg – 16 mg) daily with hydrochlorothiazide 12.5 mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs	NS [Dementia]		**BCT** NS [MMSE]			0 of 2 (no difference)	
			NS [Significant Cognitive Decline]				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]
added as needed vs. placebo daily and hydrochlorothiazide 12.5 mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed n=4,937 44 months mean followup							
Beta Blocker Results Summary k=1; n=2,401				**0 of 1 (no difference)**	**0 of 1 (no difference)**	**0 of 2 (no difference)**	
Bird, 1990 [220] atenolol 50 mg daily vs. placebo n=2,401 9 months				NS [TMT A]	NS [PAL]	0 of 2 (no difference)	NR
Combination Therapy Results Summary k=3; n=6,941	**2 of 2 favors I k=2**		**BCT 0 of 2 (no difference) k=2**	**1 of 3 favors I k=1**		**1 of 5 favors I**	
Forette, 2002 [223] (Syst-Eur trial) Antihypertensive stepwise therapy with titration with goal of lowering systolic blood pressure below 150 mmHg (step 1: nitrendipine 10-40 mg daily; step 2:	I>C [Dementia]		**BCT** NS [MMSE]			0 of 1 (no difference)	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]
enalapril 5 – 20 mg daily; step 3: hydrochlorothiazide 12.5 – 25 mg daily) vs. placebo n=3,228 3.9 years median follow up							
Forette, 1998[224] (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=3,162 2-year median follow up	I>C [Dementia]		**BCT** NS [MMSE]			0 of 1 (no difference)	NR
Gurland, 1988[226] (SHEP trial) Step therapy: step 1: chlorthalidone; step 2: reserpine, metoprolol, or hydralazine) vs. placebo n=551 1 year				NS [DSST]		1 of 3 favors I	NR
				I>C [TMT A]			
				NS [Composite][b]			

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]
ACE and Thiazide vs. placebo Results Summary k=2; n=14,985	**0 of 2 (no difference) k=2**		**BCT 0 of 3 (no difference) k=2**			**0 of 3 (no difference)**	**1 of 2 favored I k=2**
ACE and Thiazide vs. placebo							
Peters, 2008[240] (HYVET-COG) Indapamide 1.5 mg with optional perindopril (2 mg up to 4mg) vs. matching placebo n=3,845 26.4 months mean followup	NS		**BCT** NS [MMSE]			0 of 2 (no difference)	
			NS [MMSE <24 or a decline of >3 MMSE points in a year]				I>C [number of adverse events]
ADVANCE Collaborative Group, 2007[239] 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=11,140 51 months mean followup	NS		**BCT** NS [MMSE]			0 of 1 (no difference)	NS [number with serious drug reactions]
Comparative Effectiveness: ARB versus ACE Results Summary			**BCT 0 of 1 (no difference) k=1**	**0 of 1 (no difference) k=1**	**0 of 3 favored ARB 1 of 3 favored ACE**	**0 of 5 favored ARB 1 of 5 favored**	**0 of 2 (no difference)**

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]
k=3; n=17,331						**ACE**	
Hajjar, 2013 [227] Lisinopril (10 mg - 40 mg) vs. candesartan (8 mg – 32 mg) vs. hydrocholorothiazide (12.5 mg – 25 mg) n=53 6 months							NS
Andrerson, 2011[218] (ONTARGET trial) ramipril (I_1) 5 mg (increased to 10 mg after 2 weeks) daily vs. telmisartan (I_2) 80mg daily n = 17,118 56 months median follow up			**BCT** NS [Drop of 3 or more MMSE points]			0 of 1 (no difference)	NR
Forgari, 2006[222] telmisartan 80mg and hydrochlorothiazide 12.5 mg daily (I_1) vs. lisinopril 20 mg and hydrochlorothiazide 12.5 mg daily (I_2) n=160 6 months				NS [TMT B]	NS [Word List Memory]	1 of 4 favored ACE	NS
					$I_1>I_2$ [Word List Recall]		
					NS [Word List Recognition]		
ARB vs. Thiazide Results Summary k=2; n=122							**0 of 2 (no difference) k=2**
Hajjar, 2013[227] Lisinopril (10 mg -							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]
40 mg) vs. candesartan (8 mg – 32 mg) vs. hydrocholorothiazide (12.5 mg – 25 mg) n=53 6 months							
Tedesco, 1999[235] Losartan (I_1) 50 mg daily vs. hydrochlorothiazide (I_2) 25 mg daily n=69 26 months							NS
Comparative Effectiveness: Intensive vs. Standard Results Summary k=1; n=1,439	**NR**	**NR**	**BCT 0 of 1 (no difference) k=1**	**0 of 2 (no difference) k=1**	**0 of 1 (no difference) k=1**	**0 of 4 (no difference)**	**NR**
Willamson, 2014[236] (ACCORD BP trial) intensive intervention (systolic blood pressure <120 mmHg) vs. standard therapy (systolic blood pressure <140 mmHg) n=1,439 40 months			**BCT** NS [MMSE]	NS [SCWT]	NS [RAVLT]	0 of 4 (no difference)	NR
				NS [DSST]			
Comparative Effectives: Intensive vs. standard							
Antihypertensives							

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]
versus Active Comparison Results Summary k=6; n=20,162							
Hajjar, 2013[227] Lisinopril (10 mg - 40 mg) vs. candesartan (8 mg – 32 mg) vs. hydrocholorothiazide (12.5 mg – 25 mg) n=53 6 months							NS
Sato, 2013[230] (CAMUI trial) combined losartan 50 mg and hydrochlorothiazide 12.5 mg daily vs. combined amlodipine 5 mg and typical dosage of a angiotensin receptor blocker daily n=142 1 year			**BCT** NS [MMSE]			0 of 1 (no difference)	NS
Anderson, 2011[218] (ONTARGET trial) (I_1) ramipril up to 10 mg daily vs. (I_2) combined ramipril up to 10 mg daily plus telmisartan 80 mg daily n=17,078 56 months median			**BCT** NS [Drop of 3 or more MMSE points]			0 of 1 (no difference)	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]
follow up							
Fogari, 2003[221] Atenolol (I_1 50 mg with titration to 100 mg) vs. losartan (I_2 50 mg with titration to 100 mg) n=120 6 months					$I_2 > I_1$ [Word List Memory]	2 of 2 favors I_2	NS
					$I_2 > I_1$ [Word List Recall]		
Yodfat, 1996[237] (LOMIR-MCT-IL trial) Isradipine (I_1) 1.25 mg twice a day vs. methyldopa (I_2) 250 mg 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[220] atenolol 50 mg daily vs. moduretic (hydrochlorothiazide 25 mg and amiloride 2.5 mg) daily n=2,401 9 months				NS [TMT A]	NS [PAL]	0 of 2 (no difference)	NR

[a] Saxby 2008[231] evaluated composite measures of episodic memory (composed of immediate word recall, immediate word recognition, delayed word recall, delayed word recognition, picture recognition), attention (composited simple reaction time, number vigilance, choice reaction time), working memory (composted 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 TMT A & B, verbal fluency for letters F, A, and S, verbal fluency for category animals).

[b] Gurland 1988[226] evaluated a composite executive/attention/processing speed measure composed of SHORT-CARE dementia, TMT, and DSST.

ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blocker; BCT=brief cognitive test performance; C=control; DSST=Digit Symbol Substitution Test; I_1=intervention 1; I_2=intervention 2; k=number of studies included; MCI=mild cognitive impairment; mg=milligram; mmHg=millimeter of mercury; MMSE=Mini-Mental Status Examination; NS=no statistically significant difference; NR=not reported; PAL=Paired Association Learning Test; RAVLT=Rey Auditory Verbal Learning Test; SCWT=Stroop Color Word Test; TMT=Trail Making Test (Parts A & B) Shading indicates summary rows and columns.

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.[233, 234] 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 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. The study did not report any subgroup analyses. 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,[223, 224] it was a large study in which incident dementia was a relatively rare secondary outcome, and the three other trials that compared antihypertensive treatment versus placebo and reported an incident dementia outcome found no difference between treatment groups. We also found low-strength evidence of no difference between different antihypertensive treatment regimens 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. Though extensive observational data suggest that midlife but not late-life hypertension is associated with a significant increase in risk of dementia,[242] the minimal subgroup data reported from RCTs suggested that there was no difference in the effect of antihypertensive medication treatment on cognition based on participant age.

Chapter 4I. Results: Lipid Lowering Treatment

Key Messages

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

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

Eligible Studies

We identified 10 eligible publications reporting nine unique studies that compared treatment with lipid lowering medications versus control treatment to prevent age-related cognitive decline, MCI, or CATD.[193, 236, 243-250] Three publications from two studies were rated high risk of bias and excluded from our analyses.[246, 249, 250] The remaining seven studies with low to medium risk of bias were randomized controlled trials (RCTs) that enrolled a total of 23,286 adults.[193, 236, 243-245, 247, 248] 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.[251] 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.[252] 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,[253] including no protective effect with late-life statin use.[254]

Adults With Normal Cognition

Only two studies excluded participants based on any cognitive criteria; one excluded individuals with a diagnosis of clinical dementia[236] and another excluded individuals with a score on the Mini-Mental State Examination (MMSE) of <24.[247] 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 k=4	Dementia	Unable to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspected reporting bias)
	MCI	No data available.	Insufficient (no data)
	Brief cognitive test performance	Unable to draw conclusion.	Insufficient (medium study limitations, unknown precision, unknown consistency, suspected 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	Unable to draw conclusion.	Insufficient (medium study limitations, imprecise, inconsistent, suspected reporting bias)
Statin plus fenofibrate vs. statin plus placebo k=1	Dementia	No data available.	Insufficient (no data)
	MCI	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, unknown consistency, suspected 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, suspected 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, unknown consistency, suspected reporting bias)

k=number of studies included; MCI=mild cognitive impairment; n=sample size; vs.=versus

Statin Versus Placebo

Four low to medium risk of bias RCTs randomized participants to statin versus placebo and reported cognitive outcomes (n=21,484).[243-245, 247] 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,[244] 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.[247] Three studies assessed baseline cognition and found at least normal functioning.[244, 245, 247] One study reported no information about baseline cognitive function.[243] Mean baseline age ranged between 46 and 71 years in three studies reporting, while age range was 40-80 years in a fourth study.

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.[243] The same study found no difference between treatment groups in brief cognitive screening test performance at 5 years. However, the strength of evidence was 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.[247] Two other trials by the same investigators reported between-group differences favoring the placebo group for executive/attention/processing speed, but not for memory. Participants assigned to the placebo group experienced small improvements in performance across all tested cognitive domains at 6 months versus baseline that was thought to be attributable to practice effects, while participants in the statin group had similar improvements from baseline only in memory, but no change from baseline in other cognitive domains. 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 (effect sizes for between-treatment differences <0.2).[244, 245] Evidence was insufficient for no difference between treatment groups in memory at 6 months.

None of these studies reported biomarker results.

One trial reported that between treatment effects on cognitive outcomes did not differ by age category (data not shown),[247] and another reported that within the statin group a decline in cognition was only observed in those whose final low density lipoprotein (LDL) was below the study median,[244] while the other two trials reported no subgroup 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.[243] 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.[247] 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.[248] 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 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.[248] The study did not report any subgroup analyses for cognitive outcomes. 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).[236] 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. There were no consistent between-treatment differences in change in cognitive performance from baseline as a function of baseline age, gender, executive/attention/processing speed, history of cardiovascular disease, or diabetes duration. 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.[193] The study used no cognitive-related eligibility criteria.

The study reported no data on MCI or CATD 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, and no subgroup analyses for cognitive outcomes. 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Statin vs. Placebo Results Summary k=4; n=21,484	**0 of 1 (no difference) k=1**	**NR**	**BCT 0 of 2 (no difference) k=1**	**0 of 4 favored I 3 of 4 favored C k=2**	**0 of 4 favored I 1 of 4 favored C k=2**	**0 of 10 favored I 4 of 10 favored C**	**0 of 3 (no difference) k=3**
Muldoon, 2004[245] Simvastatin 10 mg daily or Simvastatin 40 mg daily vs. placebo n=308 6 months				C>I [Composite Executive/Attention/ Processing Speed 1][a]	C>I [Memory Composite 1]	0 of 3 favored I 2 of 3 favored C	1 person with drew in active therapy due to stroke
					NS [Memory Composite 2]		
Heart Protection Study, 2002[243] Simvastatin 40 mg daily vs. matching placebo n=20,536 5 years	NS [Reported number who developed dementia]		**BCT** NS [TICS]			0 of 2 (no difference)	NS [Hospitalizations]
			BCT NS [TICS <22]				
Muldoon, 2000[244] Lovastatin 20 mg daily vs. matching-placebo n=209 6 months				C>I [Composite Measure of Attention][b]	NS [Working Memory Composite]	0 of 4 favored I 2 of 4 favored C	NR
				C>I [Composite Measure Psychomotor Speed]	NS [Memory Recall Composite]		

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]
Santanello, 1997[247] lovastatin 20mg daily vs. lovastatin 40mg daily vs. placebo n=431 6 months				NS [DSST]		0 of 1 (no difference)	NS [number of events reported]
Statin Plus Ezetimibe Versus Placebo Results Summary k=1; n=34		**1 of 5 favor I k=1**	**BCT 0 of 1 (no difference) k=1**	**1 of 1 favor I k=1**	**1 of 2 favor I k=1**	**3 of 9 favor I**	
Tendolkar, 2012[248] 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		I>C [Left Amygdala Volume]	**BCT** [MMSE][c]	I>C [DSST]	NS [Dutch Version RAVLT Immediate Word Recall]	3 of 9 favor I	NR
		NS [Right Amygdala Volume]			I>C [Dutch version RAVLT Delayed Word Recall]		
		NS [Left Hippocampal Volume]					
		NS [Right Hippocampal Volume]					
		NS [White Matter Lesion Volume]					

Author Year Comparison N=	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]
Statin plus Fenofibrate versus Statin plus Placebo Results Summary k=1; n=1,538			**BCT 0 of 1 (no difference) k=1**	**0 of 2 (no difference) k=1**	**0 of 1 (no difference) k=1**	**0 of 4 (no difference)**	
Willamson, 2014[236] (ACCORD-MIND Lipid trial) Statin plus Fenofibrate vs. statin n=1538 40 months			**BCT** NS [MMSE]	NS [SCWT]	NS [RAVLT]	0 of 4 favored I	NR
				NS [DSST]			
Comparative Effectiveness k=2; n=230							
Muldoon, 2004[245d] Simvastatin 10mg daily vs. Simvastatin 40mg daily n=189 6 months							1 person with drew in active therapy due to stroke
Carlsson, 2002[193] Pravastatin 20mg daily vs. tocopherol 440 IU daily n=41 6 month followup				NS [DSST]		0 of 1 (no difference)	NS [Physical adverse events and hospitalizations]

[a]Muldoon 2004[245] evaluated composite measures. If the composite measure was significant then individual measures within the composite were tested. 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 2000[244] evaluated composite measures. If the composite measure was significant then individual measures within the composite were tested. The test of the composite measures within the attention composite: C>I [Digit Vigilance], C>I [Recurrent Words], C>I [Elithorn Maze]

[c]Tendolkar 2012[248] did not report between-group difference at followup.

[d]Muldoon 2004[245] 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 40 mg) 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)"
BCT=brief cognitive test performance; C=control; DSST=Digit Symbol Substitution Test; I=intervention; k=number of studies included; mg=milligrams; MMSE=Mini-Mental State Examination; n=sample size; NR=not reported; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; SCWT=Stroop Color Word Test; TICS=Telephone Interview for Cognitive Status; vs.=versus

Shading indicates summary rows and columns.

Adults With MCI

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

Interpreting the Findings

Among included studies, statins did not show evidence of improving or maintaining cognitive function versus placebo. Further, though of uncertain clinical significance, in two 6-month studies small improvements versus baseline in nonmemory domains from presumed practice effects were only observed in the placebo and not the statin group. The only study that reported any outcomes favoring intervention compared statin plus ezetimibe versus placebo in only 34 participants, and reported additional results showing no treatment group difference in cognitive performance. Studies were limited by followup that likely was too short to observe clinically meaningful changes in cognition in the middle-aged and older and largely cognitively normal participants.

Chapter 4J. Results: Nonsteroidal Anti-Inflammatory Drugs

Key Messages

- No evidence was available for the effect of low-dose aspirin on mild cognitive impairment (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, or to benefit multidomain neuropsychological performance or memory, with 8 years of followup after 1 to 3 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 eight eligible publications reporting four unique studies of NSAIDs to prevent age-related cognitive decline, MCI, or CATD.[255-261] Two were assessed as high risk of bias and were not used in our analysis.[260, 261] 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.[262] 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 randomized controlled trials (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.[255-259] Sample sizes were 2,528 and 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 available.	Insufficient (no data)
	MCI	No data available.	Insufficient (no data)

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
k=1	Brief cognitive test performance	No benefit in brief cognitive test performance with aspirin versus placebo long term (n=6,377; 10 years).	Low (medium study limitations, indirect, unknown consistency)
	Multidomain neuropsychological performance	No benefit in multidomain neuropsychological performance with aspirin versus placebo long term (n=6,377; 10 years).	Low (medium study limitations, indirect, unknown consistency)
	Executive/Attention/ Processing speed	No data available.	Insufficient (no data)
	Memory	No benefit in memory with aspirin versus placebo long term (n=6,377; 10 years).	Low (medium study limitations, indirect, unknown consistency)
Non-aspirin NSAIDs vs. placebo k=1	Dementia	No significant difference in dementia diagnosis with celecoxib/naproxen versus placebo (n=2,117; 8 years).	Low (medium study limitations, direct, unknown consistency)
	MCI	No data available.	Insufficient (no data)
	Brief cognitive test performance	No benefit in brief cognitive test performance with celecoxib/naproxen versus placebo long term (n=2,117; 8 years).	Low (medium study limitations, indirect, unknown consistency)
	Multidomain neuropsychological performance	No benefit with celecoxib/naproxen versus placebo in multidomain neuropsychological performance long term (n=2,117; 8 years).	Low (medium study limitations, indirect, 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)
	Memory	No benefit in memory with celecoxib/ naproxen versus placebo in long term (n=2,117; 8 years).	Low (medium study limitations, indirect, imprecise)

k=number of studies included; MCI=mild cognitive impairment; n=sample size; vs.=versus

One trial (n=6,377) compared aspirin (100 mg every other day) to placebo.[259] 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. No cognitive assessment was performed at baseline. Participants were eligible for the cognitive substudy if they were aged 65 or more and completed an initial cognitive assessment by telephone an average of 5.6 years after randomization. The primary outcome was a global score averaging performance across a battery of cognitive tests in two followup assessment up to a mean of 4 years after the initial cognitive assessment (9.6 years after randomization). 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 compared treatment groups in both mean cognitive scores at followup and in change from baseline for brief cognitive test performance, multidomain neuropsychological performance, and memory. The aspirin group performed significantly better in only one of four cognitive tests at only one of two followups, and no better than placebo in change from baseline for any cognitive performance test at the final followup.

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.[255-258] The trial had three arms comparing celecoxib (200 mg twice daily) or naproxen (220mg twice daily) with placebo. Subjects were men and women aged 70 or older with a family history (at least one first-degree relative) of CATD.

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 with either type of NSAID was found for any outcome.

Adults With MCI

The only eligible study had a high risk of bias.[260]

Interpreting the Findings

Despite the compelling epidemiological data and strong pathophysiological rationale, there is no evidence for whether NSAIDs prevent MCI or CATD, and limited available evidence shows no benefit of NSAIDs versus placebo for improving or slowing decline of cognitive performance in adults with normal cognition.

Table 4J.2. Results overview: NSAIDs versus inactive comparisons 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 Results Summary k=1; n=6,377		**BCT 0 of 1 (no difference) MNP 0 of 1 (no difference)**		**0 of 1 (no difference)**	**0 of 3 (no difference)**	
Kang, 2007[259] Aspirin vs. placebo n=6,377 10 years		**BCT** NS [TICS] **MNP** NS [Composite[1]]		NS [Composite[2]]	0 of 3 (no difference)	NR
NSAIDs Results Summary k=1; n=2,117	**0 of 2 (no difference)**	**BCT 0 of 2 (no difference) MNP 0 of 2 (no difference)**	**0 of 4 (no difference)**	**0 of 6 (no difference)**	**0 of 14 (no difference)**	
ADAPT[255-258] 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 [DS Forward] Celecoxib: NS Naproxen: NS [DS Backward]	Celecoxib: NS Naproxen: NS [HVLT] Celecoxib: NS Naproxen: NS [RBMT] Celecoxib: NS Naproxen: NS [BVMT]	0 of 14 (no difference)	Study discontinued due to increased cardiovascular risk from celecoxib

[a]TICS, category fluency, 10 words list (immediate and delayed recall), [b]EBMT; 10 words list (immediate and delayed recall), EBMT; [c]HVLT, informant-rated Dementia Severity Rating Scale, DS, Naming supermarkets, RBMT

3MS=Modified Mini-Mental State Examination; BCT=brief cognitive test performance; BVMT=Brief Visuospatial Memory Test; C=inactive control; CATD=Clinical Alzheimer's Type Disease; DS=Digit Span (Forward and/or Backward); EBMT=East Boston Memory Test; HVLT=Hopkins Verbal Learning Test; k=number of studies included; I=intervention; MNP=multidomain neuropsychological test performance; n=sample size; NS=no statistically significant difference; NSAIDs=Nonsteroidal anti-inflammatory drugs; NR=not reported; RBMT=Rivermead Behavioral Memory Test; TICS=Telephone Interview for Cognitive Status; vs.=versus

Shading indicates summary rows and columns.

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 mild cognitive impairment (MCI); evidence is insufficient for persons with normal cognition.
- Low-strength evidence shows AChEIs 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 13 eligible publications involving 10 unique studies of antidementia drugs to prevent age-related cognitive decline, MCI, or CATD.[203, 213, 263-272] All but two studies (and an additional outcome from a third study) were assessed as high risk of bias and not used in our analysis.[264-268, 270, 272, 273] All interventions used in the studies included in the analysis were 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 presented in Table 4K.1. In this small (n=28) 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.[263] The study showed no cognitive benefits in people 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 Neuropsychological Test Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Donepezil Results Summary k=1; n=28	**NR**	**NR**	**NR**	**0 of 2 (no difference) k=1**	**0 of 2 (no difference) k=1**	**0 of 4 (no difference)**	**NR**
Devi, 2007[263] Donepezil 5mg/d (6 weeks), then 10mg/d vs. placebo n=28 26 weeks				NS [COWAT]	NS [WMS-III, Logical Memory]	0 of 4 (no difference)	NR
				NS [WMS-III, Working Memory]	NS [Buschke, List Learning]		

COWAT: Controlled Word Association Test; k=number of studies included; mg/d=milligrams per day; n=sample size; NR=not reported; NS=no statistically significant difference; vs.=versus; WMS=Wecshler Memory Scale.

Shading indicates summary rows and columns.

Adults With MCI

We identified 11 eligible publications reporting eight unique studies of antidementia drug interventions versus placebo to prevent cognitive decline in adults with MCI.[203, 213, 264, 265, 267-273] All but one study were assessed as high risk of bias and not used in our analysis.[264, 265, 267-270, 272, 273] 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: Antidementia medications in adults with MCI

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
AChEI (donepezil) vs. placebo k=1	Dementia	No statistically significant difference in dementia diagnoses with donepezil versus placebo (n=769; 3 years), although improvement was noted at 18 and 24 months.	Low (medium study limitation, imprecise, unknown consistency)
	MCI	No data available.	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 limitation, 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 limitation, 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 limitation, imprecise, unknown consistency)
	Memory	No statistically significant difference in memory with donepezil versus placebo (n=769; 3 years).	Low (medium study limitation, imprecise, unknown consistency)

AChEI=acetylcholinesterase inhibitor; k=number of studies included; MCI=mild cognitive impairment; n=sample size

One randomized controlled trial (RCT) (n=769) with medium risk of bias compared donepezil to placebo in adults with MCI.[203] Petersen et al. found low-strength evidence that donepezil reduced the likelihood of progression to dementia at 1 year but not at 3 years.[203]

Petersen et al. also assessed cognition with a brief test of cognitive performance (Mini-Mental State Examination, MMSE), two tests of multidomain neuropsychological performance, one test of executive function/attention/ processing speed, and a memory composite.[203] Donepezil performed better than placebo on the MMSE for the first 2 years and on two cognitive test composites (one 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 single study with low to medium risk of bias that examined diagnostic outcomes suggests at most a modest benefit of an AChEI (donepezil) in delaying progression from MCI to CATD over 18 months to 2 years, but no benefit of AChEI versus placebo is seen at 3 years, which was the primary outcome. 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 in this population.

Several large RCTs with high risk of bias were not used in this analysis, but came to the same conclusion: there was no significant benefit of antidementia drugs on the progression of MCI to CATD, biomarkers, or on overall cognitive function. After the earlier, 3-year trial of donepezil (which showed no effects after 3 years) had shown a positive effect at 1 year,[203] donepezil was studied again in a 1-year RCT.[264] 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 Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) was seen. A 2-year RCT employing galantamine to prevent dementia[272, 273] 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 Alzheimer's disease or on cognitive function over 4 years.[265]

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.[273,272] 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 volumes[264] but a significant differences favoring drug (less volume loss) in the secondary outcome of APC in whole brain volumes.[271] While hippocampal volume loss/atrophy is associated with MCI and progression to CATD, and whole brain atrophy is seen in Alzheimer's disease, particularly in the later stages, the significance of these whole brain changes is not obvious, particularly given the negative clinical results of both trials. A number of reviews have looked at the effects of AChEIs on the progression from MCI to CADT. They used more studies than qualified for this review. Some have suggested modest initial benefit that was not sustained[274-276]. They also noted higher rates of adverse events.[275, 276]

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

Author Year Comparison N= Follow-up	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]
Donepezil Results Summary k=1; n=769	**0 of 1 (no difference) k=1**	**0 of 4 (no difference) k=1**	**BCT 0 of 1 (no difference at 3 years) k=1 MNP 0 of 2 (no difference at 3 years) k=1**	**0 of 1 (no difference) k=1**	**0 of 1 (no difference) k=1**	**0 of 9 (no difference at 3 years)**	
Petersen, 2005 [203] Jack, 2008[213] Donepezil 5mg/d (6 weeks), then 10mg/d vs. placebo n=769 3 years (MRI outcomes = High ROB)[213]	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]				

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BCT=brief cognitive test performance; C=control; I=intervention; k=number of studies included; mg/d=milligrams per day; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological test performance; mo=month; MRI=magnetic resonance imaging; n=sample size; NS=no statistically significant difference; vs.=versus.

Shading indicates summary rows and columns.

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 mild cognitive impairment (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 eight eligible studies that compared diabetes medication treatment versus control treatment to prevent age-related cognitive decline, MCI, or CATD.[67, 120, 277-282] We rated three of these studies as having high risk of bias and excluded them from our analyses.[278, 279, 281] The remaining five studies (four unique trials) enrolled a total of 15,672 adults.[67, 120, 280, 282] 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.[283] 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.[242]

Adults With Normal Cognition

Two trials, the ACCORD-MIND and the ORIGIN studies, addressed persons with presumed normal cognition but only the ACCORD-MIND study specifically reported excluding participants with preexisting clinical evidence of dementia.[284] Both trials addressed persons at high risk for cardiovascular events; both compared intensive and standard glucose control for diabetics, and both were large substudies. The ACCORD-MIND trial enrolled 2,977 older adults.[280, 282] The ORIGIN study randomized 12,537 older adults.[285] The publication 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 interventions in adults with normal cognition

Comparison	Outcome	Conclusion	Strength of Evidence (justification)
Glycemic control vs. placebo k=2	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 available.	Insufficient (no data)
	Brief cognitive test performance	A 40-month trial and a 6-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 (medium study limitations, indirect, imprecise)
	Multidomain neuropsychological performance	No data available.	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 (medium study limitations, 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 (medium study limitations, indirect, imprecise)

k=number of studies included; MCI=mild cognitive impairment; n=sample size; vs.=versus

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 Mini-Mental State Examination (MMSE).[120] However, the overall ORIGIN trial reported little difference in mean HbA1C at 6 years between the intensive and standard control groups.[285]

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.[280, 282] 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.[120] Within specific cognitive domains, these trials reported no statistically significant difference between treatment groups for change in verbal memory,[280] executive function,[120, 282] attention,[280] or processing speed.[120, 280, 282]

The ACCORD-MIND trial enrolled participants with normal cognition and measured brain MRI in a subset of participants.[280] 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.[280]

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 Results Summary k=2; n=15,514	**0 of 1 (no difference) k=1**	**1 of 2 favor I 1 of 2 favor C k=1**	**BCT 0 of 2 (no difference} k=2**	**0 of 3 (no difference) k=2**	**0 of 1 (no difference) k=1**	**1 of 8 favors I 1 of 8 favors C**	
ACCORD-MIND Trial Seaquist, 2013[282] Launer, 2011[280] Intensive glycemic control targeting HbA1c to less than 6.0% vs. standard glycemic control targeting HbA1c to 7-7.9% n=2,977 40 months		I>C [Total Brain Volume]	**BCT** NS [MMSE]	NS [DSST]	NS [RAVLT]	1 of 6 favors I 1 of 6 favors C	NS [Mortality][a]
		C>I [Abnormal White Matter]		NS [SCWT]			
Cukierman-Yaffe, 2014[120] Titrated basal insulin glargine targeting a fasting plasma glucose concentration vs. standard of care n=12,537 72 months	NS [MMSE <24, or diagnosed on report forms]		**BCT** NS [MMSE]	NS [DSST]		0 of 2 (no difference)	NR

[a]In February, 2008, increased mortality risk in the main ACCORD study led to the end of the intensive treatment and a transition of those participants to standard treatment.
BCT=brief cognitive test performance; C=control; DSST=Digit Symbol Substitution Test; HbA1c=hemoglobin A1c; I=intervention; MMSE=Mini-Mental Status Exam; NR=not reported; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; SCWT=Stroop Color Word Test; vs.=versus.

Shading indicates summary rows and columns.

Adults With MCI

Two trials evaluated the effect of glycemic control on cognition in older 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) for 6 months,[67] while Luchsinger et al. randomized 80 overweight older nondiabetic and diet controlled diabetic adults with amnestic MCI to metformin up to 1000mg twice a day versus placebo for 12 months.[277]

The Hildreth trial reported no information on the risk of CATD, but found no difference in intervention and control groups in change between baseline and 6 months in a single global measure of cognition, the cognitive domains of memory, language, visuospatial or executive function, or in any individual cognitive test.[67] The trial did not report information on biomarker outcomes or adverse events. The trial 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 Luchsinger trial reported that one person in the placebo group and none in the metformin group converted to dementia.[277] In adjusted analyses, there was no difference between groups in change from baseline in two global measures of cognition or in one measure of executive/attention/processing speed, but the metformin group had statistically significantly more improvement from baseline than the placebo group in one of two memory tests. In stratified analyses reported only for the single memory test, between group differences in the memory test were statistically significant in participants $\leq$63.7 but not >63.7 years old, those who were negative but not positive for APOE-4, those with hemoglobin A1c $\leq$6.0% but not those with >6.0%, and those with an insulin level >9 IU/dl but not those with insulin <9.0 IU/dl. There were no significant differences between treatment groups in strata defined by BMI < or $\geq$30 kg/m^2. There were no significant differences between treatment groups for change from baseline in any of the brain MRI or PET measures reported, or in change in plasma Aβ42 levels.

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

Among included studies, there was minimal to no difference between glycemic intervention and control groups in incident cognitive impairment or change in cognitive performance in adults with normal cognition (intensive versus standard control), and minimal difference in any cognitive outcomes in adults with MCI (pharmacologic monotherapy versus placebo). Because there was no substantial 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. However, results do not show that glycemic interventions lead to clinically meaningful improvements in cognition from baseline. Although the small difference in achieved glycemic control between treatment groups in the ORIGIN trial may have limited the ability of that study to observe a difference in cognitive outcomes, cognitive results also were not meaningfully different between treatment groups in the ACCORD-MIND trial despite the markedly improved glycemic control between their intervention and placebo groups.

Table 4L.3. Results overview: Antidiabetic interventions 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]
Pioglitazone Results Summary k=1; n=78			**MNP 0 of 1 (no difference) k=1**	**0 of 5 (no difference) k=1**	**1 of 4 favors I k=1**	**1 of 10 favors I**	
Hildreth, 2015[67] 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 [SCWT]	NS [RAVLT]	1 of 10 favors I	NR (there were no cases of new
				NS [TMT B]	NS [WMS, Logical Memory II]		or worsening heart failure in the treatment group)
				NS [DS Backward]	NS [Composite]		
				NS [DSST]	I>C [Visual Reproduction]		
				NS [Composite]			
Metformin Results Summary k=1; n=80		**0 of 4 (no difference) k=1**	**BCT 0 of 1 (no difference) k=1 MNP 0 of 1 (no difference) k=1**	**0 of 1 (no difference) k=1**	**1 of 3 favors I k=1**	**1 of 10 favors I**	
Luchsinger, 2016[277] Metformin 1000mg twice daily for 12 months vs. placebo n=80 1 year		NS [Posterior Cingulate-Precuneus Glucose Update]	**BCT** NS [MMSE] **MNP** NS [ADAS-Cog]	NS [DS]	I>C [Buschke Selective Reminding Test]	1 of 10 favors I	
		NS [Hippocampus Glucose Update]			NS [WMS-Revised, Logical Memory II]		

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]
		NS [Para-Hippocampus Glucose Uptake]			NS [Paragraph Recall]		
		NS [Entorhinal Cortex Glucose Uptake]					

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BCT=brief cognitive test; C=control; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution Test; I=intervention; k=number of studies; MMSE=Mini-Mental Status Exam; MNP=multidomain neuropsychological test performance; n=sample size; NR=not reported; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; SCWT=Stroop Color Word Test; TMT=Trail Making Test (Part A and/or B); vs.=versus; WMS=Wechsler Memory Scale.

Shading indicates summary rows and columns.

Chapter 4M. Results: Other Interventions

Key Messages

- Evidence was insufficient for lithium, a nicotine patch, individual piano instruction, multitask rhythmic exercise to music, sleep interventions, and social engagement.
- We found no relevant studies for depression treatments, smoking cessation, or community-level interventions.

Eligible Studies

We identified nine eligible studies of other varied interventions to prevent age-related cognitive decline, mild cognitive impairment (MCI), or CATD.[72, 79, 135, 286-291] Five studies for adults with normal cognition[79, 286-288, 291] and one for adults with MCI[72] 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 Mini-Mental State Examination (MMSE) scores or executive function were observed.[135] Adverse events were not reported. Table 4M.1 summarizes results. A conclusion table is not provided since evidence was insufficient due to limited data (single study n<500).

The remaining five 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);[288] personalized sleep plans to extend sleep for obese adults who sleep for shorter periods (n=121, 14 month followup);[286] transcranial random noise stimulation (n=25, 6 month followup);[291] guided progressive muscle relaxation tapes to improve sleep in older adults with reduced sleep quality (n=80, 12 months);[287] and group social interaction for 1 hour three times per week at a neighborhood community center for older adults (n=276, 40 weeks).[79]

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 amnestic MCI as assessed by the Mayo criteria.[289] Dosage was titrated to a level below that used for affective disorders to avoid problems of tolerability. No difference in conversion to Alzheimer's dementia 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.[290] 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.[290] 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).[72]

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 Results Summary k=1; n=134			**BCT 0 of 1 (no difference) k=1**	**0 of 2 (no difference) k=1**		**0 of 3 (no difference)**	
Hars, 2014[135] Weekly 1 hour supervised group class; multitask exercises to rhythm n=134 6 months			**BCT** NS [MMSE]	NS [CLOX-1]		0 of 3 (no difference)	NR
				NS [FAB]			

BCT=brief cognitive test; CLOX-1=Clock Drawing Test; FAB=Frontal Assessment Battery; k=number of studies included; MMSE=Mini-Mental Status Examination; n=sample size; NR=not reported; NS=no statistically significant difference.

Shading indicates summary rows and columns.

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 Neuropsychological Performance [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Other Medications Results Summary k=2; n=108	**0 of 1 (no difference) k=1**	**2 of 3 favor I k=1**	**NR**	**Unclear**	**NR**	**2 of 3 favor I**	
Newhouse, 2012[290] Nicotine 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[289] Lithium titrated to serum levels 0.25-0.5 mmol/l vs. placebo n=41 1 year	NS [Conversion to Probable AD]	I>C [Amyloid-Beta]					NS [Ischemic stroke, death due
		NS [Total Tau]					to sepsis; neither
		I>C [Phosphorylated Tau]					deemed due to treatment]

AD=Alzheimer's Disease; AEs=adverse effects; C=control; k=number of studies included; I=intervention; mg/day=milligrams per day; mmol=millimole; n=sample size; NR=not reported; NS=no statistically significant difference; vs.=versus.

Shading indicates summary rows and columns.

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

Key Messages

- Only a few (9) low or medium risk of bias studies used biomarker measures; most of those used some form of brain scan.
- The overall rate of agreement between biomarker measures and cognitive testing was 57 percent, but 90 percent of that agreement resulted from both approaches showing no effect. When the biomarker measure showed a significant result, there was agreement in 25 percent of cognitive tests conducted.

Association Between Biomarkers and Cognitive Tests

Substantial work has gone into searching for biomarkers in living persons that indicate the level of dementia activity.[292] In most cases, the biomarkers are validated by comparing the measure with a systematic clinical evaluation, but in some cases the biomarker measures may predict subsequent development of cognitive decline. The distinction between biomarkers that are used as early harbingers of incipient disease vs. those that track with disease progression is important. Imaging indices are most often used as an example of the later category but not always. cerebrospinal fluid (CSF) and blood indices are commonly used as either. Biomarkers for early identification might be of interest for those interventions with people with normal cognition and less so with MCI/dementia (and NOT expected to correlate with cognition), whereas those biomarkers that are intended to track with disease progression would be the opposite – of more interest in impaired groups and more expected to agree with observable symptoms.

KQ3 compares the biomarker measure results with cognitive testing results in the studies used for KQs 1 and 2. Only a small number of studies used both biomarker measures and cognitive testing. There were 35 biomarker measures used in 9 studies. One of the studies included two treatment arms. A few studies used only biomarker measures (and were omitted from this comparison). Several other studies included biomarker measures that were assessed as high risk of bias and not included in this analysis. Few studies used the same biomarker measure. The biomarker measures used here were all based on brain scans (MRI or PET).

Table 4N.1 shows the rate of agreement between a given biomarker measure and the cognitive domains that were simultaneously tested. The overall rate of agreement was 57 percent (144/254) but the underlying result of the biomarker played a major role in agreement. Of the 23 cases where the biomarker measure was not significant, there were 197 cognitive tests of which 130 were also not significant (66 percent). Of the 12 cases where the biomarker measure was significant, there were 57 cognitive tests of which 14 agreed with the biomarker (25 percent). There was only one study in which none of the biomarker measures nor cognitive tests were significant.[93, 94] 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.

We used a simple calculation of agreement rates between each biomarker measure and the cognitive tests used in a study to distinguish differences between experimental and control participants. For example, in a study of omega-3 fatty acids,[117] grey matter volume was found to be decreased in those receiving the intervention compared to the controls. In one instance (a test of

executive function/attention/processing speed) the cognitive test showed a similar pattern. In two other measures of executive/attention/processing speed and a memory test, it did not. Hence the rate of agreement for a finding of biomarker difference in this case was 1/4. Similarly, when the grey matter volume showed no significant difference in one study of in adults receiving resveratrol,[118] cognitive performance showed a difference in 2 out of 6 tests of cognition. Hence the agreement rate was 4/6.

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

Biomarker	Biomarkers	Diagnosis	Dementia Screens*	Executive/Attention/ Processing Speed	Memory	Agreement Rate	Intervention
MRI-grey matter volume	I>C			I>C, NS, NS	NS	1/4	Omega 3[117]
	NS				I>C, I>C, NS, NS, NS, NS	4/6	Resveratrol[118]
MRI-white matter integrity	NS			I>C, NS, NS	NS	3/4	Omega 3[117]
MRI-HC microstructure	NS				I>C, I>C, NS, NS, NS, NS	4/6	Resveratrol[118]
MRI-HC frontal	I>C				I>C, I>C, NS, NS, NS, NS	2/6	
MRI-HC parietal	I>C				I>C, I>C, NS, NS, NS, NS	2/6	
MRI-HC occipital	I>C				I>C, I>C, NS, NS, NS, NS	2/6	
MRI-total brain volume	NS	C>I, NS, NS	C>I	NS, NS, NS	NS, NS, NS, NS, NS	10/12	Estrogen[149, 175, 177, 178, 180, 293]
	NS	C>I, NS, NS	C>I	NS, NS, NS	C>I, C>I, C>I, C>I, NS	6/12	Estrogen+ progestin[149, 151, 175, 177-179]
	I>C		NS	NS, NS	NS	0/4	Glycemic control[280, 282]
MRI-ventricular volume	NS	C>I, NS, NS	C>I	NS, NS, NS	NS, NS, NS, NS, NS	10/12	Estrogen[149, 175, 177, 178, 180, 293]
	NS	C>I, NS, NS	C>I	NS, NS, NS	C>I, C>I, C>I, C>I, NS	6/12	Estrogen+ progestin[149, 151, 175, 177-179]
MRI-HC volume	NS	C>I, NS, NS	C>I	NS, NS, NS	NS, NS, NS, NS, NS	10/12	Estrogen[149, 175, 177, 178, 180, 293]
	NS	C>I, NS, NS	C>I	NS, NS, NS	C>I, C>I, C>I, C>I, NS	6/12	Estrogen+ progestin[149, 151, 175, 177-179]
MRI-whole brain cortices	NS		NS, NS		NS, NS	4/4	Multicomponent physical activity[93, 94]
MRI-medial temporal areas, including entorhinal cortex	NS		NS, NS		NS, NS	4/4	
Left HC volume	NS		NS	I>C	I>C, NS	2/4	Statins[248]
Right HC	NS		NS	I>C	I>C, NS	2/4	

Biomarker	Biomarkers	Diagnosis	Dementia Screens*	Executive/Attention/ Processing Speed	Memory	Agreement Rate	Intervention
volume							
MRI-frontal lobe volume	C>I	C>I, NS, NS	C>I	NS, NS, NS	NS, NS, NS, NS, NS	2/12	Estrogen[149, 175, 177, 178, 180, 293]
	NS	C>I, NS, NS	C>I	NS, NS, NS	C>I, C>I, C>I, C>I, NS	6/12	Estrogen+ progestin[149, 151, 175, 177-179]
Abnormal white matter	C>I		NS	NS, NS	NS	0/4	Glycemic control[280, 282]
White and grey matter	NS	C>I, NS, NS	C>I	NS, NS, NS	NS, NS, NS, NS, NS	10/12	Estrogen[149, 175, 177, 178, 180, 293]
	NS	C>I, NS, NS	C>I	NS, NS, NS	C>I, C>I, C>I, C>I, NS	6/12	Estrogen+ progestin[149, 151, 175, 177-179]
Basal ganglia	NS	C>I, NS, NS	C>I	NS, NS, NS	NS, NS, NS, NS, NS	10/12	Estrogen[149, 175, 177, 178, 180, 293]
	NS	C>I, NS, NS	C>I	NS, NS, NS	C>I, C>I, C>I, C>I, NS	6/12	Estrogen+ progestin[149, 151, 175, 177-179]
Total brain lesion volume	NS	C>I, NS, NS	C>I	NS, NS, NS	NS, NS, NS, NS, NS	10/12	Estrogen[149, 175, 177, 178, 180, 293]
	NS	C>I, NS, NS	C>I	NS, NS, NS	C>I, C>I, C>I, C>I, NS	6/12	Estrogen+ progestin[149, 151, 175, 177-179]
Posterior atrophy	I>C		NS		NS	0/2	Vitamin B[195 194, 207]
Left amygdala volume	I>C		NS	I>C	I>C, NS	2/4	Statins[248]
Right amygdala volume	NS		NS	I>C	I>C, NS	2/4	
White matter lesion volume	NS		NS	I>C	I>C, NS	2/4	
Glucose uptake (PET scan)	I>C	I>C	I>C, NS	NS, NS	I>C, NS	3/7	Cognitive training[48, 49]
Amyloid-beta	I>C	NS				0/1	Lithium[289]
Phosphorylated tau at threonine	I>C	NS				0/1	
Total tau	NS	NS				1/1	
Overall agreement rate						**144/254 (57%)**	
Agreement based on						**130/197 (66%)**	

Biomarker	Biomarkers	Diagnosis	Dementia Screens*	Executive/Attention/ Processing Speed	Memory	Agreement Rate	Intervention
both showing no significant pattern of effect (NS)							
Agreement rate when the biomarker showed a significant difference						**14/57 (25%)**	

*Includes both brief tests of cognitive performance and multidomain neuropsychological performance tests
C=control; HC=hippocampus; I=intervention; NS=no statistically significant difference

Chapter 5. Discussion

Research on interventions to prevent or slow age-related cognitive decline, mild cognitive impairment (MCI), or clinical Alzheimer's-type dementia (CATD) has focused largely on their effect on decline in measures of cognition. The reasons for this are many, including 1) meaningful investigation of dementia-onset requires either a long followup period or a large cohort of older individuals, 2) long followups in the target population face serious attrition problems due to death or comorbidities, 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 age-related cognitive decline, MCI, or CATD are often chosen because of evidence from epidemiological studies that examine actions of individuals at higher or lower than expected risk for these conditions. In other cases, theories of brain function (e.g., neuroplasticity) justify the development and testing of experimental interventions. Not all such interventions would be expected to be found to be effective in controlled experiments. This systematic review cast a wide net and only a few interventions showed any evidence of an effect, all of which raise many questions. Most of the studies showed no benefit to those receiving interventions compared to control groups. Four intervention classes show some positive results and seem the most promising for further study: cognitive training, physical activity, the selective estrogen receptor modulator (SERM) raloxifene, and B_{12} plus folic acid, although the evidence for raloxifene and B_{12} plus folic acid is lower than the others. The problems with study designs make strong conclusions difficult. Assessing the strength of evidence for negative findings is a special challenge. There is a persistent concern about Type II errors.

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

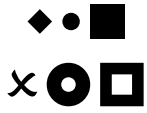
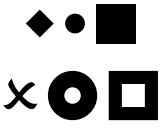
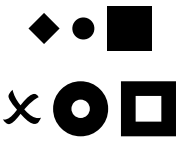
Cognitive decline is almost always a precursor of dementia. Impairment below a designated threshold helps to define CATD and/or MCI. But not all individuals with cognitive decline develop CATD, and we do not know whether interventions that show effects on selected areas of cognitive performance can also stave off dementing conditions. Presumably, the broader the effect an intervention has on multiple cognitive domains, the more likely it will also have preventive effects. But improving (or slowing the decline of) performance in one given cognitive domain does not automatically imply protection against dementia. For example, some cognitive training does seem to improve performance in the specific area of the training, but the results do not generalize to improved performance in other cognitive domains. The strongest effect of cognitive training found in this analysis was in enhancing processing speed, but extrapolating that benefit to a reduced risk of CATD is not yet established. For example, improving a person's useful field of vision can help with driving a car, and it might facilitate some instrumental activities of daily living (IADLs), but neither of those benefits necessarily slows 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. Circles show significant effects favoring interventions. Diamonds and X's show non-significant results for dementia only or composite of dementia or MCI respectively. Squares show incidences when the intervention favors the controls. 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 three different tests for memory were used by a single study, three symbols will be assigned to the memory category.

Table 5.1. Symbol sizes and related sample size information

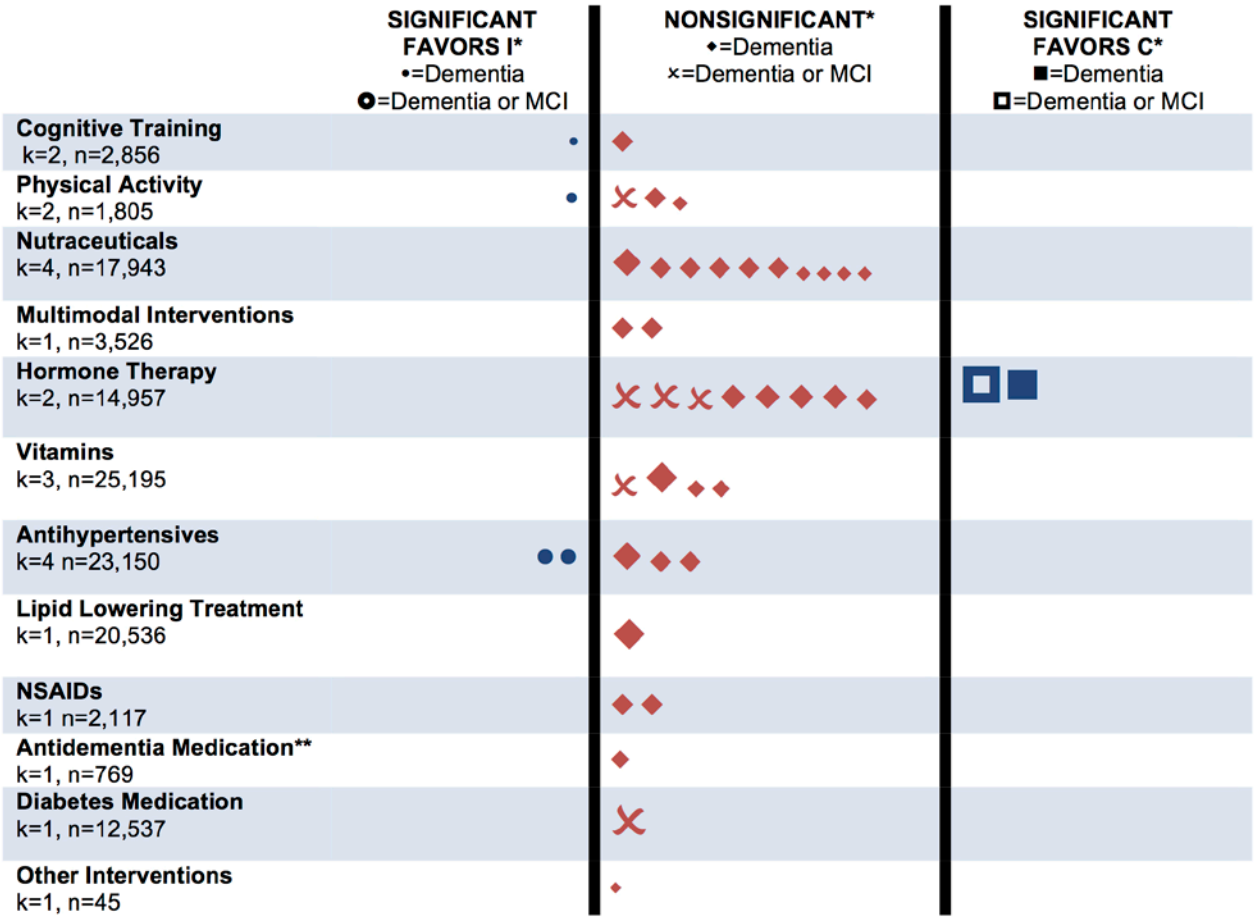
Symbol Sizes Used	Sample Sizes Represented
	**N<100**
	**N=100-500**
	**N=501-1,000**
	**N=1,001-5,000**
	**N=5,001-10,000**
	**N=10,001-15,000**
	**N=15,000+**

N=sample size

Figure 5.1 summarizes the findings on the range of interventions aimed at reducing the incidence of dementia or MCI. The preponderance of studies showed no effect. In the case of estrogen therapy, the control groups did better than the experimental groups for dementia or

composite dementia or MCI, suggesting a de facto harm. This is in contrast to the improvement in MCI alone for SERM (not shown in Figure 5.1).

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 different test measured for each outcome domain. 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. Results for CATD or MCI (per title) are shown; results for less clear categories of dementia are not shown.

** Results for the 3 year outcome.

I=intervention; C=control; k=number of studies; n=sample size; NSAIDs=nonsteroidal anti-inflammatory drugs

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 modeling 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

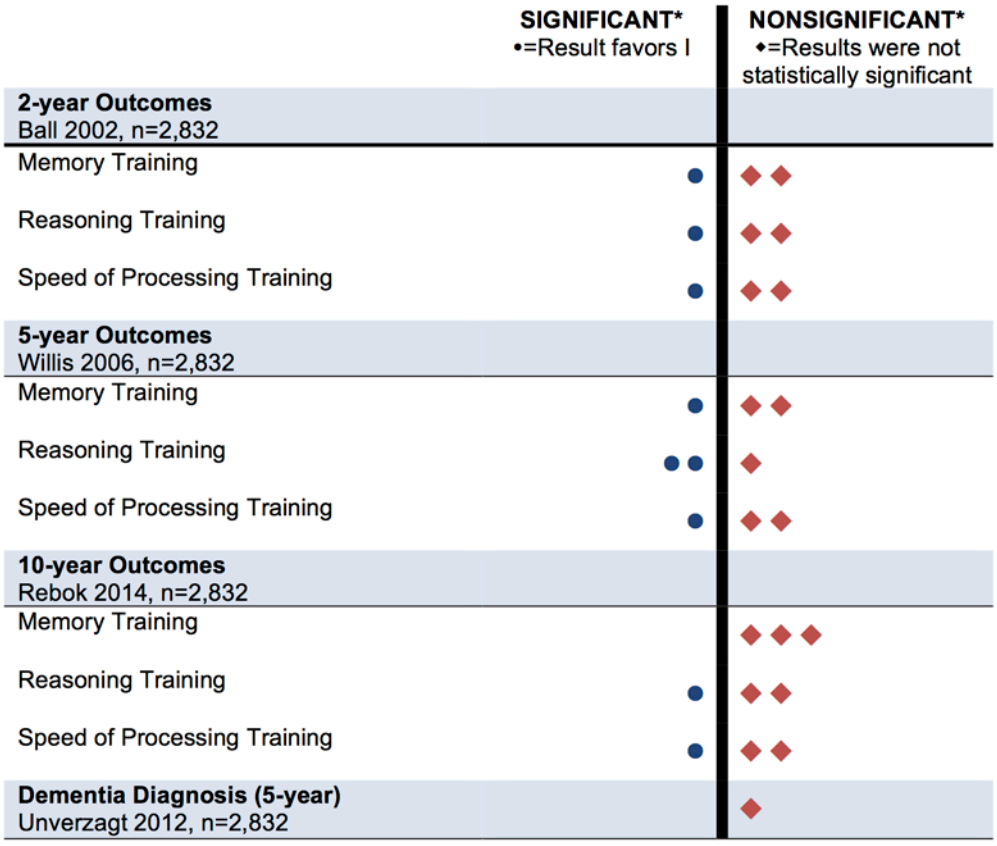
attrition, but it will make it more difficult to ascertain the relationship between the intervention and subject age.

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 participants. For the most part, the training had sustained effects (up to 2 years) on cognitive performance in the domain trained but there was little evidence of generalization to other cognitive domains. There was an effort to assess the effects of booster training, but assignment to receive a booster was not random; participants with high initial compliance received most of the boosters.

As shown in Figure 5.2, the ACTIVE study showed mixed effects. For example, across different outcomes in the memory training, one test result found significant benefit with the intervention and two did not. The positive results were in the training domain and one instance of spillover/transfer to an alternate domain. Memory did not show a statistical effect at 10 years. Otherwise the nonsignificant results were for domains not trained, showing generally a lack of generalization/transfer across domains.

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

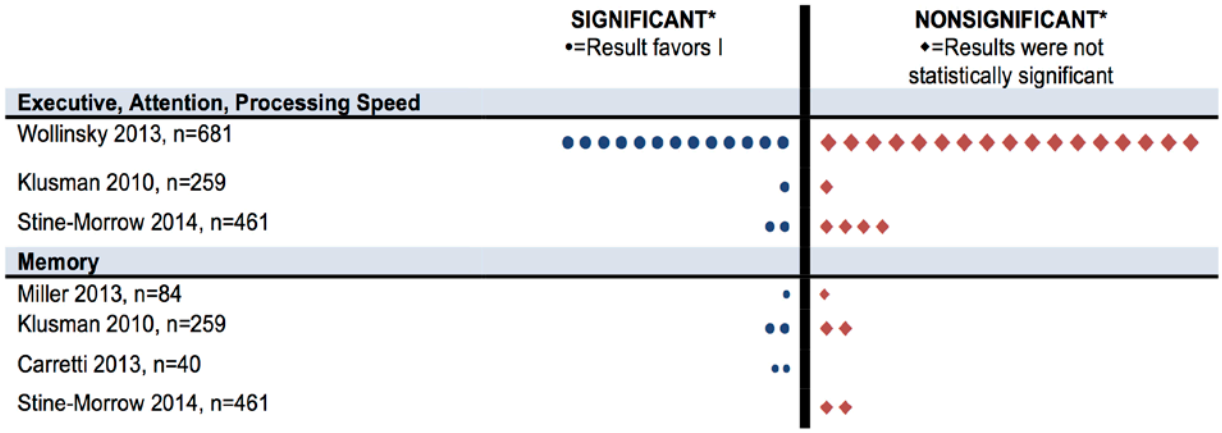


*Categorized by whether results showed statistically significant differences between groups. Each symbol represents a different test measured for each outcome domain. As described in Table 5.1, size of symbol indicates the relative sample size for test. More than one test per domain was frequently used in any given trial. At 2-years, the positive results were for the outcome that matched the domain trained; the nonsignificant results were for the outcomes that did not match the domain trained, showing generally a lack of diffusion across domains. This trend was consistent for memory and speed of processing training at 5-years and reasoning and speed of processing training at 10-years.

I=intervention; C=control; n=sample size

The other cognitive training trials showed basically the same pattern (See Figure 5.3).

Figure 5.3. Summary of the tests of cognitive performance from additional cognitive training trials other than ACTIVE for adults with normal cognition



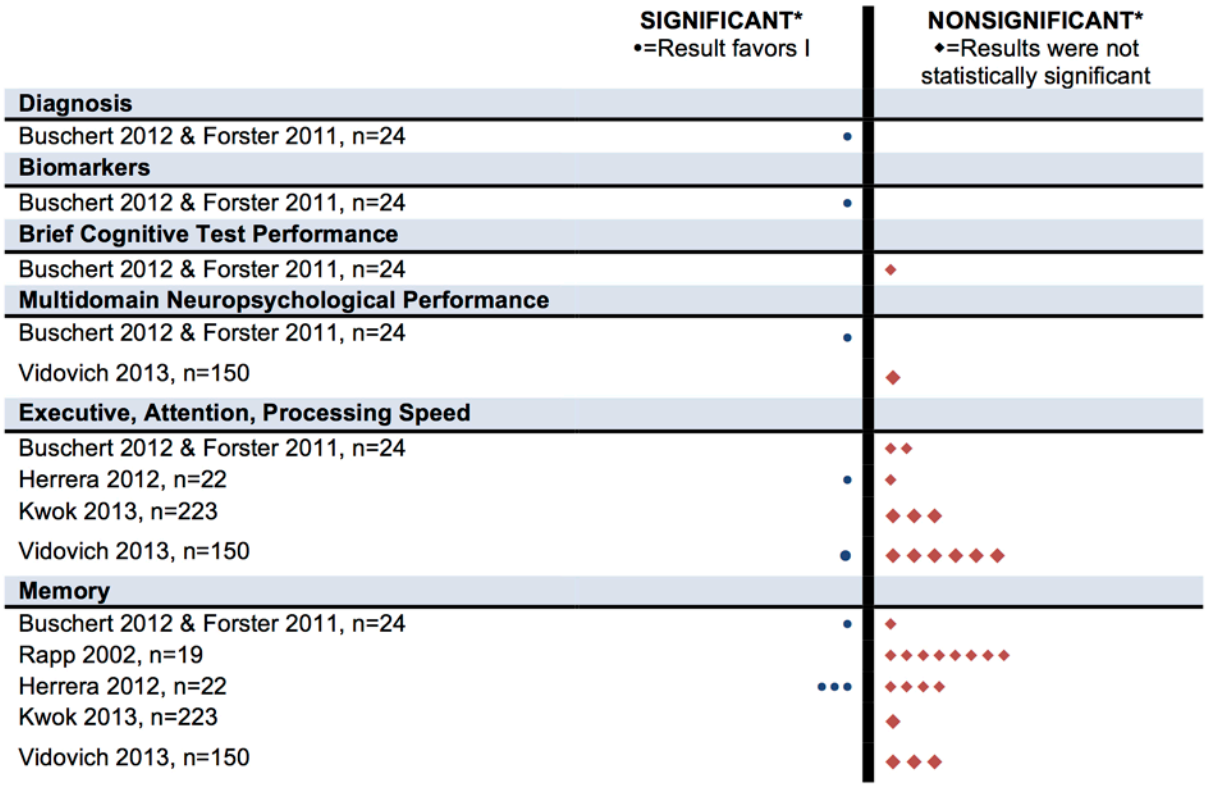
*Categorized by whether results showed statistically significant differences between groups. Each symbol represents a different test measured for each outcome domain. As described in Table 5.1, size of symbol indicates the relative sample size for test. More than one test per domain was frequently used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

I=intervention; C=control; n=sample size

The predominant pattern of the intervention studies is one of no benefit at either the cognitive domain or the dementia level. Some of this absence of effect might be attributed to inadequate statistical power, but many studies were adequately powered. Ideally, the smaller studies might be entered in a meta-analysis, but the wide variety of tests employed forced us to work at the domain level, which, as mentioned, precluded a meta-analyses. We were able to calculate Cohen D's for some of the studies but were still unable to meaningfully pool the data.

Among participants with MCI, the findings are less impressive and rely on small studies. (See Figure 5.4.) Note that two reports (of the same small number of participants), Buschert 2012 & Forster 2011, addressed multiple outcomes.

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



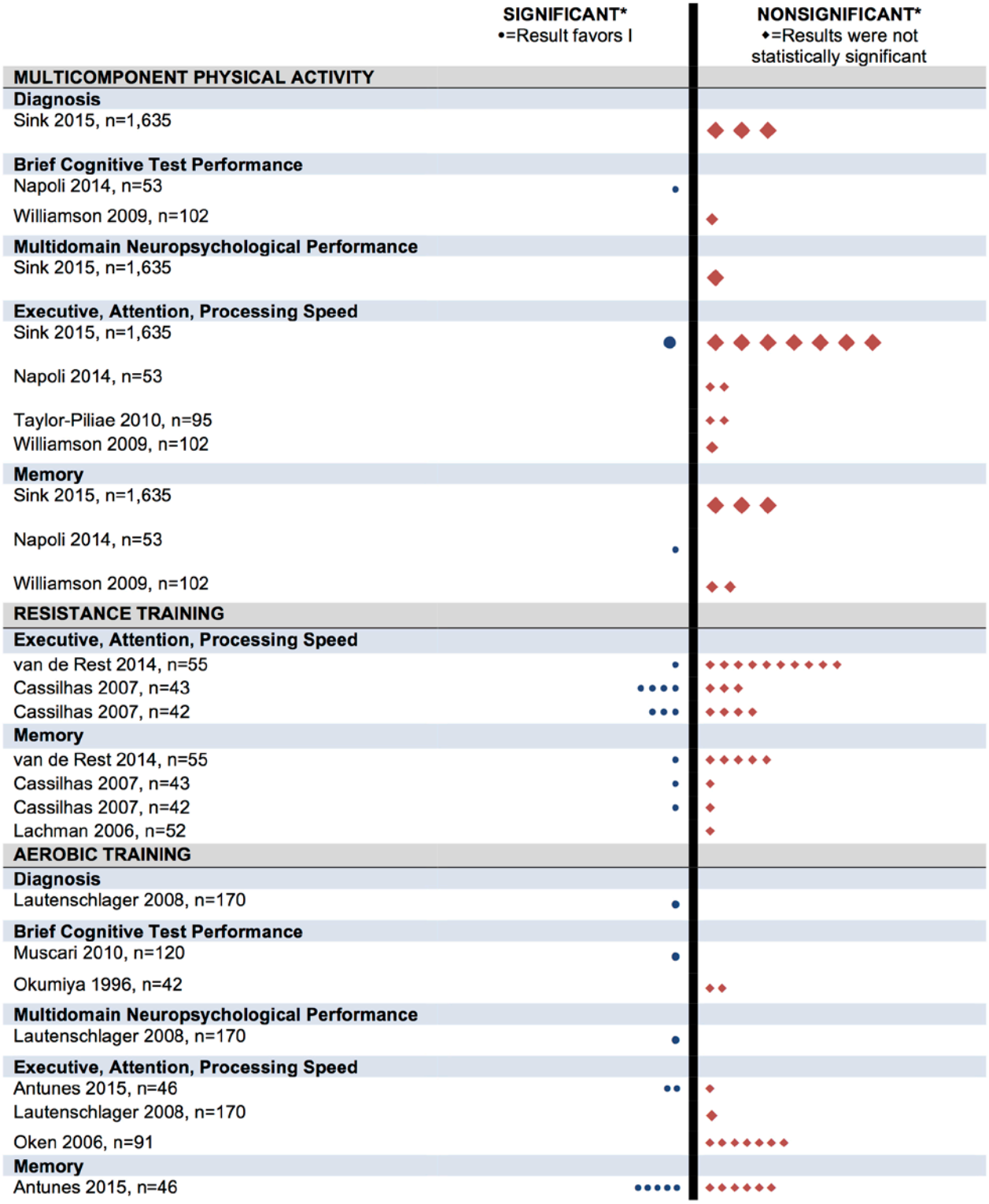
*Categorized by whether results showed statistically significant differences between groups. Each symbol represents a different test measured for each outcome domain. As described in Table 5.1, size of symbol indicates the relative sample size for test. More than one test per domain was frequently used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

I=intervention; n=sample size

Aerobic and resistance training provided the highest proportion of significant positive results among physical activity interventions. Figure 5.5 summarizes the results of these studies. It is organized by type of exercise and cognitive domain assessed. As a result, the same studies appear multiple times. As seen in the figure, 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. 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. However, if physical activity lowers risk for cognitive decline and CATD and interventions can be effectively implemented to change behaviors, these interventions likely involve long-term investment and may need to begin earlier in the aging process. Also, 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 show an overwhelming or consistent effect, but one cannot ignore the positive results. Aerobic and resistance 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 for adults with normal cognition



*Categorized by whether results showed statistically significant differences between groups. Each symbol represents a different test measured for each outcome domain. 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

While the overall findings for the remaining interventions described in Chapters 4C through 4M showed little benefit, several studies of the treatment of hypertension showed improved cognitive functioning. Given that hypertension control is already a goal for the treatment of cardiovascular disease, these positive outcomes can be viewed as a potential additional benefit from efforts to control blood pressure. Ironically, if the hypertensive treatment lowered mortality, its benefits for dementia might be underestimated because of selective attrition.

Vitamin B_{12} and folic acid also showed benefit in brief cognitive test performance and memory, but not for executive/attention/ processing speed. There were also conflicting findings for B_{12} when in combinations with other B vitamins. The other vitamins had no substantial benefit on cognition. Little or no benefit for cognitive performance was shown for multivitamins, vitamin C, vitamin D with calcium, or beta carotene (all low strength of evidence). Vitamins work differently if given to a person to address an insufficiency compared to a megadose for a person with otherwise adequate basic vitamin intake. The participants varied widely in this and other respects. In the case of B_{12}, large doses would be needed to overcome malabsorption of this vitamin for people with high homocysteine levels.

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 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 vitamin E, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and antidiabetic treatment. The argument around antihypertensive treatment is different. Some studies showed benefit and some benefit may be underestimated because of excluding post-stroke dementia studies, 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 II error. Studies that show no effect differ from non-inferiority studies, which compare effects of two interventions. Both require looking for Type II errors, which necessitates larger sample sizes than Type I 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 participants 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; B vitamins 2 of 6 tests favor I
Nutraceuticals	6: for healthy participants 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

MCI=mild cognitive impairment; I=intervention; NS=no statistically significant difference

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 are inadequate to test effectiveness of interventions to prevent these outcomes. At best, they offer some indirect evidence. Studies with longer durations and followup may experience different rates of mortality and loss to followup between intervention and comparison participants 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: intervention 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 rely on self-reported outcomes. (Unfortunately, no studies of this type that used analytic tools to simulate quasi-experimental design and address selection bias in order to test causality were identified in the searches.)

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, participants were described as having cognitive complaints but no diagnosis.

Value of Biomarkers

The evidence synthesis of measures of biomarkers and cognitive function introduces two important, related challenges. One is understanding the relationship between these outcomes and MCI or dementia incidence. Without a clear understanding of 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 biomarker measures we encountered were either used alone or in parallel with other outcomes. We limited our analysis of the agreement of biomarkers (primarily magnetic resonance imaging (MRI) and positron emission tomography (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 biomarker measures (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 biomarker measures, functional MRI, related to frequent lack of adjustment for large numbers of comparisons.[294] More needs to be known about their ability to predict the clinical course of persons with various levels of cognitive function.

Limitations of the Review Process

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

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

To address the multiplicity of cognitive performance tests used, we clustered tests into domains. Because these domains were composites of various tests with different scoring systems, meta-analysis proved unwieldy to conduct. Instead we opted to simply show the proportion of tests. We did use forest plots in some instances and calculated Cohen's D when appropriate. 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 and interpreting the strength of evidence for many studies that showed no difference was difficult, especially when we were unable to use meta-analysis to address small sample size issues. Several reviewers urged a clear distinction between the absence of strong evidence of an effect and strong evidence of no effect. We have tried to make that distinction whenever feasible.

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

Chapter 6. Conclusion

Table 6.1 provides a summary of the key messages from the results chapters detailing intervention results. Of the 13 classes of interventions examined, we found no high-strength evidence for any intervention to delay or prevent age-related cognitive decline, mild cognitive impairment (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 angiotensin converting enzyme inhibitors (AC)E and thiazide versus placebo and antiotensin receptor blockers (ARBs) versus placebo on specifically brief cognitive screening tests. We found low-strength evidence that the selective estrogen receptor modulator (SERM) raloxifene reduced risk of probable MCI, however, there was also low-strength evidence that estrogen replacement with or without progestin therapy increased the risk of MCI and CATD.

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

Although the evidence is less compelling, physical activity and perhaps vitamin B_{12} plus folic acid may also show potential benefit. While the majority of the results for physical activity showed little to no effect, the percent of results showing benefit in cognitive performance, particularly in resistance training and aerobic exercise, were unlikely to be explained solely by chance. Results for B_{12} and folic acid are more spotty and so less persuasive; vitamin B_{12} and folic acid showed benefit in brief cognitive test performance and memory, but not for executive/attention/processing speed. There were also conflicting findings for B_{12} when used in combination with other B vitamins.

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

Table 6.1. Summary of results chapters key messages

Intervention	Key Message
Cognitive Training	• Most studies addressed intermediate outcomes of cognitive training in terms of cognitive performance and a few measures of brain activity. • The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial provided the strongest and most comprehensive design to

	assess the effect of cognitive training on cognitive performance for older adults with normal cognition. Its results provide moderate-strength evidence at 2 years (but low-strength at 5 and 10 years) that cognitive training can improve cognitive function in the domain trained, but transfer to other domains was rare. There is some suggestion that processing speed training is associated with improved IADL performance, but longer term studies were rated as low strength of evidence. • Other than the ACTIVE trial, the few studies that examined CATD incidence or cognitive performance showed mixed results.
Physical Activity Interventions	• Studies of physical activity interventions examined a wide variety of activities potentially targeting different pathways to affect cognition. • Evidence is insufficient to conclude whether physical activity interventions prevent MCI or CATD incidence. • Low-strength evidence shows that multicomponent physical activity interventions offer no clear benefit in cognitive performance over attention control in adults with normal cognition. • Evidence was insufficient to conclude whether other types of physical activity interventions had benefits for cognitive outcomes in adults with normal cognition. • While the majority of results showed no significant difference, the pattern of results across very different types of physical activity interventions provides an *indication* of effectiveness of physical activity.
Nutraceutical Interventions	• Low-strength evidence suggests omega-3 fatty acids and ginkgo biloba did not reduce CATD incidence or improve cognitive performance in adults with normal cognition. • Evidence is insufficient to conclude whether resveratrol or plant sterol/stanol esters reduced CATD incidence or improved cognitive performance in adults with normal cognition. • Few studies examined the effects of nutraceuticals on adults with MCI.
Diet Interventions	• Evidence is insufficient to conclude whether protein supplementation or energy-deficit diets have an effect on cognitive performance or incidence of MCI or CATD.
Multimodal Interventions	• Evidence is insufficient to conclude whether most multimodal interventions offer benefits for cognitive performance or incidence of MCI or CATD, largely because few studies have examined interventions with similar components. • Low-strength evidence shows that a multimodal intervention composed of diet, physical activity, and cognitive training provides benefits in executive function/attention/processing speed. • Low-strength evidence shows that a multimodal intervention composed of lifestyle advice and drug treatment is not effective in reducing incidence of CATD or benefiting brief cognitive test performance or memory.
Hormone Therapy Interventions	• Hormone therapy shows mixed results of harms and benefits. • Low-strength evidence suggests that estrogen therapy may slightly increase the risk of probable MCI and CATD when the two diagnostic categories are examined together. • Low-strength evidence suggests that estrogen plus progestin therapy may slightly increase the risk of probable CATD. • Low-strength evidence suggests that raloxifene may decrease the risk of MCI but not the risk of CATD or of a combined outcome of MCI or CATD compared to placebo. • In addition to these outcomes, hormone therapy has been associated with serious adverse events, including increased risk of certain cancers and cardiovascular disease
Vitamin Interventions	• Moderate-strength evidence shows no benefit in cognitive performance for vitamin E in women. • B vitamins show mixed findings. • Low-strength evidence for folic acid (0.4 mg) plus vitamin B_{12} (0.1-0.5 mg) shows benefit in brief cognitive test performance and memory. • Moderate-strength evidence shows no benefit for folic acid (0.4 mg) plus

	B_{12} (0.1-0.5 mg) versus placebo for executive/attention/processing speed. • Low-strength evidence for vitamin B_{12} (0.02=0.5 mg), B_6 (3-10 mg), and folate (0.56-1 mg) shows no benefit for executive/attention/processing speed. • Low-strength evidence shows no benefit in cognitive performance for multivitamins, vitamin C (in women), vitamin D with calcium (in women), or beta carotene (in women). • Low-strength evidence shows no benefit in incident MCI or CATD for multivitamins or vitamin D with calcium. • In adults with MCI, low-strength evidence shows no benefit for vitamin E in incident CATD.
Antihypertensive Treatment	• Generally, low-strength evidence shows that 3 to 4.7 years of antihypertensive treatment regimens versus placebo appear to have no benefit on cognitive test performance in adults with normal cognition. • Moderate-strength evidence shows that angiotensin converting enzyme (ACE) plus thiazide versus placebo and angiotensin receptor blockers (ARBs) versus placebo have no benefit on brief cognitive screening tests. • Low-strength evidence shows that intensive versus standard antihypertensive control shows no benefit on cognitive test performance. • Low-strength evidence shows no benefit on cognitive test performance of any fixed antihypertensive treatment regimen versus another among those directly compared. • Effects of stepped multiple agent antihypertensive medication regimens to reduce risk of dementia are inconsistent; one trial showed a positive effect but three other trials found no effect of antihypertensive treatment on CATD incidence. • The only two trials that reported subgroup data found no differential effect of treatment group on cognition by participant age or other baseline characteristics.
Lipid Lowering Treatment	• Evidence was insufficient to assess the effect of 5 years of statin treatment on the risk of incident CATD or for preventing MCI. • Low-strength evidence shows a small, 6-month improvement in executive/attention/ processing speed with placebo treatment that was not found with statin treatment, presumed to be due to practice effects and of uncertain clinical significance. • Low-strength evidence shows no benefit on brief cognitive test performance, executive/attention/processing speed, or memory for statin plus fenofibrate versus statin plus placebo in adults with normal cognition. • Evidence was insufficient to assess whether effects of statins on any cognitive outcomes differ by patient age, baseline lipid level, or other characteristics.
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	• No evidence was available for the effect of low-dose aspirin on MCI or CATD incidence. • Low-strength evidence shows no benefit for low-dose aspirin on brief cognitive screening tests, multidomain neuropsychological performance, or memory, even with 10 years of use. • Low-strength evidence shows no benefit for nonsteroidal anti-inflammatory drugs (NSAIDs), including both selective and nonselective cyclooxygenase-2 (COX-2) inhibitors, to reduce CATD incidence, or to benefit multidomain neuropsychological performance or memory, with 8 years of followup after 1 to 3 years of use.
Antidementia Treatments	• Low-strength evidence shows acetylcholinesterase inhibitor (AChEI) antidementia drugs did not reduce the incidence of CATD in persons with MCI over 3 years; evidence is insufficient for persons with normal cognition. • Low-strength evidence shows AChEIs for 3 years provide no significant effect on cognitive performance in adults with MCI.
Diabetes Medication Treatment	• No studies reported on the effect of diabetes treatment on the risk of incident clinical diagnoses of MCI or CATD. • In middle-aged older adults with diabetes and presumed normal cognition, low-strength evidence shows intensive versus standard glycemic control

	had no significant effect on cognitive performance.
Other Interventions	• Evidence was insufficient for lithium, a nicotine patch, individual piano instruction, multitask rhythmic exercise to music, sleep interventions, and social engagement. • We found no relevant studies for depression treatments, smoking cessation, or community-level interventions.
Agreement of Biomarkers and Measures of Cognitive Performance	• Only a few (9) low or medium risk of bias studies for cognitive performance also used biomarker measures; most of those used some form of brain scan. • The overall rate of agreement between biomarker measures and cognitive testing was 57 percent, but 90 percent of that agreement resulted from both approaches showing no effect. When the biomarker measure showed a significant result, there was agreement in 25 percent of cognitive tests conducted.

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 mild cognitive impairment (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 for prioritizing the types of interventions that deserve 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. The full effects of hypertension control should include attention to stroke. Priority should be given to interventions that already show some promise, most notably cognitive training and physical activity. However, the decision to exclude specific stroke-related dementia may underestimate the effect of antihypertension treatment. Although it cannot be said with complete certainty that other types of interventions have no effect, work examining hormone replacement therapy, nonsteroidal anti-inflammatory drugs (NSAIDS), statins, nutraceuticals, and others has shown little promise. Moderate-strength evidence showing no benefit for vitamin E for cognitive performance support assigning low priority to this area.

Study Design/Methodology

Future trials should be designed *intentionally* to study methods of slowing and preventing age-related cognitive decline, MCI, and CATD incidence. Many studies originally designed for other purposes have added cognitive measures post-hoc. These "add-on" trials have frequently used less sophisticated measures, have not adequately evaluated baseline characteristics, and have not randomly assign participants, all of which confound data and limit conclusions.

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

In addition to dedicated trials, larger sample sizes 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 (multidomain interventions) have been initiated.[14] Three of these trials (FINGER, MAPT, PreDIVA) enrolled older adults and implemented multidomain interventions with components addressing nutrition, physical activity, cognitive training, social activity, and/or vascular risk factor management. Of the two studies with published results, while the more clinical multidomain PreDIVA trial did not find benefit,[141] results from the FINGER trial, which used a more lifestyle-based approach, were promising.[142] More studies assessing a combination of interventions would benefit the field. The key issue in designing such studies is choosing the best "package" of interventions. Current wisdom suggests that randomized controlled trials (RCTs) should use the most powerful combinations and leave the decisions about less potent versions to subsequent studies. The first critical question is whether a combination of strong interventions can achieve the goal.

Measurement

Consistent shortcomings across existing studies reveal many opportunities to improve the measurement techniques of future trials. Future research should employ a more consistent set of validated tests to assess cognitive performance. To date, cognitive outcomes have been measured using a wide array of neuropsychological tests. 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 common core 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 Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and by defining appropriate test/re-test timeframes. Although no one measure is adequate for all applications, movement towards the use of batteries with good psychometric qualities and already in common use in aging populations (such as those included in the National Alzheimer's Coordinating Center data set https://www.alz.washington.edu/WEB/forms_uds.html or drawn from the National Institutes of Health Toolbox http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox) could potentially help to narrow the field.

The baseline status of participants needs to be better measured and documented. Baseline cognitive status is variously described and often not tested. While some researchers measured baseline cognitive function as part of the trial design, the degree of measurement varied widely (e.g., brief cognitive screening versus more elaborate neuropsychological test performance). Complicating matters, some trials describe participants with terms like "normal" or "presumed healthy" while in other cases participants 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. Standardization or common understanding of such terms is lacking. The use of appropriate attention controls can help identify the effects specific to the intervention versus those that arise from other specific factors (e.g., socialization or general therapeutic relationships).

Finally, future research trials that include incident CATD as a study outcome should evaluate participants using formal diagnostic guidelines for Alzheimer's disease such as those from the National Institute on Aging (NIA) and the Alzheimer's Association.[6] Including both measures of cognitive performance and CATD incidence as study outcomes would allow researchers to better understand how these two constructs are related. Important questions 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? These questions, in turn, reflect the diagnostic criteria used to identify dementia. 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. This question still lacks consensus, and a range of values may be needed to establish what is considered clinically meaningful and to whom. Moreover, meaningful change may vary depending upon differing baseline level of function. Consistently including objective and performance-based measures of everyday function (IADLs) in future trials may help address these questions.

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Abbreviations

3MS	Modified Mini-Mental State Examination
ACE	Angiotensin converting enzyme inhibitors
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADL	Activities of daily living
AE	Adverse Events
APC	Annualized percentage change
ARB`	Antiotensin receptor blocker
AVLT	Auditory Verbal Learning Test
BCT	Brief cognitive test
BEM-144	Batterie d'Efficience Mnesique 144
BID	Twice daily
BMI	Body Mass Index
BNT	Boston Naming Test
BVMT	Brief Visuospatial Memory Test
BVRT	Benton Visual Retention Test
C	Control
CAMCOG	Cambridge Cognition Examination
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 Dementia
CDR	Clinial Dementia Rating
CEE	Conjugated equine estrogen
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence interval
CLOX-1	Clock Drawing Test
CSF	Cerebrospinal fluid
CHD	Coronary heart disease
COWAT	Controlled Oral Word Association Test
CPT	Continuous Performance Task
CT	Computerized tomography
CVFT	Category Verbal Fluency Test
CVLT	California Verbal Learning Test
DHA	Docosahexaenoic acid
DHEA	dehydroepiandrosterone
DMS48	Delayed Matching-to-Sample Task
DS	Digit Span (Forward or Backward)
DSM	Diagnostic Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
DVT	Digit Vigilance Test
EBMT	East Boston Memory Test
EPA	Eicosapentaenoic acid

ES	Effect size
FAB	Frontal Assessment Battery
FCRST	Free and Cued Selective Reminding Test
FDG-PET	Fluorodeoxyglucose positron emission tomography
fMRI	Functional magnetic resonance imaging
F-TICS	French version, Telephone Interview Cognitive Status
HC	Hippocampus
HKLLT	Hong Kong List Learning Test
HRT	Hormone replacement therapy
HVLT	Hopkins Verbal Learning Test
I	Intervention
IADL	Instrumental activities of daily living
IHAMS	Iowa Health and Active Minds Study
IOM	Institute of Medicine
ITT	Intention to treat
IU	International Units
k	Number of studies included
KQ	Key Question
LDL	Low density lipoprotein
MCI	Mild cognitive impairment
MG	Milligrams
MMSE	Mini-Mental State Examination
MNP	Multidomain neuropsychological test performance
MRI	Magnetic resonance imaging
n	Number of participants
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NR	Not reported
NS	Not significant
NSAIDs	Nonsteroidal anti-inflammatory drugs
NTB	Neuropsychological test battery
OR	Odds ratio
PALS	Paired Association Learning Test
PET	Positron emission tomography
PICOTS	Populations, Interventions, Comparisons, Outcomes, Timing, and Setting
PRM	Pattern Recognition Memory
QAD	Every other day
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for Neuropsychological Status
RBMT	Rivermead Behavioral Memory Test
RCFT	Rey-Osterrieth Complex Figure Test
RCI	Reliable Change Index
RCPM	Raven's Colored Progressive Matrices
RCT	Randomized controlled trial
ROB	Risk of bias
RT	Reaction time

SCWT	Stroop Test (color, word, interference)
SDMT	Symbol Digit Modalities Test
SERM	Selective estrogen receptor modulator
SoE	Strength of Evidence
SPECT	Single photon emission computed tomography
SWM	Spatial Working Memory
TIA	Transient ischemic attack
TICS	Telephone Interview for Cognitive Status
TICS-M	Telephone Interview for Cognitive Status-Modified
TMT	Trail Making Test (parts A and/or B)
UFOV	Useful Field of View
VP	Verbal proficiency
VR	Visual Reproduction
VRM	Verbal Recognition Memory
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

Appendix A. Search Strategies

Database: Ovid MEDLINE(R)
Search Strategy: RCTs

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1 exp Tertiary Prevention/ or exp Secondary Prevention/ or exp Primary Prevention/ (141964)
2 prevent*.ti. (216549)
3 protect*.ti. (118660)
4 delay*.ti. (51184)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (43135)
6 1 or 2 or 3 or 4 or 5 (545854)
7 lifestyle*.ti. (8489)
8 life style.ti. (1355)
9 exp Health Behavior/ (133222)
10 exp Motor Activity/ (216634)
11 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (25122)
12 exercis*.ti. (84377)
13 exp Diet/ (218815)
14 diet*.ti. (134912)
15 fruit*.ti. (16048)
16 vegetable*.ti. (7963)
17 nutrition*.ti. (74518)
18 fat*.ti. (181033)
19 caffeine.ti. (9030)
20 sodium.ti. (73002)
21 salt*.ti. (34028)
22 alcohol*.ti. (103760)
23 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (9709)
24 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (36862)
25 exp *Pharmacology, Clinical/ (1700)
26 exp Pharmaceutical Preparations/ (674904)
27 drug*.ti. (298706)
28 medication*.ti. (29416)
29 pharmacopsychiatry.ti. (51)
30 exp Psychopharmacology/ (5429)
31 lovastatin/ or simvastatin/ or pravastatin/ (11705)
32 statin*.ti. (9993)
33 exp Antihypertensive Agents/ (234730)
34 anti-hypertensive*.ti. (541)
35 antihypertensive*.ti. (10665)
36 exp Cholinesterase Inhibitors/ (44525)
37 Acetylcholinesterase inhibitor*.ti. (815)
38 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (4354)
39 cholinesterase inhibitor*.ti. (1161)
40 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (190958)
41 anti amyloid*.ti. (125)
42 antiamyloid*.ti. (26)
43 Solanezumab.ti. (15)
44 crenezumab.ti. (0)

45 gantenerumab.ti. (6)
46 crenezumab.ab. (4)
47 antiplatlet.ti. (0)
48 anti-platelet.ti. (782)
49 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (4606)
50 exp Hypoglycemic Agents/ (206876)
51 (Pioglitazone or actos or Glucophage or metformin).ti. (6739)
52 ((gonadal or sex) adj steroid*).ti. (3910)
53 exp Hormone Replacement Therapy/ (21950)
54 estrogen*.ti. (46056)
55 progest*.ti. (27523)
56 medroxyprogesterone*.ti. (1983)
57 estradiol.ti. (17656)
58 raloxifene.ti. (1169)
59 exp Cyclooxygenase 2 Inhibitors/ (10161)
60 (Celecoxib or Rofecoxib).ti. (2498)
61 exp Anti-Inflammatory Agents, Non-Steroidal/ (170835)
62 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (19958)
63 exp Dietary Supplements/ (49171)
64 supplement*.ti. (42004)
65 nutraceutical*.ti. (625)
66 exp Nootropic Agents/ (28153)
67 nootropic*.ti. (444)
68 exp Vitamins/ (279374)
69 exp Minerals/ (129537)
70 omega.ti. (7082)
71 ginkgo biloba.ti. (1700)
72 ginko biloba.ti. (6)
73 folate.ti. (7866)
74 fish oil.ti. (2892)
75 saffron.ti. (288)
76 crocus sativus.ti. (206)
77 fuzhisan.ti. (7)
78 melissa.ti. (155)
79 beta carotene.ti. (2945)
80 vitamin*.ti. (79987)
81 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (84346)
82 or/6-81 (3655158)
83 dementia/ or alzheimer disease/ (104784)
84 dement*.ti. (33084)
85 exp Cognition/ (119536)
86 exp Mild Cognitive Impairment/ or exp Cognition Disorders/ (68412)
87 memory disorders/ (16505)
88 executive funtion/ (0)
89 exp memory/ (107625)
90 cognition.ti. (7518)
91 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (31889)
92 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (1900)
93 (amyloid or tau or plasticity).ti. (44515)
94 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (15993)

95 exp Biological Markers/ (681977)
96 (83 or 86) and 95 (6502)
97 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 96 (403150)
98 82 and 97 (65610)
99 *Alzheimer Disease/pc [Prevention & Control] (1256)
100 *Mild Cognitive Impairment/pc [Prevention & Control] (48)
101 Cognition Disorders/pc [Preventions & Control] (2341)
102 or/98-101 (66756)
103 98 or 102 (66756)
104 randomized controlled trials as topic/ (100210)
105 randomized controlled trial/ (404260)
106 random allocation/ (85128)
107 double blind method/ (132506)
108 single blind method/ (21176)
109 clinical trial/ (495811)
110 clinical trial, phase i.pt. (15460)
111 clinical trial, phase ii.pt. (25039)
112 clinical trial, phase iii.pt. (10500)
113 clinical trial, phase iv.pt. (1099)
114 controlled clinical trial.pt. (89967)
115 randomized controlled trial.pt. (404260)
116 multicenter study.pt. (192213)
117 clinical trial.pt. (495811)
118 exp Clinical trials as topic/ (286404)
119 or/104-118 (1096584)
120 (clinical adj trial$).tw. (219796)
121 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (129617)
122 placebos/ (32961)
123 placebo$.tw. (159399)
124 randomly allocated.tw. (17236)
125 (allocated adj2 random$).tw. (19800)
126 120 or 121 or 122 or 123 or 124 or 125 (425064)
127 119 or 126 (1229155)
128 103 and 127 (13446)
129 limit 128 to humans (12721)
130 limit 129 to (addresses or autobiography or bibliography or biography or case reports or classical article or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or "corrected and republished article" or dataset or dictionary or directory or editorial or evaluation studies or historical article or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or observational study or patient education handout or periodical index or portraits or validation studies or video-audio media or webcasts) (838)
131 129 not 130 (11883)
132 limit 131 to yr="2009 -Current" (4830)

Database: Ovid MEDLINE(R)
Search Strategy: Observational Studies

Database: Ovid MEDLINE(R) <1946 to January Week 4 2016>
Search Strategy:

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1 exp Tertiary Prevention/ or exp Secondary Prevention/ or exp Primary Prevention/ (141964)
2 prevent*.ti. (216549)
3 protect*.ti. (118660)
4 delay*.ti. (51184)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (43135)
6 (biomarker* adj2 enrich*).ti. (11)
7 intervention*.ti. (83501)
8 program*.ti. (139255)
9 multidomain*.ti. (421)
10 multi-domain*.ti. (143)
11 multicomponent*.ti. (1987)
12 multi-component*.ti. (561)
13 multifactoral*.ti. (15)
14 multi-factoral*.ti. (2)
15 approach*.ti. (175606)
16 lifestyle*.ti. (8489)
17 life style.ti. (1355)
18 exp Health Behavior/ (133222)
19 exp Motor Activity/ (216634)
20 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (25122)
21 exercis*.ti. (84377)
22 exp Diet/ (218815)
23 diet*.ti. (134912)
24 fruit*.ti. (16048)
25 vegetable*.ti. (7963)
26 nutrition*.ti. (74518)
27 fat*.ti. (181033)
28 caffeine.ti. (9030)
29 sodium.ti. (73002)
30 salt*.ti. (34028)
31 alcohol*.ti. (103760)
32 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (9709)
33 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (36862)
34 exp *Pharmacology, Clinical/ (1700)
35 exp Pharmaceutical Preparations/ (674904)
36 drug*.ti. (298706)
37 medication*.ti. (29416)
38 pharmacopsychiatry.ti. (51)
39 exp Psychopharmacology/ (5429)
40 lovastatin/ or simvastatin/ or pravastatin/ (11705)
41 statin*.ti. (9993)
42 exp Antihypertensive Agents/ (234730)
43 anti-hypertensive*.ti. (541)
44 antihypertensive*.ti. (10665)
45 exp Cholinesterase Inhibitors/ (44525)
46 Acetylcholinesterase inhibitor*.ti. (815)

47 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (4354)
48 cholinesterase inhibitor*.ti. (1161)
49 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (190958)
50 anti amyloid*.ti. (125)
51 antiamyloid*.ti. (26)
52 Solanezumab.ti. (15)
53 crenezumab.ti. (0)
54 gantenerumab.ti. (6)
55 crenezumab.ab. (4)
56 antiplatlet.ti. (0)
57 anti-platelet.ti. (782)
58 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (4606)
59 exp Hypoglycemic Agents/ (206876)
60 (Pioglitazone or actos or Glucophage or metformin).ti. (6739)
61 ((gonadal or sex) adj steroid*).ti. (3910)
62 exp Hormone Replacement Therapy/ (21950)
63 estrogen*.ti. (46056)
64 progest*.ti. (27523)
65 medroxyprogesterone*.ti. (1983)
66 estradiol.ti. (17656)
67 raloxifene.ti. (1169)
68 exp Cyclooxygenase 2 Inhibitors/ (10161)
69 (Celecoxib or Rofecoxib).ti. (2498)
70 exp Anti-Inflammatory Agents, Non-Steroidal/ (170835)
71 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (19958)
72 exp Dietary Supplements/ (49171)
73 supplement*.ti. (42004)
74 nutraceutical*.ti. (625)
75 exp Nootropic Agents/ (28153)
76 nootropic*.ti. (444)
77 exp Vitamins/ (279374)
78 exp Minerals/ (129537)
79 omega.ti. (7082)
80 ginkgo biloba.ti. (1700)
81 ginko biloba.ti. (6)
82 folate.ti. (7866)
83 fish oil.ti. (2892)
84 saffron.ti. (288)
85 crocus sativus.ti. (206)
86 fuzhisan.ti. (7)
87 melissa.ti. (155)
88 beta carotene.ti. (2945)
89 vitamin*.ti. (79987)
90 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (84346)
91 or/1-90 (3967512)
92 dementia/ or alzheimer disease/ (104784)
93 dement*.ti. (33084)
94 exp Mild Cognitive Impairment/ or exp Cognition Disorders/ (68412)
95 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or diabil* or disable*)).ti. (23706)
96 ((impair* or disorder*) adj (cognit* or neurocognit* or memory)).ti. (576)

97 or/92-96 (175046)
98 *Alzheimer Disease/pc [Prevention & Control] (1256)
99 *Mild Cognitive Impairment/pc [Prevention & Control] (48)
100 Cognition Disorders/pc [Preventions & Control] (2341)
101 or/98-100 (3558)
102 (91 and 97) or 101 (34439)
103 exp cohort studies/ (1486668)
104 cohort$.tw. (295133)
105 controlled clinical trial.pt. (89967)
106 epidemiologic studies/ (6963)
107 (follow up adj stud$).tw. (37939)
108 longitudinal.tw. (142385)
109 (observational adj stud$).tw. (48091)
110 Comparative Study/ (1720170)
111 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 (3175113)
112 102 and 111 (7550)
113 limit 112 to humans (7069)
114 limit 113 to "all child (0 to 18 years)" (691)
115 limit 114 to "all adult (19 plus years)" (372)
116 113 not 114 (6378)
117 115 or 116 (6750)
118 limit 117 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or editorial or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or portraits or validation studies or video-audio media or webcasts) (360)
119 117 not 118 (6390)
120 limit 119 to yr="2009 - 2016" (2812)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Search Strategy: RCTs

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1 exp Tertiary Prevention/ or exp Secondary Prevention/ or exp Primary Prevention/ (0)
2 prevent*.ti. (16727)
3 protect*.ti. (9964)
4 delay*.ti. (5679)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (5717)
6 1 or 2 or 3 or 4 or 5 (37733)
7 lifestyle*.ti. (1346)
8 life style.ti. (73)
9 exp Health Behavior/ (0)
10 exp Motor Activity/ (0)
11 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (3604)
12 exercis*.ti. (7474)
13 exp Diet/ (0)
14 diet*.ti. (11652)
15 fruit*.ti. (2919)
16 vegetable*.ti. (892)
17 nutrition*.ti. (6266)
18 fat*.ti. (15032)
19 caffeine.ti. (503)
20 sodium.ti. (5610)
21 salt*.ti. (5744)
22 alcohol*.ti. (9093)
23 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (976)
24 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (3677)
25 exp *Pharmacology, Clinical/ (0)
26 exp Pharmaceutical Preparations/ (0)
27 drug*.ti. (21843)
28 medication*.ti. (3542)
29 pharmacopsychiatry.ti. (2)
30 exp Psychopharmacology/ (0)
31 lovastatin/ or simvastatin/ or pravastatin/ (0)
32 statin*.ti. (1193)
33 exp Antihypertensive Agents/ (0)
34 anti-hypertensive*.ti. (46)
35 antihypertensive*.ti. (505)
36 exp Cholinesterase Inhibitors/ (0)
37 Acetylcholinesterase inhibitor*.ti. (84)
38 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (565)
39 cholinesterase inhibitor*.ti. (89)
40 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (0)
41 anti amyloid*.ti. (18)
42 antiamyloid*.ti. (3)
43 Solanezumab.ti. (3)
44 crenezumab.ti. (1)
45 gantenerumab.ti. (0)
46 crenezumab.ab. (5)

47 antiplatlet.ti. (1)
48 anti-platelet.ti. (74)
49 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (515)
50 exp Hypoglycemic Agents/ (0)
51 (Pioglitazone or actos or Glucophage or metformin).ti. (1160)
52 ((gonadal or sex) adj steroid*).ti. (134)
53 exp Hormone Replacement Therapy/ (0)
54 estrogen*.ti. (1884)
55 progest*.ti. (985)
56 medroxyprogesterone*.ti. (51)
57 estradiol.ti. (676)
58 raloxifene.ti. (78)
59 exp Cyclooxygenase 2 Inhibitors/ (0)
60 (Celecoxib or Rofecoxib).ti. (207)
61 exp Anti-Inflammatory Agents, Non-Steroidal/ (0)
62 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (1397)
63 exp Dietary Supplements/ (0)
64 supplement*.ti. (4634)
65 nutraceutical*.ti. (127)
66 exp Nootropic Agents/ (0)
67 nootropic*.ti. (28)
68 exp Vitamins/ (0)
69 exp Minerals/ (0)
70 omega.ti. (1008)
71 ginkgo biloba.ti. (149)
72 ginko biloba.ti. (1)
73 folate.ti. (495)
74 fish oil.ti. (242)
75 saffron.ti. (81)
76 crocus sativus.ti. (55)
77 fuzhisan.ti. (1)
78 melissa.ti. (40)
79 beta carotene.ti. (163)
80 vitamin*.ti. (6567)
81 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (9325)
82 or/6-81 (152409)
83 dementia/ or alzheimer disease/ (0)
84 dement*.ti. (3196)
85 exp Cognition/ (0)
86 exp Mild Cognitive Impairment/ or exp Cognition Disorders/ (0)
87 memory disorders/ (0)
88 executive funtion/ (0)
89 exp memory/ (0)
90 cognition.ti. (1391)
91 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (4103)
92 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (216)
93 (amyloid or tau or plasticity).ti. (4251)
94 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (1579)
95 exp Biological Markers/ (0)
96 (83 or 86) and 95 (0)

97 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 96 (12603)
98 82 and 97 (1485)
99 *Alzheimer Disease/pc [Prevention & Control] (0)
100 *Mild Cognitive Impairment/pc [Prevention & Control] (0)
101 Cognition Disorders/pc [Preventions & Control] (0)
102 or/98-101 (1485)
103 98 or 102 (1485)
104 randomized controlled trials as topic/ (0)
105 randomized controlled trial/ (759)
106 random allocation/ (0)
107 double blind method/ (0)
108 single blind method/ (0)
109 clinical trial/ (472)
110 clinical trial, phase i.pt. (29)
111 clinical trial, phase ii.pt. (42)
112 clinical trial, phase iii.pt. (35)
113 clinical trial, phase iv.pt. (2)
114 controlled clinical trial.pt. (55)
115 randomized controlled trial.pt. (759)
116 multicenter study.pt. (399)
117 clinical trial.pt. (472)
118 exp Clinical trials as topic/ (0)
119 or/104-118 (1245)
120 (clinical adj trial$).tw. (26676)
121 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (9179)
122 placebos/ (0)
123 placebo$.tw. (11961)
124 randomly allocated.tw. (2339)
125 (allocated adj2 random$).tw. (2515)
126 120 or 121 or 122 or 123 or 124 or 125 (40573)
127 119 or 126 (41429)
128 103 and 127 (147)

Database: Embase Classic+Embase
Search Strategy: RCTs

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1 prevention/ or "prevention and control"/ or primary prevention/ or prophylaxis/ or protection/ (388002)
2 prevent*.ti. (292863)
3 protect*.ti. (166106)
4 delay*.ti. (70519)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (68778)
6 (biomarker* adj2 enrich*).ti. (29)
7 intervention*.ti. (128336)
8 program*.ti. (190084)
9 multidomain*.ti. (482)
10 multi-domain*.ti. (196)
11 multicomponent*.ti. (3473)
12 multi-component*.ti. (1062)
13 multifactoral*.ti. (25)
14 multi-factoral*.ti. (2)
15 approach*.ti. (256521)
16 lifestyle*.ti. (13016)
17 life style.ti. (1723)
18 exp physical activity/ (295154)
19 exp exercise/ (263840)
20 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (35810)
21 exercis*.ti. (118665)
22 exp Diet/ (271531)
23 diet*.ti. (181510)
24 fruit*.ti. (23508)
25 vegetable*.ti. (11437)
26 nutrition*.ti. (103074)
27 fat*.ti. (247795)
28 caffeine.ti. (12266)
29 sodium.ti. (99989)
30 salt*.ti. (48776)
31 alcohol*.ti. (151585)
32 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (13072)
33 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (53741)
34 exp *drug therapy/ (652263)
35 drug*.ti. (450662)
36 medication*.ti. (48020)
37 pharmacopsychiatry.ti. (90)
38 exp Psychopharmacology/ (27649)
39 lovastatin/ or simvastatin/ or pravastatin/ (44198)
40 statin*.ti. (16827)
41 exp Antihypertensive Agents/ (628950)
42 anti-hypertensive*.ti. (972)
43 antihypertensive*.ti. (16198)
44 exp Cholinesterase Inhibitors/ (83861)
45 Acetylcholinesterase inhibitor*.ti. (1226)
46 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (7323)
47 cholinesterase inhibitor*.ti. (1672)

48 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (394269)
49 anti amyloid*.ti. (214)
50 antiamyloid*.ti. (40)
51 Solanezumab.ti. (43)
52 crenezumab.ti. (2)
53 gantenerumab.ti. (9)
54 crenezumab.ab. (14)
55 antiplatlet.ti. (8)
56 anti-platelet.ti. (1311)
57 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (8156)
58 exp Hypoglycemic Agents/ (408843)
59 (Pioglitazone or actos or Glucophage or metformin).ti. (12917)
60 ((gonadal or sex) adj steroid*).ti. (4750)
61 exp Hormone Replacement Therapy/ (52856)
62 estrogen*.ti. (59100)
63 progest*.ti. (35701)
64 medroxyprogesterone*.ti. (2555)
65 estradiol.ti. (22509)
66 raloxifene.ti. (1622)
67 exp Cyclooxygenase 2 Inhibitors/ (42579)
68 (Celecoxib or Rofecoxib).ti. (3619)
69 exp Anti-Inflammatory Agents, Non-Steroidal/ (490780)
70 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (30083)
71 exp Dietary Supplements/ (72740)
72 supplement*.ti. (59036)
73 nutraceutical*.ti. (1163)
74 exp Nootropic Agents/ (98194)
75 nootropic*.ti. (693)
76 exp Vitamins/ (573824)
77 exp Minerals/ (36345)
78 omega.ti. (10406)
79 ginkgo biloba.ti. (2538)
80 ginko biloba.ti. (20)
81 folate.ti. (10490)
82 fish oil.ti. (3894)
83 saffron.ti. (625)
84 crocus sativus.ti. (434)
85 fuzhisan.ti. (12)
86 melissa.ti. (356)
87 beta carotene.ti. (3702)
88 vitamin*.ti. (113036)
89 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (127982)
90 or/1-89 (6007082)
91 *dementia/ or *alzheimer disease/ (122973)
92 (dementia or cognitive impair*).ti. (60302)
93 *Cognition/ (57927)
94 *Mild Cognitive Impairment/ (5955)
95 *memory disorders/ (2392)
96 *executive funtion/ (0)
97 exp *memory/ (86144)
98 cognition.ti. (12039)

99 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (50252)
100 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (2750)
101 (amyloid or tau or plasticity).ti. (59657)
102 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (23708)
103 exp Biological Markers/ (172233)
104 (91 or 94) and 103 (4462)
105 91 or 92 or 94 or 95 or 96 or 97 or 101 or 104 (274389)
106 *Alzheimer Disease/pc [Prevention & Control] (2840)
107 *Mild Cognitive Impairment/pc [Prevention & Control] (42)
108 106 or 107 (2870)
109 90 and 105 (57490)
110 108 or 109 (58108)
111 limit 110 to human (41595)
112 limit 111 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (1366)
113 limit 112 to (adult <18 to 64 years> or aged <65+ years>) (596)
114 (111 not 112) or 113 (40825)
115 Clinical trial/ (861651)
116 Randomized controlled trial/ (394622)
117 Randomization/ (69534)
118 Single blind procedure/ (21500)
119 Double blind procedure/ (130682)
120 Crossover procedure/ (46320)
121 Placebo/ (286985)
122 Randomi?ed controlled trial$.tw. (129567)
123 Rct.tw. (19484)
124 Random allocation.tw. (1561)
125 Randomly allocated.tw. (24259)
126 Allocated randomly.tw. (2119)
127 (allocated adj2 random).tw. (905)
128 (waitlist or wait list).tw. (4382)
129 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 (1271460)
130 Case study/ (45524)
131 Case report.tw. (324413)
132 Abstract report/ or letter/ (967648)
133 130 or 131 or 132 (1330767)
134 129 not 133 (1236125)
135 114 and 134 (9013)
136 limit 135 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or editorial or letter or note or short survey or trade journal) (2271)
137 135 not 136 (6742)
138 limit 137 to yr="2009 -Current" (2443)

Database: Embase Classic+Embase
Search Strategy: Observational Studies

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1 prevention/ or "prevention and control"/ or primary prevention/ or prophylaxis/ or protection/ (388002)
2 prevent*.ti. (292863)
3 protect*.ti. (166106)
4 delay*.ti. (70519)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (68778)
6 (biomarker* adj2 enrich*).ti. (29)
7 intervention*.ti. (128336)
8 program*.ti. (190084)
9 multidomain*.ti. (482)
10 multi-domain*.ti. (196)
11 multicomponent*.ti. (3473)
12 multi-component*.ti. (1062)
13 multifactoral*.ti. (25)
14 multi-factoral*.ti. (2)
15 approach*.ti. (256521)
16 lifestyle*.ti. (13016)
17 life style.ti. (1723)
18 exp physical activity/ (295154)
19 exp exercise/ (263840)
20 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (35810)
21 exercis*.ti. (118665)
22 exp Diet/ (271531)
23 diet*.ti. (181510)
24 fruit*.ti. (23508)
25 vegetable*.ti. (11437)
26 nutrition*.ti. (103074)
27 fat*.ti. (247795)
28 caffeine.ti. (12266)
29 sodium.ti. (99989)
30 salt*.ti. (48776)
31 alcohol*.ti. (151585)
32 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (13072)
33 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (53741)
34 exp *drug therapy/ (652263)
35 drug*.ti. (450662)
36 medication*.ti. (48020)
37 pharmacopsychiatry.ti. (90)
38 exp Psychopharmacology/ (27649)
39 lovastatin/ or simvastatin/ or pravastatin/ (44198)
40 statin*.ti. (16827)
41 exp Antihypertensive Agents/ (628950)
42 anti-hypertensive*.ti. (972)
43 antihypertensive*.ti. (16198)
44 exp Cholinesterase Inhibitors/ (83861)
45 Acetylcholinesterase inhibitor*.ti. (1226)
46 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (7323)
47 cholinesterase inhibitor*.ti. (1672)

48 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (394269)
49 anti amyloid*.ti. (214)
50 antiamyloid*.ti. (40)
51 Solanezumab.ti. (43)
52 crenezumab.ti. (2)
53 gantenerumab.ti. (9)
54 crenezumab.ab. (14)
55 antiplatlet.ti. (8)
56 anti-platelet.ti. (1311)
57 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (8156)
58 exp Hypoglycemic Agents/ (408843)
59 (Pioglitazone or actos or Glucophage or metformin).ti. (12917)
60 ((gonadal or sex) adj steroid*).ti. (4750)
61 exp Hormone Replacement Therapy/ (52856)
62 estrogen*.ti. (59100)
63 progest*.ti. (35701)
64 medroxyprogesterone*.ti. (2555)
65 estradiol.ti. (22509)
66 raloxifene.ti. (1622)
67 exp Cyclooxygenase 2 Inhibitors/ (42579)
68 (Celecoxib or Rofecoxib).ti. (3619)
69 exp Anti-Inflammatory Agents, Non-Steroidal/ (490780)
70 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (30083)
71 exp Dietary Supplements/ (72740)
72 supplement*.ti. (59036)
73 nutraceutical*.ti. (1163)
74 exp Nootropic Agents/ (98194)
75 nootropic*.ti. (693)
76 exp Vitamins/ (573824)
77 exp Minerals/ (36345)
78 omega.ti. (10406)
79 ginkgo biloba.ti. (2538)
80 ginko biloba.ti. (20)
81 folate.ti. (10490)
82 fish oil.ti. (3894)
83 saffron.ti. (625)
84 crocus sativus.ti. (434)
85 fuzhisan.ti. (12)
86 melissa.ti. (356)
87 beta carotene.ti. (3702)
88 vitamin*.ti. (113036)
89 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (127982)
90 or/1-89 (6007082)
91 *dementia/ or *alzheimer disease/ (122973)
92 (dementia or cognitive impair*).ti. (60302)
93 *Cognition/ (57927)
94 *Mild Cognitive Impairment/ (5955)
95 *memory disorders/ (2392)
96 *executive funtion/ (0)
97 exp *memory/ (86144)
98 cognition.ti. (12039)

99 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (50252)
100 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (2750)
101 (amyloid or tau or plasticity).ti. (59657)
102 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (23708)
103 exp Biological Markers/ (172233)
104 91 or 92 or 94 or 99 or 100 (177159)
105 *Alzheimer Disease/pc [Prevention & Control] (2840)
106 *Mild Cognitive Impairment/pc [Prevention & Control] (42)
107 105 or 106 (2870)
108 90 and 104 (46186)
109 107 or 108 (46804)
110 limit 109 to human (37668)
111 limit 110 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (928)
112 limit 111 to (adult <18 to 64 years> or aged <65+ years>) (353)
113 (110 not 111) or 112 (37093)
114 Clinical study/ (132584)
115 longitudinal study/ (85243)
116 prospective study/ (322344)
117 cohort analysis/ (230562)
118 (cohort adj stud*).mp. (158158)
119 (observational adj stud*).mp. (119842)
120 (follow up adj stud*).mp. (57729)
121 (epidemiologic* adj stud*).mp. (88591)
122 (cross sectional adj stud*).mp. (205524)
123 or/114-122 (1136620)
124 113 and 123 (4143)
125 limit 124 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or "conference review" or editorial or erratum or letter or note or "review" or short survey or trade journal) (1652)
126 124 not 125 (2491)
127 limit 126 to yr="2009 -Current" (1644)

Database: PsycINFO
Search Strategy: RCTs

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1 prophylaxis/ or prevention/ (14810)
2 prevent*.ti. (21271)
3 protect*.ti. (8537)
4 delay*.ti. (5830)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (7006)
6 intervention*.ti. (36138)
7 program*.ti. (35798)
8 multidomain*.ti. (22)
9 multi-domain*.ti. (34)
10 multicomponent*.ti. (176)
11 multi-component*.ti. (101)
12 lifestyle*.ti. (2645)
13 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (16817)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (126101)
15 *dementia/ or *alzheimer disease/ (35185)
16 *mild cognitive impairment/ (0)
17 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (15609)
18 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (990)
19 (amyloid or tau or plasticity).ti. (9730)
20 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (4219)
21 biological marker/ (6893)
22 dementia/ or alzheimer disease/ (39250)
23 21 and 22 (1529)
24 15 or 16 or 17 or 18 or 19 or 20 or 23 (58609)
25 14 and 24 (4017)
26 limit 25 to human (3317)
27 limit 26 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in PsycINFO; records were retained] (72)
28 limit 27 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in PsycINFO; records were retained] (12)
29 (26 not 27) or 28 (3257)
30 limit 29 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) [Limit not valid in PsycINFO; records were retained] (3257)
31 limit 30 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or editorial or letter or note or "review" or short survey or trade journal) [Limit not valid in PsycINFO; records were retained] (283)
32 30 not 31 (2974)
33 limit 32 to yr="2009 -Current" (2013)

Database: PsycINFO
Search Strategy: Observational Studies

1	prophylaxis/ or prevention/ (14810)
2	prevent*.ti. (21271)
3	protect*.ti. (8537)
4	delay*.ti. (5830)
5	((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (7006)
6	intervention*.ti. (36138)
7	program*.ti. (35798)
8	multidomain*.ti. (22)
9	multi-domain*.ti. (34)
10	multicomponent*.ti. (176)
11	multi-component*.ti. (101)
12	lifestyle*.ti. (2645)
13	((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (16817)
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (126101)
15	*dementia/ or *alzheimer disease/ (35185)
16	*mild cognitive impairment/ (0)
17	((cognit* or neurocognit* or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction*)).ti. (9474)
18	15 or 16 or 17 (41904)
19	14 and 18 (2846)
20	limit 19 to human (2537)
21	(cohort or longitudinal or prospective).ti,ab. (115078)
22	exp Longitudinal Studies/ (1595)
23	Prospective Studies/ (216)
24	21 or 22 or 23 (115252)
25	limit 24 to "reviews (best balance of sensitivity and specificity)" (53066)
26	24 not 25 (62186)
27	20 and 26 (85)
28	limit 27 to yr="2009 -Current" (55)

Cochrane Central Register of Controlled Trials

Precise search on dementia, cognitive impairment terms

Database: Ovid MEDLINE(R)
Search Strategy:

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1 exp Memory Disorders/ or exp Neuropsychological Tests/ or exp Alzheimer Disease/ or exp Cognition/ or exp Cognition Disorders/ (298451)
2 exp Alzheimer Disease/ (73521)
3 ((cognit* or memory) adj2 (impair* or declin*)).ti,ab. (58569)
4 exp Mild Cognitive Impairment/ (3643)
5 cognition.ti,ab. (34845)
6 (cognitive adj (performan* or test*)).ti,ab. (15238)
7 1 or 2 or 3 or 4 or 5 or 6 (329242)
8 exp Cardiovascular Diseases/dh, dt, rh, su, th [Diet Therapy, Drug Therapy, Rehabilitation, Surgery, Therapy] (766074)
9 exp Depression/dh, dt, th [Diet Therapy, Drug Therapy, Therapy] (21954)
10 exp Sleep Wake Disorders/dh, dt, th [Diet Therapy, Drug Therapy, Therapy] (19655)
11 (sleep adj (quality or duration or time)).ti. (2355)
12 exp Diabetes Mellitus, Type 2/dh, dt, th [Diet Therapy, Drug Therapy, Therapy] (32195)
13 8 or 9 or 10 or 11 or 12 (837027)
14 7 and 13 (8871)
15 limit 14 to (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or systematic reviews) (2669)
16 limit 15 to yr="2009 -Current" (1210)

Appendix B. Risk of Bias Assessment Tool

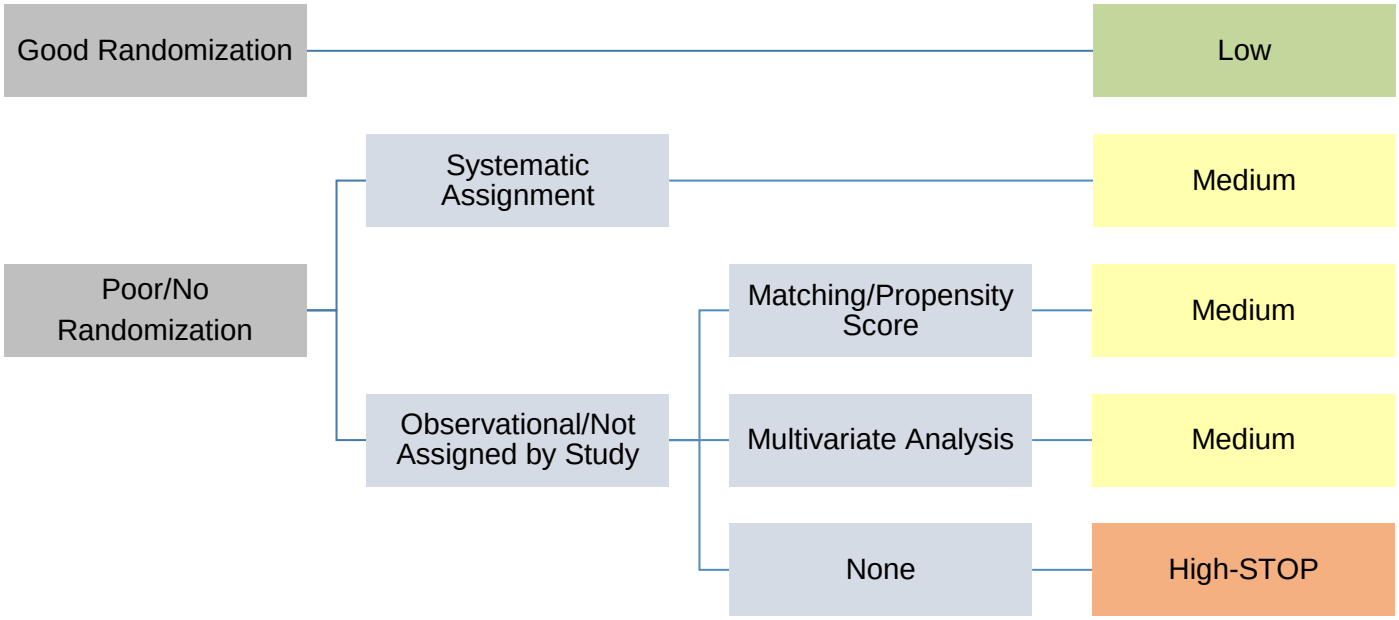
Review the methods of each trial and assess each risk of bias component as described in these instructions. You may need to have separate assessments for different outcomes (i.e. different measures; different time points may have different attrition rates). Remember, this tool is not an algorithm. Discretion must be applied.

1) Selection Bias

Systematic differences between baseline characteristics of the groups that arise from self-selection of treatments, physician-directed selection of treatments, or association of treatment assignments with demographic, clinical, or social characteristics.

- Did method of randomization create biased allocation to interventions (inadequate randomization)?
- "Good" Randomization: Random numbers table, computer random number generator
- "Poor" Randomization: Randomized based on week of the month of birthday
- No Randomization: Non-randomized clinical trial, observational study

Figure B1. Risk of bias: Selection bias

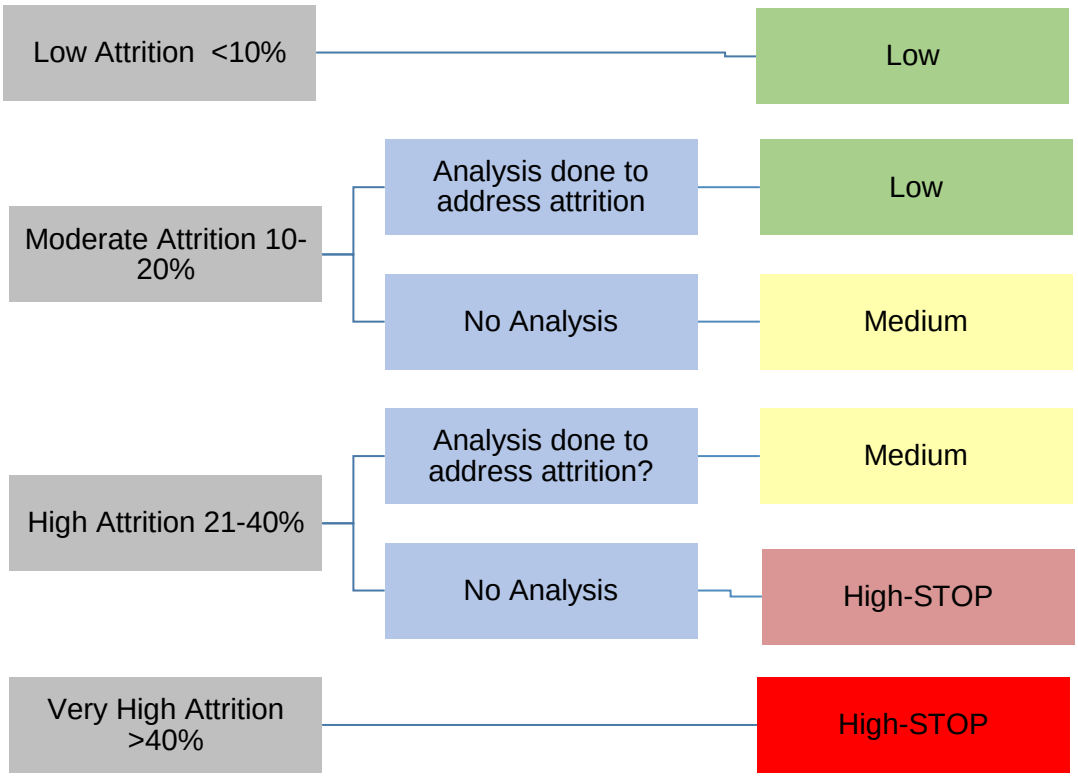


2) Attrition

Systematic differences in the loss of participants from the study and how they were accounted for in the results (e.g., incomplete followup, differential attrition). Those who drop out of the study or who are lost to followup may be systematically different from those who remain in the study. Attrition bias can potentially change the collective (group) characteristics of the relevant groups and their observed outcomes in ways that affect study results by confounding and spurious associations.

- Reasons for incomplete/missing data adequately explained?
- Do the author's attempt to address attrition in the analysis?

Figure B2. Risk of bias: Attrition



Notes

- Report attrition rate in spreadsheet.
- If a study reports outcomes at multiple intervals (e.g., 6 months, 12 months, 18 months) assess attrition at each time-point and record separately.
- Analysis should be done with appropriate method (i.e., sensitivity analysis with various scenarios; last value forward would only be appropriate for interventions that are supposed to improve the outcomes (i.e., memory training that intends to improve memory).

3) Selection and Attrition Bias Overall

Assess joint selection and attrition bias. If either selection or attrition bias is high, the risk of bias is HIGH.

Table B1. Selection and attrition bias overall

Selection Bias	Low	Low	Medium	Low	Medium	Medium	High
Attrition Bias	Low	Medium	Low	High	Medium	High	X
Action	Assess other biases	Assess other biases	Assess other biases	STOP	Assess other biases	STOP	STOP

4) Other Biases

A. Detection Bias

Systematic differences in outcomes assessment among groups being compared, including systematic misclassification of the exposure or intervention, covariates, or outcomes because of variable definitions and timings, diagnostic thresholds, recall from memory, inadequate assessor blinding, and faulty measurement techniques. Erroneous statistical analysis might also affect the validity of effect estimates.

- Were the outcome assessors blinded to the intervention ("outcome assessor blinded")?
- Was the timing of the outcome assessment similar in all groups ("comparable timing outcomes assessment")?
- Was the scale used to measure outcomes validated, reliable?
- Were outcomes measured in clinically meaningful ways?

Table B2. Detection bias

Domain	Options		Overall Rating
Outcome assessor blinded	Yes	No	All 4 Yes =Low 2 or 3 Yes = Medium 3+ No=High
Outcome assessor independent	Yes	No	
Comparable timing outcomes assessment	Yes	No	
Outcome assessment instrument/measurement quality	Yes (Adequate)	No (Inadequate)	

B. Performance Bias

Systematic differences in the care provided to participants and protocol deviation. Examples include contamination of the control group with the exposure or intervention, unbalanced provision of additional interventions or co-interventions, difference in co-interventions, and inadequate blinding of providers and participants.

Notes

- Intention-to-Treat (ITT): Includes every subject according to randomized treatment assignment. Ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization.
- Concurrent Intervention: Study participants are receiving another intervention (i.e., treatment) that is not part of the intervention being tested. Example: Participants are randomized to a physical activity intervention (or no intervention), but are also dieting.

Table B3. Performance bias

Domain	Options	Rating	Overall Rating
1a. RCTs-ITT	Yes	Low	*Low* All Low=Low 1-Low, 2-Low, 3-N/A=Low *Medium* 1-Low, 2-Low, 3-High=Medium 1-Low, 2-Medium, 3-Low=Medium 1-Low, 2-Medium, 3-N/A=Medium 1-Medium, 2-Medium, 3-N/A=Medium 1-Medium, 2-High, 3-Low=Medium 1-Medium, 2-Medium, 3-High=Medium *High* 1-High + Anything Else=High 2+ High=High
	No/Not reported	High	
1b. Obs-Adjustment for known confounders	Adequate	Low	
	Inadequate	High	
2. Concurrent intervention	Yes-Adjusted	Medium	
	Yes-Unadjusted	High	
	No	Low	
	Unclear/Not Reported	NR	
3. Participant Blinding	Yes	Low	
	No	Medium	
	N/A	N/A	

C. Reporting Bias

Systematic differences between reported and unreported findings (e.g., differential reporting of outcomes or harms, incomplete reporting of study findings, potential for bias in reporting through source of funding).

- Was a select group of outcomes reported?

Notes

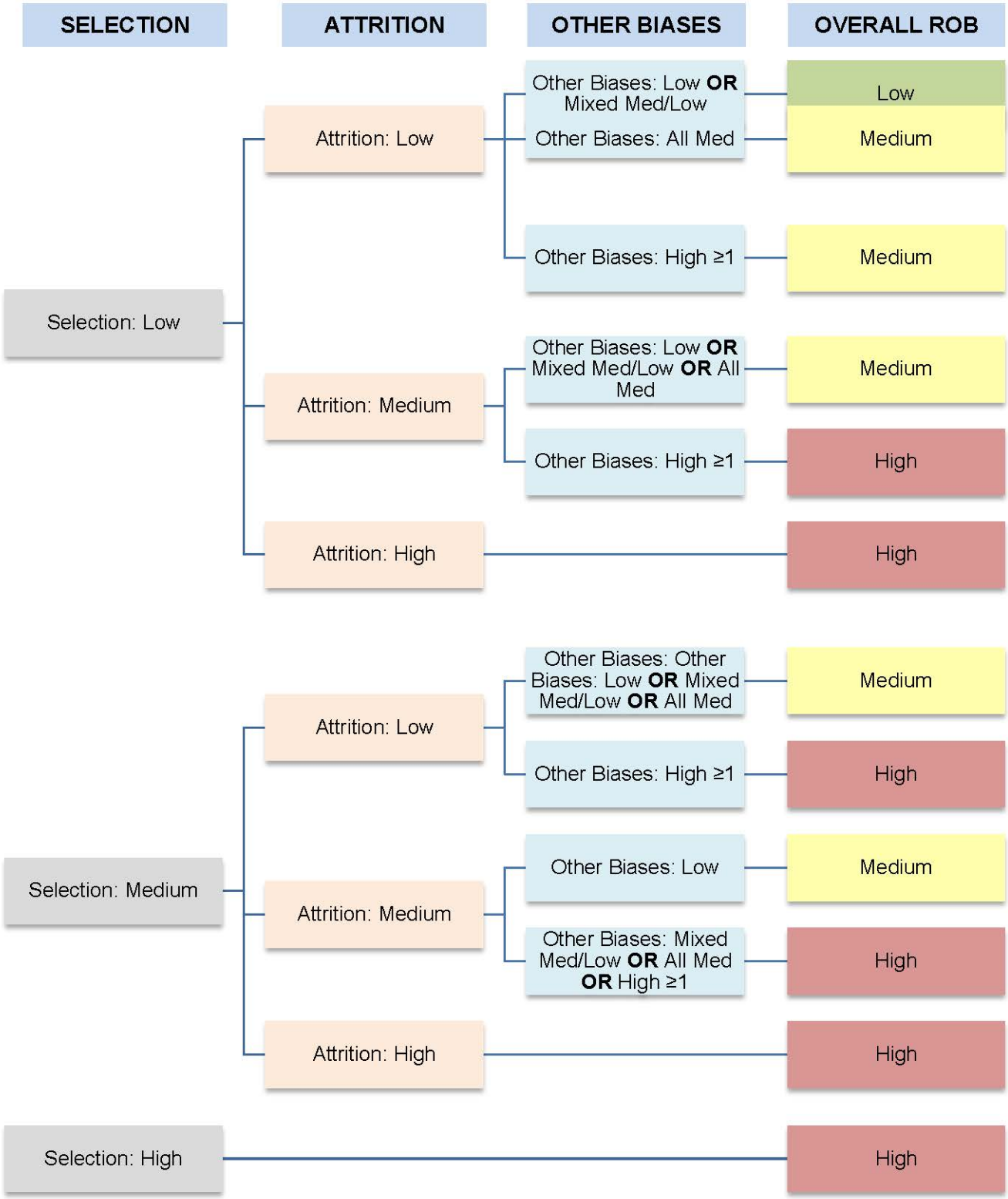
- Compare results to methods section and/ or protocol.
- Check if some results are reported in a different publication.

Table B4. Reporting bias

Domain	Options	Rating
All outcomes reported	Yes	Low
	No	Medium
	Not Reported	Medium

5) Overall Rob

Figure B5. Overall risk of bias



Appendix C. Cognitive Performance Outcomes

Appendix Table C1. Cognitive outcomes categorization

Test Names	Common Abbreviations	Cognitive Outcome Categorization
Abstraction (Shipley Inst. of Living Scales subtest)		Executive/Attention/Processing Speed
AD Cooperative Studies AD Assessment Scale - Cognitive Subscale	ADAS-Cog, ADCS-Cog	Multidomain Neuropsychological Test Performance
AD Cooperative Studies ADL in MCI Scale	ADCS-MCI-ADL	Multidomain Neuropsychological Test Performance
AD Cooperative Studies Activities of Daily Living Scale	ADCS-ADL	Multidomain Neuropsychological Test Performance
Babcock Story Recall		Memory
Benton Visual Retention Test	BVRT	Memory
Blessed Dementia Rating Scale: Blessed Information Memory Concentration	BIMC	Brief Cognitive Test Performance
Blessed Dementia Rating Scale: Blessed Rating Scale	BRS, DRS, BDS, Dementia score	Brief Cognitive Test Performance
Block Design (WAIS subtest)	BD	Visuospatial
Boston Naming Test - multiple versions: 15, 30, 60-items	BNT	Language
Brief Visuospatial Memory Test	BVMT, BVMT-R	Memory
Brixton Spatial Anticipation Test	Brixton	Executive/Attention/Processing Speed
Buschke Selective Reminding Test	SRT	Memory
California Verbal Learning Test - multiple versions	CVLT, CVLT-II	Memory
Cancellation Tests (several versions: bell, star, letter, ...)		Visuospatial
Cambridge Neuropsychological Test Automated Battery (part of the CAMDEX)	CANTAB	Multidomain Neuropsychological Test Performance
CERAD word list / list learning subtest	CERAD	Memory
Clock Drawing Tests (many versions & featured in screening tools)	CDT, CLOX	Visuospatial
Cognitive Abilities Screening Instrument	CASI	Brief Cognitive Test Performance
Consortium to Establish a Registry for Alzheimer's Disease (cognitive battery)	CERAD	Multidomain Neuropsychological Test Performance
Continuous Performance Test	CPT	Executive/Attention/Processing Speed
Corsi Block Tapping - fowards & backwards (similar		Executive/Attention/Processing Speed

to Spatial Span)		
Delis–Kaplan Executive Function System	D-KEFS	Executive/Attention/Processing Speed
Digit Span - forwards & backwards (WAIS/WMS subtest)	DS, DSp	Executive/Attention/Processing Speed
Digit Symbol Coding (WAIS subtest; inverse of Symbol Digit Modalities)	DSy	Executive/Attention/Processing Speed
East Boston Story or East Boston Memory Test	EBMT	Memory
Faces - parts I & II (WMS subtest)		Memory
Finger Tapping Test	FTT	Motor
Grip Strength / Hand Dynamometer		Motor
Grooved Pegboard		Motor
Hopkins Verbal Learning Test	HVLT, HVLT-R	Memory
Judgement of Line Orientation	JLO	Visuospatial
Letter Digit Substitution (Coding) Test	LDST	Executive/Attention/Processing Speed
Letter-Number Sequencing (most commonly a WAIS subtest)	LNS	Executive/Attention/Processing Speed
Letter Sets		Executive/Attention/Processing Speed
Logical Memory - parts I & II (WMS subtest)	LM, LMI, LMII	Memory
Matrix Reasoning (WAIS subtest)		Executive/Attention/Processing Speed
Mattis Dementia Rating Scale	MDRS, DRS	Multidomain Neuropsychological Test Performance
Maze Tracing (including Porteus Maze Test)		Executive/Attention/Processing Speed
Mini-Mental State Examination	MMSE	Brief Cognitive Test Performance
Modified Mini-Mental State Examination	3MS, 3MSE	Brief Cognitive Test Performance
Montreal Cognitive Assessment	MoCA	Brief Cognitive Test Performance
N-Back		Executive/Attention/Processing Speed
National Adult Reading Test	NART	Language
Neurobehavioral Cognitive Status Examination (original Cognistat paper test)	NCSE	Multidomain Neuropsychological Test Performance
New York University Paragraph Recall		Memory
Number Series		Executive/Attention/Processing Speed
Picture Completion (many versions, most commonly a WAIS subtest)	PC	Executive/Attention/Processing Speed; Visualspatial
Purdue Pegboard	PPT, PPBT	Motor
Raven's Progressive Matrices (several versions including Colored & Advanced)	RPM, RCPM	Executive/Attention/Processing Speed

Reaction Time Tests (many versions: simple, choice, auditory, visual...)	RT, SRT	Executive/Attention/Processing Speed
Repeatable Battery for the Assessment of Neuropsychological Status	RBANS	Multidomain Neuropsychological Test Performance
Rey Auditory Verbal Learning Test	RAVLT (may see AVLT or RVLT)	Memory
Rey-Osterrieth Complex Figure Test	CFT, RCFT, Rey-O, Rey	Memory; Visuospatial
Rivermead Behavioral Memory Test - multiple versions	RBMT, RBMT-II, RBMT-3	Memory
Self-Ordered Pointing Task(Test)	SOPT	Executive/Attention/Processing Speed
Short Portable Mental Status Questionnaire	SPMSQ	Brief Cognitive Test Performance
Short Test of Mental Status	STMS	Brief Cognitive Test Performance
Syndrom Kurztest - SKT (German)	SKT	Executive/Attention/Processing Speed; Memory
Spatial Span - forwards & backwards (WMS subtest; similar to Corsi Block Tapping)		Executive/Attention/Processing Speed
Stroop - color, word, interference (there are many versions of the Stroop)		Executive/Attention/Processing Speed
Symbol Digit Modalities Test (inverse of Digit Symbol)	SDMT	Executive/Attention/Processing Speed
Taylor Complex Figure		Memory; Visuospatial
Telephone Interview for Cognitive Status	TICS	Brief cognitive test performance
Telephone Interview for Cognitive Status, modified	TICS-M, mTICS	Brief cognitive test performance
Token Test		Language
Trail Making Test - part A	TMT A	Executive/Attention/Processing Speed
Trail Making Test - part B (or B-A, B/A, etc.)	TMT B	Executive/Attention/Processing Speed
Verbal Fluency, Phonemic/Phonological or Letter	VF, PVF, FAS, CFL, COWAT, COWA	Executive/Attention/Processing Speed; Language
Verbal Fluency, Semantic or Category	VF, SVF, animals, names, fruits/vegetables	Language
Visual Reproduction (WMS subtest)	VR, VRI, VRII, Vis Rep	Memory
Useful Field of View	UFOV	Executive/Attention/Processing Speed
Walter Reed performance assessment battery		Multidomain Neuropsychological Test Performance
Wechsler Adult Intelligence Scale - multiple versions	WAIS, WAIS-R, WAIS-III, WAIS-IV	Multidomain Neuropsychological Test Performance
Wechsler Memory Scale - multiple versions	WMS, WMS-R, WMS-III, WMS-IV	Memory
Wisconsin Card Sorting Test	WCST	Executive/Attention/Processing Speed

Appendix Table C2. Neuropsychological tests and reliable change indices

Cognitive Domain	Instrument	Measurement Properties	Reliable Change Indices
Global Cognitive Function	Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog)	Used to measure cognitive impairment in the assessment of Alzheimer's disease. Tests several cognitive domains, including memory, language, and praxis. Range: 0-70; higher scores indicate worse cognition[17]	4 pts (6 months); considered to be clinically important, but not meaningful; no established RCI's[17]
	Mini-Mental State Examination (MMSE)	11 items assessing cognitive function: orientation, registration, attention and calculation, recall, language (range 0-30) Range: 0-30; higher scores indicate better[18]	2.73 pts (3 months) 3.60 pts (5 years)[19]
	Modified Mini-Mental State Examination (3MS)	15 items: 11 from MMSE plus 4 additional items assessing long-term memory, abstract thinking, category fluency, delayed recall Range: 0-100; higher scores indicate better cognition[18]	5 pts [20] 7.41 pts (3 months) 9.82 pts (5 years)[19]
	Telephone Interview for Cognitive Status (TICS)	11 items assessing word list memory, orientation, attention, repetition, conceptual knowledge, nonverbal praxis Range: 0-41; higher scores indicate better cognition[18]	None identified
Executive, Attention, Processing Speed	Tower Test	Varying number of items assessing spatial planning, rule learning, inhibition of impulsive and perseverative responding, and the ability to establish and maintain instructional set. Subjects must construct towers using 5 circular pieces, placed onto one of 3 pegs. Towers constructed must be identical to a picture shown. Subjects are not allowed to place a larger piece on a smaller piece, and must move one piece at a time. Range: 0-30[21]	None identified
	Digit Span Forward*†	Varying number of items assessing attention efficiency and capacity: subjects asked to listen to a sequence of numbers read and then recite back in order (reported as either subscore or summary score with Digit Span Backward)	None identified; part of WAIS-III WMI and VIQ
	Digit Span Backward*†	Varying number of items assessing executive function and especially working memory: sequence of numbers read, participants asked to read sequence back in reverse order (reported as either subscore or summary score with Digit Span Forward)	None identified; part of WAIS-III WMI and VIQ
	Digit Symbol Substitution Test*	Varying number of items assessing psychomotor ability, sustained attention, processing speed and working memory: participants asked to use a key to substitute certain items within rows of numbers (Digit Symbol) or symbols (Symbol Digit Modalities) (score comprised of items completed within the specified time).	None identified; part of WAIS-III PSI and PIQ

	Stroop Interference Test	3 to 4 parts (depending on the version). Original version has 4 parts. Part 1: rows of written color names written in black ink, and the subject must say the written word. Part 2: the subject reads color names printed in colored ink, ignoring the printed color. Part 3: Subject names the colors of squares. Part 4: the subject uses the printed words from part 2, but must say the color of the ink each word is printed in instead of saying the word. Range: Time to completion and number of errors. Higher raw time and raw errors indicate worse cognition.[18]	None identified
	Trail Making Test Part A (Trails A)	Assesses visual attention and processing speed: subject asked to draw lines connecting circled numbers in sequence (score comprised of both time to complete task and number of errors made; higher score indicates lower function, unless age-scaled score is presented) Range: Time, in seconds, required for completion; higher raw scores indicate worse cognition while higher scaled scores indicate better cognition. Additionally, if error rate is reported, then higher error rates indicate worse cognition.[18]	Scores to calculate RCI: T2-T1 mean, SD: -0.96, 7.54[22]
	Vigil/Continuous Performance Task (CPT)	Varying number of items assessing sustained and selective attention. Letters flash by one at a time on a computer screen. Subject must press the spacebar after they see an 'A' followed immediately by a 'K.[18]	None identified
	Wisconsin Card Sorting Test (WCST)	Cards are presented to the subject. Subject is told to match the cards, but not how to match; however, he or she is told whether a particular match is right or wrong.[18]	None identified
Intelligence Quotient (Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed)	Wechsler Adult Intelligence Scale (WAIS)	Published battery of neuropsychological tests with varying numbers of core and optional subtests. WAIS-III assesses Verbal Comprehension (Similarities, Vocabulary, Information); Working Memory (Digit Span, Arithmetic, [Letter-Number Sequencing], [Comprehension]); Perceptual Organization (Picture Completion, Block Design, Matrix Reasoning); and Processing Speed (Digit Symbol, [Symbol Search], [Picture Arrangement], [Object Assembly]). [Bracketed] subtests are optional.[18]	VIQ: 9 pts PIQ: 11 pts FSIQ: 9 pts VCI: 11 pts POI: 13 pts WMI: 1 2pts PSI: 14 pts (WAIS-III)[23]
Memory	Wechsler Memory Scale (WMS)	Published battery of neuropsychological tests with varying numbers of core and optional tests. WMS-III assesses auditory presentation (Logical Memory I and II, Verbal Paired Associates I and II, [Letter-Number Sequencing], [Information and Orientation], [Word Lists I and II], [Mental Control], [Digit Span]) and visual presentation (Faces I and II, Family Pictures I and II, [Spatial Span], [Visual Reproduction I and II]).[18]	None identified
	Benton Visual Retention Test (BVRT)	10 items (designs) assessing visual memory and perception: subjects are shown one design at a time and asked to draw it from memory (score based on either correctness of drawing or number of errors made; higher error scores indicate lower function)	None identified

		Range: 0-10; higher scores indicate better cognition[18]	
	Rey-Osterrich Complex Figure	3 part test assessing visuospatial abilities, memory, attention, planning, and working memory (executive functions). Subject asked to reproduce a complicated line drawing 3 times: first by copying it while looking at the figure, second by reproducing it immediately afterwards from memory, and third by reproducing the figure again after a 20 to 30-minute delay[18]	Scores to calculate RCI: Copy T2-T1 mean, SD: -0.03, 1.76 Immediate Recall T2-T1 mean, SD: 2.48, 4.51 Delayed Recall T2-T1 mean, SD: 2.30, 4.32[24]
	Buschke Selective Reminding Test	12 items in one list assessing verbal recall and recognition, with a possible 12 trials. List is read aloud until subject recalls all 12 words three times in a row, or until items are read 12 total times (whichever occurs first). After a 20 to 30-minute delay, subjects are asked to recall the 12 words again. Then a recognition trial may be given, which consists of a longer list of words that is read one word at a time; subjects respond 'yes' or 'no' if the word was on the original list of 12. Range: 0-12 for each trial and the recognition score, with higher scores indicating better cognition. Also an intrusion score for the recognition portion, counting each incorrect 'yes' given; higher scores indicate worse cognition[18]	None identified
	California Verbal Learning Test (CVLT)	32 items in two lists (A & B) of 16 words assessing verbal recall and recognition: List A is presented five times for learning and List B is presented once as a distractor Range: Total Recall Score is 20-80; all other scores are z-scores -5 to +5; higher error and recency-recall index scores indicate worse cognition; all other higher scores indicate better cognition[18]	None identified
	Rey Auditory Verbal Learning Test (RAVLT)	30 items in two lists assessing verbal recall and recognition. First a list of 15 words is read aloud and subjects are asked to recall as many as possible (over 5 trials, with the list repeated each time). Then subjects are read a 15 word distractor list and asked to recall as many of the distractor words as possible (1 trial). Afterwards subjects are asked to recall as many of the original 15 words as possible (without being read the list). After a 20-minute delay period, subjects are asked to recall the original list of 15-words again (1 trial). Then a recognition trial may be given, which consists of a longer list of words that is read one word at a time; subjects respond 'yes' or 'no' if the word was on the original list of 15. Range: 0-15 for each trial (1-5, the distractor, delayed recall, and recognition) with higher scores indicating better cognition. Also an intrusion score for the recognition portion, counting each incorrect 'yes' given; higher scores indicate worse cognition.[18]	(decline; improvement) Trial 1:-2.77; 2.65 Trial 5: -3.51; 2.63 Sum 1–5: -11.64; 9.36 Interference: -3.03; 3.11 Trial 7: -4.73; 3.57 Delay: -4.96; 3.60 Recognition: -3.47; 3.69 (12 months)[25]
	Wechsler Adult Intelligence Scale (WAIS)	Published battery of neuropsychological tests with varying numbers of core and optional subtests. WAIS-III assesses Verbal Comprehension (Similarities, Vocabulary, Information); Working Memory (Digit Span, Arithmetic, [Letter-Number Sequencing], [Comprehension]); Perceptual Organization (Picture Completion, Block Design, Matrix Reasoning); and Processing Speed (Digit Symbol, [Symbol Search],	VIQ: 9 pts PIQ: 11 pts FSIQ: 9 pts VCI: 11 pts POI: 13 pts

		[Picture Arrangement], [Object Assembly]). [Bracketed] subtests are optional.[18]	WMI: 1 2pts PSI: 14 pts (WAIS-III)[23]
Language	Boston Naming Test (BNT)	60 items assessing word retrieval. Subjects are shown pictures and asked to name what they are pictures of, and receive semantic cues if needed Range: 0-60; higher scores indicate better cognition[18]	4 pts (9-15 months); 6 pts (16-24 months)Sachs, 2012 #618}
	Verbal Fluency Test	Varying number of items assessing spontaneous verbal production: subjects asked to produce as many words beginning with a specific letter (phonemic/letter fluency) or as many words in a specific category such as “animals” (semantic/category fluency) as is possible in one minute Range (phonemic fluency): sum of all admissible words for the three letters; higher scores indicate better cognition Range (semantic fluency): sum of all admissible words for the semantic categories; higher scores indicate better cognition[18]	(Decline; improvement) Letter ‘S’: -5.5; 9.8 Animals: -7.6; 10.5 (1 month)[26]

*Subtest of WAIS; †Subtest of WMS

Abbreviations: 3MS=Modified Mini-Mental State Examination; BNT=Boston Naming Test; BVRT=Benton Visual Retention Test; CERAD=Consortium to Establish a Registry for Alzheimer’s Disease; CPT=Continuous Performance Task; CVLT=California Verbal Learning Test; DKEFS=Delis-Kaplan Executive Function System; FSIQ=Full Scale IQ; MMSE=Mini-Mental State Examination; PIQ=Performance IQ; POI=Perceptual Organization Index; PSI=Processing Speed Index; RCI=Reliable Change Index; RVLT=Rey Verbal Learning Test; SDMT=Symbol Digit Modalities Test; TICS=Telephone Interview for Cognitive Status; Trails A= Trail Making Test Part A; Trails B=Trail Making Test Part B; VCI=Verbal Comprehension Index; VIQ=Verbal IQ; WAIS=Wechsler Adult Intelligence Scale; WMI=Working Memory Index; WMS=Wechsler Memory Scale

Appendix D. Excluded References

Excluded References[1-243244-316317-523524-771772-920921-1037]

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Zhitkova JV. Comparison of different doses of escitalopram in the prevention of dementia in patients with depression and moderate cognitive dysfunction associated with chronic brain ischemia. [Russian]. Zhurnal Nevrologii i Psihiatrii imeni S.S. 2015;Korsakova. 2015(8):53-60. PMID 609429789. *Not available in English*

Zhong Y, Miao Y, Jia WP, et al. Hyperinsulinemia, insulin resistance and cognitive decline in older cohort. Biomedical & Environmental Sciences. 2012 Feb;25(1):8-14. PMID 22424621. *Cohort study with inadequate sample size*

Zhong Y, Zheng X, Miao Y, et al. Effect of CYP2D6 10 and APOE polymorphisms on the efficacy of donepezil in patients with Alzheimer's disease. American Journal of the Medical Sciences. 2013 Mar;345(3):222-6. PMID 22986607. *Ineligible population*

Zhuang JP, Fang R, Feng X, et al. The impact of human-computer interaction-based comprehensive training on the cognitive functions of cognitive impairment elderly individuals in a nursing home. Journal of Alzheimer's Disease. 2013;36(2):245-51. PMID 23587747. *Ineligible population*

Ziemann U, Siebner HR. Inter-subject and inter-session variability of plasticity induction by non-invasive brain stimulation: Boon or bane? Brain Stimulation. 2015 May;8(3):662-3. PMID 2015-26434-013. *Ineligible study design*

Zieschang T, Schwenk M, Oster P, et al. Sustainability of motor training effects in older people with dementia. Journal of Alzheimer's Disease. 2013;34(1):191-202. PMID 23202438. *Ineligible population*

Zimmermann N, Netto TM, Amodeo MT, et al. Working memory training and poetry-based stimulation programs: are there differences in cognitive outcome in healthy older adults? Neurorehabilitation. 2014;35(1):159-70. PMID 24990015. *Inadequate follow up time*

Zlatic CO, Mao Y, Ryan TM, et al. FluphenazineHCl and Epigallocatechin Gallate Modulate the Rate of Formation and Structural Properties of Apolipoprotein C-II Amyloid Fibrils. Biochemistry. 2015 Jun 23;54(24):3831-8. PMID 26021642. *Ineligible study design*

Appendix E. Prospective Cohort Studies

The Health and Medicine Division (HMD) committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) provided a list of longitudinal studies that may provide evidence on interventions to prevent age-related cognitive decline, MCI, and clinical Alzheimer's-type dementia. We used Google search engine to locate, where available, the longitudinal study's website, and where not available, academic sites or curated databases that provided a description of the study. (Some longitudinal studies are hosted or conducted primarily in countries where English is not the first language; descriptions for those studies were drawn from the associated publications in the table.) Study descriptions were used to confirm the prospective cohort study design, usually interested in determining incidence or risk factors, and that treatment was not assigned.

For each study, we iteratively searched PubMed using the study name and a key word (such as "cognitive impairment" and "dementia") derived from the search algorithms in Appendix A to identify related publications. These example articles were compared to the general search results to try to identify gaps in the literature. No gaps were found. Articles that were examples of the type of publication derived from the prospective cohort study but excluded from this review are provided in the table below. The studies were excluded because treatment was not assigned and appropriate techniques to address selection bias were not employed in order to provide information on causal relationships.

Next, for each study we again iteratively searched PubMed using the study name and key words that identify an analytic method that may be applied to a prospective cohort study to simulate an experimental design by "assigning" exposure to the intervention, for example, "instrumental variable" (IV) or "Mendelian randomization." No publications were identified using this method.

As can be seen in the cohort study descriptions, many of these prospective cohort studies have been generating data for decades. The derivative publications can number in the hundreds, possibly greater than 1000 articles per cohort study. Given the potentially large number of publications, which, based on our searches, did not rise to inclusion criteria due to study design (treatment was not assigned or appropriate techniques to address selection bias were not employed in order to provide information on causal relationships), we did not provide full bibliographies for each cohort study.

Appendix Table E1. Prospective cohort studies searched for relevant literature

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
3C (Three Cities Study) France	The Three-City Study (3C Study) is a population-based longitudinal study aiming to examine the relation between vascular diseases and dementia in adults 65 years and older. http://www.three-city-study.com/the-three-city-study.php	Ancelin ML,et al. Steroid and nonsteroidal anti-inflammatory drugs, cognitive decline, and dementia. Neurobiology of Aging, 2011, doi:10.1016/j.neurobiolaging.2011.09.038.
Adult Changes in Thought Study (ACT) US	ACT is made up of 3 cohorts. Current total enrollment is 4,960. Between 1994 and 1996, the study enrolled 2,581 participants. The purpose of this cohort study is to prospectively examine the incidence of AD and dementia, as well as risk factors for those conditions. https://www.maelstrom-research.org/mica/study/act	Gray SL, et al. Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults. J Am Geriatr Soc. 2008 Feb;56(2):291-5.
Age, Gene/Environment Susceptibility – Reykjavik Study (AGES-RS) Iceland	The AGES will phenotype the surviving 12,000 members of the Reykjavik Study cohort (now 67 years and older) for quantitative traits related to diseases and conditions of old age, and collect genetic and other biologic specimens. http://www.hjartarannsokn.is/index.aspx?GroupId=346	Sigurdur Sigurdsson, et.al. Brain tissue volumes in the general population of the elderly: The AGES-Reykjavik Study, NeuroImage, Volume 59, Issue 4, 15 February 2012, Pages 3862-3870, ISSN 1053-8119, http://dx.doi.org/10.1016/j.neuroimage.2011.11.024.
Atherosclerosis Risk in Communities (ARIC) US	The Atherosclerosis Risk in Communities Study (ARIC), sponsored by the National Heart, Lung, and Blood Institute (NHLBI) is a prospective epidemiologic study conducted in four U.S. The Cohort Component of the ARIC study began in 1987, and each of the four ARIC field centers randomly selected and recruited a cohort sample of approximately 4,000 individuals aged 45-64 from a defined population in their community. A total of 15,792 participants received an extensive examination, including medical, social, and demographic data. https://www2.cscc.unc.edu/aric/desc	Lutsey PL, et. al. 2016. Obstructive Sleep Apnea and 15-Year Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Study. Sleep. 39(2):309-16.PubMed
Austrian Study of Stroke Prevention (ASPS) Austria	Community-based cohort study on vascular risk factors and brain structure and function in older adults. 2000 participants, 1000 with imaging, healthy population, aged 45 – 85 years old (non-English website)	Enzinger C, et al. Risk factors for progression of brain atrophy: 6-year follow up of the ASPS. Neurology, 2005
Baltimore Longitudinal Study of Aging (BLSA) US	The BLSA is a longitudinal study, with over 1300 participants currently and over 3100 since study inception. The aim of the study is to understand what is aging. Researchers measure physical and cognitive changes associated with aging in real time among a dedicated group of BLSA participants who come in for testing at regular intervals over the course of their lives. https://www.blsa.nih.gov/	Beydoun MA, et al. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. Journal of epidemiology and community health. 2011;65(11):949-957. doi:10.1136/jech.2009.100826.
Cache County	The study is designed to examine genetic and environmental factors associated with risk	Peters M, et al. Neuropsychiatric symptoms as

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
Study on Memory Health and Aging US	for Alzheimer's disease and other forms of dementia. Started in 1995, the study enrolled 5,092 permanent residents of the county (90%), including approximately 800 individuals aged 85 years and older. The CCMS is a longitudinal investigation of aging and Alzheimer's disease (AD) based in an exceptionally long-lived population residing in northern Utah. The elderly of Cache County have a longer life expectancy, higher educational attainment, and lower incidence of chronic disease (which can complicate the diagnosis of dementias) than other similar populations. http://www.usu.edu/epicenter/htm/studies/memorystudy	risk factors for progression from CIND to dementia: The Cache County Study. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2013;21(11):10.1016/j.jagp.2013.01.049. doi:10.1016/j.jagp.2013.01.049.
Cardiovascular Health Study (CHS) US	The Cardiovascular Health Study (CHS) is an NHLBI-funded observational study of risk factors for cardiovascular disease in adults 65 years or older. Starting in 1989, and continuing through 1999, participants underwent annual extensive clinical examinations. Measurements included traditional risk factors such as blood pressure and lipids as well as measures of subclinical disease, including echocardiography of the heart, carotid ultrasound, and cranial magnetic-resonance imaging (MRI). At six month intervals between clinic visits, and once clinic visits ended, participants were contacted by phone to ascertain hospitalizations and health status. The main outcomes are coronary heart disease (CHD), angina, heart failure (HF), stroke, transient ischemic attack (TIA), claudication, and mortality. Participants continue to be followed for these events. https://chs-nhlbi.org/	Incidence of mild cognitive impairment in the Pittsburgh Cardiovascular Health Study–Cognition Study Oscar L. et. al. October 9, 2012, 79:15 1599-1606; published ahead of print September 26, 2012, doi:10.1212/WNL.0b013e31826e25f0: 1526-632X
Chicago Health and Aging Project (CHAP) US	CHAP is a longitudinal population study of common chronic health problems of older persons, especially of risk factors for incident Alzheimer's disease, in a biracial neighborhood of the south side of Chicago. http://www.alzrisk.org/cohort.aspx?cohortID=15&rfid=2	Morris MC, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA. 2002 Jun 26;287(24):3230-7.
Coronary Artery Risk Development in Young Adults Study (CARDIA) US	The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a study examining the development and determinants of clinical and subclinical cardiovascular disease and their risk factors. It began in 1985-6 with a group of 5115 black and white men and women aged 18-30 years. The participants were selected so that there would be approximately the same number of people in subgroups of race, gender, education (high school or less and more than high school) and age (18-24 and 25-30) in each of 4 centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. http://www.cardia.dopm.uab.edu/	No relevant studies immediately found
Framingham Heart Study (note: Framingham cohorts include the Original, Offspring and	The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to CVD by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. The researchers recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts. Since 1948, the subjects have continued to return to the study every two years for a detailed medical history, physical examination, and laboratory tests. In 1971, the Study enrolled a	Karakis I, et al. Association of Serum Vitamin D with the Risk of Incident Dementia and Subclinical Indices of Brain Aging: The Framingham Heart Study. J Alzheimers Dis. 2016. Epub 2016/02/19. doi: 10.3233/jad-150991. (PubMed ID Number: 26890771).

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
Gen 3 cohorts) US	second generation - 5,124 of the original participants' adult children and their spouses - to participate in similar examinations. In 1994, the need to establish a new study reflecting a more diverse community of Framingham was recognized, and the first Omni cohort of the Framingham Heart Study was enrolled. In April 2002 the Study entered a new phase, the enrollment of a third generation of participants, the grandchildren of the Original Cohort. In 2003, a second group of Omni participants was enrolled. https://www.framinghamheartstudy.org/	
Health and Retirement Study (HRS) US	The University of Michigan Health and Retirement Study (HRS) is a longitudinal panel study that surveys a representative sample of approximately 20,000 people in America over the age of 50 every two years. http://hrsonline.isr.umich.edu/	Saczynski JS, et al. Antidepressant Use and Cognitive Decline: The Health and Retirement Study. The American journal of medicine. 2015;128(7):739-746. doi:10.1016/j.amjmed.2015.01.007.
Health, Aging and Body Composition Study (Health ABC) US	The HEALTH ABC Study will characterize the extent of change in body composition in older men and women, identify clinical conditions accelerating these changes, and examine the health impact of these changes on strength, endurance, disability, and weight-related diseases of old age. The study population consists of 3,075 persons age 70-79 at baseline with about equal numbers of men and women. Thirty-three percent of the men are African-Americans as are 46% of the women. All persons in the study were selected to be free of disability in activities of daily living and free of functional limitation (defined as any difficulty walking a quarter of a mile or any difficulty walking up 10 steps without resting) at baseline. https://www.nia.nih.gov/research/intramural-research-program/dynamics-health-aging-and-body-composition-health-abc	No relevant studies immediately found
Honolulu-Asia Aging Study (HAAS) US	The Honolulu-Asia Aging Study (HAAS) is a longitudinal epidemiologic investigation of rates, risk factors, and neuropathologic abnormalities associated with cognitive decline and dementia in aged Japanese-American men. http://www.alzrisk.org/cohort.aspx?cohortID=3&rfid=5	Taaffe, Dennis R., et al. "Physical activity, physical function, and incident dementia in elderly men: the Honolulu–Asia Aging Study." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 63.5 (2008): 529-535.
Kame Project (a cohort study of Japanese Americans in King County, Washington) US	A large population-based prospective study of Japanese Americans in King County, Washington, who were followed from 1992 to 2001, as part of the Ni-Hon-Sea Project, a cross-cultural study of prevalence and incidence rates of Alzheimer's disease and vascular dementia among Japanese populations living in Hiroshima, Japan; Oahu, Hawaii; and the metropolitan area of Seattle, Washington. http://www.alzrisk.org/cohort.aspx?cohortID=55&rfid=6	Dai Q, et al. Fruit and Vegetable Juices and Alzheimer's Disease: The Kame Project. The American journal of medicine. 2006;119(9):751-759. doi:10.1016/j.amjmed.2006.03.045.
Kungsholmen Project	The Kungsholmen Project is a longitudinal population-based study on ageing and dementia, carried out by the Stockholm Gerontology Research Center in collaboration with Aging Research Center (ARC), Karolinska Institutet. The project, which started in	Qiu C, et. al. Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. Stroke 2004;35:1810-5.

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
Sweden	1987, has gathered a 12-year long database and offers information on aging from a multidisciplinary perspective. http://www.kungsholmenproject.se/	
Leisure World Cohort Study (note: the Leisure World is now extended as the 90+ Study) US	The Leisure World Cohort Study was established to study the effect of modifiable lifestyle practices on longevity and successful aging when all residents of a California retirement community (Leisure World Laguna Hills) were mailed a postal health survey in 1981. New residents who moved into the community after this date were mailed the survey in 1982, 1983, and 1985. Of the 22,910 residents, 13,978 (61%) completed the questionnaire. The population and cohort are mostly Caucasian, well educated, upper-middle class, and elderly. https://www.mind.uci.edu/research/90plus-study/	Paganini-Hill, Annlia. "Hypertension and Dementia in the Elderly: The Leisure World Cohort Study." International journal of hypertension 2012 (2011).
Lothian Birth Cohorts UK	The Lothian Birth Cohorts of 1921 and 1936 are follow-up studies of the Scottish Mental Surveys of 1932 and 1947. The surveys had, respectively, tested the intelligence of almost every child born in 1921 or 1936 and attending school in Scotland in the month of June in those years. Therefore, tracing, recruiting and re-testing people who had taken part in the Surveys offered a rare opportunity to examine the distribution and causes of cognitive ageing across most of the human life course. The studies described here were initially set up to study determinants of non-pathological cognitive ageing; i.e. the ageing of cognitive functions largely in the normal range, and not principally dementia or other pathological cognitive disordershttp://www.lothianbirthcohort.ed.ac.uk/	No relevant studies immediately found
Mayo Clinic Study of Aging (MCSA) US	The MCSA is a population-based study that was designed to study incident mild cognitive impairment and dementia. The sampling frame included all persons aged 70–89 years who were residents of Olmsted County, Minnesota, as of October 1, 2004 (age- and sex-stratified random sample). The medical records of potential participants were formally reviewed prior to contact to exclude those with diagnoses of dementia, those in hospice care, or those considered to have conditions deemed imminently fatal. (Mayo Clinic does not appear to have a searchable site for this study.)	Vassilaki, Maria, et al. "Multimorbidity and risk of mild cognitive impairment." Journal of the American Geriatrics Society 63.9 (2015): 1783-1790.
MEMENTO France	This cohort aims at studying the evolution of a variety of potentially early signs (cognitive complaints, deficit in some domain of cognition, psycho-behavioural disturbances, changes in imaging or biological markers) of Alzheimer's disease and related dementia and to estimate the prognostic value of different markers (neuro-psychological, vascular, psychopathological, socio-educational, genetic, biological, neuro-imaging) on the progression to clinical dementia or severe cognitive deterioration stages, and then to death. http://www.memento-cohort.org/memento_web/Portals/0/Chercheurs/MEMENTO_Formulaire_AccesDonnees.pdf	No relevant studies immediately found
Minority Aging Research Study (MARS)	The Minority Aging Research Study (MARS) began in 2004 and is a study of risk factors for cognitive decline in older Blacks. Participants are recruited from community-based organizations, churches, and senior-subsidized housing facilities; the catchment area is within that of MAP. Study participation requires agreeing to detailed annual clinical	No relevant studies immediately found

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
US	evaluations and cognitive testing. Between 2004 and 2007, >350 older persons enrolled in the study. https://www.rush.edu/services-treatments/alzheimers-disease-center/minority-aging-research-study	
Monongahela Valley Independent Elders Survey (MoVIES) US	The MoVIES project investigated various aspects of normal and abnormal aging. It also studied the incidence, risk factors, and outcome in late-life dementia, including Alzheimer's disease, in a prospective community-based epidemiologic study for 15 years. The study cohort was drawn from a rural, largely blue-collar community in the mid-Monongahela Valley of Southwestern Pennsylvania. The original cohort of 1681 individuals aged 65+ years was assembled between 1987 and 1989 and was followed until 2002 with multi-stage clinical "Waves" of cognitive and risk factor screening. Screening waves were interspersed with multi-stage clinical evaluations to detect the presence of Alzheimer's and other dementias. http://www.wpic.pitt.edu/research/dementia_epidemiology/Movies/MoviesHomePage.htm	No relevant studies immediately found
Monongahela-Youghiogheny Healthy Aging Team (MYHAT) US	The MYHAT project seeks to describe the distribution of Cognitive Impairment, No Dementia (CIND) and Mild Cognitive Impairment (MCI) and related entities, their associated features, their outcomes over time, and the predictors of these outcomes. An age-stratified random community sample of approximately 2,100 was recruited and screened using cognitive, functional, and other health-related measures to identify the non-demented who are cognitively impaired. Among them, we identified subgroups meeting operational criteria for MCI of amnestic and other varieties. http://www.wpic.pitt.edu/research/dementia_epidemiology/MYHAT/MYHATHomePage.htm	Hughes TF,et al. Independent and combined effects of cognitive and physical activity on incident MCI. Alzheimers and Dement. 2015 Nov; 11(11): 1377-84. doi: 10.1016/j.jalz.2014.11.007. (PMC4536189) Ganguli M, et al. Rates and risk factors for progression to incident dementia vary by age in population cohort. Neurology, 84(1):72-80. (PMC4336092)
Multi-Ethnic Study of Atherosclerosis (MESA) US	The MESA study examines the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. From July 2000 to January 2012, MESA is a prospective population-based sample of 6,814 asymptomatic men and women aged 45-84. Approximately 38 percent of the recruited participants are white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. https://www.mesa-nhlbi.org/	No relevant studies immediately found
Northern Manhattan Study (NOMAS) US	NOMAS)is a study of the population of Washington Heights in Northern Manhattan. The ongoing study, which began in 1990, is based in the Neurological Institute of Columbia Presbyterian Hospital, located in Washington Heights. NOMAS has enrolled over 4,400 people from the surrounding community. NOMAS is the first study of its kind to focus on stroke risk factors in whites, blacks, and Hispanics living in the same community. It is helping to fill gaps in our knowledge of stroke epidemiology in minority populations.	No relevant studies immediately found

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
	http://columbianomas.org/	
Nurses' Health Study US	The Nurses' Health Studies are among the largest prospective investigations into the risk factors for major chronic diseases in women. Starting with the original Nurses' Health Study in 1976, the studies are now in their third generation with Nurses' Health Study 3 (which is still enrolling male and female nurses) and count more than 275,000 participants. http://www.nurseshealthstudy.org/	Devore, Elizabeth E., et al. "Dietary intakes of berries and flavonoids in relation to cognitive decline." Annals of neurology 72.1 (2012): 135-143. Okereke, Olivia I., et al. "Plasma C-peptide levels and rates of cognitive decline in older, community-dwelling women without diabetes." Psychoneuroendocrinology 33.4 (2008): 455-461.
Reasons for Geographic and Racial Differences in Stroke (REGARDS) US	REGARDS is an observational study of risk factors for stroke in adults 45 years or older. 30,239 participants were recruited between January 2003 and October 2007. They completed a telephone interview followed by an in-home physical exam. Measurements included traditional risk factors such as blood pressure and cholesterol levels, and an echocardiogram of the heart. At six month intervals, participants are contacted by phone to ask about stroke symptoms, hospitalizations and general health status. The study is ongoing and will follow participants for many years. http://www.regardsstudy.org/	Zhu, Wenfei, et al. "Association Between Objectively Measured Physical Activity and Cognitive Function in Older Adults—The Reasons for Geographic and Racial Differences in Stroke Study." Journal of the American Geriatrics Society 63.12 (2015): 2447-2454.
Religious Orders Study US	The Religious Orders Study is a collaborative study with Rush and other U.S. medical centers. It involves more than 1,100 older religious clergy (nuns, priests and brothers) who have agreed to medical and psychological evaluation each year and brain donation after death. Researchers are using information from the study to discover what changes in the brain are responsible for memory and movement problems. https://www.rush.edu/services-treatments/alzheimers-disease-center/religious-orders-study	Yu, Lei, et al. "The CETP I405V polymorphism is associated with an increased risk of Alzheimer's disease." Aging cell 11.2 (2012): 228-233.
Rochester Epidemiology Project (Olmsted County Study) US	The REP includes the medical records of all persons who have ever lived in Olmsted County, Minnesota between January 1, 1966 and the present, and who have given permission for their medical information to be used for research.[6] Those persons comprise more than 500,000 unique individuals and more than 6 million person years of follow-up through 2010. http://www.mayo.edu/research/centers-programs/rochester-epidemiology-project/overview	Savica, Rodolfo, et al. "Incidence of dementia with Lewy bodies and Parkinson disease dementia." JAMA neurology 70.11 (2013): 1396-1402.
Rotterdam Study Netherlands	The Rotterdam Elderly Study is a prospective cohort study in the Ommoord district in the city of Rotterdam, the Netherlands. Recruitment started in January 1990. The main objectives of the Rotterdam Study were to investigate the risk factors of cardiovascular, neurological, ophthalmological and endocrine diseases in the elderly. Up to 2008, approximately 15,000 subjects aged 45 years or over have been recruited. http://www.epib.nl/research/ergo.htm	Ruitenberg A, et al. "Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study." Annals of neurology 57.6 (2005): 789-794. Engelhart, Marianne J., et al. "Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study." Archives of neurology 61.5 (2004): 668-672.
Rush Memory and Aging Project	The Rush MAP is a companion study that is more diverse in life experience make-up than ROS. Participants are older community-dwelling persons who are recruited and	Buchman, A. S., et al. "Total daily physical activity and the risk of AD and cognitive decline in older

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
(MAP) US	followed with nearly identical annual evaluations to ROS and all agree to donate brain, spinal cord, nerve and muscle to Rush investigator's at the time of death. More than 1,350 participants have enrolled and are seen annually and have had up to 13 clinical evaluations. https://www.rush.edu/services-treatments/alzheimers-disease-center/radc-research/memory-and-aging-project-rush	adults." Neurology 78.17 (2012): 1323-1329.
The Sacramento Area Latino Study on Aging (SALSA) US	The Sacramento Area Latino Study on Aging (SALSA Study) project tracked the incidence of physical and cognitive impairment as well as dementia and cardiovascular diseases in elderly Latinos in the Sacramento, California, region. http://www.icpsr.umich.edu/icpsrweb/NACDA/studies/29323	Haan, Mary N., et al. "Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging." The American journal of clinical nutrition 85.2 (2007): 511-517.
Singapore Longitudinal Ageing Study (SLAS) Singapore	Between September 2003 and December 2005, a whole population of older adults aged 55 years and above who were Singaporean residents in contiguous precincts in the South East region of Singapore were identified from a door–to–door census and invited to participate in the Singapore Longitudinal Ageing Study (SLAS). (No identifiable website)	Ng, Tze Pin, et al. "Metabolic Syndrome and the Risk of Mild Cognitive Impairment and Progression to Dementia: Follow-up of the Singapore Longitudinal Ageing Study Cohort." JAMA neurology 73.4 (2016): 456-463.
Study of Osteoporotic Fractures (SOF) US	The multi-center Study of Osteoporotic Fractures (SOF) has 20 years of prospective data about osteoporosis that has served as the basis for many findings about osteoporosis and aging in women ≥ age 65. In addition to adjudication of fractures, SOF has tracked cases of incident breast cancer, and total and cause-specific mortalityhttp://sof.ucsf.edu/interface/	Slinin, Yelena, et al. "Cystatin C and cognitive impairment 10 years later in older women." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 70.6 (2015): 771-778.
The Sydney Memory and Ageing Study (Sydney MAS) Australia	The Sydney Memory and Ageing Study (Sydney MAS) began in 2005 to examine the clinical characteristics and prevalence of mild cognitive impairment (MCI) and related syndromes, and to determine the rate of change in cognitive function over time. It is one of the largest longitudinal studies of this kind in Australia. At the baseline assessment from 2005 to 2007, 1037 non-demented individuals aged 70-90 were recruited from two areas of Sydney, following a random approach to 8914 individuals on the electoral roll. They underwent detailed neuropsychological and medical assessments and donated a blood sample for clinical chemistry, proteomics and genomics. https://cheba.unsw.edu.au/project/sydney-memory-and-ageing-study	Heffernan, Megan, et al. "Alcohol Consumption and Incident Dementia: Evidence from the Sydney Memory and Ageing Study." Journal of Alzheimer's Disease Preprint (2016): 1-10. Sachdev, Perminder S., et al. "Risk profiles for mild cognitive impairment vary by age and sex: the Sydney Memory and Ageing Study." The American Journal of Geriatric Psychiatry 20.10 (2012): 854-865.
UK Health and Lifestyle Study UK	The Health Survey for England (HSE) is an important annual survey looking at changes in the health and lifestyles of people all over the country. Around 8,000 adults and 2,000 children take part in the survey each year. Information is collected through an interview, and if participants agree, a visit from a specially trained nurse. The surveys, which have been carried out since 1991, provide regular information that cannot be obtained from other sources. https://www.ucl.ac.uk/hssrg/studies/hse	No relevant studies immediately found
Washington-	The Washington Heights-Hamilton Heights-Inwood Community Aging Project (WHICAP)	Helzner, Elizabeth P., et al. "Contribution of

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
Heights Inwood Columbia Aging Project (WHICAP) US	is a community-based longitudinal study of aging and dementia among elderly, urban-dwelling residents. The project began enrolling patients in 1989 and has followed more than 5,900 residents over 65 years of age. The WHICAP study has enabled researchers to capture detailed information about the onset of dementia and how symptoms develop over time. http://www.alzrisk.org/cohort.aspx?cohortID=16&rfid=3	vascular risk factors to the progression in Alzheimer disease." Archives of neurology 66.3 (2009): 343-348.
Whitehall II Prospective Cohort Study UK	Whitehall II is a longitudinal, prospective cohort study of 10,308 women and men, all of whom were employed in the London offices of the British Civil Service at the time they were recruited to the study in 1985. The initial data collection included a clinical examination and self-report questionnaire. Research continues to explore the pathways and mechanisms through which social position influences health. The research group aims to build a causal model leading from social position through psychosocial and behavioural pathways to pathophysiological changes, sub-clinical markers of disease, functional change, and clinical disease. https://www.ucl.ac.uk/whitehallII	Singh-Manoux, Archana, et al. "Interleukin-6 and C-reactive protein as predictors of cognitive decline in late midlife." Neurology 83.6 (2014): 486-493. Akbaraly, Tasnime N., et al. "Metabolic Syndrome Over 10 Years and Cognitive Functioning in Late Midlife The Whitehall II study." Diabetes care 33.1 (2010): 84-89.

Appendix F. Cognitive Training Interventions

Appendix Table F1. Characteristics of eligible studies: ACTIVE trial publications

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome timing**	**Outcome** **Domain [Instrument]**
Rebok 2014[1] RCT US High	2832	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	10 years	Executive/Attention/Processing Speed [Reasoning Composite] [Speed of Processing Composite] Memory [Memory Composite]
Rebok 2013[2] RCT US High	629	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 73.5 (6.0) 77% Female 76% White Years Education, Mean (SD) 13.7 (2.7) MMSE, Mean (SD)	Verbal episodic memory training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	1 year 2 years 3 years 5 years	Memory [Memory Composite]

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome timing**	**Outcome** **Domain [Instrument]**
		27.3 (2)				
Jones, 2013[3] RCT US High	1659	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 77% Female 73% White Education, Mean (SD) 13.5 (3) MMSE, Mean (SD) 27 (2)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	5 years	Executive/Attention/Processing Speed [Reasoning Composite] [Speed of Processing Composite] Memory [Memory Composite]
Sisco 2013[4] RCT US High	1912	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 72.9 (5.4) 76% Female 72% White Years Education, Mean (SD) 13.2 (2.6) MMSE, Mean (SD) 27.3 (2)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	1 year 2 years 3 years 5 years	Memory [Rivermead Paragraph Recall Test, Verbatim Recall] [Rivermead Paragraph Recall Test, Paraphrase Recall] [HVLT, Total Recall] [AVLT, Total Recall]

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome timing**	**Outcome** **Domain [Instrument]**
Valdes 2012[5] RCT US High	195	Older adults from ACTIVE trial with psychometrically-defined MCI Age, Mean (SD) 78 (6) 67% Female 60% White Education Level, Mean (SD) 12 (2.5) Baseline Cognition NR	Speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	10 years	Executive/Attention/Processing Speed [UFOV Performance]
Unverzagt 2012[6] RCT US High		Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	5 years	Diagnosis [Dementia]
Wolinsky, 2010[7] RCT US High	1534	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over	No contact control group (study duration)	5 years	Executive/Attention/Processing Speed [Internal Locus of Control] [Chance Locus of Control] [Powerful Others Locus of Control]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		Age, Mean 73 78% Female 73% White Education Level, Mean 13 Baseline Cognition NR	5 to 6 weeks			
Wolinsky, 2010b[8] RCT US High	1804	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	2 years 3 years 5 years	Executive/Attention/Processing Speed [Reasoning Composite] [Speed of Processing Composite] Memory [Memory Composite]
Unverzagt 2007[9] RCT US High	2832	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	2 years	Executive/Attention/Processing Speed [Reasoning Composite] [Speed of Processing Composite] Memory [Memory Composite]

Study Design Country RoB	**N=**	**Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition**	**Intervention Mode Components Frequency Duration**	**Comparison Mode Components Frequency Duration**	**Outcome timing**	**Outcome Domain [Instrument]**
		88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)				
Willis 2006[10] US RCT High	2832	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	5 years	Executive/Attention/Processing Speed [Reasoning Composite] [Speed of Processing Composite] Memory [Memory Composite]
Ball 2002[11] RCT US Medium	2832	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	2 years	Executive/Attention/Processing Speed [Reasoning Composite] [Speed of Processing Composite] Memory [Memory Composite]

ACTIVE=Advanced Cognitive Training for Independent and Vital Elderly; AVLT=Auditory Verbal Learning Test; HVLT=Hopkins Verbal Learning Test; N=sample size; NR=not reported; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SD=standard deviation; US=United States

Appendix Table F2. ACTIVE Sample Loss (Based on Initial Enrollment)

	Memory	Reasoning	Speed	Control
Enrolled	711	705	712	704
Completed Training	620	627	637	
2 Years	563	555	574	584
2 Years Loss	148	150	138	120
2 Years % Loss	21%	21%	19%	17%
2 Years Deaths	6	3	9	9
2 years % Loss/Death	4%	2%	7%	8%
5 Years	472	469	490	448
5 Years Loss	239	236	222	256
5 Years % Loss	34%	33%	31%	36%
5 Years Deaths	32	41	46	46
5 Years % Loss/Death	13%	17%	21%	18%
10 Years	300	316	319	285
10 Years Loss	411	389	393	419
10 Years % Loss	58%	55%	55%	60%
10 Years Deaths	103	85	103	98
10 Years % Loss/Death	25%	22%	26%	23%

ACTIVE=Advanced Cognitive Training for Independent and Vital Elderly

Appendix Table F3. Summary risk of bias assessments: ACTIVE trial

Study	Overall Risk of Bias Assessment	Rationale
Rebok 2014[1]	High	Potential attrition bias with attrition rate of 57%.
Rebok 2013[2]	High	Potential attrition and reporting bias.
Jones 2013[3]	High	Attrition rate is greater than 21% with insufficient analysis to address potential for bias.
Sisco 2013[4]	High	Attrition rate is 33% with insufficient analysis to address potential for bias.
Valdes 2012[5]	High	Potential attrition and reporting bias.
Unverzagt 2012[6]	High	Attrition rate is 33% with insufficient analysis to address potential for bias.
Wolinsky 2010[7]	High	Potential attrition bias with attrition rate of 55%.
Wolinsky 2010b[8]	High	Attrition rate is 36% with insufficient analysis to address potential for bias.
Unverzagt 2007[9]	High	Attrition rate is greater than 21% with insufficient analysis to address potential for bias.
Willis 2006[10]	High	Attrition rate is 33% with insufficient analysis to address potential for bias.
Ball 2002[11]	Medium	Potential attrition and detection bias.

ACTIVE=Advanced Cognitive Training for Independent and Vital Elderly

Appendix Table F4. Strength of evidence assessments: ACTIVE Trial

Outcome Timing	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
2-Year Outcomes	Memory	1 (2,832)	Improvement with memory training intervention (ES=0.17). No significant differences with reasoning speed of processing training.	Medium	Indirect	Precise	Unknown	Undetected	NA	Moderate
	Reasoning	1 (2,832)	Improvement with reasoning training (ES=0.257). No significant differences with memory or speed of processing training.	Medium	Indirect	Precise	Unknown	Undetected	NA	Moderate
	Speed of Processing	1 (2,832)	Improvement with speed of processing training (ES=0.87). No significant differences with reasoning or memory training.	Medium	Indirect	Precise	Unknown	Undetected	NA	Moderate
5- and 10-Year Outcomes	Diagnosis	1 (2,832)	No statistically significant differences between intervention arms (aggregate) and control (5-Years).	High	Direct	Precise	Unknown	Undetected	NA	Insufficient
	Memory	1 (2,832)	5-Years Improvement with memory training (ES=0.23). No significant differences with reasoning speed of processing training.	High	Indirect	Precise	Unknown	Undetected	NA	Low

Outcome Timing	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			<u>10 Years</u> No statistically significant differences between intervention arms and control.							
	Reasoning	1 (2,832)	Improvement with reasoning training (5-Years: ES=0.26; 10-Years: ES=0.23). No significant differences with memory or speed of processing training.	High	Indirect	Precise	Unknown	Undetected	NA	Low
	Speed of Processing	1 (2,832)	<u>5-Years</u> Improvement with reasoning training (ES=0.15) and speed of processing training (ES=0.076). No significant differences with memory training. <u>10 Years</u> Improvement with speed of processing training (ES=0.66). No significant differences with reasoning or memory training.	High	Indirect	Precise	Unknown	Undetected	NA	Low

ACTIVE=Advanced Cognitive Training for Independent and Vital Elderly; CI=confidence interval; ES=effect size; n=sample size; NA=not applicable; SOE=strength of evidence

Appendix Table F5. Characteristics of eligible studies: other cognitive training trials in adults with normal cognition

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Corbett 2015 RCT UK High	6742	Adults over 50 with access to a computer and internet Age, Mean (SD) 58.9 (6.5) 67% Female 97% White 50% University Graduate Baseline Cognition NR	Evidence-based reasoning and problem solving cognitive training or general cognitive training - 10 minutes daily for 6 months	Internet-based tasks and games --10 minutes daily for 6 months	6 month	Executive/Attention/Processing Speed [Digit Vigilance, DSTask] Memory [PALS] [HVLT] [Spatial Working Memory]
Anderson 2014 RCT US High	62	Adults age 55 to 70 years old Age, Mean (SD) 63 (4) 55% Female Race NR Education NR Baseline Cognition NR	Brain Fitness Program, a in-home auditory-based program of six modules to increase speed and accuracy of auditory processing -1 hour/day, 5 days/week for 8 weeks	In-home educational DVDs -1 hour/day, 5 days/week for 8 weeks	6 months	Executive/Attention/Processing Speed [Visual Matching Sub-test, Woodcock-Johnson III Tests of Cognitive Abilities] Memory [Memory for Words Sub-test, Woodcock-Johnson III Tests of Cognitive Abilities]
Lampit 2014 RCT Australia High	80	Older adults without dementia who were able to use a computer and had an MMSE score greater than 23 Age, Mean (SD) 71 (6.2) 66% Female Race NR Education NR MMSE, Mean (SD) 28 (1.6)	Computerized cognitive training with 24 exercises providing training in the domains of memory, attention, response speed, executive functions and language -30-45 minute sessions, 3 times/week, over 12 weeks	National geographic videos and multiple choice questions after videos -30-45 minute sessions, 3 times/week, over 12 weeks	52 weeks	Multidomain Neuropsychological Performance [Global Cognition Composite] Executive/Attention/Processing Speed [Information Processing Speed Composite] [Executive Function Composite] Memory [Memory Composite] Language [Language Composite]
Stine-Morrow 2014[12] RCT	461	Adults without dementia or neurological impairment	Odyssey of the Mind engagement program –16 weekly meetings for 1.5	Waitlist control	8 months	Executive/Attention/Processing Speed [Processing Speed Composite] Memory [Episodic Memory Composite]

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome** **Timing**	**Outcome** **Domain [Instrument]**
US Medium		Age, Mean (SD) 23 (7.6) 75% Female Race NR Education Level, Mean (SD) 15.4 (2.6) MoCA, Mean (SD) 26 (3)	hours Home-based reasoning training -10 weekly lessons supplemented with 6 packs of crossword and Sudoku puzzles			Visuospatial [Visuospatial Composite]
Anguera 2013	80	Treatment naïve older adults Age, Mean (SD)	Neuroracer, a three dimensional video game either in single-task or multi-tasking mode -1 hour/day, 3 times/week for 4 weeks	No contact control	6 months	Executive/Attention/Processing Speed [Test of Variables of Attention, RT] [Test of Variables of Attention, RT Variability] [UFOV] Memory [Delayed-recognition Working Memory Task Ignoring Distraction RT] [Delayed-Recognition Working Memory Task Attend to Distraction RT] [Delayed-recognition Working Memory Task No Distraction RT]
Borness 2013 RCT Austrailia High	135	Full and part time staff from an Australian national public service organization Age, Mean (SD) 41.6 (13) 63.7% Female Race NR Education, Mean (SD) 13.7 (2.4) Baseline Cognition NR	Thirty-six online exercises across the domains of memory, attention, language, executive function and visuospatial abilities -20 minutes/sessions, 3 sessions/week, for 16 weeks	Videos about about the natural environment and answering multiple choice questions in a survey -20 minutes/sessions, 3 sessions/week, for 16 weeks	6 months	Executive/Attention/Processing Speed [Matrix Reasoning] [COWAT] SCWT 1] [SCWT 2] [SCWT 3] [Staged Information Processing Speed Level 1] [Staged Information Processing Speed Level 2] [Staged Information Processing Speed Level 3] [Divided Attention Indicator Alone Median Response Time] Memory [Verbal Memory, Total Accuracy] [Delayed Verbal Memory, Total Accuracy] [Non Verbal Memory, Total Accuracy] [Delayed Non Verbal Memory, Total Accuracy] Language [COWAT] Visuospatial [Visual Spatial Orientation] [Visual Sequence Comparison Thruput]

Study Design Country RoB	**N=**	**Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition**	**Intervention Mode Components Frequency Duration**	**Comparison Mode Components Frequency Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
						l [Visual Sequence Comparison Median Response Time]
Carretti 2013[13] RCT Italy Medium	40	Healthy older adults active in cultural and social activities in their neighborhood Age, Mean (SD) 70 (3.6) Sex NR Race NR Education, Mean (SD) 8.56 (4.3) Baseline Cognition NR	Six individual training sessions over 2 weeks (sessions 2-4 were training, sessions 1, 5, and 6 were for baseline, posttest, and 6 month follow-up, respectively)	Paper-and-pencil questionnaires	6 months	Memory [CWMS] [Working Memory Updating Word Span Test, Updating]
Miller 2013[14] RCT US Medium	84	Adults with no signs of dementia and a MMSE score of 24 or more Age, Mean (SD) 81.8 (6) 67% Female 96% White Years Education, Mean (SD) 16 (2.2) MMSE, Mean (SD) 28 (1.6)	Computer brain fitness program -5 days a week for 20-25 minutes/day for 8 weeks followed by 4 months of doing as many sessions as they preferred	Wait-list control -2 months wait period prior to access to intervention for 4 months	6 months	Memory [Delayed Memory Composite] [Immediate Memory Composite] Language [Language Composite]
Wolinsky 2013[15] RCT US Low	681	Adults without a diagnosis of cognitive impairment Age, Mean 57.2 68.6% Female 94.2% White 71.9% College Graduate	On-site visual speed of processing training with and without 2 hour boosters after 11 months - Five weekly, 2 hour training sessions At home visual speed of processing training -10	On-site computerized crossword game – Five weekly, 2 hour training session	1 year	Executive/Attention/Processing Speed [UFOV] [TMT A] [TMT B] [SDMT] [SCWT (Word)] [SCWT (Color)] [SCWT (Color-Word)] [COWAT] [DVT, Time] [DVT, Errors]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
		Baseline Cognition NR	hours			
Cheng 2012[16] RCT China High	270	Older adults with no evidence of significant cognitive impairment Age, Mean (SD) 70 (3.5) 48% Female Race NR Education, Mean (SD) 9.6 (3.9) Baseline Cognition NR	Multidomain training or reasoning training group cognitive training sessions –Twice a week for 12 weeks	Wait list control	6 months 12 months	Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Performance [RBANS Total Score] [RBANS Attention] [SCWT (Interference)] [SCWT (Number of Naming Errors)] [TMT A] [TMT B] Memory [RBANS Immediate Memory] [RBANS Delayed Memory] [Visual Reasoning Test] Language [RBANS Language] Visuospatial [RBANS Visuospatial/ Constructional]
Mortimer 2012[17] RCT China High	75	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Social interaction – Meeting at community center for 1 hour, 3 times/week	Inactive control with 4 check-in calls over 40 weeks	40 weeks	Biomarker [Whole Brain Volume, % of Total Intracranial Volume] Multidomain Neuropsychological Performance [Mattis Dementing Rating Scale, Total Score] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [SCWT (Word)] [SCWT (Color)] [SCWT (Color-Word)] [WAIS Similarities] [TMT A] [TMT B] [Mattis Attention Score] [Mattis Initiation Score] [Mattis Conceptualization Score] Memory [AVLT, Immediate Recall] [AVLT, Delayed Recall] [AVLT, Delayed Recognition] [RCFT, Recall] [Mattis Memory Score] Language [CVFT, Animals] [BNT] Visuospatial [Bell Cancellation Test] [RCFT, Copying] [RCFT, Recall] [CLOX-1] [Mattis Construction Score]
Szelag 2012[18] RCT Poland	30	Healthy adults between 65 and 75 years old Age, Mean (SD)	Temporal information processing training -32 hour-long sessions for 8	Non-temporal training using computer games or no	18 months	Executive/Attention/Processing Speed [Attention Measure] Memory [Spatial Span] [Delayed Matching to

Study Design Country RoB	**N=**	**Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition**	**Intervention Mode Components Frequency Duration**	**Comparison Mode Components Frequency Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
High		69 (2) 57% Female Race NR Years Education, Mean (SD) 13 (3) MMSE, Range 27-30	weeks	intervention over 8 weeks		Sample] [Pattern Recognition Memory Test]
Evers 2011[19] RCT Germany High	161	Women age 70 and over with no more than 4 errors on the MMSE Age, Mean (SD) 73.6 (4.2) 100% Female Race NR Years of Education, Mean (SD) 12 (2.6) MMSE, Mean (SD) 28.78 (0.96)	Computer course (writing, playing, calculating, surfing the Internet, emailing, drawing, image editing, and video taping)	Inactive control (live their habitual life)	6 months	Executive/Attention/Processing Speed [SCWT] [TMT B/A] Memory [RBMT, Immediate] [RBMT, Delayed Recall] [FCSRT, Short Delay] [FCSRT, Long Delay] Language [Semantic Verbal Fluency]
Borella 2010[20] RCT Italy High	40	Healthy adults with not pathologies causing possible cognitive impairments Age, Mean (SD) 69 (3) Sex NR Race NR Education, Mean (SD) 9.3 (3.7) Baseline Cognition NR	Working memory training - 3 60- minute sessions over 2 weeks	Memory questionnaires -3 60-minute sessions over 2 weeks	8 months	Executive/Attention/Processing Speed [DS Forward] [DS Backward] [SCWT (Color Incongruent, RTs] [SCWT (Color Control II, RTs)] [SCWT (Color Index, RTs)] [SCWT (Color Incongruent, Errors)] [SCWT (Color Control II, Errors)] [SCWT (Color Index, Errors)] [Pattern Comparison] Memory [CWMS] Visuospatial [Dot Matrix]
Klusmann, 2010[21] RCT Germany	168	Women older than 70 without cognitive impairment	Computer courses focusing on creative tasks and coordinative and	Living habitual life over 6 months	6 months	Executive/Attention/Processing Speed [TMT A/B] [SCWT] Memory [RBMT, Immediate] [RBMT, Delayed

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Medium		Age, Mean (SD) 74 (4) 100% Female Race NR Years Education, Mean (SD) 12 (2.6) MMSE, Mean (SD) 28.8 (0.97)	memory tasks -75 intervention units of 90 minutes over 6 months			Recall] [FCSRT, Short Delay] [FCSRT, Long Delay]
McDougall 2010[22] RCT US High	265	Non-demented older adults Age, Mean 75 79% Female 71% White Education, Mean (SD) 13.6 (3.8) Baseline Cognition MMSE, Mean 26	Small group memory training -2 times/week for a month, 12 hours total with 4, 2-hour booster sessions over 3 months following training	Health promotion training focusing on 18 topics -2 times/week for a month, 12 hours total with 4, 2-hour booster sessions over 3 months following training	6 months 14 months 26 months	Brief Cognitive Test Performance [MMSE] Memory [RBMT] [BVMT, Delayed Recall] [HVLT, Delayed Recall]
Park 2009[23] RCT South Korea High	129	Adults age 65 and over without clinically significant diseases Age, Mean (SD) 78.3 (6,22) 93% Female Race NR Years Education, Mean (SD) 4.62 (4.33) MMSE, Mean (SD) 22.14 (4.61)	Cognitive training program -12, 60-minute sessions followed by an observational period	Delayed cognitive training program -8 weeks of observation followed by cognitive training program	24 weeks	Brief Cognitive Test Performance [MMSE]
Slegers 2009[24] RCT Netherlands High	191	Healthy older adults with no prior computer experience Age NR	Small group practice with personal computer following by at home practice with a personal	No training/no intervention	12 months	Brief Cognitive Test Performance [Cognitive Failures Questionnaire] Executive/Attention/Processing Speed [Letter-Digit Substitution Test] [SCWT]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
		Sex NR Race NR Education NR MMSE, Mean (SD) 28 (1.4)	computer with at home assignments -4 hour training sessions over 2 weeks followed by home practice over 12 months			Memory [Visual Verbal Learning Test] Motor [Motor Choice RT]
Buiza 2008[25] RCT Spain High	238	Adults age 65 and over without cognitive impairment Age, Mean (SD) 74 (8) 73% Female Race NR Education NR Baseline Cognition NR	Structured and unstructured cognitive training with and without information on well-being –Weekly sessions with 180 sessions over 2 years	No training (regular daily activities)	1 year 2 years	Executive/Attention/Processing Speed [Abstraction] [TMT A] [Pho-Phonetic Fluency Execution] [Ideomotor Praxia] Memory [Immediate Memory, WMS] [Recent Logical Execution Memory, AVLT] [Short Term Memory] [Working Memory] Language [Ideomotor Praxia]
Buschkuehl 2008 RCT Switzerland High	39	High-functioning without any severe psychiatric problems Age, Mean (SD) 80 (3.3) 59% Female Race NR Education NR Baseline Cognition NR	Working memory training -45 minute sessions, 2 sessions/week for 12 weeks	Physical training with an eccentric bicycle ergometer -45 minute sessions, 2 sessions/week for 12 weeks	1 year	Executive/Attention/Processing Speed [DSST] Memory [Verbal Free Recall] [Visual Free Recall] Visuospatial [Block-Span Task]
Yesavage 2008[26] RCT US High	168	Community-dwelling adults aged 55-90 with a MMSE score between 24 and 30 Age, Mean (SD) 65 (8) 52% Female Race NR Education, Mean (SD) 16.3 (2.3) MMSE, Mean (SD)	Daily dose of 5 mg of Donepezil for 6 weeks, then increased to 10mg daily for 46 weeks; 2 weeks of cognitive training at weeks 13-14	Placebo and 2 weeks of cognitive training at weeks 13-14	1 year	Executive/Attention/Processing Speed [DSST] Memory [Word List Recall] [Name-Face Recall] [Logical Memory I Score] [Logical Memory II Score]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
		28.6 (1.2)				

AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; BVMT=Brief Visuospatial Memory Test; BVRT=Benton Visual Retention Test; CLOX-1=Clock Drawing Test; COWAT=Controlled Oral Word Association Test; DS=Digit Span (Forward and/or Backward); DVT=Digit Vigilance Test; FCSRT=Free and Cued Selective Reminding Test; HVLT=Hopkins Verbal Learning Test; MCI=mild cognitive impairment; MMSE=Mini-Mental Status Examination; N=sample size; PALS=Paired Association Learning Test; RBANS=Repeatable Battery for Neuropsychological Status; RBMT= Rivermead Behavioral Memory Test; RCFT=Rey-Osterrieth Complex Figure Test; RCT=randomized controlled trial; RoB=risk of bias; RT=Reaction Time; SCWT=Stroop Color Word Test; SD=standard deviation; SDMT=Symbol Digit Modalities Test; SOE=strength of evidence; TMT=Trail Making Test (Part A and/or B); UFOV=Useful Field of View; US=United States;

Appendix Table F6. Summary risk of bias assessments: other cognitive training trials in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Corbett 2015	High	Suspected selection bias due to process for participant recruitment and attrition bias due to attrition rate of over 40%.
Anderson 2014	High	Process for randomization is unclear and attrition rate is 22% with no analysis to address potential bias.
Lampit 2014		Attrition rate is 31% with no analysis to address potential bias.
Stine-Morrow 2014[12]	Medium	Process for randomization is unclear with potential attrition bias.
Anguera 2013	High	Suspected selection, attrition, and detection bias.
Borness 2013	High	Process for randomization is unclear and attrition rate is 35% with no analysis to address potential bias.
Carretti 2013[13]	Medium	Process for randomization is unclear with potential performance bias.
Miller 2013[14]	Medium	Process for randomization is unclear with potential attrition bias.
Wolinsky 2013[15]	Low	No suspected biases
Cheng 2012[16]	High	Potential attrition bias with attrition rate of 40%.
Mortimer 2012[17]	High	Potential selection bias due to process for randomization
Szelag 2012[18]	High	Potential selection and attrition bias.
Evers 2011[19]	High	Potential selection, attrition, and performance bias.
Borella 2010[20]	High	Process for randomization is unclear and potential detection bias.
Klusmann 2010[21]	Medium	Process for randomization is unclear with potential attrition bias.
McDougall 2010[22]	High	Potential attrition and reporting bias.
Park 2009[23]	High	Process for randomization is unclear with potential attrition and reporting bias.

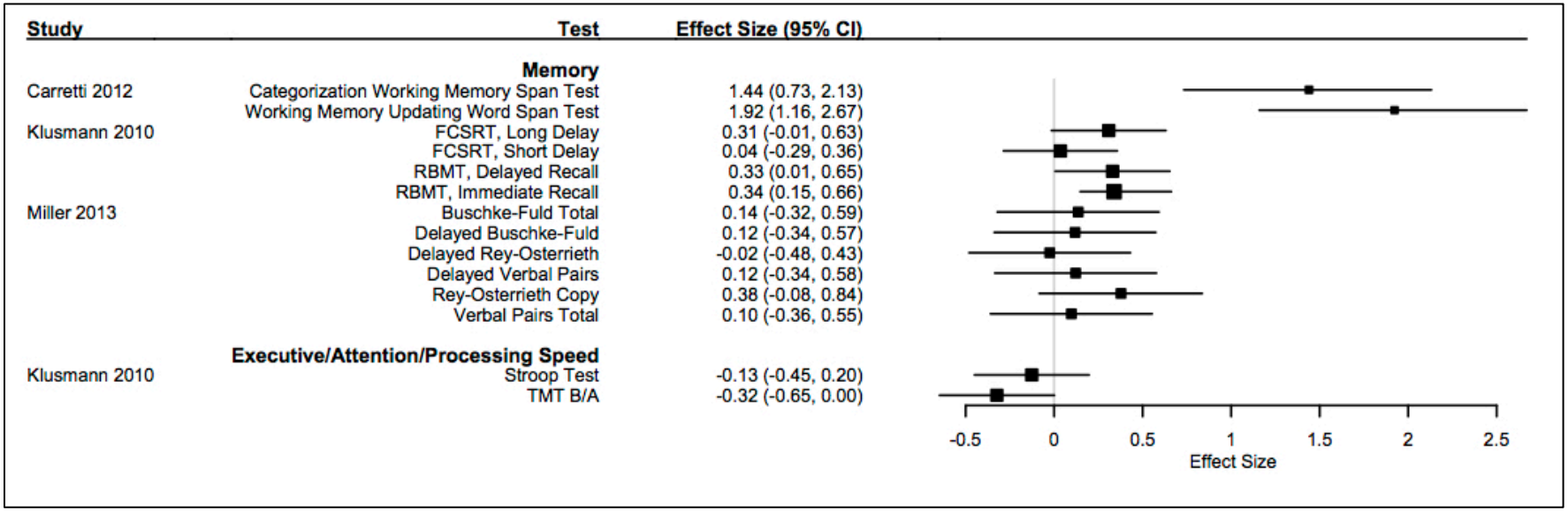
Study	Overall Risk of Bias Assessment	Rationale
Slegers 2009[24]	High	Potential reporting bias and selection bias due to process for selecting participants.
Buiza 2008[25]	High	Potential attrition, detection, and reporting bias.
Buschkuehl 2008	High	Attrition bias with an attrition rate is 44%.
Yesavage 2008[26]	High	Potential attrition bias with attrition rate of 29%.
Oswald 2006	High	Suspected selection bias due to process for randomization.

Appendix Table F7. Cognitive Training vs. Inactive Comparison, Normal Cognition: Effect Sizes for Miller 2013 (n=84), Klusmann 2010 (n=259), and Carretti 2012 (n=40)

Study	Test	Cohen's D	95% CI Lower	95% CI Upper
Miller 2013	Memory: Delayed Buschke-Fuld	0.12	-0.34	0.57
Miller 2013	Memory: Delayed Rey-Osterrieth	-0.02	-0.48	0.43
Miller 2013	Memory: Delayed Verbal Pairs, Weschler	0.12	-0.34	0.58
Miller 2013	Memory: Buschke-Fuld Total	0.14	-0.32	0.59
Miller 2013	Memory: Rey-Osterrieth Copy	0.38	-0.08	0.84
Miller 2013	Memory: Verbal Pairs Total, Weschler	0.10	-0.36	0.55
Klusmann 2010	Memory: RBMT, Immediate Recall	0.34	0.15	0.66
Klusmann 2010	Memory: RBMT, Delayed Recall	0.33	0.01	0.65
Klusmann 2010	Memory: FCSRT, Short Delay	0.04	-0.29	0.36
Klusmann 2010	Memory: FCSRT, Long Delay	0.31	-0.01	0.63
Carretti 2012	Memory: Categorization Working Memory Span Test	1.44	0.73	2.13
Carretti 2012	Memory: Working Memory Updating Word Span Test	1.92	1.16	2.67
Klusmann 2010	Executive/Attention/Processing Speed: Stroop Test	-0.13	-0.45	0.20
Klusmann 2010	Executive/Attention/Processing Speed: TMT B/A	-0.32	-0.65	0.00

CI=Confidence Interval; FCSRT= Free and Cued Selective Reminding Test; RBMT= Rivermead Behavioral Memory Test; TMT=Trail Making Test

Appendix Figure F1. Cognitive Training vs. Inactive Comparison, Normal Cognition: Plots of Effect Sizes for Miller 2013 (n=84), Klusmann 2010 (n=259), and Carretti 2012 (n=40)



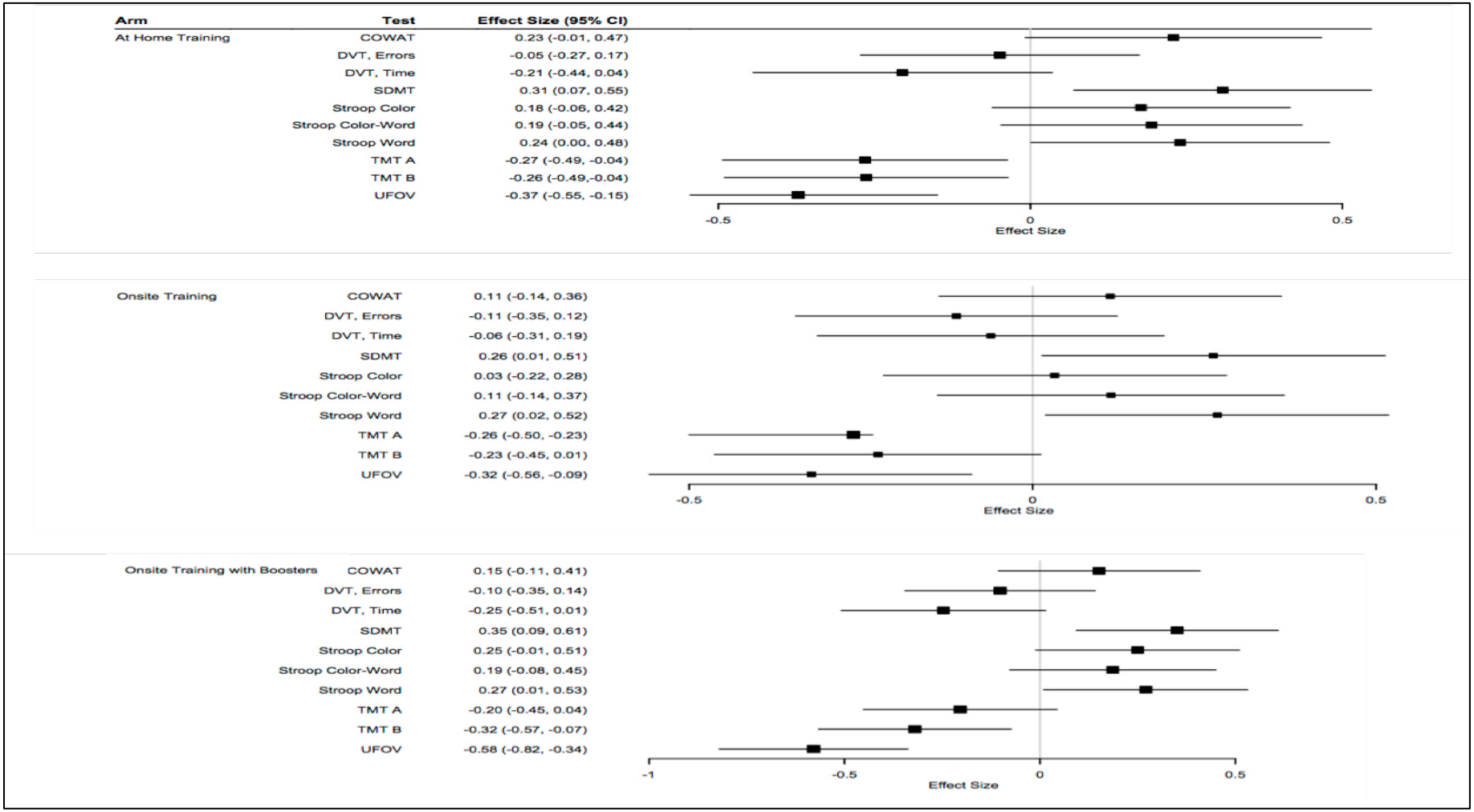
CI=Confidence Interval; RBMT= Rivermead Behavioral Memory Test; FCSRT= Free and Cued Selective Reminding Test; TMT=Trail Making Test

Appendix Table F8. Cognitive Training vs. Active Comparison, Normal Cognition: Effect Sizes for Wolinsky 2013 (n=681)

Study Arm	Test	Cohen's D	95% CI Lower	95% CI Upper
At Home Training	UFOV	-0.37	-0.55	-0.15
	TMT A	-0.27	-0.49	-0.04
	TMT B	-0.26	-0.49	-0.04
	SDMT	0.31	0.07	0.55
	Stroop Word	0.24	0.00	0.48
	Stroop Color	0.18	-0.06	0.42
	Stroop Color-Word	0.19	-0.05	0.44
	COWAT	0.23	-0.01	0.47
	DVT, Time	-0.21	-0.44	0.04
	DVT, Errors	-0.05	-0.27	0.17
Onsite Training	UFOV	-0.32	-0.56	-0.09
	TMT A	-0.26	-0.50	-0.23
	TMT B	-0.23	-0.46	0.01
	SDMT	0.26	0.01	0.51
	Stroop Word	0.27	0.02	0.52
	Stroop Color	0.03	-0.22	0.28
	Stroop Color-Word	0.11	-0.14	0.37
	COWAT	0.11	-0.14	0.36
	DVT, Time	-0.06	-0.31	0.19
	DVT, Errors	-0.11	-0.35	0.12
Onsite Training with Boosters	UFOV	-0.58	-0.82	-0.34
	TMT A	-0.20	-0.45	0.04
	TMT B	-0.32	-0.57	-0.07
	SDMT	0.35	0.09	0.61
	Stroop Word	0.27	0.01	0.53
	Stroop Color	0.25	-0.01	0.51
	Stroop Color-Word	0.19	-0.08	0.45
	COWAT	0.15	-0.11	0.41
	DVT, Time	-0.25	-0.51	0.01
	DVT, Errors	-0.10	-0.35	0.14

CI=Confidence Interval; COWAT=Controlled Oral Word Association Test; DVT=Digit Vigilance Test; SDMT= Symbol Digit Modalities Test; TMT=Trail Making Test (Parts A and B); UFOV= Useful Field of View

Appendix Figure F2. Cognitive Training vs. Active Comparison, Normal Cognition: Plots of Effect Sizes for Wolinsky 2013 (n=681)



CI=Confidence Interval; COWAT=Controlled Oral Word Association Test; DVT=Digit Vigilance Test; SDMT= Symbol Digit Modalities Test; TMT=Trail Making Test (Parts A and B); UFOV= Useful Field of View

Appendix Table F9. Characteristics of eligible studies: other cognitive training trials in adults with MCI

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Jeong 2016 RCT South Korea High	195	Adults age 50-85 diagnosed with aMCI using Peteresen criteria Age, Mean (SD) 70.3 (11) 63% Female Race NR Education, Mean (SD) 9.8 (4.4) MMSE, Mean (SD) 25.7 (2.5)	Group-based cognitive intervention -90 minute sessions, 2 times/week for 12 weeks	Wait list control	6 months	Diagnosis [CDR, Sums of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [Executive Function Composite] Memory [Logical Memory Composite] [Working Memory Composite] [Prospective Memory Test]
Jeong 2016 RCT South Korea High	197	Adults age 50-85 diagnosed with aMCI using Peteresen criteria Age, Mean (SD) 70.3 (11) 63% Female Race NR Education, Mean (SD) 9.8 (4.4) MMSE, Mean (SD) 25.7 (2.5)	Home-based cognitive intervention that invovlved homework materials (memory tasks) to be completed 5 days/week for 12 weeks	Wait list control	6 months	Diagnosis [CDR, Sums of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [Executive Function Composite] Memory [Logical Memory Composite] [Working Memory Composite] [Prospective Memory Test]
Lam 2015[27] RCT China High	277	Chinese older adults with MCI (presence of subjective cognitive complaints and objective impairments in cognitive function) Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR	Cognitive and mind-body exercises -1 hour sessions 3 times/week	Cognitively demanding activities (e.g., reading and discussing news, board games) –At least 3 sessions/weeks	8 months 12 months	Diagnosis [CDR, Sums of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Chinese Version] Memory [Delayed Recall] Language [CVFT]

Study Design Country RoB	**N=**	**Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition**	**Intervention Mode Components Frequency Duration**	**Comparison Mode Components Frequency Duration**	**Outcome timing**	**Outcome Domain [Instrument]**
		Education Level, Mean (SD) 3.9 (3.6) ADAS-cog, Mean (SD) 11.5 (3.3)				
Moro 2015 Crossover RCT Italy High	30	Adults with MCI diagnosied with Mayo criteria Age, Mean (SD) 74.8 (6.7) Sex NR Race NR Education, Mean (SD) 9.6 (4) MOCA, Mean (SD) 24.4 (3.7)	Individualized cognitive training program for 6 months followed by 6 months of no intervention - 2 sessions/week for 2 months followed by 1 sesssion/week for 4 months	No intervention for 6 months followed by 6 months of an individualzed cognitive training program -2 sessions/week for 2 months followed by 1 sesssion/week for 4 months	6 months 12 months	Brief Cognitive Test Performance [MOCA] Executive/Attention/Processing Speed [TMT B/A] [Tower of London] [Dual Task] [Attention Elevator Test] Memory [RBMT] [Listening Span Test] Language [Comprehension, Aachener Aphasie Test] [Denomination, Aachener Aphasie Test] [Repetition, Aachener Aphasie Test]
Vidovich 2015[28] RCT US Low (52 weeks) High (104 Weeks)	150	Adults age 65 years and older with MCI Age, Mean (SD) 75 (6) 54% Female 80% With High School Education Baseline Cognition NR	Cognitive activity training strategy program (attention, memory, and executive processes) -10, 90-minute sessions/week over 5 weeks; Booster telephone call at 6 months	Education about healthy aging -10, 90-minute sessions/week over 5 weeks; Booster telephone call at 6 months	52 weeks 104 weeks	Brief Cognitive Test Performance [CAMCOG-R Score] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [DS Total Score] [TMT A] [TMT B] [Symbol Search, Items Completed)] [COWAT] Memory [CVLT-II Total Recall] [CVLT-II Short Delay Free Recall] [CVLT-II Long Delay Free Recall] Language [COWAT]
Fiatarone Singh 2014[29] RCT Australia High	51	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) -100 minutes 2 days/week for 6 months	Sham cognitive training and sham exercise	6 months 18 months	Multidomain Neuropsychological Test Performance [ADAS-Cog] [Global Cognition Domain Composite] Executive/Attention/Processing Speed [WAIS Similarities] [WAIS Matrices] [COWAT] [Executive Function Domain Composite] [SDMT]

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome timing**	**Outcome** **Domain [Instrument]**
		MMSE, Mean (SD) 27 (1)				Memory [List learning Memory Sum from ADAS-Cog] Memory [BVRT] [Logical Memory, Immediate] [Logical Memory, Delayed] [Memory Domain Composite] Language [Category Fluency, Animal Naming] [COWAT]
Kwok 2013[30] RCT China Medium	223	Chinese adults aged 65 and over with subjective memory complaints Age, Mean (SD) 75 (6) 85% Female Race NR 70% Below or at primary level education MMSE. Mean (SD) 25.6 (2.6)	Cognitive therapy delivered by an occupation therapist 1 time/week, 1.5 hours each session for 12 weeks	Health-related educational lectures for 12 weeks, delivered by occupational therapist	12 months	Executive/Attention/Processing Speed [Attention Composite] [Initiation/Perseveration] [Conceptualization] Memory [Memory Composite]
Rojas 2013[31] RCT Argentina High	46	Adults with MCI based on Petersen's criteria Age, Mean (SD) 74 (10.7) 43% Female Race NR Education Level, Mean (SD) 10.54 (3.8) MMSE. Mean (SD) 27.3 (2)	Group cognitive stimulation training sessions and cognitive training –120 minutes/week over 6 months	Routine treatment with monthly consultations with doctor over 6 months	1 year	Diagnosis [CDR] Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Similarities and Matrix Reasoning] [TMT A] [TMT B] [DS Forward] [DS Backward] Memory [Signoret's Memory Battery] Language [BNT] [Verbal Fluency] [Vocabulary, WAIS] Visuospatial [Block Design]
Buschert 2012[32] Forster 2011[33] RCT Germany	24	Participants with aMCI based on Petersen's criteria Age, Mean (SD)	Group-based formal mnemonic memory training and informal cognitive and social engagement	Exercises of isolated, sustained attention – Monthly sessions for 8 months followed by	15 months 28 months	Diagnosis [Conversion to Alzheimer's Disease] Biomarker [FDG-PET Reuptake] Brief Cognitive Test Performance [MMSE]

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome timing**	**Outcome** **Domain [Instrument]**
Medium		73 (6.6) 55% Male Race NR Years Education, Mean (SD) 12.8 (5) MMSE, Mean (SD) 26.3 (2)	activities -120 minutes/week for 6 months	cross-over to intervention		Multidomain Neuropsychological Performance [ADAS-Cog] Executive/Attention/Processing Speed [TMT A/B] Memory [RBANS Memory] [RBANS, Story Recall]
Herrera 2012[34] RCT France Medium	22	Adults with a MCI based on Petersen's criteria Age, Mean (SD) 77 (1.71) 50% Female Race NR 14% With More than Secondary School MMSE. Mean (SD) 27.4 (0.5)	Computer-based memory and attention training -24, 1-hour sessions over 12 weeks	Cognitive activities (e.g., organizing lists, reading comprehension -24, 1-hour sessions over 12 weeks	6 months	Executive/Attention/Processing Speed [DS Forward] [DS Backward] Memory [Doors Recognition Subtest, Set A] [Doors Recognition Subtest, Set B] [DMS48 Test] [BEM-144 Word List Recall] [16-Item Free and Cued Reminding Test] [MMSE, Recall of 3 Words] [RCFT, Recall]
Moro 2012[35] RCT Italy High		Adults with a MCI Age, Mean (SD) 71 (8) Sex NR Race NR Education, Mean (SD) 10 (3.5) Baseline Cognition NR	Individual cognitive training sessions- 3 sessions/week for one month. 1 session/week (at home with support of caregiver) for the subsequent 5 months.	No intervention for 6 months (crossover design)	6 months 12 months	Executive/Attention/Processing Speed [Attentional Matrices] [TMT A] [Bourdon Test] [Verbal Span] [Tower of London] [Analogies] [SCWT] [TMT B/A] Memory [AVLT, Immediate Recall] [AVLT, Delayed Recall)] [Omissions] [False Recognitions] [Listening Span Test] [Story Recall] Language [CVFT]
Rapp 2002[36] RCT US Medium	19	Older adults meeting criteria for MCI based on Petersen's criteria Age, Mean (SD) 74 (6.8) 58% Female	Memory training and education –Six weekly, 2 hour group meetings with homework assignments	No memory education or training (no intervention)	6 months	Memory [Word List, Immediate] [Word List Delayed] [Shopping List Immediate] [Shopping List Delayed] [Names and Faces Immediate] [Names and Faces Delayed] [Paragraph, Immediate] [Paragraph, Delayed]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		95% White 37% With Some College MMSE. Mean (SD) 27.6 (1.7)				

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; BVRT=Benton Visual Retention Test; CAMCOG=Cambridge Cognition Examination; CDR=Clinical Dementia Rating; COWAT=Controlled Oral Word Association Test; CVFT=Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); MCI=mild cognitive impairment; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; N=sample size; NR=not reported; RBMT= Rivermead Behavioral Memory Test; RCFT=Rey-Osterrieth Complex Figure Test; RCT=randomized controlled trial; RoB=risk of bias; RT=Reaction Time; SCWT=Stroop Color Word Test; SD=standard deviation; SOE=strength of evidence; TMT=Trail Making Test (Part A and/or B); UFOV=Useful Field of View; US=United States; VP=Verbal Proficiency; VR=Visual Reproduction; VRM=Verbal Recognition Memory; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table F10. Summary risk of bias assessments: other cognitive training trials in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Jeong 2016	High	Attrition rate is 33% with no analysis to address potential bias.
Lam 2015[27]	High	Potential selection bias with attrition greater than 21%
Moro 2015	High	Suspected selection bias, unclear attrition, and suspected detection bias.
Vidovich 2015[28]	Low (52 Weeks) High (104 weeks)	Attrition rate greater than 21% at 104 weeks with no analysis to address potential bias.
Fiatarone Singh 2014[29]	High	Potential reporting bias.
Kwok 2013[30]	Medium	Potential selection, attrition, and performance bias.
Rojas 2013[31]	High	Potential selection bias with an attrition rate of 35%.
Buschert 2012[32] Forster 2011[33]	Medium	Process for randomization is unclear.
Herrera 2012[34]	Medium	Process for randomization is unclear with potential detection bias.
Moro 2012[35]	High	Potential selection, detection, and performance bias.
Rapp 2002[36]	Medium	Process for randomization unclear.

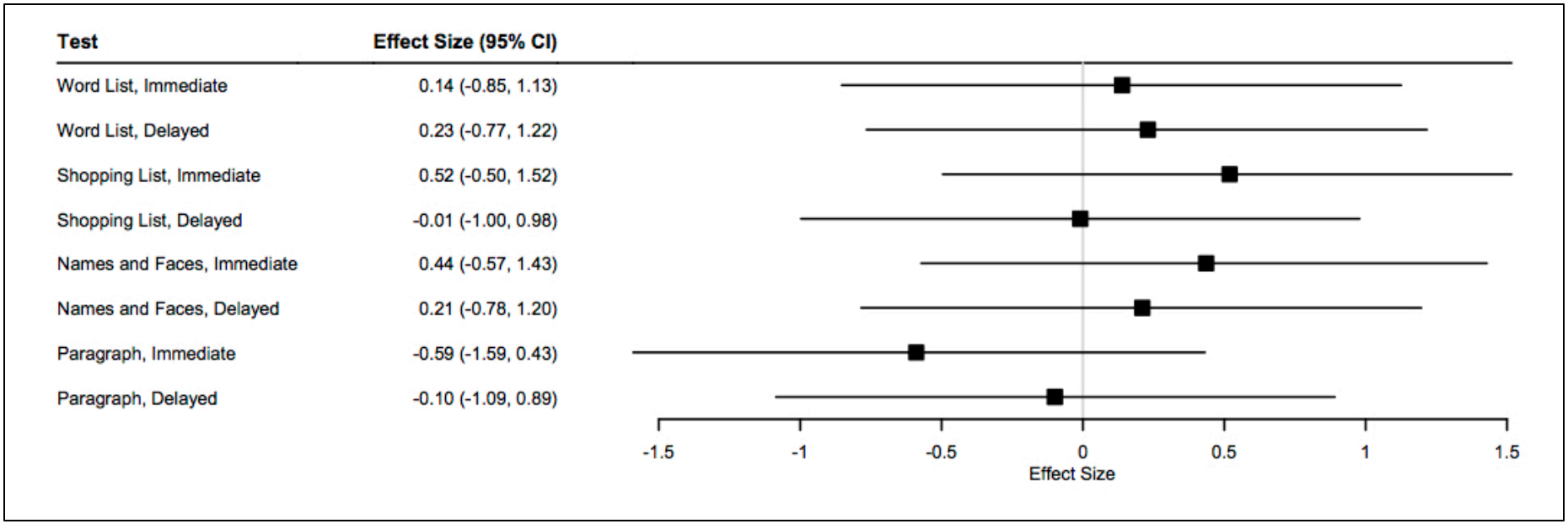
MCI=mild cognitive impairment

Appendix Table F11. Cognitive Training vs. Inactive Comparison, MCI: Effect Sizes for Rapp 2002 (n=19)

Test	Cohen's D	95% CI Lower	95% CI Upper
Word List, Immediate	0.14	-0.85	1.13
Word List, Delayed	0.23	-0.77	1.22
Shopping List, Immediate	0.52	-0.50	1.52
Shopping List, Delayed	-0.01	-1.00	0.98
Names and Faces, Immediate	0.44	-0.57	1.43
Names and Faces, Delayed	0.21	-0.78	1.20
Paragraph, Immediate	-0.59	-1.59	0.43
Paragraph, Delayed	-0.10	-1.09	0.89

CI=confidence interval; MCI=mild cognitive impairment; n=sample size

Appendix Figure F3. Cognitive Training vs. Inactive Comparison, MCI: Plot of Effect Sizes for Rapp 2002 (n=19)



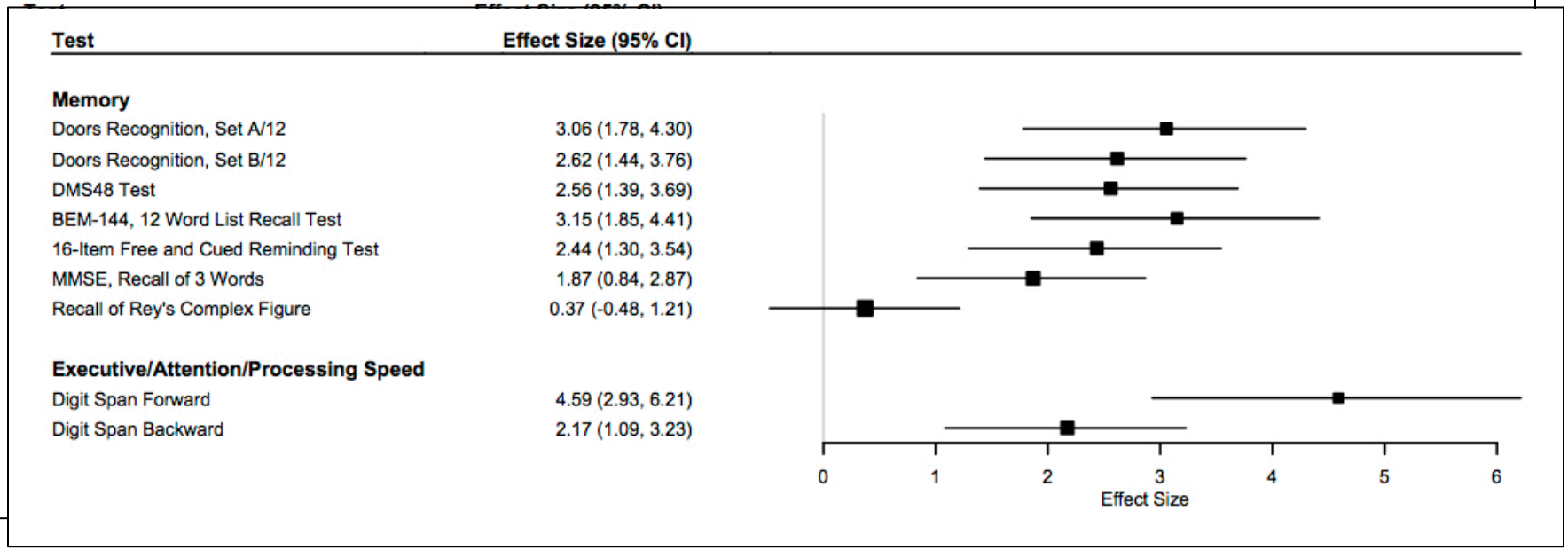
CI=confidence interval; MCI=mild cognitive impairment; n=sample size

Appendix Table F12. Cognitive Training vs. Active Comparison, MCI: Effect Sizes for Herrera 2012 (n=22)

Test	Cohen's D	95% CI Lower	95% CI Upper
Memory: Doors recognition subtest, Set A/12	3.06	1.78	4.30
Memory: Doors recognition subtest, Set B/12	2.62	1.44	3.76
Memory: DMS48 test (recognition score)	2.56	1.39	3.69
Memory: BEM-144 12-Word-List Recall Test	3.15	1.85	4.41
Memory: 16-Item Free and Cued Reminding Test	2.44	1.30	3.54
Memory: MMSE, Recall of 3 Words	1.87	0.84	2.87
Memory: Recall of Rey's Complex Figure	0.37	-0.48	1.21
Executive/Attention/Processing Speed: Digit Span Forward	4.59	2.93	6.21
Executive/Attention/Processing Speed:Digit Span Backward	2.17	1.09	3.23

CI=confidence interval; BEM-144=Batterie d'Efficience Mnesique 144; DSM48=Delayed Matching-to-Sample Task; MMSE=Mini-Mental Status Examination; n=sample size

Appendix Figure F4. Cognitive Training vs. Active Comparison, MCI: Plot of Effect Sizes for Herrera 2012 (n=22)



CI=confidence interval; BEM-144=Batterie d'Efficience Mnesique 144; DSM48=Delayed Matching-to-Sample Task; MMSE=Mini-Mental Status Examination; n=sample size

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Appendix G. Physical Activity Interventions

Appendix Table G1. Characteristics of eligible studies: physical activity interventions vs. inactive controls in adults with normal cognition

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Multicomponent Physical Activity	Bun 2015[1] Observational Japan High	1268	Cognitively normal, community-dwelling volunteers aged 65 Age, Mean (SD) 72.8 (5.1) 42% Female Race NR Years Education, Mean (SD) 10.55 (2.6) Baseline Cognition NR	Stretching, massaging, ball exercise, and easy dancing -60 minute sessions 6 times/month for 2 years	No Intervention or Nutritional supplementation (n-3 polyunsaturated fatty acid, Ginkgo biloba, leaf dry extracts, and 84 mg of lycopene) for 3 years	3 years 7 years	Diagnosis [Incident Dementia and Alzheimer's Disease, DSM-III-R and and NINCDS-ADRDA Criteria]
	Sink 2015[2] RCT USA Medium	1635	Sedentary adults without a diagnosis of dementia or significant cognitive impairment aged 70 to 89 57% aged 70 to 79 43% aged 80 to 89 67% Female 76% White	Individual physical activity training intervention focused on walking, strength, flexibility, and balance -2 center-based visits/week and 3-4 home-based activities/week for 2 years	Group health education workshops - 1 workshop/week for 26 weeks, at least once a month after for 2 years	NP battery: 2 years Computer battery: 18 or 30 months depending on enrollment	Diagnosis [Incident Dementia, Panel of Clinical Experts] [Incident MCI, Panel of Clinical Experts] [Incident MCI or Dementia, Panel of Clinical Experts] Multidomain Neuropsychological Test Performance [Composite] Executive/Attention/Processing Speed [DSST] [N-back Task, 1-back] [N-back Task, 2-back] [Eriksen Flanker Task, Congruent] [Eriksen Flanker Task, Incongruent] [Eriksen Flanker Task, Composite] [Task Switching Exercise, No] [Task Switching Exercise, Yes] Memory [HVLT, Immediate Word Recall]

			67% With a College Education 3MS, Mean (SD): 91.7 (5.4)				[HVLT, Delayed Word Recall] [HVLT, Composite]
	Napoli 2014[3] RCT US Medium	53	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White Years of Education, Mean (SD) 16.3 (3.7) 3MSE, Mean (SD) 95.7 (0.8)	Aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year	Information about healthy diet (not allowed to participate in any exercise program)	1 year	Brief Cognitive Test Performance [3MSE] Executive/Attention/Processing Speed [TMT A] [TMT B] Memory [Word List Fluency]
	Klusmann 2010[4] Evers 2011[5] RCT Germany High	167	Women age 70 and over with no more than 4 errors on the MMSE Age, Mean (SD) 73.6 (4.2) 100% Female Race NR Years of Education, Mean (SD) 12 (2.6) MMSE, Mean (SD) 28.78 (0.96)	Aerobic, endurance, strength and flexibility training, and balance and coordination training -90 minute sessions for 6 months	Inactive control (live their habitual life)	6 months	Executive/Attention/Processing Speed [SCWT] [TMT B/A] Memory [RBMT, Immediate] [RBMT, Delayed Recall] [FCSRT, Short Delay] [FCSRT, Long Delay] Language [Semantic Verbal Fluency]
	Rosano 2010[6] RCT US High	30	Sedentary older adults Age, Mean (SD) 81.1 (3.36) 40% Female Race NR	Aerobic, strength, balance, and flexibility exercises -150 minutes per week for 1 year	Successful aging sessions –Weekly sessions for 26 weeks followed by monthly sessions for duration of study	2 years	Biomarker [MRI] Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DSST]

			43% Completed High School or Equivalent MMSE, Mean (SD) 27.7 (2)				
	Taylor-Pillae 2010[7] RCT US Medium-6 mo High-12 mo	95	Sedentary adults aged 60 years or older without severe cognitive impairment Age, Mean (SD) 69.0 (5.8) 70% Female 85% White Years of Education, Mean (SD) 16.1 (2.1)	Western Exercise: Endurance, resistance/strength, and flexibility exercises- 60 minutes classes 2.times/week and home based exercise 3 times/week for 6 months, 1 class-based session/week and 3 home-based exercise sessions for the remaining 6 months	Healthy aging classes on topics including health eating, elder law, and foot and eye care - 90 minute classes 1 time/week for 6 months	6 months 12 months	Executive/Attention/Processing Speed [DS Forward] [DS Backward] Language [Animal Naming]
	Williamson 2009[8] (early results Sink 2015)[2] RCT US Medium	102	Sedentary adults aged 70-89 years with a MMSE score of 21 or more. Age, Mean (SD) 77.4 (4.3) 70.6% Female 81% White 77% with more than a high school education 3MS, Mean (SD) 90.3 (6.4)	Aerobic (walking), strength, balance, and flexibility exercises - 60 minute center-based sessions 3 times/week for 2 months -60 minute center-based sessions 2 times/per week and home-based exercise (endurance, strengthening, flexibility) at least 3 times/week for 4 months	Successful aging health education – Weekly small group sessions for 26 weeks -Monthly small group sessions for 26 weeks	12 months	Brief Cognitive Test Performance [3MS] Executive/Attention/Processing Speed [SCWT] Memory [DSST] [RAVLT]
	Liu-Ambrose 2008[9] RCT Australia 2008	74	Community-dwelling men and women age 70 years and older who attended a falls clinic Age, Mean (SD) 82.3 (6.3) 69% Female Race NR	Home-based balanced and strength training program 3 times/week for 30 minutes and and walking 2 times/week for 6 months	Guideline based-care for fall prevention	6 months	Executive/Attention/Processing Speed [TMT B] [SCWT (Color-Word)] [DS Backward]

			Education NR MMSE, Mean (SD) 28 (1.8)				
	Oswald 200610 RCT Germany High	135	Adults age 75 and older without functional cognitive or physical decline Age, Mean (SD) 79.5 (3.5) 64.8% Female 58.9% With Secondary School Education or Higher	Physical training for balance, perceptual, and motor coordination and flexibility = 30, 45 minute sessions	No intervention for duration of study	5 years	Multidomain Neuropsychological Test Performance [Composite]
	Williams 1997[11] RCT Austrailia High	374	Community-dwelling women at least 60 years old Age, Mean (SD) 71.7 (5.4) 100% Female Race NR Formal Education, Mean (SD) 9.5 (2.0) Baseline Cognition NR	Low intensity aerobic, stretching, and balance and strengthening exercises -1 hour sessions, 2 times/week for 10-12 months	Inactive control group (no organized activity)	1 year	Executive/Attention/Processing Speed [DS, WAIS] [Picture Arangement, WAIS] [Cattell's Matrices]
Resistance Training	van de Rest 2014[12] RCT Netherlands Medium	62	Frail and pre-frail adults age 65 and over Age, Mean (SD) 79 (8) 61% Female Race NR 44% With Higher Education MMSE, Mean (Range)	Resistance-type exercise program and placebo -2 sessions/week with personal supervision for 24 weeks	Usual Care and placebo for 24 weeks	24 weeks	Executive/Attention/Processing Speed [Executive Functioning Composite] [DS Forward] [DS Backward] [TMT A] [TMT B/A] [SCWT (Test 1)] [SCWT (Test 2)] [SCWT (Interference)] [Finger Precuing, Reaction Time Uncued] [Finger Precuing, Reaction Time Cued] [Information Processing Speed Composite] Memory [Word Learning Test, Immediate Recall-75 Words] [Word Learning Test,

			28 (26-30)				Delayed Recall-15 Words] [Word Learning Test, Decay] [Word Learning Test, Recognition, 30 Words] [Attention and Working Memory Composite] Language [Word Fluency, Animals] [Word Fluency, Letter P]
	Hotting 2012[13] RCT Germany High	66	Healthy, sedentary men and women aged 40-56 years Age, Mean (SD) 47.8 (4.35) 82% Female Race NR Education NR Baseline Cognition NR	Stretching and coordination training exercises -60 minute sessions 2 times/week for 6 months	Sedentary control (no exercise intervention for 6 months)	6 months	Executive/Attention/Processing Speed [D2 Test] [Zahlenverbindungstest, German] [SCWT] Memory [AVLT, German] Visuospatial [Leistungsprufystem, Subtests 8 and 9]
	Komulainen 2010[14] RCT Finland High	472	Men and women age 55 to 74 Age, Mean (SD) 66.3 (5.3) Sex NR Race NR Education, Mean (SD) 11.3 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, strength training program either 2 times/week or 3 times per week	General health advice on diet and physical activity	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
	Cassilhas 2007[15] RCT Brazil Medium	43	Sedentary males age 65-75 with a minimum MMSE score of 24 Age, Mean (SD) 68.2 (0.77) 100% Male Race NR Education NR Baseline Cognition NR	High intensity resistance training -60 minute sessions, 3 times/week for 24 weeks	Warm-up and stretching at center once a week for 24 weeks	24 weeks	Executive/Attention/Processing Speed [DS Forward] [DS Backward] [Corsi Block-Tapping, Forward] [Corsi Block-Tapping, Backward] [Corsi Block-Tapping, Similarities] [Toulouse-Pieron, Cancellations Numbers] [Toulouse-Pieron, Errors] Memory [RCFT, Copy] [RCFT, Immediate Recall]

	Cassilhas 2007[15] RCT Brazil Medium	42	Sedentary males age 65-75 with a minimum MMSE score of 24 Age, Mean (SD) 68.2 (0.77) 100% Male Race NR Education NR Baseline Cognition NR	Moderate intensity resistance training -60 minute sessions, 3 times/week for 24 weeks	Warm-up and stretching at center once a week for 24 weeks	24 weeks	Executive/Attention/Processing Speed [DS Forward] [DS Backward] [Corsi Block-Tapping, Forward] [Corsi Block-Tapping, Backward] [Corsi Block-Tapping, Similarities] [Toulouse-Pieron, Cancellations Numbers] [Toulouse-Pieron, Errors] Memory [RCFT, Copy] [RCFT, Immediate Recall]
	Lachman 2006[16] RCT US Medium	210	Sedentary, community-residing older adults with at least one disability Age, Mean (SD) 75.3 (7.4) 77.6% Female 93% White Education, Mean (SD) 14.3 (2.7) Baseline Cognition NR	Video tape of 35 minutes of resistance training -3 times/week for 6 months	No intervention for duration of study	6 months	Executive/Attention/Processing Speed [DS Backward]
Aerobic Training	Antunes 2015[17] RCT Brazil Medium	46	Healthy, sedentary men with minimum MMSE score of 24 Age, Mean(SD): 66.94 (4.65) Race NR Education NR Baseline Cognition NR	Aerobic physical fitness regime with supplementary stretching and joint flexibility exercises -60 minute sessions 3 times/week for 6 months	Maintain regular everyday activities. Instructed to not start a physical exercise program for study duration	6 months	Executive/Attention/Processing Speed [Picture Arrangement, WAIS] [Corsi Block-Tapping, Forward] [Corsi Block-Tapping, Backward] Memory [Verbal Paired Associates, Trial 1, Easy Pair] [Verbal Paired Associates, Trial 1, Hard Pair] [Verbal Paired Associates, Trial 2, Easy Pair] [Verbal Paired Associates, Trial 2, Hard Pair] [Verbal Paired Associates, Trial 3, Easy Pair] [Verbal Paired Associates, Trial 3, Hard Pair] [Verbal Paired Associates, Recall Test, Easy Pair] [Verbal Paired Associates, Recall Test, Hard Pair] [Free Word Recall, Total Words Recalled Non-Semantic] [Free Word Recall, Total Words Recalled Semantic] [Free Word

							Recall, Intrusions] [Free Word Recall, Repetitions] [Free Word Recall, Preservations]
	Satoh 2014[18] RCT Japan High	79	Physically and psychologically healthy residents age 65 and older Age, Mean (SD) 72.9 (4.6) 64% Female Race NR Years Education, Mean (SD) 10.4 (1.8) MMSE, Mean (SD) 27.6 (2.2)	Physical exercise -40, 60-minute exercise sessions over 1 year	Inactive control group (no intervention)	1 year	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Raven's Coloured Progressive Matrices] [TMT A] [TMT B] [Word Fluency] Memory [Logical Memory-I] [Logical Memory-II]
	Mortimer 2012[19] RCT China High	75	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean	Walking-50 minute group sessions 3 times/week for 40 weeks	Inactive control with 4 check-in calls over 40 weeks	40 weeks	Biomarker [Whole Brain Volume, % of Total Intracranial Volume)] Multidomain Neuropsychological Test Performance [Mattis Dementing Rating Scale, Total Score)] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [SCWT (Word)] [SCWT (Color)] [SCWT (Color-Word)] [WAIS Similarities] [TMT A] [TMT B] [Mattis Attention Score] [Mattis Initiation Score] [Mattis Conceptualization Score]

			(SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)				Memory [AVLT, Immediate Recall] [AVLT, Delayed Recall] [AVLT, Delayed Recognition] [RCFT, Copying] [RCFT, Recall] [Mattis Memory Score] Language [CVFT, Animals] [BNT] Visuospatial [Bell Cancellation Test] [RCFT, Copying] [RCFT, Recall] [CLOX-1] [Mattis Construction Score]
	Hotting 2012[13] RCT Germany High	67	Healthy, sedentary men and women aged 40-56 years Age, Mean (SD) 47.8 (4.35) 82% Female Race NR Education NR Baseline Cognition NR	Indoor cycling on stationary bikes -60 minute sessions 2 times/week for 6 months	Sedentary control (no exercise intervention for 6 months)	6 months	Executive/Attention/Processing Speed [D2 Test] [Zahlenverbindungstest, German] [SCWT] Memory [AVLT, German] Visuospatial [Leistungsprufystem, Subtests 8 and 9]
		41	Sedentary adults aged 50-72 with MMSE scores above 26 Age, Mean (SD) 59.1 (6.5) 69% Female Race NR Education, Mean (SD) 10.7 (3.5) MMSE, Mean (SD) 29.2 (2.8)	Nordic walking (intensity levels corresponding to 50–60% of maximal exertion) for 6 months	No exercise for duration of study	6 months	Memory [AVLT, German]
	Ruscheweyh 2011[20] RCT Germany Medium	42	Sedentary adults aged 50-72 with MMSE scores above 26 Age, Mean (SD) 60.3 (6.5) 65% Female Race NR Education, Mean (SD)	Gymnastics (stretching, limbering, and toning of upper and lower extremities; intensity levels corresponding to 30–40% of maximal exertion) for 6 months	No exercise for duration of study	6 months	Memory [AVLT, German]

			11.0 (3.4) MMSE, Mean (SD) 29.2 (2.8)				
	Komulainen 2010[14] RCT Finland High	470	Men and women age 55 to 74 Age, Mean (SD) 66.5 (5.3) Sex NR Race NR Education, Mean (SD) 11.4 (4.0) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, aerobic exercise program either 5 times/week for 60 min or 5 times/week for 90 min for 2 years	General health advice on diet and physical acitivity	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
	Muscari 2010[21] RCT Italy Medium	120	Healthy adults age 64-75 with a minimum MMSE of 24 Age, Mean (SD) 69.2 (2.7) 52% Male Race NR Years of Education, Mean (Range) 6.5 (5-13) MMSE, Mean (Range) 27.0 [25.9-28.0]	Group endurance exercise training (cycle ergometer, treadmill and free-body activity) -60 minute sessions 3 times/week for 1 year	Educational materials that provided suggestions to improve lifestyle. Suggestions included individualized self-administered programs to increase physical activity	12 months	Brief Cognitive Test Performance [MMSE]
	Lautenschlager 2008[22] RCT Australia Low	170	Adults reporting difficulty with memory and a MMSE score of at least 24 Age, Mean (SD): 68.7 (8.6) 51% Female Race NR Years of Education, Mean (SD)	Home-based physical activity program with behavioral intervention – At minimum 50 minutes sessions 3 times/week of moderately intense exercise for 24 weeks and a social cognitive theory-based behavioral package (workshop, manual, newsletters, and telephone calls)	Educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking. No materials on physical activity.	18 months	Diagnosis [CDR, Sum of Boxes] Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [Dsy, WAIS] [Executive Function Battery] Memory [Word List, Immediate Recall (CERAD)] [Word List, Delayed Recall (CERAD)] Language [Verbal Fluency, Delis-Kaplin

			12.4 (3.3) ADAS-Cog, Mean (SD) 7.0 (1.8)				
	Oken 2006[23] RCT US Medium	91	Generally healthy men and women age 65-85 years Age, Mean (SD) 72.3 (5.0) 74% Female 86% White Education, Mean (SD) 15.1 (2.5) Baseline Cognition NR	Walking on a track for 60 minutes once/week	Wait list control, no intervention for duration of study	6 months	Executive/Attention/Processing Speed [SCWT (Interference)] [Covert Orienting (Invalid-Valid)] [Divided Attention Threshold] [% Errors Above Threshold] [Set Shifting, Highest Shift] [Simple RT] [Choice RT] [Word List Delayed Recall] [Letter-Number Sequencing, WAIS] Memory [Word List Delayed Recall] [Letter-Number Sequencing, WAIS]
	Okumiya 1996[24] RCT Japan Medium	42	Healthy adults aged 75-87 years Age, Mean (SD) 78.8 (4.6) 57% Female Race NR Education NR MMSE, Mean (SD) 27.9 (2.6)	Aerobic exercise program -60 minutes, 2 times/week for 6 months	No exercise program for the duration of the invention	6 months	Brief Cognitive Test Performance [MMSE] [[Hasegawa Dementia Scale] Visuospatial [Visuospatial Cognitive Performance Test]
Tai Chi	Mortimer 2012[19] RCT China High	74	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD)	Tai Chi -50 minute group sessions 3 times/week for 40 weeks	Inactive control with 4 check-in calls over 40 weeks	40 weeks	Biomarker [Whole Brain Volume, % of Total Intracranial Volume)] Multidomain Neuropsychological Test Performance [Mattis Dementing Rating Scale, Total Score] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [WAIS Similarities] [TMT A] [TMT B] [SCWT (Word)] [SCWT (Color)] [SCWT (Color-Word)] [Mattis Attention Score] [Mattis Initiation Score] [Mattis Conceptualization Score] Memory [AVLT, Immediate Recall] [AVLT, Delayed Recall] [AVLT, Delayed Recognition] Memory [Mattis Memory Score] Language [CVFT, Animals] [BNT, Correct

			137.6 (7.6)				Names] [RCFT, Copying] [RCFT, Recall] Visuospatial [CLOX-1] [Bell Cancellation Test] [RCFT, Copying] [RCFT, Recall] [Mattis Construction Score]
	Nguyen 2012[25] RCT Germany High	96	Adults age 60-75 with a minimum MMSE score of 25 Age, Mean (SD) 68.98 (5.1) 50% Female Race NR 28.1% With more than 12 years of education Baseline Cognition NR	Tai Chi Exercise -60 minute sessions 2 times/ week for 6 months	Routine daily activities (instructed not to start exercise program) for study duration	6 months	Executive/Attention/Processing Speed [TMT A] [TMT B]
	Taylor-Pillae 2010[7] RCT US Medium-6 mo High-12 mo	93	Sedentary adults aged 60 years or older without severe cognitive impairment Age, Mean (SD) 69.0 (5.8) 70% Female 85% White Years of Education, Mean (SD) 16.1 (2.1)	Tai Chi -45 minutes classes 2.times/week and home based exercise 3 times/week for 6 months, 1 class-based session/week and 3 home-based exercise sessions for the remaining 6 months	Healthy aging classes on topics including health eating, elder law, and foot and eye care -90 minute classes 1 time/week for 6 months	6 months 12 months	Executive/Attention/Processing Speed [DS Forward] [DS Backward] Language [Animal Naming]

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; CDR=Clinical Dementia Rating; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; DS=Digit Span (Forward and/or Backward); DSM=Diagnostic Statistical Manual of Mental Disorders; DSST=Digit Symbol Substition Test; FCSRT=Free and Cued Selective Reminding Test; HVLT=Hopkins Verbal Learning Test; MCI=mild cognitive impairment; MMSE=Mini-Mental Status Examination; N=sample size; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RBMT= Rivermead Behavioral Memory Test; RCFT=Rey-Osterrieth Complex Figure Test; RCT=randomized controlled trial; RoB=risk of bias; RT=Reaction Time; SCWT=Stroop Color Word Test; SD=standard deviation; TMT=Trail Making Test (Part A and/or B); US=United States; WAIS=Wechsler Adult Intelligence Scale

Appendix Table G2. Characteristics of eligible studies: physical activity interventions vs. active controls in adults with normal cognition

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Resistance Training	Best 2015[26] Liu-Ambrose 2010[27] RCT Canada High	103	Women aged 65-75 years, with a MMSE score of 24 of more and a visual acutiy of at least 20/40 Age, Mean (SD) 69.6 (2.7) 100% Female Race NR 39% With a University Degree MMSE, Mean (SD) 28.6 (1.3)	Once-weekly progressive and high intensity resistance training (biceps curls, triceps extension, seated row, latissmus dorsi pull downs, leg press, hamstring curls, and calf raises; two sets of 6-8 reps)	Twice-weekly balance and tone training (stretching exercises, range of motion exercises, basic core-strength exercises including kegals, balance exercises, and relaxation techniques)	1 year 2 years	Biomarker [MRI, Cortical Gray Matter] [MRI, Cortical White Matter] [MRI, Left Hippocampus] [MRI, Right Hippocampus] Executive/Attention/Processing Speed [Latent Executive Function Composite] Memory [Memory Composite]
	Best 2015[26] Liu-Ambrose 2010[27] RCT Canada High	101	Women aged 65-75 years, with a MMSE score of 24 of more and a visual acutiy of at least 20/40 Age, Mean (SD) 69.6 (2.7) 100% Female Race NR 39% With a University Degree MMSE, Mean (SD) 28.6 (1.3)	Twice-weekly resistance training (biceps curls, triceps extension, seated row, latissmus dorsi pull downs, leg press, hamstring curls, and calf raises; two sets of 6-8 reps)	Twice-weekly balance and tone training (stretching exercises, range of motion exercises, basic core-strength exercises including kegals, balance exercises, and relaxation techniques)	1 year 2 years	Biomarker [MRI, Cortical Gray Matter] [MRI, Cortical White Matter] [MRI, Left Hippocampus] [MRI, Right Hippocampus] Executive/Attention/Processing Speed [Latent Executive Function Composite] Memory [Memory Composite]
	Hotting 2011[13] RCT Germany High	97	Healthy, sedentary men and women aged 40-56 years Age, Mean (SD) 47.8 (4.35)	Stretching and coordination training exercises -60 minute sessions 2 times/week for 6 months	Indoor cycling on stationary bikes -60 minute sessions 2 times/week for 6 months	6 months	Executive/Attention/Processing Speed [D2 Test] [Zahlenverbindungstest, German] [SCWT] Memory [AVLT, German] Visuospatial [Leistungsprufystem,

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			82% Female Race NR Education NR Baseline Cognition NR				Subtests 8 and 9]
	Cassilhas 2007[15] RCT Brazil Medium	39	Sedentary males age 65-75 with a minimum MMSE score of 24 Age, Mean (SD) 68.2 (0.77) 100% Male Race NR Education NR Baseline Cognition NR	High intensity resistance training -60 minute sessions, 3 times/week for 24 weeks	Moderate intensity resistance training -60 minute sessions, 3 times/week for 24 weeks	24 weeks	Executive/Attention/Processing Speed [DS Forward] [DS Backward] [Corsi Block-Tapping, Forward] [Corsi Block-Tapping, Backward] [Corsi Block-Tapping, Similarities] [Toulouse-Pieron, Cancellations Numbers] [Toulouse-Pieron, Errors] Memory [RCFT, Copy] [RCFT, Immediate Recall]
Aerobic Training	Eggenberger 2015[28] RCT Switzerland Medium	46	Seniors older than 70 years with an MMSE score greater than 22 Age, Mean (SD) 78.9 (5.4) 52% Female Race NR Years of Education, Mean (SD) 13.2 (1.9) MMSE, Mean (SD) 28.2 (1.4)	Virtual reality video game dancing with cognitive training -60 minute group sessions 2 times/week for 6 months	Treadmill walking with verbal memory exercise -60 minute group sessions 2 times/week for 6 months	6 months	Executive/Attention/Processing Speed [TMT A] [TMT B] [Executive Control Task] [DSST] [DS Forward] [Age Concentration Test A] [Age Concentration Test B] Memory [PALS] [Story Recall, WMS]

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
	Ferreira 2015[29] RCT Brazil High	102	Adults age 60 to 79 years with no MCI or diagnosis of dementia Age, Mean (SD) 67.1 (5.2) 87% Female Race NR MMSE, Mean (SD) 28.5 (1.5)	Supervised walking -40-50 minute sessions 3 times/ week for 6 months	Social interaction group without physical exercise or respiratory training (breathing exercises) -40-50 minute sessions 3 times/ week for 6 months	6 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DS, Vocabulary, Information, and Symbol Search, WAIS] [Corsi Block-Tapping Test] [Wisconsin Card Sorting Test] Memory [Logic Memory I and II]
	Napoli 2014[3] RCT US Medium	53	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White Years of Education, Mean (SD) 16.3 (3.7) 3MSE, Mean (SD) 95.7 (0.8)	Aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year	Diet and aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year and energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed by 6 months of weight maintenance	1 year	Brief Cognitive Test Performance [3MS] Executive/Attention/Processing Speed [TMT A] [TMT B] Memory [Word List Fluency]

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
	Mortimer 2012[19] RCT China High	74	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Walking-50 minute group sessions 3 times/week for 40 weeks	Social interaction – Meeting at community center for 1 hr 3 times/week	40 weeks	Biomarker [Whole Brain Volume, % of Total Intracranial Volume)] Multidomain Neuropsychological Test Performance [Mattis Dementing Rating Scale, Total Score] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [SCWT (Word)] [SCWT (Color)] [SCWT (Color-Word)] [WAIS Similarities] [TMT A] [TMT B] [Mattis Attention Score] [Mattis Initiation Score] [Mattis Conceptualization Score] Memory [AVLT, Immediate Recall] [AVLT, Delayed Recall] [AVLT, Delayed Recognition] [Mattis Memory Score] [RCFT, Copying] [RCFT, Recall] Language [CVFT, Animals] [BNT,Correct Names] Visuospatial [Bell Cancellation Test] [CLOX-1] [RCFT, Copying] [RCFT, Recall] [Mattis Construction Score]
	Colcombe 2011[30] RCT US High	59	Older, healthy, sedentary adults Mean Age 66.5 55% Female Race NR	Aerobic exercise (intensity based on desired peak heart rate) – 1 hour training sessions 3 times/week for 6 months	Whole body streatching and toning – 1 hour training sessions 3 times/week for 6 months	6 months	Biomarker [MRI, Gray Matter] [MRI, Regional Brain Volume]

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			Mean Education 13.8 years MMSE, Mean (SD) 29.2 (1.3)				
	Erickson 2011[31] RCT US High	120	Older adults without dementia and a score of 51 of more on the MMSE Age, Mean (SD) 66.6 (5.63) 67% Female Education NR Baseline Cognition NR	Moderate intensity walking exercise -3 days/week for 1 year	Stretching and toning exercises (muscle-toning exercises using dumbbells or resistance bands, exercises designed to improve balance, and yoga sequences) -3 days/week for 1 year	6 months 1 year	Biomarker [MRI, Hippocampal Volume] Memory [Spatial Memory Task]
	Ruscheweyh 2011[20] RCT Germany Medium	42	Sedentary adults aged 50-72 with MMSE scores above 26 Age, Mean (SD) 60.3 (6.5) 65% Female Race NR Education, Mean (SD) 11.0 (3.4) MMSE, Mean (SD) 29.2 (2.8)	Gymnastics (stretching, limbering, and toning of upper and lower extremities; intensity levels corresponding to 30–40% of maximal exertion) for 6 months	Nordic walking (intensity levels corresponding to 50–60% of maximal exertion) for 6 months	6 months	Memory [AVLT, German]
	Baker 2010[32,33] RCT US Medium	28	Individuals with abnormal glucose tolerance and normal cognitive status	Aerobic exercise (using a treadmill, stationary bicycle, or elliptical machine) -45-60 minutes sessions 4 times/week for	Stretching -45-60 minutes sessions 4 times/week for 6 months	6 months	Executive/Attention/Processing Speed [TMT B] [Task Switching] [SCWT (Interference)] [Self-Ordered Pointing Test] [Verbal Fluency]

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			Age, Mean (SD) 68.5 (6.8) 64% Female Race NR	6 months			Memory [Story Recall] [List Learning]
	Komulainen 2010[14] RCT Finland High	470	Men and women age 55 to 74 Age, Mean (SD) 66.5 (5.4) Sex NR Race NR Education, Mean (SD) 11.4 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, aerobic exercise program either 5 times/week for 60 min or 5 times/week for 90 min for 2 years	Counseling by nutritionists to modify diet to specific recommendations	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
	Komulainen 2010[14] RCT Finland High	472	Men and women age 55 to 74 Age, Mean (SD) 66.3 (5.3) Sex NR Race NR Education, Mean (SD) 11.3 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, strength training program either 2 times/week or 3 times per week	Counseling by nutritionists to modify diet to specific recommendations	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
	Smiley-Owen 2008[34] RCT US High	109	Adults age 64 or older who were npt physically active or physically fit Age, Mean (SD) 70.2 (4.7) 72% Female	Cardiovascular training 25−30 min on the aerobic exercise equipment of their choice; individualized prescriptions started at 45−60% of heart rate reserve, progressed to	Exercise training (strength, flexibility, and balance exercises) for 25−30 min -3 times week/10 months	10 months	Executive/Attention/Processing Speed [8-Choice RT Test] [SCWT] [Wisconsin Card Sort Test] [Go/No-Go Reaction Time] [Simple RT Test] [8-Choice Incompatible RT Test]

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			Race NR Education, Mean (SD) 15.9 (2.6) Baseline Cognition NR	60−70%, and were then maintained at 65−80% -3 times/week for 10 months			
	Oken 2006[23] RCT US Medium	91	Generally healthy men and women age 65-85 years Age, Mean (SD) 72.3 (5.0) 74% Female 86% White Education, Mean (SD) 15.1 (2.5) Baseline Cognition NR	Walking on a track for 60 minutes once/week	Beginner Iyengar yoga once/week for 90 minutes	6 months	Executive/Attention/Processing Speed [SCWT (Interference)] [Covert Orienting,Invalid-Valid] [Divided Attention Threshold] [% Errors Above Threshold] [Set Shifting, Highest Shift] [Simple RT] [Choice RT] [Word List Delayed Recall] [Letter-Number Sequencing, WAIS] Memory [Word list Delayed Recall] [Letter-Number Sequencing, WAIS]
	Kramer 1999[35] RCT US High	124	Sendentary adults age 60 to 75 years Age NR Sex NR Race NR Education NR Baseline Cognition NR	Walking for 6 months	Stretching and toning for 6 months	6 months	Executive/Attention/Processing Speed [Task Switching] [Response Compatability] [Stopping]
	Bluementhal 1991[36] Madden 1989[37] Crossover RCT US High	101	Sedentary adults over 60 free from coronary disease Age, Mean (SD) 67.05 (4.9) 50% Female Race NR Education, Mean	Aerobic exercise (based on a 6-bpm (beats per minute) training range equivalent to 70% maximum heart rate reserve) for 8 months. Optional aerobic intervention available for	Wait-list control for 4 months followed by aerobic exercise for 4 months. Optional aerobic intervention available for an additional 6	8 months 14 months	Executive/Attention/Processing Speed [RT Tasks] [Word-Comparison Task] [DS Forward] [DS Backward] [DSST] [TMT B] [SCWT] Memory [Short Story Module] [Randt Memory Test] [BVRT] [Selective Reminding Test] Language [Verbal Fluency]

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			(SD) 15.2 (2.4) Baseline Cognition NR	an additional 6 months.	months.		Motor [Finger Tapping Test]
Tai Chi or Yoga	Mortimer 2012[19] RCT China High	73	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Tai Chi -50 minute group sessions 3 times/week for 40 weeks	Social interaction – Meeting at community center for 1 hr 3 times/week	40 weeks	Biomarker [Whole Brain Volume, % of Total Intracranial Volume)] Multidomain Neuropsychological Test Performance [Mattis Dementing Rating Scale, Total Score] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [SCWT (Word)] [SCWT (Color)] [SCWT (Color-Word)] [WAIS Similarities] [TMT A] [TMT B] [Mattis Conceptualization Score] [Mattis Attention Score] [Mattis Initiation Score] Memory [RCFT, Copying] [RCFT, Recall] [AVLT, Immediate Recall] [AVLT, Delayed Recall] [AVLT, Delayed Recognition] [BNT, Correct Names] [Mattis Memory Score] Language [CVFT, Animals] Visuospatial [Bell Cancellation Test] [RCFT, Copying] [RCFT, Recall] [CLOX-1] [Mattis Construction Score]
	Mortimer 2012[19] RCT China High	74	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR	Tai Chi -50 minute group sessions 3 times/week for 40 weeks	Walking-50 minute group sessions 3 times/week for 40 weeks	40 weeks	Biomarker [Whole Brain Volume, % of Total Intracranial Volume)] Multidomain Neuropsychological Test Performance [Mattis Dementing Rating Scale, Total Score] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [SCWT (Word)] [SCWT (Color)] [SCWT (Color-Word)] [WAIS Similarities] [TMT A] [TMT

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)				B] [Mattis Conceptualization Score] [Mattis Attention Score] [Mattis Initiation Score] Memory [RCFT, Copying] [RCFT, Recall] [AVLT, Immediate Recall] [AVLT, Delayed Recall] [AVLT, Delayed Recognition] [BNT, Correct Names] [Mattis Memory Score] Language [CVFT, Animals] Visuospatial [Bell Cancellation Test] [RCFT, Copying] [RCFT, Recall] [CLOX-1] [Mattis Construction Score]
	Taylor-Pillae 2010[7] RCT US Medium-6 mo High-12 mo	76	Sedentary adults aged 60 years or older without severe cognitive impairment Age, Mean (SD) 69.0 (5.8) 70% Female 85% White Years of Education, Mean (SD) 16.1 (2.1)	Western Exercise: Endurance, resistance/strength, and flexibility exercises- 60 minutes classes 2.times/week and home based exercise 3 times/week for 6 months, 1 class-based session/week and 3 home-based exercise sessions for the remaining 6 months	Tai Chi -45 minutes classes 2.times/week and home based exercise 3 times/week for 6 months, 1 class-based session/week and 3 home-based exercise sessions for the remaining 6 months	6 months 12 months	Executive/Attention/Processing Speed [DS Forward] [DS Backward] Language [Animal Naming]
	Bluementhal 1991[36] Madden 1989[37] Crossover RCT US High	101	Sedentary adults over 60 free from coronary disease Age, Mean (SD) 67.05 (4.9) 50% Female Race NR Education, Mean (SD)	Yoga (60 minutes, twice a week for 4 months) followed by aerobic exercise for 4 months. Optional aerobic intervention available for an additional 6 months	Wait-list control for 4 months followed by aerobic exercise for 4 months. Optional aerobic intervention available for an additional 6 months.	8 months 14 months	Executive/Attention/Processing Speed [RT Tasks] [Word-Comparison Task] [DS Forward] [DS Backward] [Digit Symbol Subtest] [TMT B] [SCWT (Color-Word)] Memory [Short Story Module] [Randt Memory Test] [BVRT] [Selective Reminding Test] [Letter Search Task]

Physical Exercise Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			15.2 (2.4) Baseline Cognition NR				Language [Verbal Fluency] Motor [Finger Tapping Test]

3MS=Modified Mini Mental Status Examination; AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; BVMT=Brief Visuospatial Memory Test; CLOX-1=Clock Drawing Test; CVFT=Category Verbal Fluency Test; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution Test; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; N=sample size; NR=not reported; PALS=Paired Association Learning Test; RCFT=Rey-Osterrieth Complex Figure Test; RCFT=Rey-Osterrieth Complex Figure Test; RCT=randomized controlled trial; RoB=risk of bias; RT=reaction time; SCWT=Stroop Color Word Test; SD=standard deviation; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table G3. Summary risk of bias assessments: physical activity interventions in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Antunes 2015[17]	Medium	Process for randomization is unclear/poorly described.
Best 2015[26] Liu-Ambrose 2010[27]	High	Attrition rate is over 13-22% with suspected detection and reporting bias.
Bun 2015[1]	High	No randomization (participants self-selected into study arms) and attrition greater than 21%.
Eggenberger 2015[28]	Medium	Attrition rate is 20% with potential performance bias.
Ferreira 2015[29]	High	High attrition rate with suspected reporting bias.
Sink 2015[2]	Medium	Attrition 10%; potential differences in timing of certain outcomes measurements.
Napoli 2014[3]	Medium	Process for randomization is unclear and 13% attrition rate.
Satoh 2014[18]	High	Semi-randomly assigned groups and 33% attrition rate.
van de Rest 2014[12]	Medium	Attrition is 15% with potential reporting bias.
Mortimer 2012[19]	High	Suspected selection bias due to modifications post-randomization.
Nguyen 2012[25]	High	Randomization not well described with 24% attrition rate.
Colcombe 2011[30]	High	Unclear reporting of attrition with suspected detection and reporting bias.
Erickson 2011[31]	High	Unclear randomization, high attrition rate and suspected detection and reporting biases.
Hotting 2011[13]	High	Suspected selection bias due to selection procedure for control group.
Ruscheweyh 2011[20]	Medium	Attrition is 17% with potential detection bias.
Baker 2010[32, 33]	Medium	Attrition is 18% with potential reporting bias
Klusmann 2010[4] Evers 2011[5]	High	Attrition is over 25% with no analysis to address potential bias.
Komulainen 2010[14]	High	Flaw in study design related to the analysis of the data and suspected reporting bias
Muscari 2010[21]	Medium	Randomization not well described with 11% attrition rate.

Study	Overall Risk of Bias Assessment	Rationale
Rosano 2010[6]	High	Participants self-selected for inclusion for additional follow-up based on willingness to participate. High attrition rate from original study population.
Taylor-Pillae 2010[7]	High-12 mo outcomes Medium-6 mo outcomes	Randomization not well described with 21% attrition at 12 months.
Williamson 2009[8]	Medium	Potential performance and reporting bias.
Lautenschlager 2008[22]	Low	No suspected biases.
Liu-Ambrose 2008[9]	High	Attrition rate is over 21% with no analysis to address potential bias.
Smiley-Owen 2008[34]	High	Attrition rate is 27% with no analysis to address potential bias.
Cassilhas 2007[15]	Medium	Randomization not well described with potential reporting bias.
Lachman 2006[16]	Medium	Attrtion information is not reported and suspected detection bias.
Oswald 2006[10]	High	Suspected selection bias due to process for randomization.
Oken 2006[23]	Medium	Attrition rate is 13% with suspected detection bias.
Kramer 1999[35]	High	Medium risk of selection bias, no attrition data reported, and high risk of reporting bias.
Williams 1997[11]	High	Selection and attrition bias due to flaws in randomization process and high attiriton rate.
Okumiya 1996[24]	Medium	Randomization not well described with potential detection bias.
Blumenthal 1991[36] Madden 1989[37]	High	Selection bias due to flaws in crossover design and reporting bias.

Appendix Table G4. Strength of evidence assessments: physical activity interventions versus inactive control in adults with normal cognition

Physical Exercise Type	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Multicomponent Physical Activity	Dementia	1 (1,635)	OR: 0.96 [0.57 to 1.63]	Medium	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
	MCI	1 (1,635)	OR: 1.14 [0.79 to 1.62]	Medium	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
	Brief cognitive test performance	2 (155)	1 of 2 tests shows statistically significant improvement with intervention, but effect size not clinically meaningful: Napoli 2014 Difference in change from baseline (3MS): 3.0 [1.5 to 4.5] Williamson 2009 Difference in adjusted mean change from baseline (3MS): -0.86 [-3.16 to 1.44]	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient
	Multidomain neuropsychological performance	1 (1,635)	One test shows no statistically significant improvement	Medium	Indirect	Precise	Unknown consistency	Undetected	NA	Low

Physical Exercise Type	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			with intervention. <u>Sink 2015</u> Difference in mean global composite z score: 0.029 [-0.038 to 0.095]							
	Executive/ Attention/ Processing Speed	4 (1,885)	1 of 13 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
	Memory	3 (1,836)	1 of 6 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
	Biomarkers	NR								Insufficient
	Adverse Effects	NR								Insufficient
Resistance Training	Dementia	NR								Insufficient
	MCI	NR								Insufficient
	Brief cognitive test performance	NR								Insufficient
	Multidomain neuropsychological performance	NR								Insufficient
	Executive/ Attention/	2 (120)	8 of 25 tests show	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient

Physical Exercise Type	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
	Processing Speed		statistically significant improvement with Intervention							
	Memory	3 (172)	3 of 11 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient
	Biomarkers	NR								
	Adverse Effects	NR								
Aerobic Training	Dementia	Limited data	1 of 1 test shows statistically significant improvement with intervention							Insufficient
	MCI	NR								Insufficient
	Brief cognitive test performance	2 (162)	1 of 3 tests show statistically significant improvement with intervention data <u>Muscari 2010</u> MMSE, Mean Difference [95% CI] I: -0.21 [0.79, 0.37] C: -1.21 [1.83, 0.60]	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient

Physical Exercise Type	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			Okumiya 1996 MMSE (6 months, Mean (SD) I: 28.2 ± 2.3 C: 26.5 ± 3.6 Hasegawa Dementia Scale (6 months), Mean (SD) I: 28.2 ± 1.7 C: 26.5 ± 3.5							
	Multidomain neuropsychological performance	1 (170)	1 of 1 tests show statistically significant improvement with intervention data Lautenschlager 2008 ADAS-Cog (18 months), Mean Difference [95% CI] I: −0.73 [−1.27, 0.03] C: −0.04 [−0.46, 0.88]	Medium	Indirect	Precise	Unknown	Undetected	NA	Insufficient
	Executive Function	3 (307)	3 of 14 tests show statistically significant	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient

Physical Exercise Type	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			improvement with Intervention Data							
	Memory	4 (369)	6 of 18 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient
	Biomarkers	NR								Insufficient
	Adverse Effects	NR								Insufficient
Tai Chi	Dementia	NR								Insufficient
	MCI	NR								Insufficient
	Brief cognitive test performance	NR								Insufficient
	Multidomain neuropsychological performance	NR								Insufficient
	Executive Function	Limited data								Insufficient
	Memory	NR								Insufficient
	Biomarkers	NR								
	Adverse Effects	NR								Insufficient

3MS=Modified Mini Mental Status Examination; C=control; CI=confidence interval; ES=effect size; I=Intervention; ITT=intention to treat; MCI=mild cognitive impairment; mg=milligrams; n=sample size; NA=not applicable; NR=not reported; RCT=randomized controlled trial; RR=risk ratio; SD=standard deviation; SOE=strength of evidence

Appendix G Table 5. Characteristics of eligible studies: physical activity interventions vs. inactive controls in adults with MCI

Physical Exercise Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Multicomponent Physical Activity	Suzuki 2013[38] Suzuki 2012[39] RCT Japan Medium	100	Older adults with MCI and aMCI determined Peterson's criteria Age, Mean 75,7 (7.0) 22% Female Race NR Education Level, Mean (SD) 10.95 (2.55) MMSE, Mean (SD) 26.6 (2.1)	Aerobic exercises, muscle strength training, and postural balance retraining -90 minutes, 2 times/week for 6 months	Health education/health promotion classes -2 classes over 6 months	6 months	Biomarker [Medial Temporal Areas Including the Entorhinal Cortex] [Whole Brain Cortices] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog] Memory [Logical Memory I, WMS] [Logical Memory, WMS II]
	Suzuki 2012[39] (subset of Suzuki 2013[38]) RCT Japan Medium	50	Older adults with aMCI determined by education-adjusted WMS-LM II score Age, Mean 75 46% Female Race NR Education Level, Mean (SD) 10.95 (2.55) MMSE, Mean (SD)	Aerobic exercises, muscle strength training, and postural balance retraining -90 minutes, 2 times/week for 1 years	Health education/health promotion classes -3 classes over 1 year	6 months 12 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DSST] [SCWT I] [SCWT II] [LVFT] Memory [Logical Memory I, WMS] [Logical Memory, WMS II] Language [CVFT]

			26.7 (1.7)				
Resistance Training	Fiatarone Singh 2014[40] RCT Australia High	49	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Resistance Training -100 minutes 2 days/week for 6 months	Sham cognitive training and sham exercise	6 months 18 months	Multidomain Neuropsychological Performance [ADAS-Cog] [Global Cognition Domain Composite] Executive/Attention/Processing Speed [Executive Function Domain Composite] [WAIS Similarities] [WAIS Matrices] [COWAT] [SDMT] Memory [List Learning Memory Sum from ADAS-Cog] [BVRT] [Logical Memory, Immediate] [Logical Memory, Delayed] [Memory Domain Composite] Language [Category Fluency, Animal Naming] [COWAT]
Aerobic Training	Hildreth 2015[41] RCT US Medium	53	Sedentary, obese adults age 55 and over with MCI Age, Mean (SD) 65 (7) 45% Female 74% White Years of Education, Mean (SD) 16 (2) MMSE, Mean (SD) 28.6 (1.2)	Endurance exercise training –Treadmill walking for 60 minutes 3 times/week for 6 months	Maintaining current level of physical activity and placebo for study duration	6 months	Multidomain Neuropsychological Performance [ADAS-Cog] Executive/Attention/Processing Speed [Composite] [VR II, WMS] [TMT B] [DSST] [SCWT (Interference)] [DS Backward] [Picture Completion, WAIS] Memory [Composite] [Logical Memory II, WMS] [RAVLT] Language [Composite] [BNT] [Category Fluency] Visuospatial [Composite] [Block Design, WAIS] [Picture Completion, WAIS] [CLOX-1]
	Lautenschlager 2008[22] RCT Australia Low	100	Adults reporting difficulty with memory and a MMSE score of at least 24 Age, Mean (SD): 68.7 (8.6) 51% Female	Home-based physical activity program with behavioral intervention –At minimum 50 minutes sessions 3	Educational material about memory loss, stress management, healthful diet, alcohol consumption, and	18 months	Diagnosis [CDR, Sum of Boxes] Multidomain Neuropsychological Performance [ADAS-Cog] Executive/Attention/Processing Speed [Executive Function Battery] [DSST] Memory [Word List, Immediate Recall (CERAD)] [Word List, Delayed Recall (CERAD)]

			Race NR Years of Education, Mean (SD) 12.4 (3.3) ADAS-Cog, Mean (SD) 7.0 (1.8)	times/week of moderately intense exercise for 24 weeks and a social cognitive theory-based behavioral package (workshop, manual, newsletters, and telephone calls)	smoking. No materials on physical activity.		Language [Verbal Fluency, Delis-Kaplin]
	Van Uffelen 2008[42] RCT Netherlands High	179	Adults aged 70-80 years with MCI Age, Mean (SD) 75 (2.9) 47% Male Race NR Education NR MMSE, Median 29	Walking program (group-based, moderate intensity) twice weekly for 1 year	Low-intensity placebo activity group	1 year	Executive/Attention/Processing Speed [Verbal Fluency Test] [DSST] [SCWT] Memory [AVLT]

3MS=Modified Mini Mental Status Examination; ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; BVMT=Breif Visuospatial Memory Test; BVRT=Benton Visual Retention Test; CDR=Clinical Dementia Rating; CLOX-1=Clock Drawing Test; COWAT=Controlled Oral Word Association Test; CVFT=Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substition Test; DVT=Digit Vigilance Test; EBMT=East Boston Memory Test; FCSRT=Free and Cued Selective Reminding Test; HVLT=Hopkins Verbal Learning Test; MCI=Mild Cognitive Impairment; MMSE=Mini-Mental Status Examination; MRI=Magnetic Resonance Imaging; N=sample size; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RCFT=Rey-Osterrieth Complex Figure Test; RCPM=Raven's Colored Progressive Matrices; RCT=Randomized controlled trial; RoB=risk of bias; SCWT=Stroop Color Word Test; SD=standard deviation; SDMT=Symbol Digit Modalities Test; SOE=Strength of Evidence; SWM=Spatial Working Memory; TICS=Telephone Interview for Cognitive Status (TICS-M=Modified); TMT=Trail Making Test (Part A and/or B); WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table G6. Characteristics of eligible studies: physical activity interventions vs. active controls in adults with MCI

Physical Exercise Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Multicomponent Physical Activity vs. Active Control	Lam 2015[43] RCT China High	278	Older adults with MCI (determined by subjective and objective impairments in cognitive function) and without dementia Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level (Years), Mean (SD) 3.9 (3.6) Catonese MMSE. Mean (SD) 25.6 (2.3)	One stretching and toning, one mind body exercise, and one aerobic session -60 minutes per session for 1 year	Social activities - At least 3, 1-hr sessions/week	12 months	Diagnosis [CDR, Sum of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Chinese Version] Memory [Delayed recall] Language [CVFT]
	Lam 2015[43] RCT China High	292	Older adults with MCI (determined by subjective and objective impairments in cognitive function) and without dementia Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level (Years), Mean (SD) 3.9 (3.6) Catonese MMSE. Mean (SD) 25.6 (2.3)	One stretching and toning, one mind body exercise, and one aerobic session -60 minutes per session for 1 year	Cognitively demanding activities -At least 3, 1-hr sessions/week	12 months	Diagnosis [CDR, Sum of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Chinese Version] Memory [Delayed recall] Language [CVFT]

	Lam 2015[43] RCT China High	239	Older adults with MCI (determined by subjective and objective impairments in cognitive function) and without dementia Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level (Years), Mean (SD) 3.9 (3.6) Catonese MMSE. Mean (SD) 25.6 (2.3)	One stretching and toning, one mind body exercise, and one aerobic session -60 minutes per session for 1 year	Combination of cognitive and mind body exercises –At least 3, 1-hr sessions/week	12 months	Diagnosis [CDR, Sum of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Chinese Version] Memory [Delayed recall] Language [CVFT]
	Law 2014[44] RCT Australia Medium	83	Adults age 60 and older with MCI Age, Mean (SD) 73.8 (7.1) 60.2% Females Race NR 33% with Secondary or Tertiary Education MMSE, Mean (SD) 24.17 (3.29)	Functional task exercise group (FcTSim programme: 5-10 min warm-up of light stretching, 30-min core FcTSim and 5-10 min cooldown) -13 sessions in 10 weeks	Active control - cognitive training group (30 min of computer-based cognitive training and 30 min of cognitive strategy training) -6 sessions over 10 weeks	6 months	Multidomain Neuropsychological Test Performance [Neurobehavioral Cognitive Status Exam, Chinese Version] Executive/Attention/Processing Speed [TMT A, Chinse Version] [TMT B, Chinese Version] Memory [CVVLT,Immediate] [CVVLT,Delayed] Language [CVFT, Chinese Version]
Resistance Training vs. Active Control	ten Brinke 2015[45] High	56	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 75.1 (3.7) 100% Female Race NR 28% with a University Degree MMSE, Mean (SD) 26.46 (2)	Resistance Training-2 times/week for 60 minutes for 6 months Walking -2 times/week for 60 minutes for 6 months	Balance and Tone: Stretching exercises, range of motion exercises, balance exercises, functional and relaxation techniques -2 times/week for 60 minutes for 6 months	26 weeks	Biomarker [MRI] Memory [RAVLT, Total Acquisition] [RAVLT, Recall After Interference] [RAVLT, Loss After Interference] [RAVLT, Long Delay Free Recall]

	ten Brinke 2015[45] High	58	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 75.1 (3.7) 100% Female Race NR 28% with a University Degree MMSE, Mean (SD) 26.46 (2)	Resistance Training-2 times/week for 60 minutes for 6 months	Walking -2 times/week for 60 minutes for 6 months	26 weeks	Biomarker [MRI] Memory [RAVLT, Total Acquisition] [RAVLT, Recall After Interference] [RAVLT, Loss After Interference] [RAVLT, Long Delay Free Recall]
	Fiatarone Singh 2014[40] RCT Australia High	46	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Resistance Training -100 minutes 2 days/week for 6 months	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) -100 minutes 2 days/week for 6 months	6 months 18 months	Multidomain Neuropsychological Test Performance [ADAS-Cog] [Global Cognition Domain Composite] Executive/Attention/Processing Speed [Executive Function Domain Composite] [WAIS Similarities] [WAIS Matrices] [COWAT] [SDMT] Memory [List learning Memory Sum from ADAS-Cog] Language [Category Fluency, Animal Naming] [COWAT] Memory [BVRT] [Logical Memory, Immediate] [Logical Memory, Delayed] [Memory Domain Composite]
	Fiatarone Singh 2014[40] RCT Australia High	49	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Resistance Training -100 minutes 2 days/week for 6 months	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) and Resistance Training -100 minutes 2 days/week for 6	6 months 18 months	Multidomain Neuropsychological Test Performance [ADAS-Cog] [Global Cognition Domain Composite] Executive/Attention/Processing Speed [Executive Function Domain Composite] [WAIS Similarities] [WAIS Matrices] [COWAT] [SDMT] Memory [List learning Memory Sum from ADAS-Cog] Language [Category Fluency, Animal Naming] [COWAT] Memory [BVRT] [Logical Memory, Immediate] [Logical Memory,

					months		Delayed] [Memory Domain Composite]
	Nagamatsu 2013[46, 47] RCT Canada Medium High (Spatial Memory Outcome)	56	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 74.9 (3.5) 100% Female Race NR 22% with a University Degree MMSE, Mean (SD) 27.2 (1.6)	Resistance Training-2 times/week for 60 minutes for 6 months	Balance and Tone: Stretching exercises, range of motion exercises, balance exercises, functional and relaxation techniques -2 times/week for 60 minutes for 6 months	26 weeks	Memory [RAVLT, Total Acquisition] [RAVLT, Recall After Interference] [RAVLT, Loss After Interference] [RAVLT, Long Delay Free Recall]
Aerobic Training vs. Active Control	ten Brinke 2015[45] High	58	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 75.1 (3.7) 100% Female Race NR 28% with a University Degree MMSE, Mean (SD) 26.46 (2)	Walking -2 times/week for 60 minutes for 6 months	Balance and Tone: Stretching exercises, range of motion exercises, balance exercises, functional and relaxation techniques -2 times/week for 60 minutes for 6 months	26 weeks	Biomarker [MRI] Memory [RAVLT, Total Acquisition] [RAVLT, Recall After Interference] [RAVLT, Loss After Interference] [RAVLT, Long Delay Free Recall]
	Nagamatsu 2013[46, 47] RCT Canada Medium High (Spatial Memory Outcome)	58	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 74.9 (3.5) 100% Female Race NR 22% with a University Degree	Walking -2 times/week for 60 minutes for 6 months	Balance and Tone: Stretching exercises, range of motion exercises, balance exercises, functional and relaxation techniques -2 times/week for 60	26 weeks	Memory [RAVLT, Total Acquisition] [RAVLT, Recall After Interference] [RAVLT, Loss After Interference] [RAVLT, Long Delay Free Recall]

			MMSE, Mean (SD) 27.2 (1.6))		minutes for 6 months		
	Baker 2010[32, 33] RCT US High	33	Sedentary adults with amnestic MCI (single or multiple domain) based on Petersen criteria Age, Mean (Range) 70 (55-85) 52% Female Race NR Education NR MMSE, Mean (SD) 27.5 (1.9)	High-intensity aerobic exercise -4 times/week for 45-60 minutes over 6 months	Supervised stretching -4 times/week for 45-60 minutes over 6 months	6 months	Executive/Attention/Processing Speed [TMT] [SCWT] [Task Switching] Memory [Symbol Digit Modalities] [Story Recall] [List Learning] Delayed-Match-To-Sample] Language [Verbal Fluency]
Tai Chi vs. Active Control	Lam 2012[48] RCT China High	389	Adults age 65 and older with a CDR of 0.5 or aMCI with subjective cognitive complaints Age, Mean (SD) 78 (6.4) 74% Female Race NR Education Level, Mean (SD) 3.4 (3.8) MMSE, Mean (SD) 24.5 (3.0)	Training on 24-forms of simplified Tai Chi (in person for 4-6 weeks, then via home video) -30 minutes 3 times/week for 1 year	Muscle stretching and toning exercise developed by physiotherapists (in person for 4-6 weeks, then via home video) -30 minutes 3 times/week for 1 year	1 year	Diagnosis [Incident Dementia, DSM-IV criteria] Multidomain Neuropsychological Test Performance [ADAS-cog]

3MS=Modified Mini Mental Status Examination; ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; BVMT=Breif Visuospatial Memory Test; BVRT=Benton Visual Retention Test; CDR=Clinical Dementia Rating; CLOX-1=Clock Drawing Test; COWAT=Controlled Oral Word Association Test; CVFT=Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substition Test; DVT=Digit Vigilance Test; EBMT=East Boston Memory Test; FCSRT=Free and Cued Selective Reminding Test; HVLT=Hopkins Verbal Learning Test; MCI=Mild Cognitive Impairment; MMSE=Mini-Mental Status Examination; MRI=Magnetic Resonance Imaging; N=sample size; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RCFT=Rey-Osterrieth Complex Figure Test; RCPM=Raven's Colored Progressive Matrices; RCT=Randomized controlled trial; RoB=risk of bias; SCWT=Stroop Color Word Test; SD=standard deviation; SDMT=Symbol Digit Modalities Test; SOE=Strength of Evidence; SWM=Spatial Working Memory; TICS=Telephone Interview for Cognitive Status (TICS-M=Modified); TMT=Trail Making Test (Part A and/or B); WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table G7. Summary risk of bias assessments: physical activity interventions in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Hildreth 2015[41]	Medium	Attrition rate is 15% with differential attrition rates in study arms. No analysis to address potential attrition bias.

Fiatarone Singh 2014[40]	High	Suspected reporting bias. Results for intervention arms are combined in the analysis,
ten Brinke 2015[45]	High	Attrition rates is over 21% with no analysis to address potential attrition bias.
Law 2014[44]	Medium	Randomization not fully described and potential detection bias.
Nagamatsu 2013[46]	Medium Spatial Memory: High	Unaccounted differences in sample size for outcome measures. Spatial memory outcome is rated high due to high rate of attrition for outcome measure.
Suzuki 2013[38]	Medium	Attrition and suspected performance bias.
Lam 2012[48]	High	Attrition rate is over 30% with no analysis to address potential attrition bias.
Suzuki 2012[39]	Medium	Randomization not adequately described.
Baker 2010[33]	High	Suspected attrition bias and reporting bias based on reporting of study results (all results divided into subgroups, results for complete sample not reported).
Lautenschlager 2008[22]	Low	No suspected biases.
van Uffelen 2008[42]	High	Attrition rate is 16-22% with potential reporting bias

MCI=mild cognitive impairment

Appendix Table G8. Strength of evidence assessments: physical activity interventions versus inactive control in adults with MCI

Physical Exercise Type	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Multicomponent Physical Activity	Dementia	NR								
	MCI	NR								
	Brief cognitive test performance	2 (150)	1 of 3 tests show a statistically significant difference with the intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
	Multidomain neuropsychological performance	NR								
	Executive/Attention/ Processing Speed	NR								
	Memory	2 (150)	1 of 5 tests show a statistically significant difference with the intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
	Biomarkers	NR								
	Adverse Effects	NR								
Aerobic Training	Dementia	NR								
	MCI	NR								
	Brief cognitive test performance	NR								
	Multidomain neuropsychological performance	2 (153)	1 of 2 tests shows a statistically significant difference with the intervention Hildreth 2015[41]	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient

Physical Exercise Type	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			ADAS-Cog, Mean Difference from Baseline [95% CI] I: –1.6 [–4.9, 1.6] C: –0.3, [–3.5, 3.0] Lautenschlager 2008[22] ADAS-Cog, Mean Difference from Baseline [95% CI] I: −0.38 [−1.39 to 0.63] C: 0.45 [−0.46 to 1.36]							
	Executive/Attention/ Processing Speed	2 (153)	8 of 8 tests do not show a statistically significant difference with the intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
	Memory	2 (153)	5 of 5 tests do not show a statistically significant difference with the intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
	Biomarkers	NR	NA	NA	NA	NA	NA	NA	NA	NA

Physical Exercise Type	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
	Adverse Effects	2 (153)	3 of 4 reports of adverse effects do not show a statistically significant difference with the intervention.	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient

C=control; CI=confidence interval; ES=effect size; HR=hazard ratio; I=Intervention; MCI=mild cognitive impairment; mg=milligrams; n=sample size; NA=not applicable; NR=not reported; RCT=randomized controlled trial; RR=risk ratio; SD=standard deviation; SOE=strength of evidence

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Appendix H. Nutraceutical Interventions

Appendix Table H1. Characteristics of eligible studies: nutraceutical interventions in adults with normal cognition

Nutraceutical Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Omega 3 fatty acids efficacy	Boespflug 2016[1] United States RCT High	21	Individuals without dementia, diabetes, kidney disease, liver disease, serious psychiatric condition, substance abuse, or taking supplements that might affect outcome measures or interact with fish oil. Mean age (SD): 68.3 (4.94) 62.3% Female Race: NR Education: NR Mean Clinical Dementia Rating Score (SD): 0.2 (0.37)	Fish oil 2.4g daily [1.6g EPA and 0.8g DHA] and either whole fruit or freeze-dried blueberry powered for 6 months	Matching placebo for 6 months	6 months	Biomarker [fMRI] Memory [Sequential Letter N-back Working Memory]
	Cukierman-Yaffe, 2014[2] (Substudy of ORIGIN trial) RCT Multinational Medium (High for outcomes at t5 for MMSE and t6	11, 685	Adults older than 50 with dysglycaemia, with additional risk factors for cardiovascular events, not taking insulin, and taking no more than 1 oral glucose drug. Mean age (SD): 63 (7.75) 35% female 59% white	Omega 3 (EPA 465 mg+ DHA 375 mg) daily for 6 years	Placebo daily for 6 years	Median 6.2 years	Diagnosis [Incident Probable Cognitive Impairment = Reported Dementia or an MMSE score of <24] Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DSST]

	for DSS)		Education: 35% <8 years 27% 9-12 years 38% >12 years Mean MMSE (SD): 28 (2.75)				
	Mahmoudi 2014[3] Iran RCT High	199	Individuals ≥65 with normal or mild to moderate cognitive impairment. Mean age (SD): 74.63 (5.4) 54.75% Female Race: NR 68.35% Illiterate 16.6% Primary education 10.55% Secondary education 4.5% Higher education Mean MMSE (SD): 18.70 (5.25) 28.6% with normal MMSE 41.7% with mild MMSE 29.6% with moderate MMSE	Fish oil 1g daily [180mg DHA plus 120mg EPA	Matching-placebo	180 days	Brief Cognitive Test Performance [MMSE] Memory [Abbreviated Mental Test]
	Witte, 2014[4] RCT Germany Medium	80	Healthy adults aged 50-75 years Mean age (SD): 64 (± 6.5) years 46 % female Race not reported Mean education (SD) (range 0=no educ - 5=college): 4.2 (1.2) Mean MMSE (SD): 29.3 (1)	Omega 3 (fish oil, 2.2 g) daily for 6 months	Placebo capsules (sunflower oil) daily for 6 months (26 weeks)	6 months	Biomarker [MRI: Gray Matter Changes And White Matter Integrity] Executive/Attention/Processing Speed [Executive Function Composite] [Attention Composite] [Sensorimotor Speed Composite] Memory [Memory Composite]
	Stonehouse, 2013[5] RCT New Zealand High	176	Healthy adults with normal cognition aged 18-45 years & low DHA intake Mean age (SD): 33.3 (7.8) years 64% female 80% European	Omega 3 (DHA 1.16 g) daily for 6 months	Placebo daily for 6 months	6 months	Executive/Attention/Processing Speed [Composite Attention] [Reaction Time Attention] [Finding As Task] [Reaction Time Episodic Memory] [Reaction Time Working Memory] Memory [Composite Episodic

			28% secondary education 72% tertiary education Baseline global cog not reported				Memory] [Composite Working Memory]
	Geleijnse, 2012[6] RCT subset Netherlands Medium	2911	Coronary patients aged 60-80 years Mean age (SD): 69 (5.5) years 22% female Race not reported 22% elementary ed 66% secondary or higher vocational education 12% college Mean MMSE (SD): 28.2 (1.7)	Omega 3 (EPA-DHA 400 mg or ALA 200 mg) daily for 40 months (There is also an EPA-DHA + ALA arm; however, 2X2 factorial design was collapsed into combined group analysis of all EPA-DHA vs placebo and all ALA versus placebo)	Placebo daily for 40 months	40 months	Brief Cognitive Test Performance [MMSE] [Risk of Cognitive Decline based on MMSE Score]
	Andreeva, 2011[7] RCT followup France Medium	1748	Adults with normal cognition aged 45-80 with a history of ischemic heart disease Mean age (SD): 61 (8.8) years 20% female Race not reported 10% foreign-born 58% < high school Mean Isaacs Set Test (SD): 35.8 (7.5)	Omega 3 (EPA + DHA 600 mg in a 2:1 ratio) daily for 4 years or Omega 3 + Vitamin B for 4 years	Placebo for 4 years	4 years	Brief Cognitive Test Performance [F-TICS] Memory [F-TICS Memory Subscore] [F-TICS Recall Subscore]
	Dangour, 2010[8] RCT UK Medium	867	Cognitively healthy adults aged 70-79 years, MMSE ≥24 Mean age (SD): 75 (2.6) years 58% aged 70-74 42% aged 75-79 45% female Race not reported	Omega 3 (EPA 200 mg + DHA 500 mg) daily for 2 years	Olive oil capsules for 2 years	2 years	Multidomain Neuropsychological Test Performance [Composite] Executive/Attention/Processing Speed [Executive Composite] [Processing Composite] [Letter Search/Cancellation - # Correct, % of Total Attempts] [Symbol Letter Modality - # Correct] [RT, Simple] [RT, Choice] [DS Forward]

			Education: 33% no qualifications 26% O level, clerical 18% A level, college 23% other Median MMSE (IQR): 29 (28, 30)				[DS Backward] Memory [Memory Composite] [Global Delay Composite] [CVLT] [Story Recall, Immediate] [Story Recall, Delayed] [Spatial Memory, Correct Images - Immediate] [Spatial Memory, Correct Images - Delayed] Language [Verbal Fluency, Animals Named]
	Yurko-Mauro, 2010[9] RCT US Low/Medium	485	Healthy adults aged 55+ with MMSE scores >26 and a Logical Memory (WMS III) baseline score of at least 1 SD below younger adults Mean age (SD): 70 (9) years 58% female 84% white Logical memory – immediate recall (SD): 25 (6.8) Logical memory – delayed recall (SD): 11.3 (4.1)	Omega 3 (DHA 900 mg) daily for 6 months	Placebo daily for 6 months	6 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [CANTAB Stockings of Cambridge] Memory [CANTAB PAL] [CANTAB VRM – Free Recall] [CANTAB VRM - Immediate Recall] [CANTAB VRM - Delayed Recall] [CANTAB SWM] [CANTAB PRM - Delayed]
	Van de Rest, 2008[10] RCT Netherlands Low	302	Cognitively healthy (MMSE ≥21) adults aged 65+ Mean age (SD): 70 (3.5) years 45% female Race not reported Education: 9% low 54% medium 37% high Median MMSE (IQR): 28 (27-29)	Omega 3 (EPA-DHA 400 mg or 1800 mg) daily for 6 months	Placebo capsules for 6 months	6 months	Executive/Attention/Processing Speed [Executive Function Composite] [Attention Composite] [Sensorimotor Speed Composite] [TMT A] [TMT B] [Stroop Part 1] [Stroop Part 2] [Stroop Part 3 – (Part 1 + Part 2/2)] Memory [Memory Composite] Language [Word Fluency-Animals] [Word Fluency-Letter]
Ginkgo biloba efficacy	Lewis, 2014[11] RCT USA High	97	English-speaking, nonsmoking, healthy older adults aged 60+ with an MMSE score ≥ 23 Mean age (SD): 69 (7) years	Ginkgo Synergy for 6 months (2 capsules/day providing 120 mg/d Ginkgo biloba leaf, 80	Placebo (cellulose, lactose, and beet powder) for 6 months	6 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [SCWT] [TMT A] [TMT B] [DSST] Memory [HVLT]

			72% female 83% white Education: 12% ≤ high school 35% some post-high school training 25% college grad 28% ≥ master's degree No baseline cognition reported other than inclusion criteria	mg/d Gingko biloba whole extract, plus various other extracts)			Language [COWAT]
	Vellas, 2012[12] France RCT Medium	2854	Adults aged 70+ who spontaneously reported memory complaints to their primary care physician; screened and excluded diagnosed dementia, major memory impairment Mean age (SD): 76 (4.4) years 67% female Race not reported Education: 14% no formal educ 37% primary school 24% some secondary educ 24% high school diploma Mean MMSE (SD): 27.6 (1.9)	Ginkgo biloba extract (EGb761) 120 mg twice daily for at least 4 years	Matched placebo for at least 4 years	5 years	Diagnosis [Incidence Of Probable AD According to DSM-IV and NINCDS-ADRDA Criteria at 5 years]
	Snitz, 2009[13] DeKosky, 2008[14] RCT USA Low	3069 (normal cog & MCI) 2587 nor	Community-dwelling participants aged 72 to 96 years; 15% baseline MCI Mean age (SD): 79.1 (3.3) years 46% female 95% white Education mean (SD): 14.4 (3) years Mean 3MSE (SD): 93.4 (4.7)	Ginkgo biloba extract 120 mg twice daily for a median of 6.1 years	Identical appearing placebo for a median of 6.1 years	Global cognition: average annual change reported Other cognitive outcomes at year 4	Diagnosis [Incident Dementia & AD (5 categories)] Multidomain Neuropsychological Test Performance [Global Composite] Executive/Attention/Processing Speed [Executive Composite [Attention and Psychomotor Speed Composite] [TMT B] [SCWT] [TMT A] [Digit Span] Memory [Memory Compositet] [CVLT] [RCFT]

		mal cog					Visuospatial [Visuospatial Composite] [Copy Condition Of The Rey Osterrieth Figure Test] [WAIS-R Block Design] Language [Language Composite] [BNT] [Semantic Verbal Fluency]
	Dodge, 2008[15] RCT USA Medium	118	Cognitively intact subjects aged 85+ Mean age (SD): 87.5 (2) years 60% female Race not reported Mean education (SD): 14 (2.5) years Mean MMSE (SD): 28.25 (1.4)	Ginkgo biloba extract 80 mg three times daily (240 mg/d) for 3 years 6 months	Placebo	3 years 6 months	Diagnosis (estimate): [Mild Cognitive Decline Defined As Progress from CDR = 0 to 0.5] Memory [CERAD Word List Delayed Recall]
Multi-nutraceutical supplement	Strike 2016 [16] United Kingdom RCT Low	27	Non-ill community dwelling females ≥60 who could walk ≥50 m and negotiate stairs Mean age (SD): 66.8 (9.3) 100% Female Race: NR Education: NR Mean Number errors National Adult Reading Score (SD): 8.1 (4.8)	Efalex Active 50+ per day [1g DHA, 160mg EPA, 240mg Ginkgo biloba, 60mg phosphatidylserine, 20mg a-tocopherol, 1mg folic acid, and 20ug B12] for 6 months	Matching-placebo for 6 months	6 months	Executive/Attention/Processing Speed [Stockings of Cambridge, Motor Screening Task] Memory [PALS]
	Lewis, 2014[11] RCT USA High	97	Healthy older adults aged 60+ with an MMSE score ≥23 Mean age (SD): 69 (7) years 72% female 83% white Education: 12% ≤ high school 35% some post-high school training 25% college grad 28% ≥ master's No baseline cognition	OPC Synergy for 6 months (2 capsules/d providing 100 mg/d grape seed extract, 50 mg/d green tea extract, 50 mg/d bilberry fruit, dried buckwheat leaf and juice, green tea leaf powder, and dried carrot root plus Catalyn	Placebo (cellulose, lactose, and beet powder) for 6 months	6 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [SCWT] [TMT A] [TMT B] [DSST] Memory [HVLT-R] Language [COWAT]

			reported other than inclusion criteria	(4 tablets/d providing 312 IU/d vitamin D, 1600 IU/d vitamin A, 5.3 mg/d vitamin C, 0.3 mg/d thiamine, 0.3 mg/d riboflavin, 1.3 mg/d vitamin B6, defatted wheat germ, carrot (root), and various other ingredients) for 6 months			
Resveratrol efficacy	Witte, 2014[17] RCT Germany Medium	46	Healthy overweight older adults aged 50-80 years Mean age (SD): 64 (6) years 64% female Race not reported Mean education (SD): 17 (3) years Mean MMSE (SD): 29 (1)	Resveratrol (200 mg/d) for 6 months	Placebo for 6 months	6 months	Biomarker [MRI: Volume, Microstructure, and Functional Connectivity of the Hippocampus] Memory [AVLT Retention] [AVLT Delayed Recall] [AVLT Recognition] [AVLT Learning Ability] [AVLT 5th Learning Trial]
Plant sterols/ plant stanols efficacy	Schiepers, 2009[18] RCT Netherlands Medium	57	People aged 43-69 years taking statins Mean age (SD): 60 (7) years 42% female Race not reported 39% low education Baseline cognition not reported	Margarines enriched with plant sterol esters (2.5 g/d) or plant stanol esters (2.5 g/d) for 7 years (85 weeks)	Control margarine for 7 years (85 weeks)	7 years (85 weeks)	Executive/Attention/Processing Speed [Simple Information Processing Speed Composite] [Complex Speed Composite] Memory [Memory Composite]
Omega 3 comparative effectiveness	Andreeva, 2011[7] RCT France Medium	1748	People with normal cognition aged 45-80 with a history of ischemic heart disease Mean age (SD): 61 (8.8) years 20% female 10% foreign-born 58% < high school	Omega 3 (EPA + DHA 600 mg in a 2:1 ratio) daily for 4 years or Omega 3 + Vitamin B for 4 years	Omega 3 + Vitamin B for 4 years or Vitamin B for 4 years	4 years	Brief Cognitive Test Performance [F-TICS] Memory [F-TICS-m Subscore] [F-TICS-m Recall Subscore]

			diploma Mean F-TICS-m (SD): 28.5 (4.8)				
	Chew, 2015[19] RCT USA High	3501	Adults at risk for developing macular degeneration Mean age (SD): 72.7 (± 7.7) years 57.5% female 97% white 29% ≤ high school 49% ≥ some college 22% postgraduate Mean TICS (SD): 33 (3.4)	Long-chain polyunsaturated fatty acids (1 g, specifically DHA 350 mg and EPA 650 mg) for 5 years	No long-chain polyunsaturated fatty acids (other groups) for 5 years	Yearly for 5 years	Brief Cognitive Test Performance [TICS Total Score] Multidomain Neuropsychological Test Performance [Composite] Executive/Attention/Processing Speed [Backwards Counting] [Verbal Fluency – Animal, Letter & Alternating] Memory [Wechsler Logical Memory I & II] [TICS Word List Recall] Language [Verbal Fluency – Animal] [Verbal Fluency – Letter] [Verbal Fluency – Category]
Lutein/ Zeaxanthin	Chew, 2015[19] RCT USA High	3501	Adults at risk for developing age-related macular degeneration Mean age (SD): 72.7 (± 7.7) years 57.5% female 97% white 29% ≤ high school 49% ≥ some college 22% postgraduate Mean TICS (SD): 33 (3.4)	Lutein (10mg)/ zeaxanthin (2mg) daily 5 years	No Lutein/zeaxanthin (other groups) for 5 years	Yearly for 5 years	Brief Cognitive Test Performance [TICS Total Score] Multidomain Neuropsychological Test Performance [Composite] Executive/Attention/Processing Speed [Backwards Counting] [Verbal Fluency – Animal, Letter & Alternating] Memory [Wechsler Logical Memory I & II] [TICS Word List Recall] Language [Verbal Fluency – Animal] [Verbal Fluency – Letter] [Verbal Fluency – Category]
Multi-nutraceutical supplement	Bun, 2015[20] Open label intervention study (observational) Japan High	825	People aged 65+ Mean age (SD): 72 (5) years 42% female Race not reported Mean education (SD): 10 (2.5) years Baseline cog exclusion score < 1.5 SD on ≥ 1 domain of the 5-cog test after adjustment	Nutritional supplementation (n-3 polyunsaturated fatty acid, Ginkgo biloba, leaf dry extracts, and lycopene) for 3 years	No nutritional supplementation (exercise and inactive control groups)	3 years	Diagnosis [Diagnosis of AD]

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; ALA=alpha-linolenic acid; AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; BVMT=Breif Visuospatial Memory Test; BVRT=Benton Visual Retention Test; CAMCOG=Cambridge Cognition Examination; CDR=Clinical Dementia Rating; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CLOX-1=Clock Drawing Test;

COWAT=Controlled Oral Word Association Test; CVFT=Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DHA=docosahexaenoic acid; DS=Digit Span (Forward and/or Backward); DSM=Diagnostic Statistical Manual of Mental Disorders; DSST=Digit Symbol Substition Test; DVT=Digit Vigilance Test; EBMT=East Boston Memory Test; EPA=eicosapentaenoic acid; FCSRT=Free and Cued Selective Reminding Test; F-TICS=French Version, Telephone Interview Cognitive Status; HVLT=Hopkins Verbal Learning Test; MCI=mild cognitive impairment; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; n=sample size; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease; NR=PALS=Paired Association Learning Test; PRM=Pattern Recognition Memory; RAVLT=Rey's Auditory Verbal Learning Test; RBANS=Repeatable Battery for Neuropsychological Status; RBMT= Rivermead Behavioral Memory Test; RCFT=Rey-Osterrieth Complex Figure Test; RCPM=Raven's Colored Progressive Matrices; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SCWT=Stroop Color Word Test; SD=Standard Deviation; SDMT=Symbol Digit Modalities Test; SOE=Strength of Evidence; SWM=Spatial Working Memory; TICS=Telephone Interview for Cognitive Status (TICS-M=Modified); TMT=Trail Making Test (Part A and/or B); VP=Verbal Proficiency; VR=Visual Reproduuction; VRM=Verbal Recognition Memory; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Table H2. Summary risk of bias assessments: nutraceuticals interventions in adults with normal cognition

Nutraceutial Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
Omega 3 fatty acids efficacy	Boespflug, 2016[1]	High	Attrition > 20% without appropriate analysis to correct for potential bias
	Cukierman-Yaffe, 2014[2]	Medium	Attrition >20% at some time points; sensitivity analysis conducted
	Mahmoudi, 2014[3]	High	Includes people with dementia, MCI and normal cognition
	Witte, 2014[4]	Medium	Unclear randomization procedures; attrition >10% without analysis to account for possible bias
	Stonehouse, 2013[5]	High	Attrition >20% without analysis to conduct for possible bias
	Geleijnse, 2012[6]	Medium	Unclear randomization procedures; attrition
	Andreeva, 2011[7]	Medium	Subset of RCT followup using participants with a history of cardiovascular disease. Original RCT baseline measures on subset – no differences between groups.
	Dangour, 2010[8]	Medium	Attrition >10% without analysis to correct for potential bias
	Yurko-Mauro, 2010[9]	Medium	Attrition >10% without appropriate analysis; unclear whether assessor was independent)
	van de Rest, 2008[10]	Low	
Ginkgo biloba efficacy	Lewis, 2014[11]	High	Attrition >25% without analysis
	Vellas, 2012[12]	Medium	Attrition >30% (analysis conducted)
	Snitz, 2009[13] DeKosky, 2008[14]	Medium	High attrition, but analysis conducted to correct for potential bias
	Dodge, 2008[15]	Medium	Attrition >10% without analysis; possible detection bias (unclear outcome assessment blinding/independence)
Multi-nutraceutical efficacy	Strike, 2016[16]	Low	
	Lewis, 2014[11]	High	Attrition >25% without appropriate analysis
Resveratrol efficacy	Witte, 2014[17]	Medium	Unclear randomization procedures; unclear whether outcome assessor was blinded and independent
Plant sterols or plant stanols	Schiepers 2009[18]	Medium	Unclear randomization procedures; unclear whether outcome assessor was blind to treatment
Comparative effectiveness	Andreeva, 2011 (Omega 3)[7]	Medium	Subset of RCT followup using participants with a history of cardiovascular disease. Original RCT baseline measures on subset – no differences between groups.
	Chew, 2015[19] (Omega 3 & Lutein/Zeaxanthin)	High	Unclear randomization procedures; high attrition; reporting bias due to discrepancies in number randomized in 2 study papers
	Bun, 2015[20] (Multi-nutraceutical supplement)	High	Participants not randomized; high attrition

MCI=mild cognitive impairment; RCT=randomized controlled trial

Appendix Table H3. Strength of evidence assessments: nutraceutical interventions in adults with normal cognition

Nutraceutical Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Omega 3 fatty acids versus inactive control	Dementia	1 (12,536)	0 of 1 tests show statistically significant improvement with intervention Cukierman-Yaffe 2014[2] Hazard ratio for incident cognitive impairment (composite of either incident dementia diagnosis of follow-up MMSE <24): 0.93 [0.86 to 1.0]	High	Direct	Precise	Unknown	Undetected	N/A	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		NR							Insufficient
	Brief cognitive test performance (6 months to 6 years)	4 (16,431)	0 of 9 tests show statistically significant improvement with intervention (no differences between	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low

			groups) <u>Cukierman-Yaffe, 2014</u>[2] Rate of change from baseline MMSE: 0.0013 [-0.0165, 0.0191] <u>Geleijnse, 2012</u>[6] *EPA-DHA* Difference in change from baseline MMSE: 0.05 [-0.07, 0.17] Risk of moderate/ severe cognitive decline (decrease of ≥3 MMSE pts or incidence of cognitive decline or dementia): OR 1.03 [0.84, 1.26] Risk of							

			severe cognitive decline (decrease of ≥5 MMSE pts or incidence of cognitive decline or dementia): OR 0.99 [0.73, 1.34] *ALA* Difference in change from baseline MMSE: 0.14 [-0.04, 0.32] Risk of moderate /severe cognitive decline: OR 0.90 [0.74, 1.10] Risk of severe cognitive decline: OR 0.88 [0.65, 1.19] <u>Andreeva,</u>							

			2011[7] No statistically significant effects of group assignment on cognitive function. Difference in mean F-TICS-m scores are not reported. Yurko-Mauro, 2010[9] Difference in change from baseline MMSE treatment vs. placebo: 0 [-0.30, 0.30]							
	Multidomain neuropsychological performance (2 years)	1 (744)	0 of 1 test shows statistically significant improvement with intervention (no differences between groups) Dangour, 2010[8] Difference	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low

			in change from baseline (measure of global cognitive function) treatment vs placebo: -0.01 [-0.05, 0.04]							
	Executive/ Attention/ Processing Speed (6 months to 2 years)	5 (5079)	2 of 31 favor I	Medium	Indirect	Imprecise	Consistent (2 I>C from n=548 over 6 months; 29 NS from 5079 over 6 years)	Undetected	NA	Low
	Memory (6 months to 4 years)	5 (3428)	3 of 25 favor I	Medium	Indirect	Imprecise	Consistent (3 I>C from 1 study of n=483; 22 from all)	Undetected	NA	Low
Ginkgo biloba versus inactive control	Dementia (5-6 years)	2 (5407)	0 of 5 tests show statistically significant differences between intervention and control groups. Vellas, 2012[12] Incidence of probable AD by year of study (hazard not proportional by time) 1 year: HR	Medium	Direct	Imprecise	Consistent	Undetected	NA	Low

			0.72 [0.32-1.61] 2 years: HR 1.66 [0.81-3.40] 3 years: HR 1.11 [0.51-2.43] 4 years: HR 0.57 [0.19-1.69] ≥5 years: HR 0.49 [0.25-0.96] DeKosky, 2008[14] Incidence of dementia: All dementia: HR 1.05 [0.84-1.30] AD without vascular dementia: HR 1.13 [0.86-1.48] AD with vascular dementia: HR 1.12 [0.72-1.74] Total AD: HR 0.13 [0.90-1.42] Vascular dementia without AD: HR 0.36 [0.13-1.00]							
	MCI	Single trial <500	Limited Data							Insufficient (limited

		participants								data)
	Brief cognitive test performance	NR								Insufficient (no data)
	Multidomain neuropsychological performance (6 years)	1 (3069) (includes 482 MCI; 15.7% total)	0 of 1 (no statistically significant differences between groups) Snitz, 2009[13] Results of linear mixed models: Treatment effect (overall difference in z scores ginkgo vs. placebo): mean (95% CI): 0.015 [-0.018, 0.047] Treatment x time interaction: annual difference in rates of change between ginkgo and placebo: mean (95% CI): -0.002 [-	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low

			0.009, 0.005]							
	Executive/ Attention/ Processing Speed (6 years)	1 (3069) (includes 482 MCI; 15.7% total)	0 of 5 (no differences)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
	Memory (3.5 to 6 years)	2 (3187)	0 of 4 (no differences)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
Multi-nutraceutical supplement efficacy	Dementia	NR								
	MCI	NR								
	Biomarkers	NR								
	Brief Cognitive Test Performance	NR								
	Multidomain Composites	NR								
	Executive/ Attention/ Processing Speed	Single study with sample size < 500								
	Memory	Single study with sample size < 500								
Omega 3 versus B Vitamins	Dementia	NR								Insufficient (no data)
	MCI	NR								Insufficient (no data)
	Biomarkers	NR								Insufficient (no data)
	Brief Cognitive Test Performance	1 (885)	0 of 1 test show statistically significant differences	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low
	Multidomain Composites	NR								Insufficient (no data)
	Executive/ Attention/ Processing Speed	NR								Insufficient (no data)

	Memory	1 (885)	0 of 2 tests show statistically significant differences	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low
Omega 3 versus Omega 3 + B Vit	Dementia	NR								Insufficient (no data)
	MCI	NR								Insufficient (no data)
	Biomarkers	NR								Insufficient (no data)
	Brief Cognitive Test Performance	1 (877)	0 of 1 test show statistically significant differences	Medium	Indirect	Imprecise	Unknown	Undetected		Low
	Multidomain Composites	NR								Insufficient (no data)
	Executive/ Attention/ Processing Speed	NR								Insufficient (no data)
	Memory (4 years)	1 (877)	0 of 2 tests show statistically significant differences	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low

AD=Alzheimer's disease; ALA=alpha-linolenic acid; C=control; CI=confidence interval; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; F-TICS=French version, Telephone Interview Cognitive Status; HR=hazard ratio; I=intervention; MCI=mild cognitive impairment; MMSE=Mini Mental Status Examinatrion; NA=not applicable; NR=not reported; OR=odds ratio; SOE=strength of evidence

Appendix Table H4. Characteristics of eligible studies: Intervention type in adults with MCI

Nutraceutical Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Omega 3 fatty acids efficacy	Lee, 2013[21] RCT Malaysia Medium	36	Low SES people aged 60+ with MCI Mean age (SD): 65 (4) years 77% female Race not reported Mean education (SD): 5.9 (3) years Mean MMSE (95% CI): 26.7 (25.7-27.5)	Omega 3 fatty acids (DHA 430 mg and EPA 150 mg) daily for 1 year	Placebo capsules daily for 1 year	1 year	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Executive Function Attention Composite] [DSST] [DS Forward] [DS Backward] Memory [Memory Composite] [VR I] [VR II] [RAVLT, Immediate Recall] [RAVLT, Delayed Recall] Visuospatial [Visuospatial Skills Composite] [Clock Drawing Test] [Matrix Reasoning] [Block Design]
Ginkgo biloba efficacy	Gavrilova, 2014[22] RCT Russia Low	160	People with MCI who scored at least 6 on the 12-item Neuropsychiatric Inventory (NPI) Mean age (SD): 64 (7) 62% female Race not reported Mean education (SD): 9.7 (0.9) years Mean MMSE (SD): 25.7 (1.4)	Ginkgo biloba (EGb 761) 240 mg daily for 6 months	Placebo tablet for 6 months	6 months	Executive/Attention/Processing Speed [TMT A] [TMT B]
	DeKosky, 2008[14] RCT USA Medium	3069 (total) 482 MCI	For full sample: Community-dwelling participants aged 72 to 96 years; 15% baseline MCI Mean age (SD): 79.1 (3.3) years 46% female 95% white Education mean (SD): 14.4	Ginkgo biloba extract 120 mg twice daily for a median of 6.1 years	Identical appearing placebo for a median of 6.1 years	Global cognition: average annual change reported	Diagnosis: Incident Dementia & AD (5 categories)

			(3) years Mean 3MSE (SD): 93.4 (4.7)				
Omega 3 fatty acids comparative effectiveness	Sinn, 2011[23] RCT Australia High	50	People aged 65+ with MCI Mean age (SD): 74 (5) years 33% female Race not reported Average education: slightly under year 12 Mean MMSE (SD): 27 (2.5)	Omega 3 supplementation Diet rich in EPA (1.67 g EPA + 0.16 g DHA daily) or DHA (1.55 DHA + 0.40 g EPA daily) or n-6 PUFA linoleic acid (PUFA linoleic acid 2.2 g) daily for 6 months	Other groups (a diet rich in EPA, or DHA, or 6-6 PUFA linoleic acid)	6 months	Executive/Attention/Processing Speed [DS Forward] [DS Backward] [Letter-Number Sequencing] [TMT A] [TMT B] [SCWT] Memory [RAVLT] Language [Verbal Fluency]

AD=Alzheimer's disease; DHA= docosahexaenoic acid; DS=Digit Span (Forward and/or Backward); EPA=eicosapentaenoic acid; g=grams; MCI=mild cognitive impairment; MMSE=Mini-Mental Status Examination; N=sample size; NR=not reported; PUFA=polyunsaturated fatty acids; RAVLT=Rey's Auditory Verbal Learning Test; RCT=randomized controlled trial; RoB=risk of bias; SCWT=Stroop Color Word Test; SD=standard deviation; VR=Rerbal Recognition

Appendix Table H5. Summary risk of bias assessments: nutraceuticals in adults with MCI

Nutraceutical Type	Study	Overall Risk of Bias Assessment	Rationale
Omega 3 fatty acids efficacy	Lee 2013[21]	Low/Medium	Possible detection bias (unclear outcomes assessment)
Ginkgo biloba	Gavrilova, 2014[22]	Low	
	DeKosky, 2008[14]	Low	
Omega 3 fatty acids comparative effectiveness	Sinn, 2012[23]	High	Randomization not well described; attrition > 25% without appropriate analysis to account for possible bias

MCI=mild cognitive impairment

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Appendix I. Diet Interventions

Appendix Table I1. Characteristics of eligible studies: nutrition/lifestyle interventions in adults with normal cognition

Diet Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Caloric restriction diet interventions	Martin 2007[1] RCT USA High	48	Overweight adults aged 25 to 50 with a BMI ≤25 and <30 Mean age: 38 56% Female 63% White Education: NR Baseline cognition: NR	1) calorie restriction (25% calorie restriction based on baseline energy requirements); food provided at a center weeks 1-12, and 22-24, diets self-selected in weeks 13-22 2) calorie restriction + structured exercise (12.5% calorie restriction + 12.5% increase in energy expenditure via structured exercise) 3) very low-calorie diet (890 kcal/d liquid formula diet until 15% of body weight is lost, followed by weight maintenance)	Weight maintenance diet	6 months	Executive/Attention/Processing Speed [Conners' CPT-II] Memory [RAVLT] [ACT] [BVRT]
Energy restriction diet interventions	Napoli 2014[2] RCT Italy Medium	107	Obese (BMI ≥30), sedentary adults with stable body weight aged ≥65 Mean age: 70 Sex: 63% Female Race: 85% White Mean education: 16 years Baseline cognition: NR	1) Diet: calorie restriction; counseling; goal setting; 10% weight loss with maintenance 2) Exercise: counseled on weight maintenance; multicomponent exercise 3 times/week 3) Diet + Exercise: both interventions	Information control: general nutrition information; instructed not to make changes to daily routine	1 year	Multidomain Neuropsychological Test Performance [3MS] Executive/Attention/Processing Speed [TMT A] [TMT B] Language [Word List Fluency]

	Brinkworth 2009[3] RCT Australia High	118	Adults aged 24 to 64 years with abdominal obesity and at least 1 additional metabolic syndrome risk factor Mean age: 50 Sex: NR Race: NR Education: NR Mean 3MS (SE): 96.3 (0.8) control 96 (0.6) diet only 95.6 (0.8) diet-exercise	Energy-restricted, planned, isocaloric, very low carbohydrate, high fat (LC) diet	High-carbohydrate, low-fat diet with individual counseling for first 8 weeks.	1 year	Executive/Attention/Processing Speed [DS Backward] [Inspection Time]
Mediterranean Diet interventions	Valls-Pedret 2015[4] PREDIMED RCT Spain High	447	Adults aged 55 to 80 with no cardiovascular disease, but high vascular risk Mean age: 67 51% Women Mean education: 7 years Baseline global cog: NR	1) Mediterranean Diet high consumption plant-based foods, fish and seafood; low consumption of dairy, meat, processed grains; regular moderate alcohol (red wine with meals preferred) plus extra-virgin olive oil 2) Mediterranean Diet + mixed nuts	Information control (leaflet about low-fat diets)	5 years	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [Color Trail Test Part 1] [Color Trail Test Part 2] Memory [RAVLT, Total Learning And Delayed Recall] [Verbal Paired Associates] Language [Verbal Fluency]
	Martinez-Lapiscina 2013(a)[5] PREDIMED RCT Spain High	1055	Adults aged 55 to 80 with no cardiovascular disease, but high vascular risk Mean age: 67 55% Female Race: NR Education: >8 years: 29% Baseline global cog: NR	1) Mediterranean Diet high consumption plant-based foods, fish and seafood; low consumption of dairy, meat, processed grains; regular moderate alcohol (red wine with meals preferred) plus extra-virgin olive oil 2) Mediterranean Diet + mixed nuts	Information control (leaflet about low-fat diets)	6.5 years	Diagnosis [Incidence of MCI] Brief Cognitive Test Performance [MMSE] Visuospatial [Clock Drawing Test]
	Martinez-Lapiscina	285	Adults aged 55 to 80 with no	1) Mediterranean Diet high consumption plant-	Information control (leaflet about low-	6.5 years	Diagnosis [Incidence of MCI] Brief Cognitive Test Performance [MMSE]

	2013(b)[6] PREDIMED (subgroup) RCT Spain High		cardiovascular disease, but high vascular risk Mean age: 67 55% Female Race: NR Mean education: 9 years Baseline global cog: NR	based foods, fish and seafood; low consumption of dairy, meat, processed grains; regular moderate alcohol (red wine with meals preferred) plus extra-virgin olive oil 2) Mediterranean Diet + mixed nuts	fat diets)		Executive/Attention/Processing Speed [TMT A] [TMT B] [DS Forward] [DS Backward] Memory [RAVLT, Immediate And Delay] [Verbal Paired Associates] [RCFT] Language [Similarities] [Semantic Verbal Fluency Test-Animals] [Phonemic Verbal Fluency Test] [BNT] Visuospatial [Clock Drawing Test] [RCFT]
	Komulainen 2010[7] RCT Finland High	450	Men and women age 55 to 74 Age, Mean (SD) 66.3 (5.3) Sex NR Race NR Education, Mean (SD) 11.3 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Counseling by nutritionists to modify diet to specific recommendations	General health advice on diet and physical activity	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
Protein supplement interventions	van der Zwaluw 2014[8] RCT Netherlands Medium	65	Elderly adults aged ≥65 and an elevated plasma Hcy level (12-50 µmol/L) Mean age: 80 55% Female Education: Low: 9% (protein) and 0% (placebo) Middle: 59% (protein) and 55% (placebo) High: 32% (protein) and 45% (placebo) Mean MMSE (IQR): 29 (26-30) protein 28 (26-30) placebo	Protein drink (15mg of protein) twice daily	Placebo drink	24 weeks	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DS Forward] [Digit Span Backward] [TMT A] [TMT B] [SCWT] [DSST] [Reaction Time Test] Memory [Word Learning Test] Language [Letter Fluency]

	Wouters-Wesseling 2005[9] RCT USA High	101	White adults aged ≥65 and a BMI ≤25 kg/m2) Mean age: 83 58% Female 100% White Education: ≤6 years: 50% (intervention) 38% (placebo) 7-9 years: 35% (intervention) 47% (placebo) >9 years 15% (intervention) 15% (placebo) Baseline global cog: NR	125-ml enriched drink containing 30%–150% of the U.S. Recommended Daily Allowance of vitamins and minerals, with enhanced amounts of antioxidants, and containing 250 kcal energy in a daily dose	Placebo drink	6 months	Memory [Recognition Memory Test for Words] Language [Category Fluency] [Word Learning Test]

3MS=Modified Mini Mental Status Examination; BVRT=Benton Visual Retention Test; cog=cognitive; N=sample size; DS=Digit Span (Forward and/or Backward); NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation; SE=standard error; TMT=Trail Making Test (Part A and/or B); US=United States

Appendix Table I2. Summary risk of bias assessments: diet interventions in adults with normal cognition

Diet Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
Caloric restriction diet	Martin 2007[1]	High	Method of randomization unclear. High reporting bias due to unclear results
Energy restriction diet	Napoli 2014[2]	Medium	Method of randomization unclear. 13% attrition with no sensitivity analysis.
	Brinkworth 2009[3]	High	Method of randomization unclear. Attrition 44%
Mediterranean Diet	Valls-Pedret 2015[4]	High	Attrition 25% with no sensitivity analysis

	Martinez-Lapiscina 2013(a)[5]	High	Attrition 51%
	Martinez-Lapiscina 2013(b)[6]	High	Poor randomization
	Komulainen 2010[7]	High	Flaw in study design related to the analysis of the data and suspected reporting bias
Protein supplement	van der Zwaluw[8]	Low	Did not report if outcome assessor was blinded or independent
Nutrient supplement	Wouters-Wesseling[9]	High	Attrition 34%

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Appendix J. Multimodal Interventions

Appendix Table J1. Characteristics of eligible studies: multimodal interventions vs. inactive controls in adults with normal cognition

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Physical Activity and Diet	Lehtisalo 2016[1] RCT Finland High	364	Overweight or obese adults with impaired glucose intolerance Age, Mean (SD) 55.1 (6.8) 60% Female Race NR 34% With Higher Education Baseline Cognition NR	Seven initial counseling sessions followed by sessions every 3 months with nutritionist on Individualized dietary, physical activity, and weight and voluntary supervised exercise sessions for 4 years.	General health advice at baseline.	4 years	Executive/Attention/Processing Speed [TMT A] Memory [CERAD Total Score]
	Napoli 2014 [2] RCT US Medium	55	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White Years of Education, Mean (SD) 16.3 (3.7) 3MS, Mean (SD) 95.7 (0.8)	Diet and aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year and energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed by 6 months of weight maintenance	Information about healthy diet (not allowed to participate in any exercise program)	1 year	Brief Cognitive Test Performance [3MS] Executive/Attention/Processing Speed [TMT A] Executive/Attention/Processing Speed [TMT B] Language [Word List Fluency]
	Komulainen 2010[3] RCT Finland High	470	Men and women age 55 to 74 Age, Mean (SD) 66.3 (5.3) Sex NR Race NR	Individualized, independent, aerobic exercise program either 5 times/week for 60 min or 5 times/week for 90	General health advice on diet and physical activity	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			Education, Mean (SD) 11.3 (3.9) MMSE, Mean (SD) 27.6 (2.1)	min for 2 years and counseling by nutritionists to modify diet to specific recommendations			Composite] Visuospatial [Visual Performance Composite]
	Komulainen 2010[3] RCT Finland High	470	Men and women age 55 to 74 Age, Mean (SD) 66.3 (5.3) Sex NR Race NR Education, Mean (SD) 11.3 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, strength training program either 2 times/week or 3 times per week and counseling by nutritionists to modify diet to specific recommendations	General health advice on diet and physical activity	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
	Martin 2007[4] RCT US Medium	24	Overweight adults aged 25 to 50 years Age, Mean (SD) 37.5 (1.9) 56% Female 62.5% White Education NR Baseline Cognition NR	Individual-based calorie restriction (12.5% reduction) and structured exercise (12.5% increase in energy expenditure) for 6 months	Weight maintenance for 6 months	6 months	Executive/Attention/Processing Speed [CPT-II, Beta (Response Style)] [CPT-II, Omissions] [CPT-II, Detectability] [CPT-II, RT] [CPT-II, RT SE] [CPT-II, Commissions] [CPT-II, Perseverations] [CPT-II, RT Block Changes] Memory [RAVLT, Trial I-V] [RAVLT, Trial B] [RAVLT, Trial VI] [RAVLT, Delayed Recall] [RAVLT, Recognition] [Auditory Consonant Trigram, 9 sec] [Auditory Consonant Trigram, 18 sec] [Auditory Consonant Trigram, 36 sec] [BVRT, Correct Deviation] [BVRT, Error Deviation]
Physical Activity and Cognitive Training	Hars 2014[5] RCT Switzerland Medium	134	Community dwelling adults age 65 and older with an increased risk of falling, balance	Structured music-based multitask exercise classes (walking while following changes to	Maintain usual lifestyle habits for 6 months (delayed intervention)	6 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [FAB] [Sensitivity to Inference Subtest, FAB]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			impairment, or frailty. Age, Mean (SD) 75.5 (7) 96% Female Race NR 18% With High School Education MMSE, Mean (SD) 26.1 (2.9)	rhythmic patterns in piano music and handling objects) -60 minute sessions, 1 session/per week for 25 weeks			Visuospatial [CLOX-1]
	Tesky 2011[6] RCT Germany High	307	Adults age 65 + with no previous dementia or MCI diagnosis Age, Mean (SD) 71 (6) 73% Female Race NR Years Education, Mean (SD) 10.4 (1.8) ADAS-cog, Mean (SD) 7.15 (2.7)	Group cognitive stimulating leisure activities (8 weekly sessions and 2 booster sessions after 16 weeks post-intervention) with nutritional education and physical activity (courses on gymnastics, walking, yoga)	Usual care for Booklet on training topics (received at the end of the study)	32 weeks	Diagnosis [CDR] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [TMT A] [TMT B]
	Oswald 2006[7] RCT Germany High	375	Adults age ≥75 years without functional, cognitive or physical decline Age, Mean (SD) 79.5 (3.5) 64.8% Female 58.9% Secondary school education or higher	Memory training (90 minutes sessions) and gymnastic exercises (45 minute sessions), 30 sessions total	No intervention for duration of study	5 years	Multidomain Neuropsychological Test Performance [Composite]
	Carlson 2008[8] RCT US High	149	Cognitively intact older adults with a MMSE of ≥24 Age, Mean (SD)	Experience Corps Program-Cognitive activity (reading to children and library	Wait-list control	8 months	Executive/Attention/Processing Speed [TMT A] [TMT B] Memory [Word List Memory, Immediate

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			69 (6) 90% Female 95% African American Education, Mean (SD): 11.5 (3) years MMSE, Mean (SD) 25.1 (3)	service), physical activity, and social engagement for 15 hrs/week over a school year			Recall] [Word List Memory, Delayed Recall] [RCFT, Copy Score] [RCFT, Delayed Recall] Visuospatial [RCFT, Copy Score] [RCFT, Delayed Recall]
Physical Activity, Diet, and Cognitive Training	Ngandu 2015[9] RCT Finland Low	1260	Individuals age 60–77 years with a CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. Age, Mean (SD) 69.5 (4.6) Race NR Years Education, Mean (SD) 10.0 (3.4) MMSE, Mean (SD) 26.7 (2)	Individual and group nutritional intervention, individualized aerobic (1-3 times/week) and strength training (2-5 times/week) programs, group and individual cognitive training, and management of metabolic and vascular risk factors (via lifestyle changes) for 2 years.	General health advice	2 years	Multidomain Neuropsychological Test Performance [NTB, Total Score] Executive/Attention/Processing Speed [NTB, Executive Functioning] [NTB, Processing Speed] Memory [NTB, Memory] [NTB, Abbreviated Memory]
Physical Activity and Protein Supplementation	van de Rest 2014[10] RCT Netherlands Medium	58	Frail and pre-frail adults age 65 and over Age, Mean (SD) 77.8 (8.5) 62% Female 34% with Higher Education Race NR MMSE, Mean (Range) 28.5 (21-30))	Resistance-type exercise program and protein supplementation -2 sessions/week with personal supervision for 24 weeks	Usual Care (no exercise) and protein supplementation for 24 weeks	24 weeks	Executive/Attention/Processing Speed [Executive Functioning Composite] [DS Forward] [DS Backward] [TMT A] [TMT B/A] [SCWT (Test 1)] [SCWT (Test 2)] [SCWT (Interference)] [Finger Precuing, Reaction Time Uncued] [Finger Precuing, Reaction Time Cued] [Information Processing Speed Composite]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
							Memory [Word Learning Test, Immediate Recall-75 Words] [Word Learning Test, Delayed Recall-15 Words] [Word Learning Test, Decay] [Word Learning Test, Recognition, 30 Words] [Attention and Working Memory Composite] Language [Word Fluency, Animals] [Word Fluency, Letter P]
Goal Setting	Clare 2015[11] RCT UK Medium	46	Individuals aged 50 and over, living and functioning independently in the community Age, Mean (SD) 68.21 (7.92) 86.7% Female Race NR Year of Education, Mean (SD) 13.33 (2.93) Baseline Cognition NR	Goal Setting: Structured goal-setting process using Bangor Goal Setting Interview during 90 minute session. Participant set 5 goals for the coming year relating to physical activity, cognitive activity, physical health, diet, or social engagement. OR Goal Setting and Mentoring: Goal setting with five, bimonthly follow-up mentoring calls from researchers to review progress, discuss obstacles, and reinforce	Information: 90-minute session with interview where information was provided about activities and health.	1 year	Brief Cognitive Test Performance [Montreal Cognitive Assessment] Executive/Attention/Processing Speed [TMT] Memory [CVLT, Immediate Recall] [CVLT, Delayed Recall] Language [Verbal Fluency, Delis-Kaplan Executive Function System]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
				success.			
Occupational Therapy	Clark 2012[12] RCT US High	460	Individuals aged 60 years or older with no overt signs of dementia or psychosis. 52% Age 75 or older 37.4% White 16.7% with 4 or more years of college Baseline Cognition NR	Lifestyle-based occupational therapy intervention –Weekly 2 hour small group sessions for 6 months and 10 individual 1 hour sessions	No treatment	6 months	Executive/Attention/Processing Speed [Reaction Time, Visual Search Task] [DSST] Memory [CERAD, Immediate Recall] [CERAD, Delayed Recall] [CERAD, Recognition]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Care Management	Lee 2014[13] RCT South Korea High	1,115	Community-dwelling adults aged 60 and over Age. Mean (SD) 77.1 (2.5) 78.6% Female Race NR 21.9 % Middle school or higher MMSE, Mean (SD) 24.1 (1.7)	Telephonic or in-person care management including providing educational materials, counseling regarding health behavior, and recommendations for physical activity - Monthly or bi-monthly for 18 months	Standard care (no care management)	18 months	Brief Cognitive Test Performance [MMSE]
Cognitive Training and acetylcholinesterase inhibitor	Yesavage 2008[14] RCT US High	168	Community-dwelling adults aged 55-90 with a MMSE score between 24 and 30 Age, Mean (SD) 65 (8) 52% Female Race NR Education, Mean (SD) 16.3 (2.3) MMSE, Mean (SD) 28.6 (1.2)	Daily dose of 5 mg of Donepezil for 6 weeks, then increased to 10mg daily for 46 weeks; 2 weeks of cognitive training at weeks 13-14	Placebo and 2 weeks of cognitive training at weeks 13-14	1 year	Executive/Attention/Processing Speed [DSST] Memory [Word List Recall] [Name-Face Recall] [Logical Memory I Score] [Logical Memory II Score]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Lifestyle Advice and Drug Treatment	Moll van Charante 2016[15] RCT Netherlands Medium	3526	Community-dwelliing adults without dementia Age, Mean (SD): 74.5 (2.5) 55% Female 96% White 62% 7-12 Years of Education Baseline cog NR	Visits to a practice nurse to assess cardiovascular risk and receive lifestyle advice, every 4 months for 6 years. Medication prescribed as needed.	Usual care (defined by standards for cardiovascular risk management) for 6 years.	6 years	Diagnosis [All-Cause Dementia] [AD] Brief Cognitive Test Performance [MMSE] Memory [Visual Association Test A]

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; CDR=Clinical Dementia Rating; CLOX-1=Clock Drawing Test; cog=cognition; CPT=Conners' Continuous Performance Test-II; MMSE=Mini-Mental Status Examination; N=sample size; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RCFT=Rey-Osterrieth Complex Figure Test; RCT=randomized controlled trial; RoB=risk of bias; sec=seconds; SCWT=Stroop Color Word Test; SD=standard deviation; TMT=Trail Making Test (Part A and/or B); US=United States

Appendix Table J2. Characteristics of eligible studies: multimodal interventions vs. active controls in adults with normal cognition

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Physical Activity and Diet vs. Diet	Napoli 2014 [2] RCT US Medium	647	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White	Diet and aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year and energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed	Diet - Energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed by 6 months of weight maintenance	1 year	Brief Cognitive Test Performance [3MS] Executive/Attention/Processing Speed [TMT A] [TMT B] Language [Word List Fluency]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			Years of Education, Mean (SD) 16.3 (3.7) 3MS, Mean (SD) 95.7 (0.8)	by 6 months of weight maintenance			
	Komulainen 2010[3] RCT Finland High	470	Men and women age 55 to 74 Age, Mean (SD) 66.5 (5.4) Sex NR Race NR Education, Mean (SD) 11.4 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, aerobic exercise program either 5 times/week for 60 min or 5 times/week for 90 min for 2 years and counseling by nutritionists to modify diet to specific recommendations	Counseling by nutritionists to modify diet to specific recommendations	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
	Komulainen 2010[3] RCT Finland High	470	Men and women age 55 to 74 Age, Mean (SD) 66.3 (5.3) Sex NR Race NR Education, Mean (SD) 11.3 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, strength training program either 2 times/week or 3 times per week and counseling by nutritionists to modify diet to specific recommendations	Counseling by nutritionists to modify diet to specific recommendations	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
	Martin 2007[4] RCT US Medium	24	Overweight adults aged 25 to 50 years Age, Mean (SD) 37.5 (1.9) 56% Female	Individual-based calorie restriction (12.5% reduction) and structured exercise (12.5% increase in energy expenditure) for 6 months	Calorie restriction (25% restriction) for 6 months	6 months	Executive/Attention/Processing Speed [CPT-II, Beta (Response Style)] [CPT-II, Omissions] [CPT-II, Detectability] [CPT-II, RT] [CPT-II, RT Standard Error] [CPT-II, Commissions]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			62.5% White Education NR Baseline Cognition NR				[CPT-II, Perseverations] [CPT-II, RT Block Changes] Memory [RAVLT, Trial I-V] [RAVLT, Trial B] [RAVLT, Trial VI] [RAVLT, Delayed Recall] [RAVLT, Recognition] [Auditory Consonant Trigram, 9 sec] [Auditory Consonant Trigram, 18 sec] [Auditory Consonant Trigram, 36 sec] [BVRT, Correct Deviation] [BVRT, Error Deviation]
	Martin 2007[4] RCT US Medium	24	Overweight adults aged 25 to 50 years Age, Mean (SD) 37.5 (1.9) 56% Female 62.5% White Education NR Baseline Cognition NR	Individual-based calorie restriction (12.5% reduction) and structured exercise (12.5% increase in energy expenditure) for 6 months	Low-calorie diet (890 kcal/d liquid formula diet until 15% of body weight is lost, followed by weight maintenance) for 6 months	6 months	Executive/Attention/Processing Speed [CPT-II, Beta (Response Style)] [CPT-II, Omissions] [CPT-II, Detectability] [CPT-II, RT] [CPT-II, RT Standard Error] [CPT-II, Commissions] [CPT-II, Perseverations] [CPT-II, RT Block Changes] Memory [RAVLT, Trial I-V] [RAVLT, Trial B] [RAVLT, Trial VI] [RAVLT, Delayed Recall] [RAVLT, Recognition] [Auditory Consonant Trigram, 9 sec] [Auditory Consonant Trigram, 18 sec] [Auditory Consonant Trigram, 36 sec] [BVRT, Correct Deviation] [BVRT, Error Deviation]
Physical Activity and Diet vs. Physical Activity	Napoli 2014 [2] RCT US Medium	54	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White	Diet and aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year and energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed	Aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year	1 year	Brief Cognitive Test Performance [3MS] Executive/Attention/Processing Speed [TMT A] [TMT B] Language [Word List Fluency]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			Years of Education, Mean (SD) 16.3 (3.7) 3MS, Mean (SD) 95.7 (0.8)	by 6 months of weight maintenance			
	Komulainen 2010[3] RCT Finland High	468	Men and women age 55 to 74 Age, Mean (SD) 66.5 (5.4) Sex NR Race NR Education, Mean (SD) 11.4 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, aerobic exercise program either 5 times/week for 60 min or 5 times/week for 90 min for 2 years and counseling by nutritionists to modify diet to specific recommendations	Individualized, independent, aerobic exercise program either 5 times/week for 60 min or 5 times/week for 90 min for 2 years	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]
	Komulainen 2010[3] RCT Finland High	470	Men and women age 55 to 74 Age, Mean (SD) 66.3 (5.3) Sex NR Race NR Education, Mean (SD) 11.3 (3.9) MMSE, Mean (SD) 27.6 (2.1)	Individualized, independent, strength training program either 2 times/week or 3 times per week and counseling by nutritionists to modify diet to specific recommendations	Individualized, independent, strength training program either 2 times/week or 3 times per week	2 years	Brief Cognitive Test Performance [MMSE] Memory [Immediate Memory Composite] [Delayed Memory Composite] Language [Verbal Performance Composite] Visuospatial [Visual Performance Composite]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Physical Activity and Cognitive Training vs. Physical Activity and Cognitive Training	Eggenberger 2015[16] RCT Switzerland Medium	89	Seniors older than 70 years with an MMSE score greater than 22 Age, Mean (SD) 78.9 (5.4) 52% Female Race NR Years of Education, Mean (SD) 13.2 (1.9) MMSE, Mean (SD) 28.2 (1.4)	Virtual reality video game dancing with cognitive training -60 minute group sessions 2 times/week for 6 months	Treadmill walking with verbal memory exercise -60 minute group sessions 2 times/week for 6 months	6 months	Executive/Attention/Processing Speed [TMT A] [TMT B] [Executive Control Task] [DS Forward] [DSST] [Age Concentration Test A] [Age Concentration Test B] Memory [Paired-Associates Learning] [Story Recall, WMS]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Physical Activity and Cognitive Training vs. Physical Activity	McDaniel 2014[17] RCT US High	96	Adults age 55 to 75 without dementia or MCI Age, Mean (SD) 65 (8) 67% Female 88% White Years Education, Mean (SD) 16 (2) MMSE, Mean (SD) 29 (1)	Treadmill walking or exercise bicycle program (45-50 minute sessions 3 times/week) for 6 months and cognitive training 3 days/week for 8 weeks	Low-intensity home exercise program focusing on flexibility for 6 months and in-person health education for 8 weeks	6 months	Executive/Attention/Processing Speed [SCWT Part 1] [SCWT Part 2] [DSST] [TMT A] [TMT B] Memory [Logical Memory Immediate] [Logical Memory Delayed, Wechsler] [Virtual Week (5-min Break)] [Memory for Health Information Part 1] [Memory for Health Information Part 2]
	McDaniel 2014[17] RCT US High	96	Adults age 55 to 75 without dementia or MCI Age, Mean (SD) 65 (8) 67% Female 88% White Years Education, Mean (SD) 16 (2) MMSE, Mean (SD) 29 (1)	Treadmill walking or exercise bicycle program (45-50 minute sessions 3 times/week) for 6 months and cognitive training 3 days/week for 8 weeks	Treadmill walking or exercise bicycle program -45-50 minute sessions 3 times/week for 6 months	6 months	Executive/Attention/Processing Speed [SCWT Part 1] [SCWT Part 2] [DSST] [TMT A] [TMT B] Memory [Logical Memory Immediate] [Logical Memory Delayed, Wechsler] [Virtual Week (5-min Break)] [Memory for Health Information Part 1] [Memory for Health Information Part 2]

Intervention Type	Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
	McDaniel 2014[17] RCT US High	96	Adults age 55 to 75 without dementia or MCI Age, Mean (SD) 65 (8) 67% Female 88% White Years Education, Mean (SD) 16 (2) MMSE, Mean (SD) 29 (1)	Treadmill walking or exercise bicycle program (45-50 minute sessions 3 times/week) for 6 months and cognitive training 3 days/week for 8 weeks	Low-intensity home exercise program focusing on flexibility for 6 months and cognitive training 3 days/week for 8 weeks	6 months	Executive/Attention/Processing Speed [SCWT Part 1] [SCWT Part 2] [DSST] [TMT A] [TMT B] Memory [Logical Memory Immediate] [Logical Memory Delayed, Wechsler] [Virtual Week (5-min Break)] [Memory for Health Information Part 1] [Memory for Health Information Part 2]

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; CDR=Clinical Dementia Rating; CLOX-1=Clock Drawing Test; cog=cognition; CPT=Conners' Continuous Performance Test-II; MMSE=Mini-Mental Status Examination; N=sample size; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RCFT=Rey-Osterrieth Complex Figure Test; RCT=randomized controlled trial; RoB=risk of bias; sec=seconds; SCWT=Stroop Color Word Test; SD=standard deviation; TMT=Trail Making Test (Part A and/or B); US=United States; WMS=Wechsler Memory Scale

Appendix Table J3. Summary risk of bias assessments: multimodal interventions in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Lehtisalo 2016[1]	High	High rate of attrition with no analysis to address risk of bias.
Moll van Charante 2016[15]	Medium	Potential for bias due to high dropout rate across all study arms.
Clare 2015[11]	Medium	Potential performance and detection bias.
Eggenberger 2015[16]	Medium	Attrition rate is 20% with potential performance bias.
Ngandu 2015[9]	Low	No significant risk of bias detected.
Hars 2014[5]	Medium	Process for randomization is unclear and attrition rate is 16%.
Lee 2014[13]	High	High potential for bias due to over 50% attrition.
McDaniel 2014[17]	High	Process for randomization is unclear with suspected reporting bias.
Napoli 2014[2]	Medium	Process for randomization is unclear and 13% attrition rate.
van de Rest 2014[10]	Medium	Attrition is 15% with potential reporting bias.
Clark 2012[12]	High	Attrition rate is greater than 21% with no analysis to address potential bias.
Tesky 2011[6]	High	Attrition rate is greater than 21% with no analysis to address potential bias.
Komulainen 2010[3]	High	Flaw in study design related to the analysis of the data and suspected reporting bias
Carlson 2008[8]	High	Attrition rate is greater than 21% with no analysis to address potential bias.
Yesavage 2008[14]	High	Attrition rate is greater than 21% with no analysis to address potential bias.
Martin 2007[4]	Medium	Process for attrition is unclear with potential detection bias.
Oswald 2006[7]	High	Suspected selection bias due to process for randomization.

Appendix Table J4. Strength of evidence assessments: multimodal interventions versus inactive control in adults with normal cognition

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
Physical activity and diet vs. inactive control	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test Performance									
	Multidomain Neuropsychological Performance	NR								
	Executive Function	2 (79)	1 of 10 tests shows a statistically significant difference with intervention.	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient
	Memory	NR								
	Biomarkers	NR								
	Adverse Effects	NR								
Physical activity, diet, ad cognitive training vs. inactive control	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test Performance	NR								
	Multidomain Neuropsychological Performance	1 (1260)	1 of 1 test show a statistically significant difference with intervention. Ngandu 2015[9] NTB, Difference between groups per year [95% CI]	Low	Indirect	Precise	Unknown	Undetected	NA	Low

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
			0.022 [0.002, 0.042]							
	Executive Function	1 (1260)	2 of 2 tests show a statistically significant difference with intervention. Ngandu 2015[9] NTB Executive Functioning, Difference between groups per year [95% CI] 0.027 [0.001, 0.052] NTB Processing Speed, Difference groups per year [95% CI] 0.030 [0.003, 0.057]	Low	Indirect	Precise	Unknown	Undetected	NA	Low
	Memory	1 (1260)	1 of 2 tests shows a statistically significant difference	Low	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
			with intervention. Ngandu 2015[9] NTB Memory, Difference between groups per year [95% CI] 0.015 [-0.017, 0.048] NTB Abbreviated Memory, Difference between groups per year [95% CI] 0.038 [0.002, 0.073]							
	Biomarkers	NR								
	Adverse Effects	NR								
Lifestyle advice with drug treatment vs. inactive control	Dementia	1 (3526)	No difference with intervention in dementia incidence. Moll van Charante 2016[15]	Medium	Direct	Precise	Unknown	Undetected	NA	Low

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
			All-cause Dementia Hazard Ratio, [95% CI] 0.92 [0.71, 1.19] Alzheimer's Disease, Hazard Ratio [95% CI] 1.05 [0.78, 1.41]							
	MCI	NR								
	Brief Cognitive Test Performance	1 (3526)	1 of 1 tests shows no diference with intervention Moll van Charante 2016[15] MMSE, Adjusted mean difference [95% CI] -0.02 [-0.14 0.10]	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
	Multidomain Neuropsychological Performance	NR								
	Executive Function	NR								
	Memory	1 (3526)	1 of 1 tests shows no	Medium	Indirect	Precise	Unknown	Undetected	NA	Low

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
			diference with intervention Moll van Charante 2016[15] Visual Association Test A, Adjusted mean difference [95% CI] -0·02 [-0.09, 0.04]							
	Biomarkers	NR								
	Adverse Effects	1 (3526)	No difference in serious adverse effects between intervention and control group. Moll van Charante 2016[15] Serious adverse events (hospital admissions), Hazard Ratio (p-value) 0.96 (p=0.56)	Medium	Indirect	Precise	Unknown	Undetected	NA	Low

C=control; CI=confidence interval; I=intervention; MCI=mild cognitive impairment; MMSE=MMSE=Mini-Mental Status Examination; n=sample size; NA=not applicable; NR=not reported; NTB=Neuropsychological Test Battery; RCT=randomized controlled trial; SD=standard deviation

Appendix Table J5. Strength of evidence assessments: multimodal interventions versus active comparison in adults with normal cognition

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
Physical activity and diet vs. diet	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test Performance									
	Multidomain Neuropsychological Performance	NR								
	Executive Function	2 (90)	18 of 18 tests show no statistically significant difference with intervention.	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
	Memory	NR								
	Biomarkers	NR								
	Adverse Effects	NR								

C=control; CI=confidence interval; I=intervention; MCI=mild cognitive impairment; NA=not applicable; NR=not reported; vs.=versus

Appendix Table J6. Characteristics of eligible studies: multimodal interventions vs. inactive controls in adults with MCI

Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Fiatarone Singh 2014[18] RCT Australia High	51	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) and Resistance Training -100 minutes 2 days/week for 6 months	Sham cognitive training and sham exercise	6 months 18 months	Multidomain Neuropsychological Test Performance [ADAS-Cog] [Global Cognition Domain Composite] Executive/Attention/Processing Speed [Executive Function Domain Composite] [WAIS Similarities] [WAIS Matrices] [COWAT] [SDMT] Memory [Memory Domain Composite] [List Learning Memory Sum from ADAS-Cog] [BVRT] [Logical Memory, Immediate] [Logical Memory, Delayed] Language [Category Fluency, Animal Naming] [COWAT]
Johari 2014[19] RCT Malaysia High	35	Individuals with MCI based on Petersen criteria Age, Mean (SD) 65.7 (3.8) 54.3% Female 83% Malay 94% with Formal Education MMSE, Mean (SD) 27 (3)	Nutrition and lifestyle education (7 guidelines) – Monthly sessions for 12 months	No education, supplementation with placebo capsule containing 1000 mg corn oil (taken 3 times a day for 12 months)	12 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [DSST] [Matrix Reasoning] Memory [VR I] [VR II, Delayed] [RAVLT] Visuospatial [Block Design] [CLOX-1]

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; BVRT=Benton Visual Retention Test; COWAT=Controlled Oral Word Association Test; MCI=mild cognitive impairment; mg=milligrams; MMSE=Mini-Mental Status Examination; N=sample size; NR=not reported; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation; SDMT=Symbol Digit Modalities Test; VR=Visual Reproduction; WAIS=Wechsler Adult Intelligence Scale;

Appendix Table J7. Characteristics of eligible studies: multimodal interventions vs. active controls in adults with MCI

Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Kobe, 2016[20] RCT Germany High	35	MCI patients diagnosed according to Mayo criteria Age, Mean (SD) 70 (6.2) 64% Male Years of Education, Mean (SD) 16.3 (3.5) MMSE, Mean (SD) 28.2 (1.4)	Aerobic exercise (45 minutes twice a week), cognitive stimulation (cognitive stimulating leisure activities and memory strategies; 12, 90 minute sessions), and omega-3 FA supplementation (2200 mg) for 6 months	Non-aerobic exercise (45 minutes twice a week) and omega-3 FA supplementation (2200 mg) for 6 months.	6 months	Brief Cognitve Test Performance [MMSE] Executive/Attention/Processing Speed [Composite] [Attention Composite] Memory [Composite]
Lam 2015[21] RCT China High	263	Chinese older adults with MCI (presence of subjective cognitive complaints, and objective impairments in cognitive function) Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level, Mean (SD) 3.9 (3.6) ADAS-cog, Mean (SD) 11.5 (3.3)	Cognitive and mind-body exercises -1 hour sessions 3 times/week	Social activities (e.g., tea gathering, film watching) –At least 1 hour sessions 3 times/week	8 months 12 months	Diagnosis [CDR, Sums of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Chinese Version] Memory [Delayed Recall] Language [CVFT]

Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Lam 2015[21] RCT China High	277	Chinese older adults with MCI (presence of subjective cognitive complaints, and objective impairments in cognitive function) Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level, Mean (SD) 3.9 (3.6) ADAS-cog, Mean (SD) 11.5 (3.3)	Cognitive and mind-body exercises -1 hour sessions 3 times/week	Cognitively demanding activities (e.g., reading and discussing news, board games) –At least 3 sessions/weeks	8 months 12 months	Diagnosis [CDR, Sums of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Chinese Version] Memory [Delayed Recall] Language [CVFT]
Lam 2015[21] RCT China High	279	Chinese older adults with MCI (presence of subjective cognitive complaints, and objective impairments in cognitive function) Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level, Mean (SD) 3.9 (3.6) ADAS-cog, Mean (SD) 11.5 (3.3)	Cognitive and mind-body exercises -1 hour sessions 3 times/week	Stretching and toning, mind body exercise (e.g., Tai Chi), and aerobic exercise -1 session/week of each type, 60 minutes/session	8 months 12 months	Diagnosis [CDR, Sums of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Chinese Version] Memory [Delayed Recall] Language [CVFT]

Study Design Country RoB	N=	Population Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Fiatarone Singh 2014[18] RCT Australia High	51	Adults age 55 and older with aMCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) and Resistance Training -100 minutes 2 days/week for 6 months	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) -100 minutes 2 days/week for 6 months	6 months 18 months	Multidomain Neuropsychological Test Performance [Global Cognition Domain Composite] [ADAS-Cog] Executive/Attention/Processing Speed [Executive Function Domain Composite] [WAIS Similarities] [WAIS Matrices] [COWAT] [SDMT] Language [Category Fluency, Animal Naming] [COWAT] Memory [List Learning Memory Sum from ADAS-Cog] [BVRT] [Logical Memory, Immediate] [Logical Memory, Delayed] [Memory Domain Composite]
Fiatarone Singh 2014[18] RCT Australia High	49	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) and Resistance Training -100 minutes 2 days/week for 6 months	Resistance Training -100 minutes 2 days/week for 6 months	6 months 18 months	Multidomain Neuropsychological Test Performance [Global Cognition Domain Composite] [ADAS-Cog] Executive/Attention/Processing Speed [Executive Function Domain Composite] [WAIS Similarities] [WAIS Matrices] [COWAT] [SDMT] Memory [List Learning Memory Sum from ADAS-Cog] [BVRT] [Logical Memory, Immediate] [Logical Memory, Delayed] [Memory Domain Composite] Language [Category Fluency, Animal Naming] [COWAT]

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; CDR=Clinical Dementia Rating; CVFT=Category Verbal Fluency Test; MCI=mild cognitive impairment; MMSE=Mini-Mental Status Examination; N=sample size; NR=not reported; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation; SDMT=Symbol Digit Modalities Test; WAIS=Wechsler Adult Intelligence Scale

Appendix Table J8. Summary Risk of Bias Assessments: Multimodal interventions in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Kobe 2016[20]	High	Suspected selection, attrition, and detection bias.
Lam 2015[21]	High	Attrition rate is higher than 21% with no analysis to address potential bias.
Fiatarone Singh 2014[18]	High	Suspected reporting bias. Results for intervention arms are combined in the analysis,
Johari 2014[19]	High	Process for randomization not described, potential detection bias, and potential performance bias due to concurrent intervention.

MCI=mild cognitive impairment

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Appendix K. Hormone Interventions

Appendix Table K1. Characteristics of eligible studies: hormone interventions vs. inactive controls in adults with normal cognition

Homone Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
HRT-Estrogen	Henderson 2016[1] RCT USA Medium (2.5 years) High (5 years)	567	Healthy postmenopausal women Mean age (SD) (early menopause): 55.5 (4.1) years Mean age (SD) (late menopause): 64.4 (6) years 100% female 71% White 79% college graduate Baseline cognition: NR	Oral estrogen therapy (17 beta-estradiol, 1 mg/day) for a mean duration of 57 months	Identically appearing placebo for a mean duration of 57 months	2.5 & 5 years	Multidomain Neuropsychological Test Performance [Global Cognition Composite] Executive/Attention/Processing Speed [Executive Functions Composite] Memory [Verbal Episodic Memory]
	Wroolie 2015[2] Rasgon 2014[3] RCT USA Medium (cognitive outcomes) High (MRI)	64	Postmenopausal women aged 49-69 years at risk of developing dementia Mean age (SD): 58 (5) years Race: NR Mean education (SD): 16 (2) years Baseline cog: NR	Continued estrogen-based hormone therapy (17 beta-estradiol or conjugated equine estrogen) for 2 years after an average of 10 years of use	Discontinuation of estrogen therapy for 2 years after an average of 10 years of use	2 years	Biomarker [PET scan to assess changes on regional cerebral metabolism] Executive/Attention/Processing Speed [Attention/Working Memory/Processing Speed Composite] [Executive Function Composite] Memory [Verbal Memory Composite] [Visual Memory Composite] [Subjective Memory Composite]
	Espeland 2013[4] Espeland 2010[5] Coker 2009[6] Resnick 2009[7]	2947	Community dwelling postmenopausal women aged 65-80 years, free of probable dementia at enrollment 45% aged 65-69 37% aged 70-74	Estrogen (conjugated equine estrogen 0.625 mg) daily	Placebo daily	Varied 5.7 – 8+ years	Diagnosis [Incidence of Probable Dementia] [Incidence of MCI] Biomarker [MRI: Total Brain Volume] [MRI: Ventricle Volume] [MRI: Hippocampal Volume] [MRI: Frontal Lobe Volume] [MRI: White and Gray Matter (outside of basal ganglia)] [MRI:

	Resnick 2009[8] Resnick, 2006[9, 10] Shumaker 2004[11] Rapp 2003[12] (Women's Health Initiative sub-studies) Medium		18% aged 75+ 100% female 85% White Education 31% ≤ high school 42% > some college 27% ≥ college Mean 3MSE (SD): 94.6 (4.8)				Basal Ganglia] [MRI: Total Brain Lesion Volume] Brief Cognitive Test Performance [3MS] [TICS] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [TMT A] [TMT B] Memory [BVRT] [CVLT] [EBMT] Language [Primary Mental Abilities-Verbal] [Verbal Fluency] Visuospatial [Card Rotations Test] Motor [Finger Tapping, Dominant Hand] [Finger Tapping, Non-Dominant Hand]
	Gorenstein 2011[13] RCT Brazil Medium	65	Healthy, postmenopausal women aged 40-59 years Mean age: 26.5 100% female Race not reported Mean education (SD): 9.1 (4) years Baseline cog: NR	Estrogen (conjugated equine estrogens 0.625 mg/day) for 6 months	Placebo for 6 months	6 months	Executive/Attention/Processing Speed [DS Forward] [DS Backward] [DSST] [3-min Reasoning Test, Correct] [3-min Reasoning Test, Time] Memory [PALS, Easy] [PALS, Difficult] [Immediate Verbal Recall] [Delayed Verbal Recall] [Free Recall of Words]
	Pefanco 2007[14] RCT USA Medium	57	Healthy postmenopausal women aged 65 and older Mean age (SD): 75(5) years 100% female Race: NR 77% college graduate Baseline cognition: NR	Micronized 17-beta estradiol 0.25 mg/day for 3 years	Placebo for 3 years	3 years	Executive/Attention/Processing Speed [COWAT] [Animal Naming] [TMT A] [TMT B] [Wisconsin Test] [Total Perservative Error] [Digital Written Score] Memory [Immediate Recall] [Delayed Recall] [Fuld Object Memory Evaluation] [Total Recall Trial 5] [Total Recall, 5-Minute Delay] [Total Recognized 5-Delay] [Wechsler Logical Memory 1] [Verbal Paired Association 1] [Visual Representation 1] [Logical Memory 2] [Verbal Paired Association 2] [Visual Representation] [Recognition Total Score 1] [Recognition Total Score 2] [Recognition Total Score 3] Language [BNT] Visuospatial [RCFT]
	Yaffe 2006[15] RCT USA	417	Postmenopausal women aged 60 to 80 years Mean age (SD): 66.8 (5)	Weekly transdermal patch that	Placebo patch for 2 years	2 years	Brief Cognitive Test Performance [3MS] Executive/Attention/Processing Speed

	Low		years 100% female 93% White 73% ≥ high school Baseline cognition (3MS):Mean (SD): 96.8 (3.4)	delivers 0.014 mg estradiol/day for 2 years			[TMT B] Memory [Logical Memory, Immediate] [Logical Memory, Delayed] [Brief Visuospatial Memory Test, Immediate] [Brief Visuospatial Memory Test, Delayed] [Word List, Memory] [Word List, Recall] Language [BNT] [Verbal Fluency]
HRT-estrogen + progestin	Kantarci 2016[16] Gleason 2015[17] RCT USA Medium (cognitive tests) High (MRI)	505	Healthy postmenopausal women aged 52 to 65 years Mean age (SD): 52.5 (2.6) years 100% female 77% White 73% college graduate Baseline cognition (3MS):Mean (SD): 96.6 (4.3)	Low dose oral conjugated equine estrogen 0.45 mg daily plus cyclical micronized progesterone 200 mg capsule or transdermal estradiol (200 mg daily) plus cyclical micronized progesterone	Placebo	4 years	Biomarker [MRI] Brief Cognitive Test Performance [3MS] Executive/Attention/Processing Speed [Visual Attention & Executive Function Composite] Memory [Verbal Learning & Memory Composite] [Auditory Attention & Working Memory Composite] Language [Speeded Language & Mental Flexibility]
	Espeland 2013[4] Espeland 2010[5] Coker 2009[6] Resnick 2009[8] Resnick 2006[9] Espeland 2004[10] Shumaker 2004[11] Shumaker 2003[18] Rapp 2003[12] RCT (Women's Health Initiative substudies)	4532	Community dwelling postmenopausal women aged 65-80 years, free of probable dementia at enrollment 45% aged 65-69 37% aged 70-74 18% aged 75+ 100% female 85% White Education 31% ≤ high school 42% > some college 27% ≥ college Mean 3MSE (SD): 94.7 (4.5)	Estrogen (conjugated equine estrogen 0.625 mg) daily with progestin (medroxyprogesterone acetate 2.5 mg) daily	Placebo daily	Average 7 years	Diagnosis [Incidence of Probable Dementia] [Incidence of MCI] Biomarker [MRI: Total Brain Volume] [MRI: Ventricle Volume] [MRI: Hippocampal Volume] [MRI: Frontal Lobe Volume] [MRI: White and Gray Matter (outside of basal ganglia)] [MRI: Basal Ganglia] [MRI: Total Brain Lesion Volume] Brief Cognitive Test Performance [3MS] [TICS] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [TMT A] [TMT B] Memory [BVRT] [CVLT] [EBMT] Language [Primary Mental Abilities-Verbal] [Verbal Fluency] Visuospatial [Card Rotations Test] Motor [Finger Tapping, Dominant Hand] [Finger Tapping, Non-Dominant Hand]

	USA Medium						
	Davison 2013[19] RCT Australia Medium	23 13 (MRI)	Healthy postmenopausal women aged 49-55 years Mean age: 53 100% women Race: NR Education: NR Baseline cognition: NR	Estrogen (oral estradiol + progestin (drospirenone) for 6 months	Placebo for 6 months	6 months	Executive/Attention/Processing Speed [Groton Maze Learning Task] [CogState Identification] [CogState Detection Speed] [Mental Rotation] Memory [Groton Maze Recall] [CogState International Shopping List, Learn] [CogState International Shopping List, Recall] [CogState Continued Paired Associate Learning] Visuospatial [Mental Rotation]
	Alhola 2010[20] RCT Finland High	32	Premenopausal (aged 45-51 years) and postmenopausal (aged 58-70 years) women Mean age pre-menop (SD): 48 (1.5) Mean age post-menop (SD): 63 (2.5) 100% female Race: NR Mean education (years): 15 years Mean MMSE (SD): 27 (1.5)	Estrogen + progestin daily for 6 months	Placebo daily for 6 months	6 months	Executive/Attention/Processing Speed [Verbal Functions, Similarities] [Digit Span] [Counting] [Digit Symbol] [CogniSpeed, SRT] [CogniSpeed, 2-CRT] [CogniSpeed, 10-CRT] [CogniSpeed, Subtraction] [CogniSpeed, Verification] [CogniSpeed, Vigilance] [Stroop Congruence] [Stroop Incongruence] [PASAT, Easy, Correct] [PASAT, Easy, Correct Consecutive] [PASAT, Difficult, Correct] [PASAT, Difficult, Correct Consecutive] [Shared Attention Dual Task Efficiency, Cancellation] [Shared Attention Dual Efficiency, Counting] [Shared Attention Dual Task Smaller Percentage, Efficiency] Memory [RAVLT, Trial 1] [RAVLT, Trial 2] [RAVLT, Trial 3] [RAVLT, Immediate Recall] [RAVLT, Delayed Recall] [Benton Visual Retention, Immediate Recall] [Benton Visual Retention, Delayed Recall] Visuospatial [Block Design] [Cancellation]
	Maki 2009[21] RCT USA High	66	Midlife women aged 61-87 years with ≥ 35 weekly hot flashes Mean age (SD): 53 (4.5) years	Estrogen + progestin (0.625 mg conjugated equine estrogen + 2.5 mg	Placebo for 1 year	1 year	Executive/Attention/Processing Speed [DS Forward] [DS Backward] [Brief Test of Attention] [Finding As Test] Memory [CVLT, Total Learning] [CVLT, Short-Delay Free Recall] [CVLT, Long-

			100% female 45% White Education: NR Baseline cog: NR	medroxyprogesterone acetate) for 1 year			Delay Free Recall] [Logical Memory Subtest-WMS – Immediate Total Score] [Logical Memory Subtest-WMS – Delayed Total Score] [BVRT] Language [Letter Fluency Test] Visuospatial [Modified Card Rotations Test]
	Tierney 2009[22] RCT Canada Medium	142	Older postmenopausal women with normal to mildly impaired memory functioning (**28% had MCI at baseline**) Mean age (SD): 75 (6) years 100% female 90% White Education mean (SD): 13 (3) years) Mean MMSE (SD): 28 (1.5)	Estrogen + progestin (1 mg 17-B estradiol daily and 0.35 mg norethindrone 3 days/week) for 2 years	Placebo daily for 2 years	2 years	Memory [CVLT, Short Delay Recall]
	Grady 2002[23] USA RCT Medium	1063	Postmenopausal women with coronary disease Mean age (SD): 66.8 (6.3) years 100% female 91% White Mean education (SD): 12.7 (2.7) years Baseline cognition: NR	Conjugated estrogen (0.625 mg) plus medroxyprogesterone acetate (2.5 mg) daily for a mean of 4.2 (± 0.4) years	Identical placebo daily for a mean of 4.2 (± 0.4) years	Mean 4.2 (± 0.4 years)	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [TMT B] Memory [Word List Memory] [Word List Recall] Language [Verbal Fluency] [BNT]
	Binder[24] USA RCT High	67	Postmenopausal women aged 75 to 91 years Mean age (SD): 81 (4) years 100% female 86% White 30% college graduate Baseline cognition: NR	Conjugated estrogen (0.625 mg/day) plus trimonthly medroxyprogesterone acetate (5 mg/day) for 9 months	Placebo for 9 months	9 months	Executive/Attention/Processing Speed [TMT A] [TMT B] Memory [Weschler Associate Learning and 20 Min Delayed Recall] Language [Word Fluency, Animal] Visuospatial [Cancellation Random Letter and Random Figure Tests]
HRT-DHEA	Kritz-Silverstein 2008[25] USA RCT Medium	225	Healthy men & women aged 55 to 85 years Mean age (SD): 68 (8) years 53% female Race: NR	Oral DHEA supplementation 50 mg/day for 1 year	Placebo daily for 1 year	1 year	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [TMT B] Memory [Word List] [Word List Recall] Language [Verbal Fluency] [BNT]

			Mean education (SD): 16 (2.4) years Median 3MS (IQR): 96 (5)				
HRT-Testosterone	Vaughn 2007[26] RCT USA High	69	Men aged 65 to 83 years without evidence of cognitive impairment and baseline testosterone levels below 350 ng/dL Mean age: NR 0% female Race: NR Education: NR Baseline cognition: mean NR but participants had baseline MMSE scores ≥ 28	Testosterone enanthate 200 mg intramuscularly every 2 weeks or testosterone enanthate 200 mg intramuscularly every 2 weeks plus finasteride 5 mg/day orally	Placebo (sesame oil injections) plus placebo pill daily	3 years	Executive/Attention/Processing Speed [DS Forward] [DS Backward][TMT A] [TMT B] Memory [BBVRT # Correct] [BVRT # Errors] [Selective Reminding Test, Total Recall] [Selective Reminding Test, Long-Term Storage] [Selective Reminding Test, Consistent Long-Term Retrieval] [Selective Reminding Test, Delayed Recall] [Selective Reminding Test, # of Intrusions] Visuospatial [Judgment of Line Orientation]
	Kenny 2002[27] RCT USA High	67	Men aged 65-87 years with low biotesterone levels Mean age (SD): 75.5 (4.5) years 0% female Race: NR 65% ≥ college Baseline cognition: NR	Testosterone (transdermal testosterone patch 2-2.5 mg daily)	Placebo patch	1 year	Executive/Attention/Processing Speed [Digit Span] [DSST] [TMT A] [TMT B]
Selective estrogen receptor modulator (SERM)	Yaffe 2005[28] Yaffe 2001[29] RCT USA Medium	7478	Postmenopausal women with osteoporosis Mean age (SD): 68 (7) years 100% female 95% white Mean education (SD): 12 (4) years Baseline cognition: NR	Raloxifene 60 mg or 120 mg daily for 3 years	Oral placebo daily	3 years	Diagnosis [MCI] [Alzheimer's Disease] [Any Type of Dementia] [Dementia or MCI] Executive/Attention/Processing Speed [Short Blessed] [TMT A] [TMT B] Memory [Word List Memory] [Word List Recall] Language [Word List Fluency]
	Nickelsen 1998[30] RCT USA Medium	143	Postmenopausal women aged 45-75 years with osteoporosis Mean age: 68 years 100% female Race: NR Education: NR Baseline cognition: NR	Raloxifene 60 mg or 120 mg daily for 1 year	Placebo for 1 year	1 year	Executive/Attention/Processing Speed [Walter Reed Performance Assessment Battery (PAB) 2-Letter Search] [Walter Reed PAB: 6-Letter Search] [Walter Reed PAB: 4-Choice Serial Reaction Time] Memory [MAC Battery: Name-Face Association, Total Acquisition] [MAC Battery: Name-Face Association,

							Delayed Recall] [MAC Battery: First-Last Name Association, Delayed Recall] [MAC Battery: First-Last Name Association, Total Acquisition] [MAC Battery: Facial Recognition, Number Before 1st Error] [Telephone Number Recall, Before Interference] [Telephone Number Recall, After Interference]
Soy	Henderson 2012[31] RCT USA Low	350	Healthy postmenopausal women aged 45-92 years Mean age (SD): 61 (7) years 100% female 63% White 60% college graduate Baseline cognition: NR	Soy (isoflavone rich soy protein 25 g) daily for 2.5 years	Milk protein-matched placebo for 2.5 years	2.5 years	Multidomain Neuropsychological Test Performance [Cognitive Composite] Executive/Attention/Processing Speed [Executive/Expressive/Visuospatial Factor Composite] [SDMT] [TMT B] [Shipley Abstraction] [Letter-Number Sequencing] Memory [Verbal Episodic Memory Composite] [CVLT, Immediate Recall] [CVLT, Delayed Recall] [Visual Episodic Memory Composite] [EBMT, Immediate Recall] [EBMT, Delayed Recall] [Visual Episodic Memory Composite] Language [Category Fluency] [BNT] Visuospatial [Block Design] [Judgment of Line Orientation]
	Gleason 2009[32] RCT USA Medium	30	Older women aged 62-89 years without dementia Mean age (SD): 74 (7) years 100% female Race: NR Mean education (SD): 16.5 (3) years Mean MMSE (SD): 29 (1)	Soy isoflavonea 100 mg/d for 6 months	Matching placebo tablets for 6 months	6 months	Executive/Attention/Processing Speed [Stroop Color Word Test] [TMT B] [Mazes] [Language Fluency, Letter] Memory [Buschke Selective Reminding Test] [Buschke Selective Reminding Test, Total of Learning Trials – Words] [Buschke Selective Reminding Test, Learning Slope, Trial 5 vs. Trial 1] [Delayed Recall, Words] [Paragraph Recall Test, Total Immediate Recall] [Paragraph Recall Test, Total Delayed Recall] [Rey Complex Figure Test, Immediate Recall] [Rey Complex Figure Test, Delayed Recall] [Visual Spatial Learning Test, Total Correction Positions + Designs] [Visual Spatial Learning Test, Learning Slope Position + Design, Trial 5 Vs. Trial 1] [Visual

							Spatial Learning Test, Learning Slope Incorrect Designs] Language [BNt] [Language Fluency, Letter & Category] Visuospatial [RCFT] [Grooved Pegboard
	Ho 2007[33] RCT China Medium	191	Generally healthy women aged 55-76 years Mean age (SD): 65 (6) years 100% female Race: NR 30% secondary education 17% postsecondary education Mean MMSE (SD): 28 (1.9)	Soy (soy-derived isoflavones 80 mg) daily for 6 months	Identical appearing placebo daily for 6 months	6 months	Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [Composite Cognitive Score, including all cognitive test scores] Executive/Attention/Processing Speed [Color Trail I] [Color Trail II] [DSST] Memory [Hong Kong List Learning Test (HKLLT), Trials 1-5] [HKLLT, Short Delay Recall] [HKLLT, Long Delay Recall] [VR I] [VR II] [VR, Copy] Language [BNT] [Verbal Fluency, Categories] Motor [Finger Tapping, Right] [Finger Tapping, Left]
	Casini 2006[34] RCT crossover Italy High	78	Postmenopausal women Mean age (SD): 50 (4.1) years 100% female Race: NR Education: NR Baseline cog: NR	Soy (soy-derived isoflavones 60 mg) daily for 6 months	Identical appearing placebo daily for 6 months	6 months	Executive/Attention/Processing Speed [Digit Symbol Text, Pairs Recalled Correctly] [Digit Symbol Text, Time (sec)] [Digit Symbol Text, Raw Scores] [DS Backward] [DS Forward] [Visual Scanning Test, Time] [Visual Scanning Test, Total Correct] [Visual Scanning Test, Errors]
	Kreijkamp-Kaspers 2004[35] RCT Netherlands Medium	202	Healthy postmenopausal women aged 60 to 75 years Mean age (SD): 66.5 (4.7) years 100% female Race: NR Baseline MMSE (SD): 27.6 (1.6)	Soy (soy-derived isoflavones 99 mg) daily for 12 months	Total milk protein for 12 months	1 year	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [TMT A] [TMT B] [DSST] [Verbal Fluency, Letter N] [Verbal Fluency, Letter A] Memory [RAVLT, Immediate Recall] [RAVLT, Delayed Recall] [RAVLT,Recog] [Doors Test] Language [Verbal Fluency, Letter N] [Verbal Fluency, Letter A] [Verbal Fluency, Animals] [Verbal Fluency,

							Occupations] [BNT]
	Kritz-Silverstein 200336 RCT USA Low	56	Postmenopausal women aged 55 to 74 yearsl, not using estrogen therapy Mean age (SD): 60 (5) years 100% female 86% White Mean education (SD): 15 (2.5) years Mean MMSE (SD): 29 (1.2)	Soy (soy-extracted isoflavones (110 mg) daily for 6 months	Identical appearing placebo daily for 6 months	6 months	Executive/Attention/Processing Speed [TMT A] [TMT B] Memory [Logical Memory I, Immediate] [Logical Memory II, Delayed] Language [Category Fluency]
Red clover	Maki 2009[21] RCT USA High	66	Midlife women aged 61-87 years with ≥ 35 weekly hot flashes Mean age (SD): 53 (4.5) years 100% female 45% White Education: NR Baseline cog: NR	Red clover (an ethanolic extract of the aerial parts of red clover, 398 mg/day standardized to 120 mg isoflavone aglycones) or an ethanolic etract of black cohosh below ground parts (128 mg day)	Placebo for 1 year	1 year	Executive/Attention/Processing Speed [DS Foward] [DS Backward] [Brief Test of Attention] [Finding A's Test] Memory [CVLT, Total Learning] [CVLT, Short-Delay Free Recall] [CVLT, Long-Delay Free Recall] [Logical Memory Subtest-WMS – Immediate Total Score] [Logical Memory Subtest-WMS – Delayed Total Score] [BVRT] Language [Letter Fluency Test] Visuospatial [Modified Card Rotations Test]
	Howes 2004[37] RCT crossover USA Medium	30	Postmenopausal women aged 60 + with memory complaints Mean age: NR 100% female Race: NR Baseline cognition: NR, but MMSE score of 27+ was required	An extract of aglycone isoflavones from red clover	Placebo	6 months	Executive/Attention/Processing Speed [Arithmetic Test] [TMT A] Block Design Test] [DSST] Memory [Digit Recall Test] [Memory 1 Test] [Memory 2 Test] [Verbal Memory 1 Test] [Verbal Memory 2 Test] [Visual Memory 1 Test] [Visual Memory 2 Test] Language [BNT] [FAS Test] [Animals Naming Test] [Similarities Test]

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; BVMT=Brief Visuospatial Memory Test; BVRT=Benton Visual Retention Test; CDR=Clinical Dementia Rating; CLOX-1=Clock Drawing Test; cog=cognition; COWAT=Controlled Oral Word Association Test; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substition Test; DVT=Digit Vigilance Test; EBMT=East Boston Memory Test; FCSRT=Free and Cued Selective Reminding Test; F-TICS=French Version, Telephone Interview Cognitive Status; HVLT=Hopkins Verbal Learning Test; MCI=mild cognitive impairment; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; N=sample size; NR=not reported; PALS=Paired Association Learning Test; PRM=Pattern Recognition Memory; RAVLT=Rey's Auditory Verbal Learning Test;

RBMT= Rivermead Behavioral Memory Test; RCFT=Rey-Osterrieth Complex Figure Test; RCPM=Raven's Colored Progressive Matrices; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SCWT=Stroop Color Word Test; SD=Standard Deviation; SDMT=Symbol Digit Modalities Test; SOE=Strength of Evidence; SWM=Spatial Working Memory; TICS=Telephone Interview for Cognitive Status (TICS-M=Modified); TMT=Trail Making Test (Part A and/or B); VP=Verbal Proficiency; VR=Visual Reproduuction; VRM=Verbal Recognition Memory; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table K2. Summary risk of bias assessments: hormone interventions vs. inactive controls in adults with normal cognition

Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
HRT-estrogen efficacy	Henderson 2016[1]	Medium/High	Medium attrition (10%) at 2.5 years; high attrition (30%) at 5 years without correction for possible bias; unclear whether outcome assessor was independent
	Wroolie 2015[2] Rasgon 2014[3]	Medium	Medium (16%) attrition for cognitive outcomes; high (30%) attrition for MRI without correction to account for possible bias; participants not blinded to treatment
	Espeland 2013[4] Espeland 2010[5] Coker 2009[6] Resnick 2009[7] Resnick 2009[8] Resnick, 2006[9, 10] Shumaker 2004[11] Rapp 2003[12] (Women's Health Initiative sub-studies) Medium	Medium	Medium attrition (rate varies by specific outcome); possible detection bias for some outcomes
	Gorenstein 2011[13]	Medium	Medium attrition (19%) without correction to account for possible bias; unclear whether outcome assessor was independent
	Pefanco 2007[14]	Medium	Medium (21%) attrition with some analysis to account for possible bias; unclear whether outcome assessor was independent
	Yaffe 2006[15]	Low	
HRT-estrogen + progestin efficacy	Kantarci 2016[16] Gleason 2015}[17]	Medium (cognitive outcomes) High (MRI)	Medium attrition (10%) at 2.5 years; high attrition (30%) at 5 years
	Espeland 2013[4] Espeland 2010[5] Coker 2009[6] Resnick 2009[8] Resnick 2006[9] Espeland 2004[10] Shumaker 2004[11] Shumaker 2003[18] Rapp 2003[12] RCT (Women's Health Initiative substudies) USA Medium	Medium	Medium attrition (rate varies by specific outcome); possible detection bias for some outcomes

	Davison 2013[19]	Medium	Attrition (17%) without analysis to account for possible bias; unclear whether outcome assessor independent
	Alhola 2010[20]	High	Attrition (>25%) from original randomization without analysis to account for possible bias
	Maki 2009[21]	High	High attrition (>25%) without appropriate analysis
	Tierney 2009[22]	Low/Medium	Unclear whether outcome assessor independent
	Grady 2002[23]	Medium	Medium attrition (20%) without appropriate analysis; unclear whether outcome assessor independent
	Binder 2001[24]	High	High attrition (22%) without appropriate analysis; unclear whether outcome assessor independent
DHEA efficacy	Kritz-Silverstein 2008[25]	Medium	Randomization not well described; medium attrition (15%) without appropriate analysis; unclear whether outcome assessor independent
HRT-testerone efficacy	Vaughn 2007[26]	High	High attrition (33%) without appropriate analysis; unclear whether outcome assessor independent
	Kenny 2002[27]	High	Randomization not well described; high attrition (34%) without appropriate analysis; unclear whether outcome assessor independent
SERM efficacy	Yaffe, 2005[28] Yaffe, 2001[29]	Medium	Medium attrition without appropriate analysis; unclear whether outcome assessor independent
	Nickelsen 1998[27]	Medium	Randomization not well described; unclear whether outcome assessor blinded and independent
Soy efficacy	Henderson 2012[31]	Low	
	Gleason 2009[32]	Medium	Randomization not well described; medium (12%) attrition without appropriate analysis; unclear whether outcome assessor blinded
	Ho 2007[33]	Medium	Medium attrition (12%) without appropriate analysis; unclear whether outcome assessor independent
	Casini 2006[34]	High	Unclear whether baseline cognitive tests were performed (no baseline data presented); unclear whether outcome assessor independent
	Kreijkamp-Kaspers 2004[35]	Medium	Medium attrition (24%) with some analysis; unclear whether outcome assessor independent
	Kritz-Silverstein 2003[36]	Low	
Red clover efficacy	Maki 2009[21]	High	High attrition (>25%) without appropriate analysis
	Howes, 2004[37]	Medium	Unclear whether outcome assessor blinded and independent; participants may have been unblinded to treatment during crossover

DHEA=dehydroepiandrosterone; RCT=randomized controlled trial;

Appendix Table K3. Characteristics of eligible studies: hormone interventions vs. active controls in adults with normal cognition

Hormone Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
HRT-estrogen + progestin vs. tibolone	Pan 2003[38] RCT Taiwan Medium	50	Healthy postmenopausal women Mean age (SD): 52 (4) years 100% female Race: NR Mean MMSE (SD): 26.6 (2.3)	Estrogen + progestin (conjugated equine estrogen 0.625 mg/day + metheylprogresterone acetate 5 mg/day) for 6 months	Tibolone 2.5 mg/day for 6 months	6 months	Brief Cognitive Test Performance [MMSE] [Cognitive Abilities Screening Instrument]
HRT-estrogen + testosterone vs. estrogen	Moller 2013[39] Moller 2010[40] RCT crossover Sweden Medium	50	Women aged 45-60 years with surgically-induced menopause Mean age (SD): 54 (2.9) years 100% female Race: NR Baseline global cognition: NR	Estrogen + testosterone (estradiol valerate 2 mg/day + testosterone undecanoate 40 mg/day) for 6 months	Estrogen (estradiol valerate 2 mg/day) plus placebo	6 months	Executive/Attention/Processing Speed [DSST, used To assess "cognitive fatigue," = difference between the # of digits produced during the first 30 seconds and last 30 seconds of a 90 second session] [Digit Symbol, Free Recall of Words] [Digit Symbol, Paired Recall of Symbols] [Digit Symbol, % Spatial Errors] Memory [Logical Story, Immediate Recall] [Logical Story, Delayed Recall]
SERM Tamoxifen vs. Raloxifene	Legault 2009[41] RCT US High	1498	Healthy postmenopausal women aged 65+ with increased risk of breast cancer, without dementia Mean age (SD):	Tamixofen 20 mg/d daily for up to 5 years	Raloxifene 60 mg daily for up to 5 years	Up to 5 years	Brief Cognitive Test Performance [3MS] Executive/Attention/Processing Speed [DS Forward] [DS Backward] Memory [BVRT] [CVLT] Language [Primary Mental Abilities-Verbal] [Verbal Fluency, Letter] [Verbal Fluency, Semantic] Visuospatial [Card Rotations]

			70 (4.2) years 100% female 94% White 34% some college 34% college graduate 67% 3MSE ≤ 95 23% 3MSE 90-94 10% 3MSE < 90				Motor [Finger Tapping]
SERM/HRT - Tamoxifen or Raloxifene vs. CEE	Espeland 2010[42] RCT USA High	6461 (WHI & Co-STAR trial participants)	Women aged 65-80 years who participated in the WHI or CoSTAR trials Age, years (approx.) 65-59: 51% 70-74: 34% 75+: 15% 100% female % white: 90% Education: 7% < high school 25% high school graduate 38% some college 30% college grad Baseline 3MS (SD): 95 (4.25)	Congugated equine estrogen 0.625 with or without medroxyprogesterone for at least 3 years	Tamoxifen (20 mg/d) or raloxifene (60 mg/d) for at least 3 years (There were also Placebo arms in both trials included in the analysis)	Mean follow-up: 4.6 years (range 1-8) years	Brief Cognitive Test Performance [3MS]

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; DHEA=dehydroepiandrosterone; BVRT=Benton Visual Retention Test; Co-STAR=The Study of Tamoxifen and Raloxifene Cognitive Substudy; DS=Digit Span (Forward and/or Backward); CVLT=California Verbal Learning Test; DSST=Digit Symbol Substitution Test; HRT=hormone replacement therapy; mg/d=milligrams per day; N=sample size; NR=not reported; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation; SERM=selective estrogen receptor modulator; vs.=versus; WHI=Women's Health Initiative

Appendix Table K4. Summary risk of bias assessments: hormone interventions vs. active controls in adults with normal cognition

Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
HRT-estrogen vs. estrogen + progestin	Pan 2003[38]	Medium	Medium attrition (20%) without appropriate analysis to correct for potential bias
HRT-estrogen vs. estrogen + testosterone	Moller 2010[39] Moller 2013[40]	Medium	Medium attrition (12%) without appropriate analysis to correct for possible bias
SERM Tamoxifen vs. Raloxifene	Legault 2009[41]	High	High attrition
Raloxifene vs. CEE	Espeland 2010[42]	High	Considerable variation in study populations included in analysis; original studies already included in review

CEE=conjugated equine estrogen; HRT=hormone replacement therapy; SERM=selective estrogen receptor modulator; vs.=versus

Appendix Table K5. Strength of evidence assessments: hormone therapies in adults with normal cognition

Hormone Intervention type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Components	SOE
HRT-estrogen	Dementia	1 (2947)	1 of 2 tests show statistically significant differences between groups (favoring placebo) (p=0.04) Shumaker 2004[11] (WHI) Probable Dementia: Not significant HR: 1.49 [0.83, 2.66] Probable Dementia or Mild Cognitive Impairment: C>I HR: 1.38 [1.01, 1.89]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
	MCI	1 (2947)	Shumaker 2004[11] MCI: Not significant HR: 1.34 [0.95, 1.89]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
	Brief Cognitive Test	2 (3364)	1 of 3 tests favors C Espeland 2004[10] (WHI) Mean difference in change from baseline 3MSE scores, estrogen group minus placebo (p=0.04): Mean [95% CI]: -0.26 [-0.52, 0] Yaffe 2006[15] Mean difference in change from baseline 3MS scores, estrogen group minus placebo, baseline 3MS ≤ 90 (p=0.53): Mean [95% CI]: -1.21 [-5.05, 2.64]	Medium	Indirect	Precise	Consistent	Undetected	NA	Low

			Mean difference in change from baseline 3MS scores, estrogen group minus placebo, baseline 3MS > 90 (p=0.18): Mean [95% CI]: -0.30 [-0.74, 0.14]							
	Multidomain Composite	1 (567)	0 of 1 (no differences)	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient
	Executive/ Attention/ Processing Speed	6 (2056)	2 of 19 favor I	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
	Memory	6 (2056)	2 of 35 favor I	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
HRT-estrogen + progestin	Dementia	1 (4532)	1 of 2 tests show statistically significant differences between groups Shumaker 2003[18] (WHI) Probable Dementia: C>I HR: 2.05 [1.21, 3.48] Probable Dementia or MCI: NS HR: 1.37 [0.99, 1.89]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
	MCI	1 (4532)	No statistically significant differences between groups Shumaker 2003[18] (WHI) MCI: NS HR: 1.07 [0.74, 1.55]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
	Brief Cognitive Test	3 (6288)	One of four tests favors placebo: Gleason 2015[17] Beta estimates for estrogen versus placebo groups not statistically significant: p=0.18 (conjugated	Medium	Indirect	Precise	Consistent	Undetected	NA	Low

			equine estrogen + progesterone versus placebo) p=0.84 (transdermal estradiol + progesterone versus placebo) Rapp 2003[12] (WHI) Statistically significant in favor of placebo. Mean difference between treatment groups (estrogen + progestin – placebo) in 3MS [95% CI]: -0.063 [-0.120, -0.006]; p=0.03 Grady 2002[23] Difference between groups in post-intervention 3MS scores [95% CI]: -0.4 [-1.1, 0.4]; p=0.36 [**NOTE: no baseline/pre-test was conducted**, making it impossible to determine the actual difference between groups]							
	Multidomain Composite	NR								
	Executive/ Attention/ Processing Speed	5 (3404)	1 of 11 tests was statistically significant in favor of placebo	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
	Memory	5 (3404)	4 of 17 tests favor C	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
DHEA	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test	Single trial <500 participants								

	Multidomain Composite	NR								
	Executive function/attention/processing speed	Single trial <500 participants								
	Memory	Single trial <500 participants								
SERM	Dementia	1 (5386)	Yaffe 2005[28] Relative risk of cognitive impairment, SERM (60 & 120 mg doses) vs. placebo: no significant differences Alzheimer's disease: NS (either group) RR (60 mg): 0.82 [0.39, 1.71] RR (120 mg): 0.52 [0.22, 1.21] Any type of dementia NS (either group) RR (60 mg): 0.90 [0.47, 1.74] RR (120 mg): 0.91 [0.47, 1.76] Dementia or MCI NS (either group) RR (60 mg): 1.12 [0.84, 1.49] RR (120 mg): 0.73 [0.53, 1.01]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
	MCI	1 (5386)	Yaffe 2005[28] Relative risk of cognitive impairment, SERM (60 & 120 mg doses) vs. placebo MCI: Significant (p=0.04) at 120 mg dose; not significant at 60 mg I>C (lower risk in	Medium	Direct	Precise	Unknown	Undetected	NA	Low

			SERM group) RR (60 mg): 1.18 [0.85, 1.64] RR (120 mg): 0.67 [0.46, 0.98]							
	Brief Cognitive Test	NR								
	Multidomain Composite	NR								
	Executive function/attention/processing speed	2 (5877)	0 of 6 (no differences)	Medium	Indirect	Precise	Consistent	Undetected	NA	Low
	Memory	2 (5739)	0 of 9 (no differences)	Medium	Indirect	Precise	Consistent	Undetected	NA	Low
Soy	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test	2 (393)	0 of 2 (no differences)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
	Multidomain Composite	2 (541)	0 of 3 (no differences)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
	Executive/ Attention/ Processing Speed	5 (829)	2 of 14 tests favor C	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
	Memory	5 (829)	5 of 31 tests favor I 1 of 31 tests favors C	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
Red clover	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test	NR								
	Multidomain Composite	NR								

	Executive/ Attention/ Processing Speed	Single trial <500 participants								
	Memory	Single trial <500 participants								

C=control; CI=confidence interval; I=intervention; HR=hazard ratio; MCI=mild cognitive impairment; mg=milligrams; n=sample size; NA=not applicable; NR=not reported; NS=not significant; RR=relative risk; RoB=risk of bias; SD=standard deviation; SERM=selective estrogen receptor modulator; vs.=versus; WHI=Women's Health Initiative

Appendix Table K6. Characteristics of eligible studies: hormone interventions vs. inactive controls in adults with MCI

Hormone Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
HRT-testesterone	Cherrier 2010[43] RCT US Medium	22	Men aged 60-90 years with both MCI and low serum testosterone levels Mean age (SD): 70.5 (8) years 0% female Race NR Education NR Mean 3MS (SD) 92.5 (6.7)	Testosterone gel 50-100 mg/d with a target total T level of 500 to 900 ng/dL	Placebo gel daily for 6 months	6 months	Executive/Attention/Processing Speed [Letter-Number Sequencing, Total Score] [Letter-Number Sequencing, Span] [Computerized Simple RT, 2-Second Interval] [Computerized Simple RT, 5-Second Interval] [Computerized Choice RT, 2-Second Interval] [Computerized Choice RT, 5-Second] [Mental Rotation] Memory [RAVLT, Immediate] [RAVLT, Short Delay] [RAVLT, Long Delay] [Story Recall, Immediate] [Story Recall, Delay] [Visual Spatial Learning Test, Immediate & Delayed] Language [Verbal Fluency] Visuospatial [Route Test, Immediate] [Route Test, Delay] [Complex Design Construction]
Soy	Kato-Kataoka 2010[44] RCT Japan Medium	78	People aged 50-69 years with MCI Mean age (SD): 60 (1) years 48% female Japanese Mean education (SD): 14 (0.4) years Mean MMSE (SD) 27.8 (0.4)	Soybean derived phosphatidylerine (Soy-PS) 100 mg or 300 mg daily for 6 months	Placebo for 6 months	6 months	Brief Cognitive Test Performance [MMSE] [Hasegawa Dementia Scale] Memory [RBMT]

3MS=Modified Mini Mental Status Examination; MCI=mild cognitive impairment; mg=milligrams; mg/d=milligrams per day; MMSE=Mini-Mental Status Examination; N=sample size; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RBMT= Rivermead Behavioral Memory Test; RCT=randomized controlled trial; RoB=risk of bias; RT=reaction time; SD=standard deviation; vs.=versus

Appendix Table K7. Summary risk of bias assessments: hormone interventions vs. inactive controls in adults with MCI

Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
HRT-testosterone	Cherrier 2015[43]	Medium	Medium attrition (14%) without appropriate analysis; unclear whether outcome assessor independent
Soy	Kato-Kataoka 2010[44]	Medium	Unclear whether outcome assessor blinded and independent; possible concurrent intervention

MCI=mild cognitive impairment

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Appendix L. Vitamin Interventions

Appendix Table L1. Characteristics of eligible studies: vitamins in adults with normal cognition

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
Multivitamins	Chew 20151 Age-related Eye Disease Study 2 RCT USA High	3501	Adults at risk for developing late age-related macular degeneration Age 73 Female 58% White 97% Black 1% Asian <1% American Indian <1% Native Hawaiian or Pacific Islander <1% Other <1% Education ≤ High school 29% ≥ Some college 49% Postgrad 22% Baseline cognition: TICS 33	Vitamin C (500 mg) Vitamin E (400 IU) Beta carotene (15 mg) Zinc (80 or 25 mg) daily for 5 years	No beta carotene or no zinc	5 years	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Test Performance [Composite] Executive/Attention/Processing [Animal Category] [Letter Fluency] [Alternating Fluency] [DS Backward] Memory [WMS-III Logical Memory Part I and II] [Recall Paragraph] Language [Animal Category] [Letter Fluency] [Alternating Fluency]
	Grodstein 2013[2] Physicians' Health Study II RCT USA Medium: followup 1 and 3 High: followup 3 and 4 (time in years NR)	5947	Substudy of Physicians' Health Initiative recruited men physicians without serious disease aged 65+ 65-74 72% 75-84 26% 85+ 2% Female 0% Race NR Education 100% medical school Baseline cognition	Multivitamin (Centrum Silver) daily for approximately 13 years	Placebo	8.5 years (mean)	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Test Performance [Composite] Memory [Memory Composite] Language [Category Fluency]

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
			TICS 34				
	Kesse-Guyot 2011[3] Supplementation in Vitamins and Mineral Antioxidants 2011 RCT France High	4447	Healthy adults aged 45-60 Age 52 Female 48% Race NR Education: Primary 21% Secondary 40% University 39% Baseline cognition NR	Vitamin C (120 mg) Vitamin E (30 mg) Beta carotene (6 mg) Selenium (100 µg) Zinc (20 mg) daily for 6 years	Placebo	6 years	Executive/Attention/Processing Speed [TMT] [DS Forward] [DS Backward] Memory [RI-48] Language [Verbal Fluency] [Semantic Fluency] [Phonetic Fluency]
	McNeill 2007[4] Mineral and Vitamin Intervention Study RCT Scotland Low	910	Aged 65+ and not taken vitamins, minerals or fish oil in prior 3 months Age 72 Female 48% Race NR Education: 7 years Baseline cognition NR	Supplement containing 11 vitamins & 5 minerals: Vitamin A (800 µg) B vitamins (1 µg B_{12}; 200 µg folic acid; 1.4 mg thiamin; 1.6 mg riboflavin; 18 mg niacin; 6 mg pantothenic acid) Vitamin C (60 mg) Vitamin D (5 µg) Vitamin E (10 mg) Pyridoxine (2 mg) Iron (14 mg) Iodine (150 µg)	Placebo	1 year	Executive/Attention/Processing Speed [DS Forward] Language [Verbal Fluency Test]

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
				Copper (0.75 mg) Zinc (15 mg) Manganese (1 mg) daily for 1 year			
	Wolters 2005[5] RCT Germany Low	220	Healthy women aged 60+ not taking vitamins in prior 2 months Age 63 Female 100% Race NR Education: No secondary school 35% Grammar school 43% High school grad 22% Baseline cognition NR	B vitamins (0.4 mg folic acid; 9 µg cobalamin; 0.2 mg biotin; 35 mg niacin; 16 mg pantothenic acid; 3.2 mg riboflavin; 2.4 mg thiamine) Vitamin C (150 mg) Vitamin E (36 mg) Beta carotene (9 mg) Magnesium (50 mg) Selenium (60 µg) Daily for 6 months	Placebo	6 months	Executive/Attention/Processing Speed [WAIS-III Symbol Search Subtest] Kurztest fuer Allgemeine Intelligenz] Memory [Berliner Amnesie Test]
	Yaffe 2004[6] Age-Related Eye Disease Study RCT USA High	2,166	Elderly adults Age 75 Female NR Race NR Education NR Baseline cognition NR	Vitamin C (500 mg) Vitamin E (400 IU) Beta carotene (15 mg) Zinc (80 mg) Copper (2 mg) Daily for 7 years	Placebo	7 years	Diagnosis [MCI] Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Buschke Selective Reminding Test] [DS Backward] Memory [Logical Memory Parts I and II, Wechsler Memory Scale-Revised, Immediate Recall] Language [Category Fluency] [Letter

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
							Fluency]
	Heart Protection Study 2002[7] RCT UK Medium	20,536	Aged 40-80 with substantial risk of death from coronary heart disease in next 5 years. Some were concurrently taking simvastatin, which was the primary study drug. Age 70+: 28% Female 25% Race NR Education NR Baseline cognition NR	Vitamin E (600 mg) Vitamin C (250 mg) Beta carotene (20 mg) daily for 5 years	Placebo	5 Years	Diagnosis [Dementia, MCI] Brief Cognitive Test Performance [TICS]
	Cockle 2000[8] RCT UK High	139	Healthy, elderly, free-living adults Age 70 Female 63% Race NR Education NR Baseline cognition: MMSE 29	Vitamin A (palmitate 3334 IU) B vitamins (4 mg folic acid; 2 mg d-biotin; 180 mg nicotinamide; 14 mg thiamine mononitrate; 16 mg riboflavin; 22 mg pyridoxine; 0.03 mg B_{12}) Vitamin C (600 mg) Vitamin E (100 mg dl-alpha-tocopherol acetate) Daily for 6 months	Placebo	6 months	Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [Syndrom Kurztest, Alice Heim's 4 and 5 Tests of General Intelligence] Executive/Attention/Processing Speed [Choice Reaction Time] Memory [Sternberg Memory Scanning Task, Word Scan Task] Language [National Adult Reading Test]

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
	Smith 1999[9] RCT UK High	110	Healthy adults aged 60-80 and with MMSE 18+ Age 67 Female 54% Race NR Education NR Baseline cognition NR	Vitamin C (500 mg) Vitamin E (400 mg) Beta carotene (2 mg) daily for 1 year	Placebo	1 year	Executive/Attention/Processing Speed [Logical Reasoning Task, Simple Reaction Time Task, Repeated-digits Vigilance Task, Focused Attention Task, Categoric Search Task] Memory [Free Recall Task, Delayed Recognition Memory Task]
Folic acid	Durga 2007[10] Folic Acid and Carotid Intimamedia Thickness Trial RCT Netherlands Low	818	Age 50-70, high homocysteine levels likely due to suboptimal folate concentrations. Age 60 Female 29% Race NR Education NR Baseline cognition: MMSE 29	Folic acid (0.8 mg) Daily for 3 years	Placebo	3 years	Multidomain Neuropsychological Test Performance [Composite] Executive/Attention/Processing Speed [SCWT] [LDST] [Concept Shifting Test (modified TMT)] Memory [RAVLT] Language [Verbal Fluency Test]
Folic acid + B_{12}	van der Zwaluw 2014[11] B-vitamins for the Prevention of Osteoporotic Fractures RCT Netherlands Low	2919	Aged 65+ with elevated homocysteine levels, able to make own decisions and compliant Age 74 Female 50% Race NR Education: Low 51% Medium 21% High 26% Baseline cognition: MMSE 28	Folic acid (400 mg) Vitamin B_{12} (500 mg) Daily for 2 years	Placebo	2 years	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Composite] [Composite: Information Processing Speed] Memory [Composite: Episodic Memory [RAVLT] Language [Verbal Fluency Test]
	Walker 2012[12] RCT Australia Low	900	Age 60-74 with elevated psychological distress, did not exercise or take vitamins	Folic acid (0.4 mg) Vitamin B_{12} (0.1 mg)	Placebo	2 years	Brief Cognitive Test Performance [TICS] Executive/Attention/Processing Speed [TICS Orientation/Calculation & Attention] Memory [TICS Immediate & Delayed

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
			Age 66 Female 60% Race NR Education 14 years Baseline cognition: TICS-m 27	Daily for 2 years			Recall And Semantic Memory]
Folate/folic acid + B_6 + B_{12}	Andreeva 2011[13] Supplementation with Folate, vitamins B_6 and B_{12} and/or Omega-3 fatty acids RCT France Low	1248	Age 45-70 with heart disease Age 61 Female 58% Race NR Education: Less than high school diploma 37% Baseline cognition: Isaac set test: 35.8	Folate (0.56 mg) Vitamin B_6 (3 mg) Vitamin B_{12} (0.02 mg) Daily for 4 years	Placebo	4 years	Brief Cognitive Test Performance [TICS French version] Memory [TICS Memory & Recall]
	Brady 2009[14] VA HOST RCT USA High	659	Veterans aged 21+ with advanced chronic kidney disease Age 64 Female 2% White 49% Black 37% Hispanic 11% Other 3% Education NR Baseline cognition: TICS 32	Folic acid (40 mg) Vitamin B_6 (100 mg) Vitamin B_{12} (2 mg) Daily for 6 years	Placebo	1 year	Brief Cognitive Test Performance [TICS]
	Kang 2008[15] Women's Antioxidant and Folic Acid Cardiovascular Study	5,442	Female health professionals aged 40+ with heart disease or 3+ risk factors Age 71 Female 100%	Folic acid (2.5 mg) Vitamin B_6 (50 mg) Vitamin B_{12} (1 mg)	Placebo	5.4 years	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Test Performance [Composite] Memory [Composite] Language [Category Fluency]

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
	RCT USA High		Race NR Education: Nursing degree: 70% Bachelor's degree or higher: 30% Baseline cognition: TICS 34	Daily for 5.4 years			
	McMahon 2006[16] RCT New Zealand Low	276	Age 65+ with healthy cognition and homocysteine at least 13 micromoles/liter Age 74 Female 44% Race NR Education: <3 years secondary 35% ≥3 years secondary 11% Tertiary 54% Baseline cognition: MMSE 29	Folate (1 mg) Vitamin B_{12} (0.5 mg) Vitamin B_6 (10 mg) Daily for 2 years	Placebo	2 years	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Raven's Progressive Matrices] [TMT B] [COWAT] Memory [RAVLT] [Paragraph Recall, WMS] Language [Category Word Fluency] [National Adult Reading Test] [COWAT]
Vitamin E	Kang 2009[17] The Women's Antioxidant and Cardiovascular Study RCT USA Low: followup 1-3 High: followup 4 (exact time in years NR)	2824	Women aged 40+ with CVD or 3+ coronary risk factors who are part of the larger RCT; this sub-study included women aged 65+ Age 69 Female 100% Race NR Education: Technical nursing degree 70% Bachelor's or higher 30% Baseline cognition NR	Vitamin E (402 mg) Every other day for 9 years	Placebo	5.4 years (4 follow up calls)	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Test Performance [Composite] Memory [Composite] Language [Category Fluency Test]
	Kang 2006[18] Women's Health	6377	Women age 65+ Age 72	Vitamin E (600 IU)	Placebo	4 years	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
	Study RCT USA Low		Female 100% Race NR Technical nursing degree 68% Bachelor's or higher 32% Baseline cognition: TICS 34	Every other day for 10 years			Performance [Composite] Memory [Composite] Language [Category Fluency Test]
Vitamin C	Kang 2009[17] The Women's Antioxidant and Cardiovascular Study RCT USA Low: followup 1-3 High: followup 4 (exact time in years NR)	2824	Women aged 40+ with CVD or 3+ coronary risk factors who are part of the larger RCT; this sub-study included women aged 65+ Age 69 Female 100% Race NR Education: Technical nursing degree 70% Bachelor's or higher 30% Baseline cognition NR	Vitamin C (500 mg) Daily for 9 years	Placebo	5.4 years (4 follow up calls)	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Test Performance [Composite] Memory [Composite] Language [Category Fluency Test]
Vitamin D + Calcium	Rossom 2012[19] Women's Health Initiative Calcium and Vitamin D Trial RCT USA Low: 7 years High: 8 years	4143	Participants in the Women's Health Initiative Memory Study Age 71 Female 100% Race: White 88% Black 6% Hispanic 3% Asian 2% Native American 1% Education: <High school 7%	Calcium carbonate (1000 mg) Vitamin D_3 (400 IU) Daily for 8 years Optional use of calcium (1000 mg) Vitamin D (600 mg)	Placebo	7.8 years (mean)	Diagnosis [Probable Dementia or MCI] Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DS Forward] [DS Backward] Memory [CVLT] [BVRT] Language [Letter & Category Fluency, Primary Abilities Vocabulary] Motor [Finger Tapping] Visuospatial [Card Rotations]

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
			High school grad 22% >High school 40% College grad 31% Baseline cognition: MMSE-m 95				
Beta carotene	Kang 2009[17] The Women's Antioxidant and Cardiovascular Study RCT USA Low: followup 1-3 High: followup 4 (exact time in years NR)	2824	Women aged 40+ with CVD or 3+ coronary risk factors who are part of the larger RCT; this sub-study included women aged 65+ Age 69 Female 100% Race NR Education: Technical nursing degree 70% Bachelor's or higher 30% Baseline cognition NR	Beta carotene (50 mg) Every other day for 9 years	Placebo	5.4 years (4 follow up calls)	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Test Performance [Composite] Memory [Composite] Language [Category Fluency Test]

µg=microgram (1000 µg=1 mg) (1000 µg=1 g); BVRT=Benton Visual Retention Test; COWAT=Controlled Oral Word Association Test; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); IU=internal units; mg=milligrams; MCI=mild cognitive impairment; MMSE=Mini Mental Status Exam; N=sample size; NR=not reported; RAVLT=Rey's Auditory Verbal Learning; RCT=randomized controlled trial; SCWT=Stroop Color Word Test; TICS=Telephone Interview Cognitive Status; TMT=Trail Making Test (Part A and/or B); vs=versus; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table L2. Characteristics eligible studies: B vitamin combinations vs. active control in adults with normal cognition

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention** **Duration**	**Comparison**	**Outcome timing**	**Outcome** **Domain [Instrument]**
Stott 2005[20] RCT UK Medium	185	Age 65+ and history of ischemic vascular disease. Age 74 Female 56% Race NR Education NR Baseline cognition: TICS-m: 26	1) folic acid (2.5 mg)/B_{12} (0.4 mg) 2) B_2 (25 mg) 3) B_6 (25 mg) 4) folic acid/B_{12} + B_2 5) folic acid/B_{12} + B_6 6) B_2 + B_6 7) folic acid/B_{12} + B_2 + B_6 Daily for 3 months	Placebo	6 months and 1 year	Brief Cognitive Test Performance [TICS] Executive/Attention/Processing Speed [SDMT]

µg=microgram (1000 µg=1 mg) (1000 µg=1 g); IU=internal units; mg=milligrams; NR=not reported; SDMT=Symbol Digit Modalities Test; RCT=randomized controlled trial; TICS=Telephone Interview for Cognitive Status; UK=United Kingdom

Appendix Table L3. Summary risk of bias assessments: vitamins in adults with normal cognition

Vitamin Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
Multivitamins	Chew 2015[1]	High	Randomization methods unclear, reported attrition (19%) conflicting with related publication, concurrent intervention not controlled for.
	Grodstein 2013[2]	Medium at followup 2 High at followup 3+	Randomization and blinding methods adequate, attrition 11% at second followup (medium), 31% at third followup (high) and 60% and final followup (high) with no missing data imputation, independent outcome assessor unclear.
	Kesse-Guyot 2006[3]	High	Randomization unclear, attrition 35% with no missing data imputation.
	McNeill 2007[4]	Low	Randomization and blinding methods adequate, attrition unclear but likely 15%, ITT, all outcomes reported.
	Wolters 2005[5]	Low	Randomization and blinding methods unclear, comparable outcome assessment timing between groups, blinding likely adequate, concurrent interventions unclear.
	Yaffe 2004[6]	High	Randomization and allocation methods likely adequate, attrition 40%.
	Heart Protection Study 2002[7]	Medium	Randomization methods adequate, attrition unclear but used survival analyses, outcome assessor blinding and independence unclear, ITT.
	Cockle 2000[8]	High	Randomization methods unclear, attrition 35%, missing data imputation methods inappropriate.
	Smith 1999[9]	High	Randomization methods unclear, attrition not reported, blinding methods adequate, ITT not reported.
B Vitamins	van der Zwaluw 2014[11]	Low	Randomization methods adequate, attrition 24% with no missing data imputation, outcome assessor not independent, all outcomes reported.
	Walker 2012[12]	Low	Randomization methods adequate, blinding unclear, attrition 16% at two year followup and no missing data imputation, outcome assessor independence unclear.
	Andreeva 2011[13]	Low	Adequate randomization and blinding, low attrition in this followup study, ITT.

Vitamin Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
	Brady 2009[14]	High	Attrition 25-27% and no missing data imputation.
	Kang 2008[15]	High	Subset of randomized trial studied, attrition at timepoint 4 48%, confounder controlling likely inadequate, linding methods unclear.
	Durga 2007[10]	Low	Randomization and allocation methods adequate, attrition 3% at 3-year followup, all outcomes reported clearly.
	McMahon 2006[16]	Low	Randomization and blinding methods adequate, outcome assessor independence unclear, ITT not reported.
	Stott 2005[20]	Medium	Randomization and blinding methods adequate, attrition 10%, outcome assessor independence unclear.
Vitamin E	Kang 2009[17]	Low at followup 3 High at final followup	Attrition 12% at third followup (medium) and 20% by final followup (high), outcome assessment timing not comparable between groups, ITT unclear.
	Kang 2006[18]	Low	Randomization unclear, attrition 20% and no missing data imputation, outcome assessment timing unclear.
Vitamin C	Kang 2009[17]	Low at followup 3 High at final followup	Attrition 12% at third followup (medium) and 20% by final followup (high), outcome assessment timing not comparable between groups, ITT unclear.
Vitamin D + Calcium	Rossom 2012[19]	Low at followup 7 High at followup 8	Randomization and blinding methods adequate, outcome assessor independent, ITT, all outcomes reported.
Beta carotene	Kang 2009[17]	Low at followup 3 High at final followup	Attrition 12% at third followup (medium) and 20% by final followup (high), outcome assessment timing not comparable between groups, ITT unclear.

ITT=intention to treat

Appendix Table L4. Strength of evidence assessments: vitamins in adults with normal cognition

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Multivitamin vs. placebo	Dementia	1 (20,469)	1 test showed no statistically significant improvement Heart Protection Study 2002[7] Dementia diagnosis 0.3% vs 0.3%	Medium	Direct	Unclear	Unknown	Suspected	NA	Low
	MCI	1 (20, 469)	1 test showed no statistically significant improvement Heart Protection Study 2002[7] MCI diagnosis 23.7% vs 24.2%	Medium	Direct	Unclear	Unknown	Suspected	NA	Low
	Brief Cognitive Test Performance Grodstein 2013[2]: Followup 2 (time NR) Heart Protection Study 2002[7]: 5 years	2 (25,765)	2 tests showed no statistically significant improvement Grodstein 2013[2] TICS, between groups difference from longitudinal models of mean cognitive performance 0.10 (-0.05 to 0.24) Heart Protection Study 2002[7] TICS-m, between groups mean difference at followup (time NR) 0.02 (SE 0.07)	Medium	Indirect	Imprecise	Consistent	Suspected	NA	Insufficient

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
	Multidomain Neuropsychological Performance Grodstein 2013[2]: Followup 2 (time NR)	1 (5296)	1 test showed no statistically significant improvement Grodstein 2013[2] Composite z-score, between groups difference from longitudinal models of mean cognitive performance -0.01 (-0.05 to 0.03)	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
	Executive/ Attention/ Processing Speed McNeill 2007[4]: 1 year Wolters 2005[5] 6 months	2 (992)	3 tests showed no statistically significant improvement McNeill 2007[4] Digit span forwards, mean difference -0.1 (-0.3 to 0.2) Wolters 2005[5] Kurtztest fuer Allgemeine Intelligenz, between groups change from baseline* -1 [NR] WAIS-III symbol search, between groups change from baseline* 0 [NR]	Low	Indirect	Unclear	Consistent	Undetected	NA	Low
	Memory Grodstein 2013[2]:	2 (5516)	2 tests showed no statistically significant	Medium	Indirect	Unclear	Consistent	Undetected	NA	Low

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
	Followup 2 (time NR) Wolters 2005[5]: 6 months		improvement Grodstein 2013[2] Composite z-score, between groups difference from longitudinal models of mean cognitive performance 0.00 (-0.05 to 0.04) Wolters 2005[5] Berliner Amnesit Test, between groups change from baseline* -0.8 [NR]							
	Adverse Effects		NR							
B vitamins: folic acid vs. placebo	Dementia		NR							
	MCI		NR							
	Brief Cognitive Test Performance Durga 2007[10]: 3 years		NR							
	Multidomain Neuropsychological Performance	1 (818)	1 test showed statistically significant improvement with intervention Composite, between groups change from baseline 0.05 [0.004 to 0.096] p=0.03	Low	Indirect	Precise	Unknown	Suspected	NA	Insufficient
	Executive/ Attention/	1 (818)	1 of 3 tests showed statistically	Low	Indirect	Imprecise	Inconsistent	Suspected	NA	Insufficient

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
	Processing Speed		significant improvement with control Composite: sensorimotor speed, between groups change from baseline 0.06 [-0.001 to 0.13] p=0.055 Composite: complex speed, between groups change from baseline 0.04 [-0.05 to 0.12] p=0.4 LDST, between groups change from baseline 0.09 [0.016 to 0.16] p=0.02							
	Memory	1 (818)	1 test showed statistically significant improvement with intervention RAVLT, between groups change from baseline 0.13 [0.03 to 0.23] p=0.01	Low	Indirect	Precise	Unknown	Suspected	NA	Insufficient
	Adverse Effects		NR							
B vitamins: folic acid + B_{12} vs. placebo	Dementia		NR							
	MCI		NR							
	Brief Cognitive Test Performance	2 (3456)	1 of 2 tests showed statistically	Low	Indirect	Precise	Inconsistent	Suspected	NA	Insufficient

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
	van der Zwaluw 2014[11]: 2 years Walker 2012[12]: 2 years		significant improvement with intervention van der Zwaluw 2014[11] MMSE, between groups change from baseline* 2.0 [NR] p=0.05 Walker 2012[12] TICS-m total, time by intervention effect size 0.17 [NR] p=0.03							
	Multidomain Neuropsychological Performance		NR							
	Executive/ Attention/ Processing Speed	2 (3456)	11 tests showed no statistically significant improvement van der Zwaluw 2014[11] Executive functioning composite, between groups change from baseline* 0.07 [NR] Attention/working memory composite, between groups change from baseline* -0.03 [NR] Information processing speed	Low	Indirect	Unclear	Consistent	Suspected	NA	Medium

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			composite, between groups change from baseline* -0.01 [NR] DS Forward, between groups change from baseline* -0.1 [NR] DS Backward, between groups change from baseline* 0.0 [NR] Trails B/A, between groups change from baseline* 0.0 [NR] Stroop I&II, between groups change from baseline* 0.4 [NR] Stroop Interference, between groups change from baseline* -1.6 [NR] Symbol digit modalities, between groups change from baseline* -0.1 [NR] Walker 2012[12] TICS-m orientation/calculati						

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			on NR; NS TICS-m attention NR; NS							
	Memory Walker 2012[12]: 2 years	2 (3456)	2 of 7 tests showed statistically significant improvement with intervention <u>van der Zwaluw 2014[11]</u> Memory composite, between groups change from baseline* 0.03 [NR] RAVLT-immediate recall, between groups change from baseline* 0.2 [NR] RAVLT-delayed recall, between groups change from baseline* 0.1 [NR] RAVLT recognition, between groups change from baseline* 0.0 [NR] <u>Walker 2012[12]</u> TICS-m immediate recall, time by intervention effect size 0.15 (p<0.05) TICS-m delayed	Low	Indirect	Unclear	Inconsistent	Suspected	NA	Low

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			recall, time by intervention effect size 0.18 (p=0.01) TICS-m semantic memory NR							
	Adverse Effects		NR							
B vitamins: folate + B_6 + B_{12} vs. placebo	Dementia		NR							
	MCI		NR							
	Brief Cognitive Test Performance Andreeva 2011[13]: 4 years McMahon 2006[16]: 2 years	2 (1124)	2 tests showed no statistically significant improvement <u>Andreeva 2011[13]</u> TICS-m total (French), between groups difference at followup* -0.4 [NR] <u>McMahon 2006[16]</u> MMSE, adjusted between groups change from baseline -0.09 [-0.30 to 1.13] p=0.42	Low	Indirect	Precise	Consistent	Suspected	NA	Low
	Multidomain Neuropsychological Performance		NR							
	Executive/ Attention/ Processing Speed	1 (253)	1 of 2 tests showed statistically significant improvement **with control** <u>McMahon 2006[16]</u> Trails B, adjusted	Low	Indirect	Imprecise	Inconsistent	Suspected	NA	Insufficient

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			between groups change from baseline 1.08 [1.02 to 1.14] p<0.01 Raven's Progressive Matrices, adjusted between groups change from baseline -0.31 [-0.81 to 0.19] p=0.22							
	Memory	2 (1124)	4 tests showed no statistically significant improvement Andreeva 2011[13] TICS-m memory (French), between groups difference at followup* 0.0 [NR] TICS-m recall (French), between groups difference at followup* -0.1 [NR] McMahon 2006[16] RAVLT, adjusted between groups change from baseline -0.35 [-0.85 to 0.14] p=0.16 WMS paragraph recall, adjusted	Low	Indirect	Imprecise	Consistent	Suspected	NA	Low

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			between groups change from baseline -0.88 [-1.98 to 0.21] p=0.12							
	Adverse Effects		NR							
Vitamin E vs. placebo	Dementia		NR							
	MCI		NR							
	Brief Cognitive Test Performance Kang 2009[17]: Followup 3 (~4 years) Kang 2006[18]: 4 years	2 (7497)	2 tests showed no statistically significant improvement Kang 2009[17] TICS, between groups change from baseline -0.08 [-0.37 to 0.21] p=0.61 Kang 2006[18] TICS, between groups change from baseline 0.04 [-0.12 to 0.21]	Low	Indirect	Precise	Consistent	Suspected	NA	Moderate
	Multidomain Neuropsychological Performance	2 (7497)	2 tests showed no statistically significant improvement Kang 2009[17] Composite, between groups change from baseline z-score -0.02 [-0.09 to 0.05] p=0.55 Kang 2006[18]	Low	Indirect	Precise	Consistent	Suspected	NA	Moderate

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			Composite, between groups change from baseline z-score 0.00 [-0.04 to 0.04]							
	Executive/ Attention/ Processing Speed		NR							
	Memory	2 (7497)	2 tests showed no statistically significant improvement Kang 2009[17] Composite, between groups change from baseline z-score -0.01 [-0.08 to 0.06] p=0.61 Kang 2009[17] Composite, between groups change from baseline z-score 0.01 [-0.03 to 0.05]	Low	Indirect	Precise	Consistent	Suspected	NA	Moderate
	Adverse Effects	1 (2271)	Kang 2009[17] None	Low	Direct	Unclear	Unknown	Suspected	NA	Insufficient
Vitamin C vs. placebo	Dementia		NR							
	MCI		NR							
	Brief Cognitive Test Performance ~4 years Kang 2009[17]: Followup 3 (~4 years)	1 (2271)	1 test showed no statistically significant improvement TICS, between groups change from baseline	Low	Indirect	Imprecise	Unknown	Suspected	NA	Low

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			0.15 [-0.14 to 0.44] p=0.31							
	Multidomain Neuropsychological Performance	1 (2271)	1 test showed no statistically significant improvement Composite, between groups change from baseline z-score 0.05 [-0.01 to 0.12] p=0.1	Low	Indirect	Imprecise	Unknown	Suspected	NA	Low
	Executive/ Attention/ Processing Speed		NR							
	Memory	1 (2271)	1 test showed statistically significant improvement with vitamin C, but effect size was not clinically meaningful. Composite, between groups change from baseline z-score 0.07 [0.00 to 0.13] p=0.05	Low	Indirect	Imprecise	Unknown	Suspected	NA	Low
	Adverse Effects	1 (2271)	No adverse effects were reported, but no statistics were presented	Low	Direct	Unclear	Unknown	Suspected	NA	Insufficient
Vitamin D + calcium vs. placebo	Dementia Rossom 2012[19]: 7.8 years	1 (4122)	1 test showed no statistically significant	Low	Direct	Precise	Unknown	Suspected	NA	Low

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			difference Incidence of probable dementia or MCI (pooled), hazard ratio 0.94 (0.72 to 1.24) p=0.68							
	MCI	1 (4122)	See above							
	Brief Cognitive Test Performance 7 years	1 (41)	1 test showed no statistically significant improvement MMSE-m, unadjusted between group change from baseline -0.05 (SE 0.17) p=0.77	Low	Indirect	Imprecise	Unknown	Suspected	NA	Insufficient
	Multidomain Neuropsychological Performance		NR							
	Executive/ Attention/ Processing Speed	1 (4122)	1 test showed no statistically significant improvement Digit span forwards and backwards (pooled), adjusted standardized between groups change from baseline 0.02 (SE 0.04) p=0.46	Low	Indirect	Precise	Unknown	Suspected	NA	Low
	Memory	1 (4122)	2 tests showed no statistically	Low	Indirect	Imprecise	Consistent	Suspected	NA	Low

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			significant improvement California Verbal Learning Test, adjusted standardized between groups change from baseline -0.05 (SE 0.04) p=0.15 Benton Visual Retention Test, adjusted standardized between groups change from baseline -0.02 (SE 0.04) p=0.66							
	Adverse Effects		NR							
Beta carotene vs. placebo	Dementia		NR							
	MCI		NR							
	Brief Cognitive Test Performance Kang 2009[17]: Followup 3 (~4 years)	1 (2271)	1 test showed no statistically significant improvement TICS, between groups change from baseline 0.14 [-0.15 to 0.43] p=0.35	Low	Indirect	Imprecise	Unknown	Suspected	NA	Low
	Multidomain Neuropsychological Performance	1 (2271)	1 test showed no statistically significant improvement Composite,	Low	Indirect	Precise	Unknown	Suspected	NA	Low

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			between groups change from baseline z-score 0.01 [-0.06 to 0.07] p=0.82							
	Executive/ Attention/ Processing Speed		NR							
	Memory	1 (2271)	1 test showed no statistically significant improvement Composite, between groups change from baseline z-score 0.02 [-0.04 to 0.09] p=0.50	Low	Indirect	Precise	Unknown	Suspected	NA	Low
	Adverse Effects	1 (2271)	No adverse effects were reported, but no statistics were presented	Low	Direct	Unclear	Unknown	Suspected	NA	Insufficient

*calculated by EPC

BCT=brief cognitive screening test; BVRT=Benton Visual Retention Test; C=control; CI=confidence interval; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution Test; DSy=Digit Symbol Coding; EMBT=East Boston Memory Test; HVLT-R=Hopkins Verbal Learning Test-Revised; I=intervention; k=numer of studies; LDST=Letter Digit Substitution Test; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; MNP=multidomain neuropsychological test performance; n=sample size; NA=not applicable; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; SDMT=Symbol Digit Modalities Test; Stroop=Modified Stroop; TICS=Telephone Interview for Cognitive Status (TICS-m=modified); TMT=Trail Making Test (parts A and or B); WAIS=Wechsler Adult Intelligence Scale

Appendix Table L5. Characteristics of eligible studies: vitamins vs. inactive control in adults with MCI

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
Multivitamins	Naeini 2014[22] RCT Iran Low	256	Adults aged 60-75 with MCI (MMSE 21-26) Age 67 Female 53% Race NR Education: Primary 16% Secondary 11% Diploma 40% University degree 33% Baseline cognition: MMSE 24	Vitamin E (300 mg) Vitamin C (400 mg) Daily for 1 year	Placebo	1 year	Brief Cognitive Test Performance [MMSE]
B vitamins	Remington 2015[23] RCT US High	34	Community-dwelling adults with MCI Age 66 Female NR Race NR Education: 15 years Baseline cognition NR	Folic acid (0.4 mg) Vitamin B_{12} (6 µg) Vitamin E (30 IU) SAM (S-adenosyl methionine 400 mg) ALCAR (acetyl-Lcarnitine 500 mg) NAC (N-acetyl cysteine 600 mg) Two doses daily for 6 months	Placebo	6 months	Brief Cognitive Test Performance [Mattis Dementia Rating Scale] Visuospatial [CLOX-1]
	Smith 2010[24] deJager 2012[25] Duouad 2013[26] Oulhaj 2016[27] RCT UK Low	266	Adults aged 70+ diagno-sed with MCI (Peterson's criteria) Age 77 Female 47% Race NR Mean years of education: 15 Baseline cognition: MMSE 28 TICS 25	Folic Acid (0.8 mg) Vitamin B_6 (20 mg) Vitamin B_{12} (0.5 mg) Daily for 2 years	Placebo	2 years	Biomarker [Posterior Brain Atrophy, Rate of Atrophy] Brief Cognitive Test Performance [MMSE] Memory [HVLT] Language [Category Fluency Test] Visuospatial [CLOX-1]

Vitamin Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
	van Uffelen 2008[28] RCT Netherlands High	152	Community-dwelling adults with MCI aged 70-80 Age 75 Female 44% Race NR Education: Low 58% Medium 25% High 17% Baseline education: MMSE 29	Folic acid (5 mg) Vitamin B_6 (50 mg) Vitamin B_{12} (0.4 mg) Daily for 1 year	Placebo	1 year	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Verbal Fluency Test] [DSST] [SCWT] Memory [RAVLT] Language [Verbal Fluency Test]
Vitamin E	Petersen 2005[29] Jack 2008[30] RCT USA Low (Petersen) High (Jack)	516	Adults aged 55-90 with degenerative amnestic MCI Age 73 Female 47% Race NR Education NR Baseline cognition: MMSE 27	Vitamin E (2000 IU) Daily for 3 years (study included a donepezil arm)	Placebo	3 years	Diagnosis [Possible or Probable AD] [CDR Sum of Boxes, AD] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [from Composite Battery, presumed to be DS Backward, SDMT, Number Cancellation, Maze Tracing] Memory [from Composite Battery, presumed to be New York University Paragraph Recall Test] Language [from Composite Battery, presumed to be BNT, Category Fluency] Visuospatial [from Composite Battery, presumed to be CLOX-1]

µg=micrograms (1000 µg=1 mg) (1000 µg=1 g); AD=Alzheimer's disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR=Clinical Dementia Rating; CLOX-1= Clock Drawing Test; DSST=Digit Symbol Substitution Test; HVLT=Hopkins Verbal Learning Test; IU=internal units; MCI=mild cognitive impairment; mg=milligrams; MMSE=Mini Mental Status Exam; NR=not reported; RAVLT=Rey Auditory Verbal Learning Test; RCT=randomized controlled trial; SCWT=Stroop Color Word Test; SDMT=Symbol Digit Modalities Test; US=United States

Appendix Table L6. Summary risk of bias assessments: vitamins in adults with MCI

Intervention	Study	Overall Risk of Bias Assessment	Rationale
Multivitamins	Naeini 2014[22]	Low	Randomization methods unclear, blinding methods adequate, attrition low, ITT not reported.
B vitamins	Oulhaj 2015[27]	Low	Randomization methods adequate, attrition 16%, blinding and outcome assessment methods unclear but likely reported in previous publications.
	Remington 2015[23]	High	Randomization methods unclear, attrition 45% at 6 month followup with no missing data imputation.
	Douaud 2013[26]	Low	Randomization and blinding methods adequate, attrition low, all outcomes reported.
	de Jager 2012[25]	Low	Randomization methods adequate, attrition 16% for cognitive outcomes and no missing data imputation, blinding methods likely adequate, all outcomes reported.
	Smith 2010[24]	Low	Randomization and blinding methods adequate, attrition low for primary outcome and medium for secondary outcomes, ITT, comparable outcome assessment timing between groups.
	van Uffelen 2008[28]	High	Randomization and allocation methods adequate, attrition 16%, outcome assessor blinding unclear, outcomes inexplicably reported stratified by gender (not reported overall).
Vitamin E	Jack 2008[30]	High	Randomization and allocation methods unclear, volunteer cohort of original randomized trial, attrition 33%.
	Petersen 2005[29]	Low	Randomization and blinding methods adequate, attrition 30% but performed appropriate sensitivity analyses, ITT.

ITT=intention to treat; MCI=mild cognitive impairment

Appendix Table L7. Strength of evidence assessments: vitamins vs. inactive control in adults with MCI

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Vitamin E vs. placebo	Dementia Peterson 2005[29]: 3 years	1 (516)	2 tests showed no statistically significant decrease in diagnosis of Alzheimer's disease with vitamin E, Diagnosis, between groups probability of progression to Alzheimer's disease HR=1.02 [0.74 to 1.41] p=0.91 CDR Sum of Boxes, between groups change from baseline (z-score)* 0.03 [NR]	Medium	Direct	Imprecise	Consistent	Undetected	NA	Low
	Brief Cognitive Test Performance	1 (516)	1 test showed no statistically significant improvement with vitamin E MMSE, between	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			groups change from baseline (z-score)* 0.55 [NR]							
	Multidomain Neuropsychological Performance	1 (516)	1 test showed no statistically significant improvement with vitamin E ADAS-Cog, between groups change from baseline (z-score)* 0.85 [NR]	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient
	Executive/ Attention/ Processing Speed	1 (516)	1 composite test showed no statistically significant improvement with vitamin E Composite, between groups change from baseline (z-score)* 0.0 [NR]	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient
	Memory	1 (516)	1 composite test showed no statistically	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient

Vitamin Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
			significant improvement with vitamin E Composite, between groups change from baseline (z-score)* -0.03 [NR]							
	Adverse Effects	1 (516)	No significant difference between groups for withdrawals 28% vs. 25%* RR*=1.10 [0.83 to 1.46] p=0.52	Medium	Direct	Imprecise	Unknown	Undetected	NA	Low

*calculated by EPC

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR=Clinical Dementia Rating; HR=hazard ratio; k=number of studies; MMSE= Mini-Mental Status Exam; n=sample size; NA=not applicable; NR=not reported; RR=relative risk

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Appendix M. Antihypertension Treatment

Appendix Table M1. Characteristics of eligible studies: antihypertension interventions in adults with normal cognition

Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cog	Intervention (INT) Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome measurement timing	Outcome (Instrument)
ACE and Thiazide Efficacy	Peters 2008[1] (HYVET-COG) RCT Multinational Medium	3,845	Adults aged ≥80 years with an average sitting systolic blood pressure between 160 mmHg and 200 mmHg and an average standing systolic blood pressure ≥140 mmHg, and a sitting diastolic blood pressure of ≤110 mmHg. Normal cognition. Mean age (SD): 83.5 (3.1) 61% Female Race: NR 27% no education 28% primary education 29% secondary education 12% higher education 3% more than higher education Median MMSE (range): 26 (15 – 30)	Indapamide 1.5 mg with optional perindopril (2mg up to 4 mg)	Matching-placebo	2.2 years mean follow up	Diagnosis [Committee-reported diagnosis of dementia] Brief Cognitive Test Performance [MMSE, cognitive decline defined as MMSE <24 or a decline of >3 MMSE points in a year]

	Patel 2007[2] ADVANCE Collaborative Group 2007[2] RCT Multinational Low	11,140	Adults diagnosed with type 2 diabetes at the age ≥30 years, and were aged ≥55 years at study entry. Patients also need to have a history of cardiovascular disease or at risk for cardiovascular disease. Normal cognition. Mean age (SD): 66 (7) 43% Female Race: NR Education: NR Median MMSE (range): NR	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	Matching-placebo and open label perindopril up to 4 mg.	4.3 yeas mean follow up	Diagnosis Brief Cognitive Test Performance [MMSE]
ARB Efficacy	Anderson 2011[3] (TRANSCEND trial) RCT Multinational Medium	5926	Adults aged ≥55 years with evidence of coronary artery, peripheral vascular, or cerebrovascular disease or diabetes with end-organ damage, intolerance to ACE inhibitors, and normal cognition. Mean age (SD): 66.9 43% Female 61% European ethnic origin 62% ≥9 years of education Median MMSE (IRQ): 29 (27 – 30)	Telmisartan 80 mg daily	Placebo daily	56 months median follow up	Brief Cognitive Test Performance [Cognitive decline - drop of 3 or more MMSE points]

	Saxby 2008[4] (single center in SCOPE trial) RCT United Kingdom Medium	257	Hypertensive adults aged 70 to 89 years with systolic blood pressure of 160 to 179 mmHg and diastolic blood pressure of 90 to 99 mmHg and normal cognition. Mean age (SD): 76 (4) 54% Female Race: NR Mean years education (SD): 10 (2) Mean MMSE (SD): 29 (1)	Candesartan (8 mg – 16 mg) daily with hydrochlorothiazide 12.5 mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed.	Placebo daily and hydrochlorothiazide 12.5 mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed.	44 months mean follow up	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Composite] Memory [Composite]
	Lithell 2003[5] Skoog 2005[6] (SCOPE trial) RCT Multinational Medium	4937	Hypertensive adults aged 70 to 89 years with systolic blood pressure of 160 to 179 mmHg and diastolic blood pressure of 90 to 99 mmHg and normal cognition with results stratified by low (MMSE 24 – 28) and high (29 – 30) cognitive function. Mean age (SD): 76 (NR) 64% female Race: NR 10% less than primary school education 44% primary school education 40% more than primary school education 6% University	Candesartan (8mg – 16 mg) daily with hydrochlorothiazide 12.5 mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed.	Placebo daily and hydrochlorothiazide 12.5mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed.	44 months mean follow up	Diagnosis Brief Cognitive Test Performance [MMSE]

			education Mean MMSE (SD): 28.5 (NR)				
Beta Blocke Efficacyr	Perez-Stable 2000[7] RCT United States High	312	Adults aged 18 to 59 with diastolic blood pressure between 90 and 104 mmHg and normal cognition.	Propranolol (40 mg first three days then 80 mg daily as tolerated then increased up to 400 mg daily)	Placebo daily	12 months	Executive/Attention/Processing Speed [Stimulus Evaluation/Response Selection, CPT, DSST] Memory [CVLT]
	Bird 1990[8, 9] RCT United Kingdom Medium	2401	Adults aged 65 to 74 with systolic blood pressure of 160 to 209 mmHg and diastolic blood pressure of <114 mmHg, and normal cognition. Mean age (SD): 70.3 (2.7) 58% Female Race: NR Education: NR Cognition: NR	Atenolol 50 mg daily	Placebo daily	9 months	Executive/Attention/Processing Speed [TMT] Memory [PALS]
Combination therapy Efficacy	Forette 2002[10] (Syst-Eur trial 1 & 2) RCT and open-label follow up Multinational Medium	3228	Adults aged >60 years with systolic blood pressure of 160 to 219 mmHg and diastolic blood pressure <95 mmHg and normal cognition. Median age (range): 68 (60-92) Sex: NR Race: NR Mean age (SD) on leaving school: 16.7 (4.5) Cognition: NR	Antihypertensive stepwise therapy with titration with goal of lowering systolic blood pressure by 20 mmHg or below 150 mmHg (step 1: nitrendipine 10 -40 mg daily; step 2: enalapril 5 – 20 mg daily; step 3: hydrochlorothiazide 12.5 – 25 mg daily)	Placebo daily (in open-label phase offered active treatment)	3.9 years median follow up	Diagnosis Brief Cognitive Test Performance [MMSE]
	Forette 1998[11] (Syst-Eur trial	3162	Adults >60 years with systolic blood	Antihypertensive stepwise therapy	Placebo daily	2 years median follow up	Diagnosis Brief Cognitive Test

	1) RCT Multinational Medium		pressure of 160 to 219 mmHg and diastolic blood pressure <95 mmHg and normal cognition. Mean age (SD): 69.9 (6.4) Sex: NR Race: NR Mean age (SD) on leaving school: 16.2 (4.4) Median MMSE (range): 29 (15-30)	with titration with goal of lowering systolic blood pressure by 20 mmHg or below 150 mmHg (step 1: nitrendipine 10 -40 mg daily; step 2: enalapril 5 – 20 mg daily; step 3: hydrochlorothiazide 12.5 – 25 mg daily)			Performance [MMSE]
	Applegate 1994[12, 13] (SHEP trial) RCT United States High	4736	Adults >60 years with systolic blood pressure of 160 to 220 mmHg and diastolic blood pressure <90 mmHg and normal cognition. Mean age (range): 72 (60 – 94) 57% Female 86% White Mean years of education (SD): 11.7 (NR) 0.4% Evidence of cognitive impairment	Step therapy: step 1: chlorthalidone (12.5 – 25 mg); step 2: atenolol (25 – 50 mg) or reserpine (0.05 – 0.1 mg).	Placebo daily	5 year average follow up	Diagnosis Brief Cognitive Test Performance [SHORT-CARE Dementia] Executive/Attention/Processing Speed [DSST] Memory [Addition Test] [Finding A's Test] [Delayed Recognition Span Test] Language [BNT] Visuospatial [Letter Sets Test]
	Gurland 1988[14] (SHEP feasibility trial) RCT United States Medium	551	Adults >60 years with systolic blood pressure >160 mmHg and diastolic blood pressure <90 mmHg and normal cognition. Mean Age: NR Sex: NR 83% White Education: NR Cognition: NR	Step therapy: step 1: chlorthalidone; step 2: reserpine, metoprolol, or hydralazine)	Placebo	1 year	Diagnosis Executive/Attention/Processing Speed [TMT] [DSST] [Composite Battery[b]]

Comparative Effectiveness ARB versus ACE	Hajjar 2013[15] RCT United States Medium	53	Adults aged ≥60 years with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or receiving antihypertensive medications and normal cognition. Mean age (SD): 72 (7) 57% Female 70% White 19% ≤High school Mean MMSE (SD): 26 (2)	I_1:Lisinopril 10 mg with titration to 40 mg I_2: Candesartan 8 mg with titration to 32 mg I_3: Hydrochlorothiazide 12.5 mg with titration to 25 mg If systolic blood pressure of less than 140 mmHG and diastolic blood pressure of less than 90 mmHG not get then long-acting nifedipine (30 mg increased to 90 mg) was added followed by long-acting metoprolo (12.5 mg to 50 mg).		6 months	Executive/Attention/Processing Speed [TMT] [DS Test] Memory [HVLT]
	Andrerson 2011[3] (ONTARGET trial) RCT Multinational Medium	17118	Adults aged ≥55 with evidence of coronary artery, peripheral vascular, or cerebrovascular disease or diabetes with end-organ damage, and normal cognition. Mean age (SD): 66 (7.2) 27% Female 73% European ethnic origin 67% ≥ 9 years of education Median MMSE (IQR): 29 (27 – 30)	Ramipril 5mg (increased to 10 mg after 2 weeks) daily	Telmisartan 80 mg daily	56 months median follow up	Brief Cognitive Test Performance [Cognitive decline - drop of 3 or more MMSE points]
	Forgari 2006[16] RCT open-	160	Adults aged 61 to 75 with systolic	Telmisartan 80 mg and	Lisinopril 20 mg and	6 months	Executive/Attention/Processing Speed [TMT B]

	label Italy Low		blood pressure >140 mmHg diastolic blood pressure ≥95 and <110 mmHg, and normal cognition. Mean age (SD): 68 (5.5) 54% Female Race: NR Education: NR Cognition: NR	hydrochlorothiazide 12.5 mg daily	hydrochlorothiazide 12.5mg daily		Memory [Word-List Memory Test] [Word-List Recall Test] [Word-List Recognition Test] Language [BNT] [Name Animals]
Comparative Effectiveness ARB versus Thiazide	Hajjar 2013[15] RCT United States Medium	53	Adults aged ≥60 years with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or receiving antihypertensive medications and normal cognition. Mean age (SD): 72 (7) 57% Female 70% White 19% ≤High school Mean MMSE (SD): 26 (2)	I_1:Lisinopril 10 mg with titration to 40 mg I_2: Candesartan 8 mg with titration to 32 mg I_3: Hydrochlorothiazide 12.5 mg with titration to 25 mg If systolic blood pressure of less than 140 mmHG and diastolic blood pressure of less than 90 mmHG not get then long-acting nifedipine (30 mg increased to 90 mg) was added followed by long-acting metoprolo (12.5 mg to 50 mg).		6 months	Executive/Attention/Processing Speed [TMT, DSST] Memory [HVLT-R]
	Tedesco 1999[17] RCT Italy Low	69	Adults aged 30 to 73 with mild-to-moderate essential hypertension: diastolic blood pressure of 90 to 114 mmHg and normal cognition.	Losartan 50 mg daily	Hydrochlorothiazide de 25 mg daily	26 months	Brief Cognitive Test Performance [MMSE]

			Mean age (SD): 55 (11) 48% Female Race: NR Mean years education (SD): 9.1 (4) Mean MMSE (SD): 23 (3)				
Comparative Effectiveness – Unique comparisons	Williamson 2014[18] (ACCORD BP trial) RCT United States Medium	1439	Middle-aged and older adults with diabetes at high risk of cardiovascular events and systolic blood pressure of 130 to 180 mmHg and normal cognition. Mean age (SD): 62 (5.8) 55% Female 66% White 13% <High school 26% High school graduate 36% Some college 25% college graduate or more Median MMSE (25th and 75th percentile): 28 (26-29)	Intensive intervention (systolic blood pressure <120 mm Hg)	Standard therapy (systolic blood pressure <140 mm Hg)	40 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [SCWT] [DSST] Memory [RAVLT]
	Hajjar 2013[15] RCT United States Medium	53	Adults aged ≥60 years with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or receiving antihypertensive medications and normal cognition. Mean age (SD): 72 (7) 57% Female 70% White	I_1:Lisinopril 10mg with titration to 40 mg I_2: Candesartan 8 mg with titration to 32 mg I_3: Hydrochlorothiazide 12.5mg with titration to 25 mg If systolic blood pressure of less		6 months	Executive/Attention/Processing Speed [TMT] [DSST] Memory [HVLT-R]

			19% ≤High school Mean MMSE (SD): 26 (2)	than 140 mmHG and diastolic blood pressure of less than 90mmHG not get then long-acting nifedipine (30 mg increased to 90 mg) was added followed by long-acting metoprolo (12.5 mg to 50 mg).			
	Sato 2013[19] (CAMUI trial) RCT open-label Japan Low	142	Hypertensive adults aged ≥65 years that had not attained the blood pressure goal (systolic blood pressure <140 mmHg and or diastolic blood pressure >90 mmHg) with monotherapy with typical dosage of ARB and normal cognition. Mean age (SD): 74 (6.2) Sex: NR Race: NR Education: NR Mean MMSE (SD): 26.7 (3)	Combined losartan 50mg and hydrochlorothiazide 12.5 mg daily in quarterly visits if blood pressure goals not obtained titration was undertaken	Combined amlodipine 5mg and typical dosage of a angiotensin receptor blocker daily during quarterly visits if blood pressure goals not obtained titration was undertaken	12 months	Brief Cognitive Test Performance [MMSE]
	Andrerson 2011[3] (ONTARGET trial) RCT Multinational Medium	17078	Adults aged ≥55 years with evidence of coronary artery, peripheral vascular, or cerebrovascular disease or diabetes with end-organ damage, and normal cognition. Mean age (SD): 66 (7.2) 27% Female 73% European	Ramipril 5mg (increased to 10mg after 2wks) daily	Combined ramipril 5 mg (increased to 10mg after 2wks) daily and telmisartan 80 mg daily	56 months median follow up	Brief Cognitive Test Performance [Cognitive decline - drop of 3 or more MMSE points]

			ethnic origin 67% ≥ 9 years of education Median MMSE (IRQ): 29 (27 – 30)				
	Forgari 2003[20] RCT Italy Low	120	Adults aged 75 to 89 with mild to moderate essential hypertension: systolic blood pressure <200 mmHg and diastolic blood pressure of 90 to 105 mmHg. Normal cognition. Mean age (SD): 83 (4.3) 56% Female Race: NR Mean years education (SD): 8.6 (4.1) Cognition: NR	Atenolo 50 mg with titration to 100 mg	Losartan 50 mg with titration to 100 mg	6 months	Memory [Word-List Test] [Memory Word Recall Test] Language [Word-List Frequency]
	Yodfat 1996[21] RCT Israel Low	368	Males aged 40 to 65 with essential hypertension: diastolic blood pressure of 95 to 105 mmgHg. Normal cognition. Mean age (SD): 52 (7.6) 100% Male Race: NR Education: NR Cognition: NR	I_1:Isradipine 1.25 mg twice a day (dose doubled if normotension not achieved at 4 weeks and if normotension not achieved at 6 weeks captopril 25mg daily) I_2: Methyldopa 250 mg twice a day (dose doubled if normotension not achieved at 4 weeks and if normotension not achieved at 6 weeks captopril 25 mg daily)	placebo twice a day	12 months	Language [Semantic Memory]
	Bird 1990[8]	2446	Adults aged 65 to	I_1: Atenolol 50mg	Placebo	9 months	Executive/Attention/Processing

	RCT United Kingdom Medium		74 with systolic blood pressure of 160 to 209 mmHg and diastolic blood pressure of <114 mmHg, and normal cognition. Mean age (SD): 70.3 (2.7) 58% Female Race: NR Education: NR Cognition: NR	daily I_2: Moduretic (hydrochlorothiazide 25mg and amiloride 2.5mg) daily			Speed [TMT] Memory [PALS]
	Goldstein 1990[22] RCT United States High	690	Men aged >60 with mild-to-moderate hypertension and normal cognition. Mean Age: NR 100% Male Race: NR Mean years of education (SD): 10.6 (NR) Cognition: NR	Hydrochlorothiazide 25mg once or twice a day if target blood pressure not achieved (<90 mmHg and ≤5 mmHg decline from baseline) randomly assigned to additional therapy (hydralazine 50-200 mg daily, methyldopa 550-2,000 mg daily, metoprolol 100-400 mg daily, and reserpine 0.05-0.25mg daily).	Hydrochlorothiazide 50mg once or twice a day if target blood pressure not achieved (<90 mmHg and ≤5 mmHg decline from baseline) randomly assigned to additional therapy (hydralazine 50-200mg daily, methyldopa 550-2,000 mg daily, metoprolol 100-400 mg daily, and reserpine 0.05-0.25mg daily).	1 year	Executive/Attention/Processing Speed [TMT] [Symbol Digit (no. correct)] [Time Estimation] [Digit Span] Memory [BVRT [Immediate and Delayed Logical Memory] PALS] [Complex Cognition Composite] [Memory composite] Language [Token Test, Controlled word production] Motor [Halstead Finger Tapping [Motor Speed Composite] Visuospatial [Hooper Visual Organization]

[a] Saxby 2008[4] evaluated a composite measures of episodic memory (composed of immediate word recall, immediate word recognition, delayed word recall, delayed word recognition, picture recognition), attention (composited simple reaction time, number vigilance, choice reaction time), working memory (composted 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 1988[14] evaluated a composite executive/attention/processing speed measure composed of SHORT-CARE dementia, Trail Making, and Digit Symbol test.

ACE=angiotensin converting enzyme inhibitors; BNT=Boston Naming Test; DSST=Digit Symbol Substitution Test; HVLT=Hopkins Verbal Learning Test; IQR=interquartile range; mg=milligrams; mmHg=millimeter of mercury; MMSE=Mini-Mental Status Examination; N=sample size; NR=not reported; PALS=Paired Association Learning Test; RAVLT=Rey's Auditory Verbal Learning Test; RCT=randomized controlled trial; RoB=risk of bias; SCWT=Stroop Color Word Test; SD=standard deviation; TMT=Trail Making Test (Part A and/or B)

Appendix Table M2. Summary risk of bias assessments: antihypertensives in adults with normal cognition

Intervention	Study	Overall Risk of	Rationale

Type		Bias Assessment	
ACE and Thiazide versus Placebo	Peters 2008[1]	Medium	Attrition 19%
	ADVANCE Collaborative Group 2007 [2]	Low	
ARB versus Placebo	Anderson 2011[3]	Medium (TRANSCEND)	Attrition 12%
	Saxby 2008[4]	Medium	Attrition 13%
	Lithell 2003[5], Skoog 2005[6]	Medium	Attrition 32%
Beta Blocker versus Placebo	Perez-Stable 2000[7]	High	Attrition 34%
	Bird 1990[8]	Medium	Attrition 11%
Combination Therapy versus Placebo	Forette 2002[10]	Medium	Attrition unclear and outcome assessor not independent
	Forette 1998[11]	Medium	Attrition 14%
	Applegate 1994[9, 12]	High	Attrition 25%
	Gurland 1988[14]	Medium	Attrition 12%
ARB versus ACE	Anderson 2011[3]	Medium (ONTARGET)	Attrition 12%
	Hajjar 2013[15]	Medium (6 month outcomes) High (12 month outcomes)	Medium: Attrition 11% High: Attrition 42%
	Fogari 2006[16]	Low	
ARB versus Thiazide	Hajjar 2013[15]	Medium (6 month outcomes) High (12 month outcomes)	Medium: Attrition 11% High: Attrition 42%
	Tedesco 1999[17]	Low	
Comparative Effectiveness – Unique Comparisons	Williamson 2014[18]	Medium High (MIND substudy)	Medium (ACCORD BP trial): Attrition 13% High (ACCORD BP MIND trial): Attrition 24% among those in the intensive intervention
	Hajjar 2013[15]	Medium (6 month outcomes) High (12 month outcomes)	Medium: Attrition 11% High: Attrition 42%
	Sato 2013[19]	Low	
	Anderson 2011[3]	Medium (ONTARGET)	Attrition 12%

	Fogari 2003[20]	Low	
	Yodfat 1996[21]	Medium	Attrition 19%
	Bird 1990[8]	Medium	Attrition 11%
	Goldstein 1990[22]	High	Attrition 52%

ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blocker

Appendix Table M3. Strength of evidence assessments: antihypertensives in adults with normal cognition

Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Antihypertension (ACE and Thiazide)	Dementia	2 (14,985)	0 of 2 tests show statistically significant improvement Peters 2008 (HYVET-COG)[1] Diagnosis HR: 0.86 [0.67 to 1.09] ADVANCE Collaborative Group 2007[2] Relative risk reduction diagnosis: -4% [-64% to 33%]	Medium	Direct	Imprecise	Consistent	Suspected	NA	Low
	MCI	NR								Insufficient
	Brief Cognitive Test	2 (14,985)	0 of 3 tests show statistically significant improvement Peters 2008 (HYVET-COG))[1] Cognitive decline (MMSE <24 or a decline of >3 MMSE points in a year HR: 0.93 [0.82 to 1.05]	Medium	Indirect	Precise	Consistent	Suspected	NA	Moderate

			Mean MMSE change score in indapamide and perindopril 0.07 (SD 4.0) versus placebo -1.1 (SD 3.9) p = 0.08 ADVANCE Collaborative Group 2007[2] Relative risk reduction cognitive function: 2% [-9% to 12%]							
	Multidomain Composites	NR								Insufficient
	Executive/Attention/Processing Speed	NR								Insufficient
	Memory	NR								Insufficient
	Serious Adverse Events	2 (14,985)	1 of 2 tests show statistically fewer adverse events Peters 2008 (HYVET-COG)[1] Number of adverse events in indapamide and perindopril (358) vs placebo (448) p <0.001 ADVANCE Collaborative Group 2007[2] Number of adverse drug reactions in	Medium	Direct	Precise	Unknown	Suspect	NA	Low

			perindopril and indapamide (47) and placebo (31).							
Antihypertension (ARBs)	Dementia	1 (4937)	0 of 1 tests show statistically significant improvement <u>Lithell 2003[5] and Skoog 2005[6] (SCOPE)</u> Dement events per 1000 patient years candesartan (6.8) vs control (6.3) p > 0.20	Medium	Direct	Precise	Unknown	Suspect	NA	Low
	MCI	NR								Insufficient
	Brief Cognitive Test	2 (10,863)	0 of 3 tests show statistically significant improvement: <u>Anderson 2011[3] (TRANSCEND)</u> OR cognitive decline (drop of 3 or more MMSE points) Telmisartan vs placebo 1.10 [0.95 to 1.27] <u>Saxby 2008[4] (single center in SCOPE)</u> Difference in mean change from baseline to closeout visit (MMSE) candesartan (baseline 28.7 to closeout visit 28.3) vs placebo (baseline 28.9 to closeout visit 28.5) p-value = 0.94	Medium	Indirect	Precise	Consistent	Suspect	NA	Moderate

			for change in MMSE between groups. Lithell 2003[5] and Skoog 2005[6] (SCOPE) Difference in mean change (MMSE) candesartan vs placebo 0.15 [-0.08 to 0.38]							
	Multidomain Composites	NR								Insufficient
	Executive/ Attention/ Processing Speed	1 (257)	1 of 3 tests show statistically significant improvement with Intervention	Medium	Indirect	Unknown	Inconsistent	Suspect	NA	Insufficient
	Memory	1 (257)	1 of 2 tests show statistically significant improvement with Intervention Saxby 2008[4] (single center in SCOPE) Coefficient (SD) for decline in episodic memory for candesartan 0.14 (1.38) and placebo -0.22 (1.21). p = 0.04. Coefficient (SD) for decline in working memory for candesartan 0.0014 (0.012) and placebo 0.0010 (0.012). p = 0.90.	Medium	Indirect	Unknown	Inconsistent	Suspect	NA	Insufficient
	Serious Adverse	1 (5,926)	Lithell 2003[5] and Skoog 2005[6]	Medium	Direct	Unknown	Unknown	Suspect	NA	Insufficient

	Events		(SCOPE) No difference adverse events reported between groups							
Antihypertension (Beta blocker)	Dementia	NR								Insufficient
	MCI	NR								Insufficient
	Brief Cognitive Test	NR								Insufficient
	Neuropsychological Performance	NR								Insufficient
	Executive/ Attention/ Processing Speed	1 (1859)	0 of 1 tests show statistically significant improvement with Intervention	Medium	Indirect	Unknown	Unknown	Suspect	NA	Insufficient
	Memory	1 (1859)	0 of 2 tests show statistically significant improvement with Intervention	Medium	Indirect	Unknown	Inconsistent	Suspect	NA	Insufficient
	Serious Adverse Events	NR								Insufficient
Antihypertension (Combination therapy)	Dementia	2 (3779)	Forette 1998[11] (Syst-Eur 1) Forette 2002[10] (Syst-Eur 1 & 2) 2011 RR 0.50 (95%CI, 0.24-1.00) reduction in the rate of dementia for treatment vs. placebo	Medium	Direct	Imprecise	Unknown	Suspect	Low	Insufficient
	MCI	NR								Insufficient
	Brief Cognitive Test	1 (3228)	0 of 2 tests show statistically significant improvement:	Medium	Indirect	Precise	Consistent	Suspect	NA	Low

			Forette 2002[10] (Syst-Eur 1 & 2) 2011 Change in MMSE score at year 1 [treatment 0.10 (SD 1.44) control 0.16 (SD 1.52); p = 0.28], year 2 [treatment 0.17 (SD 1.64) control 0.15 (SD 1.69); p = 0.75], year 3 [treatment 0.17 (SD 1.82) control 0.14 (SD 1.85); p = 0.73] Forette 1998[11] (Syst-Eur 1) MD MMSE 0.07 [-0.09 to 0.23]							
	Executive Function	1 (551)	1 of 3 tests show statistically significant improvement	Medium	Indirect	Imprecise	Inconsistent	Suspect	NA	Insufficient
	Memory	NR								Insufficient
	Serious Adverse Events	NR								Insufficient
Antihypertension (ARB versus ACE)	Dementia	NR								Insufficient
	MCI	NR								Insufficient
	Brief Cognitive Test	1 (17,118)	0 of 1 test show statistical significant improvement Anderson 2011[3] (ONTARGET) cognitive decline (drop of 3 or more MMSE points) telmisartan vs	Medium	Indirect	Precise	Unknown	Suspect	NA	Low

			ramipril RR 0.97 [0.89 to 1.06]							
	Neuropsychological Performance	NR								
	Executive Function	1 (160)	0 of 1 test show statistically significant improvement	Medium	Indirect	Unknown	Unknown	Suspect	NA	Insufficient
	Memory	1 (160)	1 of 2 tests show statistically significant improvement	Low	Indirect	Unknown	Unknown	Suspect	NA	Insufficient
	Serious adverse events	1 (160)	0 of 1 test show statistically significant difference Forgari 2006[16] No difference in adverse events	Low	Direct	Unknown	Unknown	Suspect	NA	Insufficient
ARB versus Thiazide	Dementia	NR								Insufficient
	MCI	NR								Insufficient
	Biomarkers	NR								Insufficient
	Global Cognition	NR								Insufficient
	Executive Function	NR								Insufficient
	Memory	NR								Insufficient
	Serious adverse events	2 (122)	0 of 2 test show statistically significant difference Hajjar 2013[15] No difference in adverse events Tedesco 1999[17] No difference in adverse events	Medium	Direct	Unknown	Unknown	Suspect	NA	Insufficient
Intensive blood	Dementia	NR	NR							Insufficient

pressure control (systolic blood pressure <120 mm Hg) versus standard blood pressure control (standard therapy (systolic blood pressure <140 mm Hg))	MCI	NR	NR							Insufficient
	Brief Cognitive Test	1 (1439)	0 if 1 test show statistically significant difference Williamson 2014[18] (ACCORD BP trial) MD MMSE 0.05 [-0.20 to 0.29]	Medium	Indirect	Precise	Unknown	Suspect	NA	Low
	Multidomain Neuropsychological Performance	NR								
	Executive Function	1 (1439)	0 of 2 tests show statistically significant difference	Medium	Indirect	Imprecise	Consistent	Suspect	NA	Low
	Memory	1 (1439)	0 of 1 test show statistically significant difference	Medium	Indirect	Precise	Unknown	Suspect	NA	Low
	Serious adverse events	NR								Insufficient
(I_1) Ramipril up to 10 mg daily vs. (I_2) combined ramipril up to 10 mg daily and telmisartan 80 mg daily	Dementia	NR								Insufficient
	MCI	NR								Insufficient
	Screening Tools	1 (17,078)	0 if 1 test shows statistically significant difference Anderson 2011[3] (ONTARGET) OR cognitive decline (drop of 3 or more MMSE points) combined ramipril and telmisartan vs. ramipril 0.95 [0.88 to 1.04]	Medium	Indirect	Precise	Unknown	Suspect	NA	Low
	Multidomain Composites	NR								Insufficient
	Executive	NR								Insufficient

	Function									
	Memory	NR								Insufficient
	Serious adverse events	NR								Insufficient

ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blocker; C=control; CI=confidence interval; MCI=mild cognitive impairment; mg=milligrams; MMSE=Mini Mental Status Exam; NA=not applicable; NR=not reported; OR=odds ratio; SD=standard deviation; vs=versus

Appendix Table M4. Characteristics of eligible studies: antihypertension interventions in adults with MCI

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cog	Intervention (INT) Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome measurement timing	Outcome (Instrument)
Starr 1996[23], 2005[24] (HOPE trial) RCT United Kingdom Medium	81	Adults aged 70 to 85 with median systolic blood pressure of 160 to 220 mmHg and diastolic blood pressure of 100 to 120 mmHg, or median systolic blood pressure of 180 to 220 mmHg and diastolic blood pressure of ≥85 mmHg. Mild cognitive impairment. Mean age (range): 76.1 (70-84) 65% Female Race: NR Education: NR Mean MMSE (range): 26.1 (20-28)	Captopril 12.5mg twice a day	Bendrofluazide 2.5 mg once a day	26 weeks	Executive/Attention/Processing Speed [TMT A, RCPM] Memory [Logical Memory Immediate] [Delayed Memory Immediate] [Anomalous Sentences Repetition Test] [PALS]

NR=not reported; MCI=mild cognitive impairment mg=milligrams; PALS=Paired Association Learning Test; RCPM = Raven's Colored Progressive Matrices; RCT=randomized controlled trial; TMT A = Trail Making Test Part A

Appendix Table M5. Summary risk of bias assessments: antihypertension in adults with mild cognitive impairment

Study	Overall Risk of Bias Assessment	Rationale
Starr 1996[23], 2005[24]	Medium	Attrition 12%

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Appendix N. Lipid Lowering Treatment

Appendix Table N1. Characteristics of eligible studies: lipid lowering interventions in adults with normal cognition

Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cog	Intervention (INT) Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome measurement Timing	Outcome (Instrument)
Statins Versus Placebo	Trompet 2010[1, 2] RCT Multinational High	5804	Adults aged 70 to 82 years with preexisting vascular disease or at increased risk of vascular disease and normal cognition. Mean age (SD): 75 (3) 52% Female Race: NR Mean years of education (SD): 15.1 (2) Mean MMSE (SD): 28 (1.5)	Pravastatin	Placebo	42 months mean follow up	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [SCWT] [Letter-Digit Coding Test] Memory [15-Picture Learning Test Immediate And Delayed]
	Parale 2006[3] Observational India High	97	Adults age ≥40 years with cardiovascular indications for statin use and normal cognition. Mean age (SD): 56.5 (8) 67% Female Race: NR Mean years education (SD): 11 (2.9) Mean MMSE (SD): 28.4 (1.8)	Atorvastatin 10 mg daily	Placebo	6 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DSST] [DVT] [TMT B] Memory [Picture-Word Learning] [COWAT] [Auditory Vigilance] Adverse Events
	Muldoon 2004[4] RCT	308	Adults aged 35 to 70 years with low-density lipoprotein cholesterol level between	Simvastatin 10 mg daily or Simvastatin 40 mg	Placebo	6 months	Executive/Attention/Processing Speed[a] [Composite] Memory [Memory Composite 1]

	United States Medium		160 and 220 mg/dL and normal cognition. Mean age (SD): 53.7 (9.1) 52% Female 86% White Mean years education (SD): 14.8 (3.4) Mean Digit Vigilance (errors), and Recurring Words (errors): 6.6, 81.84.	daily			[Memory Composite 2] Adverse Events
	Heart Protection Study 2002[5] RCT United Kingdom Medium	20,536	Adults aged 40-80 years with total cholesterol concentrations ≥ 135 mg/dL and with substantial 5-risk of death from coronary heart disease and normal cognition. 28% > 70 years 28% Female Race: NR Education: NR Mean TICS-M (SD): 24.07 (NR)	Simvastatin 40 mg daily	Matching-placebo	5 years mean follow up	Diagnosis Brief Cognitive Test Performance [TICS] Adverse Events [Hospitalizations]
	Muldoon 2000[6] RCT United States Medium	209	Adults aged 24 to 60 with hypercholesterolemia (serum low-density-lipoprotein cholesterol level ≥160 md/dL) and normal cognition. Mean age (SD): 46.4 (8.9) 46% Female 88% White Mean years education (SD): 15 (3) Mean Digit Span (SD), Digit Symbol (SD), Trailing Making B (SD): 7 (1.3), 11.8 (2.5), 65 (21).	Lovastatin 20 mg daily	Matching placebo	6 months	Executive/Attention/Processing Speed[b] [Composite Measure of Attention] [Composite of Mental Flexibility] [Composite Measure of Psychomotor Speed] Executive/Attention/Processing Speed[b] Memory [Working Memory Composite] [Memory Retrieval Composite]
	Santanello 1997[7] RCT United States Medium	431	Adults aged ≥65 years with low-density lipoprotein-cholesterol >159 md/dL and < 221 mg/dL and normal cognition and MMSE ≥ 24.	(l_1) lovastatin 20 mg daily (l_2) lovastatin 40 mg daily	Placebo	6 months	Executive/Attention/Processing Speed [DSST] Adverse Events [Number of Events]

			Mean age (SD): 71.2 (NR) 71% Female 24% White Education: NR Mean Digit Symbol Substation Score (SD): 41.86 (13.88)				
Statin Plus Ezetimibe Versus Placebo	Tendolkar 2010[8] RCT Netherlands Low	34	Elderly stroke-free patients with chronic or paroxysmal atrial fibrillation and normal cognition. Mean age (SD): 74 (4) 24% Female Race: NR Education: NR Mean MMSE (SD): 27.4 (2)	Atorvastatin 20mg for 2 weeks then increased to 40mg, after 4 weeks ezetimibe 10mg was added. Standard anticoagulant therapy	Matching-placebo and standard anticoagulant therapy	1 year	Biomarker [Brain Volume Change] Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DSST] Memory [Dutch Modified Version RAVLT] Immediate and Delayed Word Recall]
	Statin Plus Fenofibrate Versus Statin Plus Placebo						
	Willamson 2014[9] (ACCORD Lipid trial) RCT United States Medium	1538	Middle-aged and older adults with diabetes at high risk of cardiovascular events with low-density lipoprotein cholesterol levels of less than 100 mg/dL and normal cognition. Mean age (SD): 62.5 (5.7) 38.9% Female 73% White 13% <High school 25% High school graduate 33% Some college 28% college graduate or more Median MMSE (25th and 75th percentile): 28 (26-29)	Fenofibrate plus statin	Placebo plus statin	40 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [SCWT] [DSST] Memory [RAVLT]
Comparative Effectiveness	Muldoon 2004[4] RCT United States Medium	189	Adults aged 35 to 70 years with low-density lipoprotein cholesterol level between 160 and 220 mg/dL and normal cognition. Mean age (SD): 53.7 (9.1)	Simvastatin 10 mg daily	Simvastatin 40 mg daily	6 months	Executive/Attention/Processing Speed[a] [Composite 1] [Composite 2] Memory [Memory Composite] Adverse Events

			52% Female 86% White Mean years education (SD): 14.8 (3.4) Mean Digit Vigilance (errors), and Recurring Words (errors): 6.6, 81.84.				
	Carlsson 2002[10] RCT-Crossover United States Medium	41	Adults ≥70 years with low-density lipoprotein-cholesterol ≥140 mg/dl and tri-glyceride levels ≤140 mg/dl and normal cognition. Mean age (SD): 76.3 (4.3) 68% Female Race: NR Education: NR Mean Digit Symbol Substitution (SD): 42.45 (9.69)	Pravastatin 20 mg daily	Tocopherol 440 IU daily	6 months	Executive/Attention/Processing Speed [DSST] Adverse Events [Physical Adverse Events] [Hospitalizations]

[a]Muldoon 20043 grouped tests into composite measures and if there was a significant difference in the composite measure individual items were evaluated. The composite measures were: 1) composite Executive/Attention/Processing Speed 1: Elithorn mazes, digit vigilance, recurring words, grooved pegboard; 2) memory composite 1: mirror tracing, 4-word short term memory, 3) memory composite 1: digit symbol, stroop interference, trail making B, digit span, complex figure, letter rotation;
[b]Muldoon 20005 grouped tests into composite measures and if there was a significant difference in the composite measure individual items were evaluated. The composite measures were: 1) composite measure of attention: digit vigilance, letter rotation, digit span, recurring words; 2) composite measure of psychomotor speed: grooved pegboard, Elithorn Maze, Digit Symbol; 3) composite of mental flexibility: Stroop Interference, Trail Making Digit Vigilance, Letter Rotation; 4) working memory composite: Associative Learning, Digit Span, 5) memory retrieval composite: Controlled Oral Word Association, Digit Symbol Recall, Verbal Recall, Complex Figure.
DVT=Digit Vigilance Test; COWAT=Controlled Oral Word Association Test; DSST=Digit Symbol Substitution Test; IU=international units; mg=milligrams; MMSE=Mini-Mental State Examination; NR=not reported; RCT=randomized controlled trial; RAVLT=Rey's Auditory Verbal Learning Test; SCWT = Stroop Color Word Test; SD=standard deviation; TICS=Telephone Interview for Cognitive Status

Appendix Table N2. Summary risk of bias assessments: lipid lowering treatment in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Williamson 2014[9] (ACCORD Lipid trial)	Low (ACCORD Lipid-MIND trial) High (ACCORD Lipid-MIND MRI sub-trial)	Low (ACCORD Lipid-MIND trial) High (ACCORD Lipid MIND MRI sub-trial): Attrition 21%
Tendolkar 2012[7]	Low	

Trompet 2010[1, 2]	High	Attrition 25%
Parale 2006[3]	High	Method of randomization and performance bias
Muldoon 2004[4]	Medium	Reporting bias
Heart Protection Study 2002[5]	Medium	Attrition unclear, detection bias
Muldoon 2000[6]	Medium	Reporting bias
Santanello 1997[6]	Medium	Attrition 15%
Carlsson 2002[10]	Medium	Attrition 12%

Appendix Table N3. Strength of evidence assessments: lipid lowering interventions in adults with normal cognition

Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Statins Versus Placebo	Dementia	1 (20,536)	0 of 1 tests shows statistically significant improvement: Heart Protection Study 20025 Number in statins versus placebo who developed dementia during follow up: 31 [0.3%] vs. 31 [0.3%]	Medium	Direct	Unknown	Unknown	Suspect	NA	Insufficient
	MCI	NR								Insufficient
	Biomarkers	NR								Insufficient
	Brief Cognitive tesT	1 (20,53	0 of 1 tests shows statistically significant	Medium	Indirect	Unknown	Unknown	Suspect	NA	Insufficient

		6)	improvement: Heart Protection Study 2002[5] Mean difference TICS-M [SE]: 0.02 [0.07] Percent of participant classified as cognitively impaired statins versus placebo: 23.7% vs. 24.2%							
	Multidomain Composites	NR								
	Executive/ Attention/ Processing Speed	3 (948)	0 of 4 tests shows statistically significant improvement for statins. 3 of 4 tests shows statically significant improvement for placebo. Muldoon 20044 Mean difference composite Executive/Attention/Processing Speed [CI]: 0.18 [0.07 to 0.29] Muldoon 20006 Mean difference in change composite Executive/Attention/Processing Speed [95% CI]: 0.18 [0.06 to 0.31] Mean difference in change composite psychomotor speed [95% CI]: 0.17 [0.05 to 0.28] Santanello 19977 Mean change DSST [SD] placebo 0.33 [13.06], lovastatin 20 mg -0.80 [13.28], and lovastatin 40 mg 1.66 [8.98]. P-value for difference between groups 0.66	Medium	Indirect	Imprecise	Inconsistent	Suspect	NA	Low
	Memory	2 (517)	0 of 4 tests shows statistically significant	Medium	Indirect	Imprecise	Inconsistent	Suspect	NA	Insufficient

			improvement for statins. 1 of 4 tests shows statically significant improvement for placebo.							
	Serious Adverse Events	2 (20,967)	1 of 17 test shows a statistically significant difference: Heart Protection Study 2002[5] Number of hospitalization in statins versus placebo. NS Santanello 1997[7] Abdominal pain %: placebo 4.4, lovastatin 20 mg 5.8, lovastatin 40 mg 9.6. P-value for difference between groups <0.01 For 15 other common symptoms no difference reported.	Medium	Direct	Unknown	Consistent	Suspect	NA	Insufficient
Fenofibrate plus statin versus placebo plus statin	Dementia	NR								Insufficient
	MCI	NR								Insufficient
	Biomarkersa	NR								Insufficient
	Screening	1 (1,538)	0 of 1 tests shows statistically significant improvement: Williamson 2014[9] (ACCORD Lipid trial) Mean difference MMSE 0.07 [95% CI]: [-0.17 to 0.31]	Low	Indirect	Precise	Unknown	Suspect	NA	Low
	Multidomain Composites									
	Executive/Attention/ Processing Speed	1 (1,538)	0 of 2 tests shows statistically significant improvement	Low	Indirect	Imprecise	Consistent	Suspect	NA	Low
	Memory	1 (1,538	0 of 1 tests shows statistically significant	Low	Indirect	Precise	Unknown	Suspect	NA	Low

		)	improvement							
	Serious Adverse Events	NR								Insufficient

[a] Williamson 2014 [8] (ACCORD Lipid trial) reported total brain volume but data was excluded from analysis due to high risk of bias (attrition 21%).
C=control; CI=confidence interval; DSST=Digit Symbol Substitution Test; MCI=mild cognitive impairment; mg=milligrams; MMSE=Mini-Mental Status Examination; I=intervention; NA=not applicable; NR=not reported; TICS=Telephone Interview for Cognitive Status (TICS-m=modified);

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Appendix O. Nonsteroidal Anti-Inflammatory Drugs

Appendix Table O1. Characteristics of eligible studies: NSAIDs in adults with normal cognition

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention**	**Comparison**	**Outcome** **Timing**	**Outcome** **Domain [Instrument]**
ADAPT Group[1-5] RCT USA 10 years[4] High 8 years Medium 5 years Medium 4 years 2008: Medium 2007: Medium	10 years 1689 8 years 2117 5 years 2071 4 years 2528	Adults aged 70+ with normal cognition and at least 1 first-degree relative with AD-like dementia **Age** (median) 70-74: 55% 75-79: 32% 80-84: 11% 85+: 2% **Sex** 46% **Race** White: 97% Black: 2% Hispanic: 1% **Education** Less than high school: 4% High school degree: 20% College, no degree: 27% College degree: 19% Postgrad: 30% **Baseline cognition** (median) Adjusted 3MS: 95.0	Celecoxib (200 mg BID) or naproxen (220 mg BID)	Placebo	10 years 8 years[1] 5 years[2] 4 years[3, 4]	**10 years** Brief Cognitive Test Performance [3MS] Multidomain Neuropsychological Test Performance [Composite: HVLT-R, Informant-Rated Dementia Severity Rating Scale, Digit Span, Naming Supermarkets, RBMT] Executive/Attention/Processing Speed [Digit Span] Memory [HVLT] [RBMT] Language [Generative Verbal Fluency] **8 years** Diagnosis [Alzheimer's Disease] **5 years** Diagnosis [Alzheimer's Disease] Biomarker [CSF tau : Ab1-42] **4 years** Diagnosis [Alzheimer's Disease] Brief Cognitive Test Performance [3MS] Multidomain Neuropsychological Test Performance [Composite: HVLT-R, Informant-Rated Dementia Severity Rating Scale,

						Digit Span, Naming Supermarkets, RBMT] Executive/Attention/Processing Speed [Digit Span] Memory [HVLT] [RBMT]
Small, 2008[6] RCT USA High	88	Middle-aged and older volunteers with normal cognition and self-reported age-related memory complaints **Age** 58 **Sex** 38% **Race** NR **Education** (mean years) 15 **Baseline cognition** (median) MMSE: 29.2	Celecoxib 200 mg or 400 mg QD	Placebo	1.5 years	Executive/Attention/Processing Speed [TMT A] [TMT B] [DSST] [Stroop Interference Kaplan Version] [F.A.S. Letter Fluency Test] Memory [Buschke Selective Reminding Test Total And Delayed Recall] [WMS Verbal Paired Associations] [BVRT] Language [BNT] [Animal Naming Test] Visuospatial [WAIS-III Block Design Test] [RCFT]]
Kang, 2007[7] RCT USA Medium	6377	Normal cognition, women aged 65+ participating in healthy study **Age** 72 **Sex** 100% **Race** NR **Education** Licensed vocational or registered nurse/associates degree: 67% Bachelors/masters/doctorate degree: 33% **Baseline cognition** TICS: 34	Aspirin (100 mg QAD)	Placebo	10 years	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Test Performance [Composite: TICS, Category Fluency, 10 Words List Immediate And Delayed Recall, EBMT] Memory [Composite: 10 Words List Immediate And Delayed Recall, EBMT]

3MS=Modified Mini-Mental State Examination; BID=twice daily; EBMT=East Boston Memory Test; mg=milligrams; n=sample size; NP=Neuropsychological; NR=not reported; QAD=every other day; QD=every day; SD=standard deviation; RCT=randomized controlled trial; RBMT= Rivermead Behavioral Memory Test; RCFT=Rey-Osterrieth Complex Figure Test; USA=United States; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table O2. Summary risk of bias assessments: NSAIDs in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
ADAPT Group[1-5]		
10 year	High	Attrition > 40%
8 year	Medium	Attrition 39% but use survival and sensitivity analyses; unclear if concurrent interventions
5 year	Medium	Attrition 18% but use survival analysis; participant and outcome assessor blinding methods unclear
4 year (2008 publication)	Medium	Attrition 20%; unclear if concurrent interventions
4 year (2007 publication)	Low	Attrition 15% but use survival analysis; unclear if concurrent interventions
Small, 2008[6]	High	Attrition 44%
Kang, 2007[7]	Medium	Attrition 29%; outcome assessor independence unclear; unclear if concurrent interventions

NSAIDS=Nonsteroidal Antiinflammatory Drugs

Appendix Table O3. Strength of evidence assessments: NSAIDs in adults with normal cognition

Intervention Type	Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Aspirin vs. Placebo	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test Performance 10 years	1 (6377)	0 of 1 tests showed no statistically significant difference. TICS, mean difference from baseline -0.02 [-0.19 to 0.14]	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
	Multidomain Neuropsychological Performance 10 years	1 (6377)	0 of 1 tests showed no statistically significant difference. Composite, mean difference from baseline 0.0 [-0.04 to 0.04]	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
	Executive/ Attention/ Processing Speed	NR								
	Memory 10 years	1 (6377)	0 of 1 test showed no statistically significant difference. Composite,	Medium	Indirect	Precise	Unknown	Undetected	NA	Low

			mean difference from baseline -0.02 [-0.06 to 0.02]							
	Adverse Effects	NR								
Non-aspirin (Celecoxib 200 mg BID; Naproxen 220 mg BID) **vs. Placebo**	Dementia 8 years	1 (2117)	0 of 2 tests at longest follow-up showed no significant difference. Adjusted HR for Alzheimer's disease Celecoxib: 1.03 [0.72 to 1.50] p=0.86 Naproxen: 0.92 [0.62 to 1.35] p=0.66	Medium	Direct	Precise	Unknown	Undetected	NA	Low
	MCI	NR								
	Brief Cognitive Test Performance 4 years	1 (2528)	0 of 2 tests showed no statistically significant difference. Adjusted 3MS, generalized estimating equation regression vs placebo (B coefficient) Celecoxib: -0.20 [-0.47 to 0.07] p=0.14 Naproxen: -0.19 [-0.47 to	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient

			0.09] p=0.19							
	Multidomain Neuropsychological Performance4 years	1 (2528)	0 of 2 tests showed no statistically significant difference. <u>Composite, generalized estimating equation regression vs placebo (B coefficient)</u> Celecoxib: -0.004 [-0.04 to 0.03] p=0.84 Naproxen: -0.03 [-0.07 to 0.01] p=0.09	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
	Executive/ Attention/ Processing Speed 4 years	1 (2528)	0 of 4 tests show no statistically significant improvement with intervention <u>Digit Span Forward, generalized estimating equation regression vs</u>	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low

			placebo (B coefficient) Celecoxib: -0.05 [-0.19 to 0.09] p=0.48 Naproxen: -0.03 [-0.17 to 0.11] p=0.69 Digit Span Backward, generalized estimating equation regression vs placebo (B coefficient) Celecoxib: 0.03 [-0.11 to 0.18] p=0.64 Naproxen: -0.09 [-0.23 to 0.05] p=0.22							
	Memory 4 years	1 (2528)	0 of 6 tests show no statistically significant improvement with intervention Hopkins Verbal Learning Test, generalized estimating equation regression vs placebo (B	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low

			coefficient) Celecoxib: 0.12 [-0.06 to 0.30] p=0.20 Naproxen: -0.04 [-0.23 to 0.16] p=0.70 Rivermead Behavioral Memory Test, generalized estimating equation regression vs placebo (B coefficient) Celecoxib: -0.06 [-0.29 to 0.18] p=0.64 Naproxen: -0.13 [-0.37 to 0.11] p=0.28 Brief Visuospatial Memory Test-Revised, generalized estimating equation regression vs placebo (B coefficient) Celecoxib: 0.05 [-0.14 to 0.23] p=0.62 Naproxen: -							

			0.07 [-0.26 to 0.12] p=0.45							
	Adverse Effects	NR								

3ME=Modified Mini-Mental State Examination; k=number of studies; MCI=mild cognitive impairment; n=sample size; NP=neuropsychological; NA=not applicable; NR=not reported; RCT=randomized controlled trial; SD=standard deviation;

Appendix Table O4. Characteristics of eligible studies: NSAIDs in adults with MCI

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex** **Race** **Education** **Baseline Cog**	**Intervention**	**Comparison**	**Outcome Timing**	**Outcome Domain [Instrument]**
Thal, 2005[8] RCT USA High	1457	People aged 65+ with 8+ years of education and met criteria for MCI **Age** 75 **Sex** 32% **Race** NR **Education** (years) <11: 10% 12-17: 77% 18+: 13% **Baseline cognition** MMSE: 27.4 ADAS-Cog: 9.3	Rofecoxib 25 mg QD	Placebo	4 years	Brief Cognitive Test Performance [MMSE] [ADAS-Cog] Memory [Buschke Selective Reminding Test (Summed And Delayed)]

3ME=Modified Mini-Mental State Examination; ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; BID=twice daily; Cog=cognition; MCI=mild cognitive impairment; N=sample size; NP=neuropsychological; NR=not reported; QD=daily; NSAIDS=Nonsteroidal Antiinflammatory Drugs; RCT=Randomized Controlled Trial; RoB=risk of bias; SD=Standard Deviation;USA=United States

Appendix Table O5. Summary risk of bias assessments: NSAIDs in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Thal, 2005[8]	High	Attrition 45%

MCI=mild cognitive impairment; NSAIDS=Nonsteroidal Antiinflammatory Drugs

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Appendix P. Antidementia Drugs

Appendix Table P1. Characteristics of eligible studies: antidementia interventions in adults with normal cognition

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Gavrilova 2011[1] Observational Russia High	110	Adults aged 55 to 85 with MMSE scores above 26, signs of cognitive deficit corresponding to stage 3 on the Global Deterioration Scale (GDS), and assessments of 0.5 on the Clinical Dementia Rating (CDR) scale Mean age: 67 years 74% Female Race: NR Education: NR Mean MMSE (SD): 28.4 (0.1)	Cerebrolysin (two courses per year for 3 years [lasting 4 weeks each] of 30ml cerebrolysin infusions in 100ml of physiological saline), or Cavinton (two courses per year for three years [lasting 4 weeks each] of 5 mg three times daily	Groups compared to one-another	3 years	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [Forward Number Naming] [Reverse Number Naming] [Frontal Dysfunction Battery] [Wechsler Scale, Sound and Categorical Associations] Memory [Delayed 10-Word Reproduction] Language [Boston Naming Test] Visuospatial [CLOX-1]
Devi 2007[2] RCT USA Medium	28	Postmenopausal women aged 46 to 60 without depression Mean age: 54 100% female 75% White Education: 100% ≥16 years Baseline global cognition: NR	Donepezil 5mg daily for 6 weeks, then 10mg daily (if tolerated) for the remaining 20 weeks	Placebo daily for 6 months	6 months	Executive/Attention/Processing Speed [WMS-III, Working Memory] Memory [WMS-III, Logical Memory] [Buschke Selective Reminding Test, List Learning] Language [Boston Diagnostic Aphasia Examination, naming] [WAIS-III, Vocabulary] Language [COWAT]

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BEM= Batterie d'Efficience Mnesique; BVRT=Benton Visual Retention Test; CDR=Change in Dementia Rating; CLOX-1=Clock Drawing Test; COWAT=Controlled Oral Word Association Test; CVFT=Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DS=Digit Span; DSM=Diagnostic Statistical Manual of Mental Disorders; FDG-PET=; MCI=Mild Cognitive Impairment; MMSE=Mini

Mental Status Exam; n=sample size; NR=not reported; RBANS=Repeat Battery for the Assessment of Neuropsychological Status; RCT=randomized controlled trial; RoB=risk of bias; SCWT=Stroop Test; SD=Standard Deviation; TMT=Trail Making Trial (Parts A and/or B); USA=United States; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table P2. Summary risk of bias assessments: antidementia drug interventions in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Antidementia		
Gavrilova 2011[1]	High	Systematic assignment instead of randomization. Attrition 20% without appropriate analysis to account for potential bias.
Devi 2007[2]	Medium	Attrition 14% in treatment group. Outcome assessor not independent.

Appendix Table P3. Characteristics of eligible studies: antidementia interventions in adults with MCI

Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Donepezil efficacy	Doody 2009 [3] Schuff 2011[4] (subset of Doody 2009) RCT USA High	821	Healthy adults with MCI aged 45 to 90 who expressed a memory complaint Mean age: 70 45% female 87% White Education: 0-7 years: <1% 8-15 years: 53% >15 years: 47% MMSE ≤ 28: 84%	Donepezil 5mg daily for 6 weeks, then 10mg daily for the remaining 42 weeks	Placebo daily for 48 weeks, with a 3-week single-blind run-in period	48 weeks	Biomarker [MRI: APC in Hippocampal Volume; Changes in Whole Brain Atrophy, Ventricular Atrophy, and Cortical Atrophy] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [SDMT] [DS Backward]
	Petrella 2009[5] RCT USA High	13	Healthy adults with MCI aged 55 to 90 with MMSE scores of at least 24 and without depressive	Donepezil 5mg daily for 6 weeks, followed by 10 mg daily for the remaining 4	Placebo daily for 6 months	6 months	Biomarker [fMRI: Changes in Dorsolateral Prefrontal Activation and Ventrolateral Prefrontal Cortex Activation] Brief Cognitive Test Performance [MMSE]

			symptoms Mean age: 68 Sex: NR Race: NR Mean education: 16 Mean MMSE (SD): 28.3 (1.7)	months and 2 weeks			Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [DSST] [DS Backward]] Memory [NYU Delayed Recall]
	Petersen2005[6] Jack, 2008[7] RCT USA Medium High (MRI outcomes)	769	Adults with amnestic MCI aged 55 to 90 with impaired memory, a Logical Memory Delayed-recall score approximately 1.5 to 2 SD below an education-adjusted norm, a Clinical Dementia Rating (CDR) of 0.5, and a score of 24 to 30 on the MMSE Mean age: 73 46% Female Race: NR Education: NR Mean MMSE (SD): 27.27 (1.8) Mean ADAS-cog (SD): 11.26 (4.4) original 17.72 (6.1) modified	Donepezil 5mg daily for 6 weeks, followed by 10 mg daily for the remainder of the study	Placebo	3 years	Diagnosis [Clinical Criteria of the NINCDS-ADRDA] Biomarker [MRI: APC in Hippocampus, Entorhinal Cortex, Whole Brain, and Ventricle; Rate of Hippocampal Atrophy] [MRI and Cognitive Performance Correlation] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Original] [ADAS-Cog, Modified] Executive/Attention/Processing Speed [Composite Measure] Language [Composite Measure] Memory [Composite Measure] Visuospatial [Composite Measure]
	Salloway 2004[8] RCT USA High	270	Healthy adults aged 55 to 90 with MCI, a documented memory complaint, and MMSE scores ≥ 24, global Clinical Dementia Rating (CDR) score of 0.5 with memory box scores of 0.5 or 1, no more than two box scores other than memory rated as high as 1, and no box score rated greater than 1 Mean age: 72 42% female 94% White Mean education: 15 Mean MMSE (SD): 27.5 (2)	Donepezil 5mg daily for 42 days, then 10mg daily for the remainder of the study	Placebo daily for 2 years	2 years	Multidomain Neuropsychological Test Performance [ADAS-Cog, Modified] Executive/Attention/Processing Speed [DS Backward] [SDMT] [Maze Test] Memory [NYU Paragraph Test] Language [BNT] [Verbal Fluency]

Donepezil & antidepressant efficacy	Reynolds 2011[9] RCT USA High	130	Adults at least 65 years of age with normal cognition or MCI, and with remitted depression (a score of 15 or higher on the 17-item Hamilton Rating Scale for Depression)	Donepezil (mean of) 7.8mg daily for 2 years plus antidepressant pharmacotherapy with supportive depression care management (12 to 16 weeks)	Placebo for 2 years	2 years	Multidomain Neuropsychological Test Performance [Composite of all Tests] Executive/Attention/Processing Speed [Composite] Memory [Composite] Language [Composite] Visuospatial [Composite]
Rivastigmine efficacy	Feldman 2007[10] RCT USA High	508	Adults aged 55 to 85 with MCI (having a global CDR score = 0.5, NYU Delayed Paragraph Recall <9, 17-item HAM-D score <13, and HAM-D Item 1 [depressed mood] score =1) Mean age: 70 52% female Race: NR Mean education: 11 Mean MMSE (SD): 27 (2.7)	Rivastigmine 1mg daily for 2 weeks, then 3-12mg daily (increases of 3mg at minimum of 4-week intervals) until end of study or progression to AD; latter group could continue with starting dose of 3mg daily irrespective of treatment assignment	Placebo daily for 4 years	Until diagnosis of AD, up to 4 years	Diagnosis [Time to AD] Brief Cognitive Test Performance [MMSE]
Galantamine efficacy	Peters 2012[11] RCT Germany High	232	Adults with amnestic MCI Mean age: 68 Sex: NR Race: NR Education: NR Mean MMSE (SD): 27 (2.4)	Galantamine 8mg twice daily, galantamine (8mg) and memantine (10mg) twice daily	Placebo	2 years	Multidomain Neuropsychological Test Performance [ADAS-Cog]
		990	Adults ≥ 50 years with MCI, a CDR score of 0.5 and CDR memory score ≥0.5 Mean age: 70 55% famale 95% White Education: NR Median ADAS-cog/MCI (range): 16	Galantamine 4 mg twice daily for 1 month, then 8 mg twice daily. If well tolerated, dose could be titrated to 12 mg twice daily, but could be lowered back to 8 mg twice daily after 1 month, if necessary. The dose selected at month 3	Placebo daily for 2 years	2 years	Biomarker [MRI: Hippocampal Atrophy] Diagnosis [CDR] Multidomain Neuropsychological Test Performance [CDR-Sum of Boxes] [ADAS-Cog/MCI] Executive/Attention/Processing Speed [DSST]

				(8 or 12 mg twice daily) was fixed for the remainder of the study (23 months)			
	Winblad 2008[12] Prins 2014[13] RCT (2) USA High	1058	Adults ≥ 50 years with a CDR score of 0.5 and CDR memory score ≥0.5 Mean age: 70 44% female 95% White Education: NR Median ADAS-cog/MCI (range): 17.5 (1-63)	Galantamine 4 mg twice daily for 1 month, then 8 mg twice daily for 1 month. If well tolerated, dose could be titrated to 12 mg twice daily, but could be lowered back to 8 mg twice daily after 1 month, if necessary. The dose selected at month 3 (8 or 12 mg twice daily) was fixed for the remainder of the study (23 months)	Placebo daily for 2 years	2 years	Multidomain Neuropsychological Test Performance [ADAS-Cog/MCI] Executive/Attention/Processing Speed [DSST]

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; BNT=Boston Naming Test; CDR=Clinical Dementia Rating; COWAT=Controlled Oral Word Association Test; DS=Digit Span (Forward and/or Backward); DSST=Digit Symbol Substitution Test; N=sample size; NR=not reported; NYU=New York University; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation; SDMT=Symbol Digit Modalities Test; USA=United Statse

Appendix Table P4. Summary risk of bias assessments: antidementia drug interventions in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Doody 2009[3] Schuff 2011[4]	High	High attrition (39%)
Petrella 2009[5]	High	Poor randomization. Attrition 13%.
Petersen 2005[6] Jack 2008[7]	Medium/High	Medium attrition (30%) for cognitive outcomes with sensitivity analysis; high attrition (33%) for MRI
Salloway 2004[8]	High	High attrition (24%) without appropriate analysis
Reynolds 2011[9]	High	High atttrition (30%)O with sensitivity analysis; groups not described so not clear whether randomization held
Feldman 2007[10]	High	High attrition (35%)
Peters 2012[11]	High	Method of randomization unclear. Attrition not clearly reported; likely greater than 50%.
Winblad 2008[12] Prins 2014[13]	High	High attrition (35%)

MCI=mild cognitive impairment

Appendix Table P5. Strength of evidence assessments: antidementia medication versus placebo control in adults with MCI

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Dementia	1 (769)	No reduction in dementia diagnoses with donepezil Petersen 2005[6] (Donepezil) Hazard Ratio for risk of progression to AD (3 years): 0.8 [0.57 to 1.13]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
MCI	NR								
Biomarkers	NR								
Brief cognitive test performance	1 (769)	0 of 1 tests show statistically significant improvement at 3 years Petersen 2005[6] (Donepezil) Mean change from baseline in MMSE (SD) scores: Difference in mean [CI] change: -0.44 [-1.11 to 0.23]	Medium	Indirect	Precise	Unknown	Undetected	NA	Low

Multidomain neuropsychological performance	1 (769)	0 of 2 tests show statistically significant improvement at 3 years Petersen 2005[6] (Donepezil) Mean change from baseline in ADAS-cog original (SD) scores: Difference in mean [CI] change: 0.06 [-1.07 to 1.19] Mean change from baseline in ADAS-cog (SD) modified scores: Difference in mean [CI] change: 0.6 [-0.79 to 1.99]	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
Executive/Attention/Processing Speed	1 (769)	0 of 1 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient
Memory	1 (769)	0 of 1 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient

C=control; CI=confidence interval; ES=effect size; HR=hazard ratio; I=Intervention; ITT=intention to treat; MCI=mild cognitive impairment; mg=milligrams; n=sample size; NA=not applicable; NR=not reported; RCT=randomized controlled trial; RR=risk ratio; SD=standard deviation; SOE=strength of evidence

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Appendix Q. Diabetic Medication Treatment

Appendix Table Q1. Characteristics of eligible studies: diabetic medication treatments in adults with normal cognition

Intervention type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Glycemic control efficacy	Cukierman-Yaffe 2014[1] (Substudy of ORIGIN trial) RCT Multinational Medium (High for outcomes at t5 for MMSE and t6 for DSS)	15077	Adults older than 50 with dysglycaemia, with additional risk factors for cardiovascular events, not taking insulin, and taking no more than 1 oral glucose drug Mean age: 63 65% Male 59% White Mean MMSE (SD): 27.93 (2.74) MMSE group 27.50 (2.79) DSST group	Titrated basal insulin glargine targeting a fasting plasma glucose concentration of 5.3 mmol/L or lower – injected in evenings until target values achieved, then injected at least twice per week	Standard approaches to glycemic control (continuation of pre-randomization therapy)	Median 6.2 years	Diagnosis [MMSE<24, Report Forms] Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DSST]
	Seaquist 2013[2] RCT (Substudy of ACCORD trial) USA Medium	2977	Adults aged 55 to 80 with type 2 diabetes, high HbA1c concentrations (>7.5%, >58 mmol/mol), and high risk for cardiovascular disease events Mean age: 63 47% Women	Intensive glycemic control targeting HbA1c to less than 6.0% for 40 months	Standard glycemic control targeting HbA1c to 7-7.9% for 40 months	40 months	Executive/Attention/Processing Speed [DSST]

			70% White Mean MMSE (IQR): 28 (26-29)				
	Launer 2011[3] RCT (Substudy of ACCORD trial) USA Medium	2977	Adults aged 55 to 80 with type 2 diabetes, high HbA1c concentrations (>7.5%, >58 mmol/mol), and high risk for cardiovascular disease events Mean age: 63 47% Women 70% White Mean MMSE (IQR): 28 (26-29)	Intensive glycemic control targeting HbA1c to less than 6.0% for 40 months	Standard glycemic control targeting HbA1c to 7-7.9% for 40 months	40 months	Biomarker [MRI: Total Brain Volume] Executive/Attention/Processing Speed [SCWT] [DSST] Memory [RAVLT]
	Cheatham 2009[4] RCT USA High	42	Healthy overweight (BMI 25-29.9 kg/m^2) adults aged 20 to 42 without depression or diabetes Mean age: 35 Sex: NR Race: NR Education: NR Baseline global cog: NR	High glycemic load energy-restricted diet (116g/1000 kcal), or a low glycemic load energy-restricted diet (45g/1000 kcal) for 6 months	Groups compared to one-another	6 months	Executive/Attention/Processing Speed [Visual Reaction Time Test] [Repeated Acquisition Test] [Scanning Visual Vigilance Test] Language [Grammatical Reasoning Test]
	Luchsinger 2011[5] RCT USA High	2169	Adults at least 55 years of age with type 2 diabetes Mean age: 71 61% Female 52% White Education: 53% Elementary 29% High School 16% College	Diabetes case management (target HgbA1c was ≤7%, or ≤8% for participants with reduced life expectancy and/or severe hypoglycemic unawareness; BP goal was <130/85 mmHg, or <125/75 mmHg in the	Usual care - care from primary care physicians without guidance from study personnel; primary care physicians were mailed diabetes care guidelines for 5 years	Up to 5 years (mean 3.5)	Multidomain Neuropsychological Test Performance [Comprehensive Assessment and Referral Evaluation (CARE), Diagnostic Scale]

			Baseline global cog: NR	presence of proteinuria (>1g/24h) or renal insufficiency; in 2003 BP goal changed to <130/80 mmHg, except for proteinuria or renal insufficiency; LDL goals were < 130 mg/dl for primary prevention, and <100 mg/dl for those with cardiovascular disease) implemented by a diabetes nurse via telemedicine unit in participant's home in coordination with primary care physician for 5 years			
Lifestyle advice & glycemic control efficacy	Koekkoek 2012[6] RCT Netherlands High	252	Adults aged 50 to 70 years with type II diabetes Mean age: 60 61% Female Race: NR Education: 10 years Baseline global cog: NR	Lifestyle advice (regarding diet, physical activity, and smoking); HbA1c level had to be kept <53 mmol/mol (a biguanide, prandial glucose regulator or sulphonylurea) and had to be altered when HbA1c was >48 mmol/mol., Antihypertensive treatment with an ACE inhibitor if needed, and blood pressure treatment with calcium channel blockers, thiazides or beta-blockers if needed (6 years)	Routine care (GPs were informed about diagnostic test results and patients received treatment according to the current guidelines of the Dutch College of GPs) for 6 years. Also reference group of spouses and acquaintances of the patients, without diabetes, was recruited and matched for age, sex, and education level	6 years	Executive/Attention/Processing Speed [DS Forward] [DS Backward] [DSST] [Corsi Block-Tapping Test Forward] [Corsi Block-Tapping Test Backward] [SCWT I] [SCWT II] [SCWT IIK] [TMT A] [TMT B] [Brixton Spatial Anticipation Test] Memory [RAVLT, Trials 1-5 And Delayed Recall And Recognition] [Location Learning Test, Trials 1-5 and Learning Index and Delayed Trial] [Complex Figure Test Delay] Language [Letter Fluency] [Category Fluency]

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BEM= Batterie d'Efficience Mnesique; BVRT=Benton Visual Retention Test; CDR=Change in Dementia Rating; COWAT=Controlled Oral Word Association Test; CVFT= Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DS=Digit Span; DSM=Diagnostic Statistical Manual of Mental Disorders; FDG-PET=; MCI=Mild Cognitive Impairment; MMSE=Mini Mental Status Exam; NR=not reported ; RBANS=Repeat Battery for the Assessment of Neuropsychological Status; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SCWT=Stroop Test; SD=Standard Deviation; TMT=Trail Making Trial; WAIS=Wechsler Adult Intelligence Scale

Appendix Table Q2. Summary risk of bias assessments: diabetic medication treatment in adults with normal cognition

Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
Glycemic control efficacy	Cukierman-Yaffe 2014[1]	Medium (High for MMSE outcomes at year 5)	Attrition not clearly reported and sensitivity analysis performed only for the Digit Symbol Substitution cohort. Participants and outcome assessors not blinded
	Seaquist 2013[2]	Medium (Table 4 and 5 analyses) High (other analyses)	Medium: Attrition not clearly reported. High: unclear if evaluations done by treatment assignment
	Launer 2011[3]	Medium	Attrition 13%. Participants and outcome assessors not blinded
	Luchsinger 2011[5]	High	Attrition not clearly reported. Participants not blinded
	Cheatham 2009[4]	High	Method of randomization not clear. High attrition due to technical difficulties with encrypted data.
Lifestyle advice & glycemic control efficacy	Koekkoek 2012[6]	High	Attrition 26%

MMSE=Mini-Mental Status Examination

Appendix Table Q3. Strength of evidence assessments: diabetic medication treatments versus standard of care/standard glycemic control in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Dementia	1 (12537)	0 of 1 tests show statistically significant improvement with intervention Cukierman-Yaffe 2014[1] Hazard ratio for incident cognitive impairment (composite of either incident dementia diagnosis of follow-up MMSE <24): 0.93 [0.86 to 1.0]	High	Direct	Precise	Unknown	Undetected	N/A	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		NR							
Biomarkers	1 (2977)	1 of 2 tests show statistically significant improvement with intervention Launer 2011[3] Difference in decline in mean total brain volume: -13.0 vs. -17.7 cm3 (mean difference 4.6 cm^3 [2.0 to 7.3] (favors intervention) Difference in geometric mean abnormal white matter at follow-up: 1.10 cm^3 [1.02 to 1.19]	Medium	Indirect	Precise	Inconsistent	Undetected	N/A	Insufficient

		(favors control)							
Brief cognitive test performance	2 (15514)	0 of 2 tests show statistically significant improvement: Cukierman-Yaffe 2014[1] Difference in least-squares mean raw MMSE score: 0.0037 [-0.0144 to 0.0217] Launer 2011[3] Difference in mean raw MMSE score: -0.01 [-0.18 to 0.16]	Medium	Indirect	Imprecise	Consistent	Undetected	N/A	Low
Multidomain neuropsychological performance		NR							
Executive Function	2 (15514)	0 of 3 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Consistent	Undetected	N/A	Low
Memory	1 (2977)	0 of 1 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Unknown	Undetected	N/A	Low

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BEM= Batterie d'Efficience Mnesique; BVRT=Benton Visual Retention Test; CDR=Change in Dementia Rating; COWAT=Controlled Oral Word Association Test; CVFT= Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DS=Digit Span; DSM=Diagnostic Statistical Manual of Mental Disorders; FDG-PET=; MCI=Mild Cognitive Impairment; MMSE=Mini Mental Status Exam; NR=not reported ; RBANS=Repeat Battery for the Assessment of Neuropsychological Status; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SCWT=Stroop Test; SD=Standard Deviation; TMT=Trail Making Trial; WAIS=Wechsler Adult Intelligence Scale

Appendix Table Q4. Characteristics of eligible studies: diabetic medication treatments in adults with MCI

Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Pioglitazone efficacy	Hildreth 2015[7] RCT USA Low	78	Sedentary community-dwelling obese adults at least 55 years of age with MCI (90% had MCI) and without diabetes Mean age: 66 57% Female 88% White Education: 16 years Mean MMSE (SD): 28.4 (1.3) pioglitazone group 28.8 (1.3) placebo group	Pioglitazone 30mg daily for 1 month, then 45mg daily as tolerated for 5 months	Placebo for 6 months	6 months	Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [Composite] [SCWT] [TMT B] [DS Backward] [DSST] Memory [Composite] [RAVLT] [WMS Logical Memory II] [VR] Language [Composite] [BNT] [Category Fluency] Visuospatial [Composite] [WAIS-R, Block Design] [CLOX-1]
Metformin efficacy	Luchsinger 2016[8] RCT USA Medium	80	Overweight or obese (BMI at least 25 kg/m^2) adults aged 55 to 90 years, untreated diabetes, with aMCI Mean age: 64 53% Female 30% White Education Level (Years), Mean (SD): Metformin: 13.8 (3.4) Placebo: 13.1 (4.5) Mean ADAS-Cog (SD):	Metformin 1000mg twice daily for 12 months	Placebo daily for 12 months	12 months	Biomarker [PET and MRI] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [DS Backward] Memory [Bushcke Selective Reminding Test] [WMS Logical Memory II Delayed] [Paragraph Recall]

			Metformin: 12 (4.0) Placebo: 14.6 (6.1)				

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BEM= Batterie d'Efficience Mnesique; BVRT=Benton Visual Retention Test; CDR=Change in Dementia Rating; COWAT=Controlled Oral Word Association Test; CVFT= Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DS=Digit Span; DSM=Diagnostic Statistical Manual of Mental Disorders; FDG-PET=; MCI=Mild Cognitive Impairment; MMSE=Mini Mental Status Exam; NR=not reported ; RBANS=Repeat Battery for the Assessment of Neuropsychological Status; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SCWT=Stroop Test; SD=Standard Deviation; TMT=Trail Making Trial; WAIS=Wechsler Adult Intelligence Scale

Appendix Table Q5. Summary risk of bias assessments: diabetic medication treatment in adults with MCI

Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
Pioglitazone efficacy	Hildreth 2015[7]	Low	
Metformin efficacy	Luchsinger 2016[8]	Medium	Attrition 19%

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Appendix R. Other Interventions

Appendix Table R1. Characteristics of eligible studies: other interventions in adults with normal cognition

Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Other Medications	Newhouse 2012[1] RCT US Medium	74	Non-smoking adults ≥55 with MCI (determined by subjective and objective impairments in cognitive function) Age, Mean (SD) 76 (7.6) 39% Female Race NR Years of Education, Mean (SD) 15.9 (2.7) MMSE, Mean (SD) 27.4 (2.0)	Transdermal nicotine patch 15 mg/day for 6 months	Placebo	6 months	Diagnosis [CDR] Multidomain Neuropsychological Test Performance [Cognitive Drug Research Battery] Executive/Attention/Processing Speed [Connors Continuous Performance Test] [Immediate and Delayed Paragraph Recall Test, NYU Version] [DSST]
	Forlenza 2011[2] RCT Brazil Medium	45	Community-dwelling adults ≥60 diagnosed with amnestic MCI per Mayo criteria Age, Mean (SD) 72.5 (5.9) Sex NR Race NR Years of education, Mean (SD) 10.5 (5.3) ADAS-Cog Score, Mean (SD) 10.9 (5.9)	Lithium titrated to serum levels 0.25-0.5 mmol/l (lower than dose for affective disorders); daily doses for 12 months	Placebo	12 months	Diagnosis [CDR, Sum of Boxes] Biomarker [Amyloid-Beta] [Phosphorylated Tau At Threonine] [Total Tau] Multidomain Neuropsychological Test Performance [ADAS-Cog] Executive/Attention/Processing Speed [TMT A] [TMT B] Memory [CERAD Delayed Recall] [CERAD Figure Recall] Memory [Sequence of Letters and Numbers Score] (Cognitive Performance outcomes compared only baseline to endpoint within group, not between group)
Music Interventions	Hars 2014[3] Secondary analysis of	134	Adults ≥65 at increased risk of falling	Weekly 1 hour supervised group class; multitask	Inactive control	6 months	Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [TMT A]

Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
	RCT Switzerland Medium		Age, Mean (SD) 75 (7) 96.5% Female Race NR Education, 15% primary, 67% middle, 18% highschool MMSE, Mean (SD) 26.1 (2.9)	exercises to rhythm			Visuospatial [CLOX-1]
	Bugos 2007[4] US RCT High	31	Musically naïve older adults Age, Mean (SD) 70.5 (5.6) 81% Females Race NR Years of Education, Mean (SD) 16.4 (NR) No baseline cognitive screen	Individualized piano instruction ½ hour per week and independent practice 3 hours per week for 6 months. (Music theory instruction component)	Inactive control	9 months	Multidomain Neuropsychological Test Performance [WAIS] Executive/Attention/Processing Speed [TMT A] [TMT B]
Sleep interventions	Lucassen 2014[5] US RCT High	121	Short-sleeping (<6.5 hours/night), obese (BMI 30-55 kg/m2) adults Age, Mean (SD) 41.1 (7) 76% Female 60% Black Years of Education NR No baseline cognitive screen	Sleep extension (up to 7.5 hours/night) with life-style modifications using personalized sleep plans	Continue current sleep habits; habits reviews every 2 months	Median 14 months	Multidomain Neuropsychological Test Performance [WAIS] Executive/Attention/Processing Speed [TMT A] [TMT B] [Wisconsin Card Sort Test] Memory [RCFT] [CVLT] Language [Verbal Fluency] Visuospatial [RCFT] Motor [Grooved Peg Board]
	Sun 2013[6] RCT China High	80	Adults ≥60 years with reduced sleep quality (Pittsburgh Sleep Quality Index >5) Age, Mean (SD)	Sleep hygiene educational pamphlet; guided progressive muscle relaxation	Sleep hygiene educational pamphlet	12 months	Brief Cognitive Test Performance [MMSE] Memory [Weschler Memory Scale, Chinese Revised]

Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			69 (8) 74.7% Female Race NR 1.3% high school or above MMSE, Mean (SD) 24.2 (3.7)	tape (unclear frequency and duration; presumably daily for 12 months)			
Social Engagement	Lam 2015[7] RCT China High	276	Older adults with MCI (determined by subjective and objective impairments in cognitive function) and without dementia Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level (Years), Mean (SD) 3.9 (3.6) Catonese MMSE. Mean (SD) 25.6 (2.3)	Cognitive group (board games, reading/discussing newspapers) at least 3, 1-hr sessions/week	Social activities - At least 3, 1-hr sessions/week	12 months	Diagnosis [CDR, Sum of Boxes] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Test Performance [ADAS-Cog, Chinese Version] Memory [Delayed Recall] Language [CVFT]
	Mortimer 2012[8] RCT China High	74	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean	Group social interaction for 1 hour 3 times per week at a neighborhood community center	Inactive control with 4 check-in calls over 40 weeks	40 weeks	Biomarker [Whole Brain Volume, % of Total Intracranial Volume] Multidomain Neuropsychological Test Performance [Mattis Dementing Rating Scale, Total Score] Executive/Attention/Processing Speed [DS Forward] [DS Backward] [SCWT, Word] [SCWT, Color] [SCWT, Color-Word] [WAIS Similarities] [TMT A] [TMT B] [Mattis Attention Score] [Mattis Initiation Score] [Mattis Conceptualization Score] Memory [RCFT, Copying] [RCFT, Recall] [AVLT, Immediate Recall] [AVLT, Delayed Recall] [AVLT, Delayed Recognition] [Mattis

Intervention Type	Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
			(SD) 137.6 (7.6)				Memory Score] Language [Category Verbal Fluency, Animals] [BNT] Visuospatial [Bell Cancellation Test] [RCFT, Copying] [RCFT, Recall] [CLOX-1] [Mattis Construction Score]
Transcranial random noise stimulation	Snowball, 2013{Snowball, 2013 #795} United Kingdom RCT High	29 (4 excluded due to drop-out)	Adults with normal or corrected-to-normal vision, no history of psychiatric illness. Mean age (SD): 21 (SD~2.7) 59% Female Race: NR Education: NR No baseline cognition	Transcranial random noise stimulation by DC stimulator-Plus device, noise in high-frequency band, for 20 minutes per day for 5 days	Sham procedure: current applied for 30 seconds after upward ramping and then terminated for 5 days	6 months	Executive/Attention/Processing Speed [Arithmetic Calculation And Drill] [Mental Rotation Task] [Attention Network Test]

3MSE=Modified Mini Mental Status Examination; AD=Alzheimer's disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CVLT=California Verbal Learning Test; CDR=Change in Dementia Rating; COWAT= Controlled Oral Word Association Test; DSM=Diagnostic and Statistical Manual of Mental Disorders; MMSE=Mini-Mental State Examination; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; N=sample size; NR=not reported; RCT=randomized controlled trial;RoB=risk of bias; SD=standard deviation; TMT=Trails Making Test (A and/or B); WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table R2. Summary risk of bias assessments: other interventions in adults with normal cognition and MCI

Intervention Type	Study	Overall Risk of Bias Assessment	Rationale
Other Medications	Newhouse 2012[1]	Medium	Method of randomization unclear. Likely selective outcome reporting
	Forlenza 2011[2]	Medium	Method of randomization unclear.
Music	Hars 2014[3]	Medium	Method of randomization unclear. 16% attrition with no sensitivity analysis.
	Bugos 2007[4]	High	Method of randomization unclear. Attrition 21%.
Sleep	Lucassen 2014[5]	High	Method of randomization unclear. Attrition 39%.
	Sun 2013[6]	High	Attrition 51%
	Lam 2015[7]	High	Method of randomization unclear. Attrition 22% at 8 months, 24% at 1 year.
	Mortimer 2012[8]	High	Suspected selection bias due to modifications post-randomization.
Transcranial random noise stimulation	Snowball 2013	High	Method of randomization not reported. 52% (only 12/25 available for recall). Outcome assessor not blinded.

MCI=mild cognitive impairment

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Appendix S. Biomarkers

Appendix Table S1. Relationship between biomarkers and cognitive performance and incidence outcomes in adults with normal cognition

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Cognitive Training		**None reported**					
Physical Activity		**None reported**					
Nutraceuticals							
Omega 3 versus Placebo							
Witte, 2014[1] Omega 3 (fish oil LC-n3-FA) 2.2 g daily vs placebo n=65 6 months		**I>C [MRI - grey 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 [DS Forward]			
Resveratrol versus Placebo							
Witte 2014[2] Resveratrol 200 mg daily versus placebo n=46 6 months (Resveratrol belongs to a group of plant compounds called polyphenols with possible antioxidant		NS [MRI-total grey matter volume]			**I>C [Memory Composite: AVLT Retention, Delayed Recall, Recognition, Learning Ability, 5th Learning Trial]**	5 of 11 favor I	
		NS [MRI-HC microstructure]			**I>C [AVLT Retention]**		

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
properties)							
		I>C [MRI- functional capacity, HC frontal]			NS [AVLT Delayed Recall]		
		I>C [MRI- functional capacity, HC parietal]			NS [AVLT Recognition]		
		I>C [MRI- functional capacity, HC occipital]			NS [AVLT Learning Ability]		
					NS [AVLT Fifth Learning Trial]		
Diet Types		**None Reported**					
Multimodal Interventions		**None Reported**					
Other Health/ Lifestyle Intervention		**None Reported**					
Hormone Therapies							
HRT- Estrogen versus Placebo							
Women's Health Initiative (WHI) substudies	NS [Probable Dementia] n=2947	NS [MRI - total brain volume] n=520	**BCT C>I [3MS] N=2947**	NS [Letter Fluency] n=886	NS [BVRT Errors] n=886	2 of 16 favors C	Increased risk of probable dementia in women taking

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Coker, 2009[3] **Resnick, 2009a**[4] **Resnick, 2009b**[5] **Espeland, 2004**[6] **Shumaker, 2004**[7] **Rapp, 2003**[8] Estrogen daily Mean followup varies by outcome up to 8 years	NS [MCI] n=2947	NS [MRI - ventricle volume] n=520		NS [DS Forward] n=886	NS [CLVT Total List A Trials] n=886		estrogen. Increased risk of global cognitive
	C>I [Probable Dementia or MCI] n=2947	NS [MRI - hippocampal volume] n=520		NS [DS Backward] n=886	NS [CVLT Total List B] n=886		decline in women taking estrogen.
		C>I [MRI- frontal lobe volume] n=520			NS [CVLT Short Delay Free] n=886		
		NS [White & grey matter] n=520			NS [CVLT Long Delay Free] n=886		
		NS [Basal ganglia] n=520					
		NS [Total brain lesion volume] n=520					
HRT – Estrogen + Progesterone versus Placebo							
Women's Health Initiative (WHI) Coker, 2009[3] **Resnick, 2009a** [4] **Resnick, 2009b** [5] **Espeland, 2004** [6] **Shumaker, 2004** [7] **Rapp, 2003**[8] Estrogen + progestin daily Mean followup varies by outcome	**C>I [Probable Dementia] n=4532**	NS [MRI - total brain volume] n=883	**BCT C>I [3MS] n=4532**	NS [Letter Fluency] n=1416	**C>I [BVRT Errors] n=1416**	5 of 16 favor C	In addition to increased risk of probable dementia and
	NS [MCI] n=4532	NS [MRI - ventricle volume] n=883		NS [DS Forward] n=1416	**C>I [CLVT Total List A Trials] n=1416**		memory decline, women taking estrogen +
	NS	NS		NS	NS		progestin

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
up to 8 years	[Probable Dementia or MCI] n=4532	[MRI - hippocampal volume] n=883		[Digits Backward] n=1416	[CVLT Total List B] n=1416		experienced more strokes than women taking placebo
		NS [MRI - frontal lobe volume] n=883			**C>I [CVLT Short Delay Free] n=1416**		
		NS [White and grey matter] n=883			**C>I [CVLT Long Delay Free] n=1416**		
		NS [Basal ganglia] n=883					
		NS [Total brain lesion volume] n=883					
Vitamins							
Vitamin B versus Placebo							
Douaud 2013[9] de Jager 2012[10] Smith 2010[11] Vitamin B (folic acid + B12 + B6) n=266 MRI n=166 2 years		I>C [Reduction of posterior atrophy]	NS [MMSE]		NS [HVLT]	1 of 3 favor I	NR
Antihypertensive Treatment		**None reported**					

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Lipid Lowering Treatment							
Atorvastatin versus Placebo							
Tendolkar 2010[12] 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		**I>C [Left amygdala volume]**	NS **BCT** [MMSE]	**I>C [Digit Symbol Substitution]**	NS [Dutch Modified Version of the RAVLT Immediate Word Recall]	3 of 9 favor I	
		NS [Right amygdala volume]			**I>C [Dutch Modified version of the RAVLT Delayed Word Recall]**		
		NS [Left hippocampal volume]					
		NS [Right hippocampal volume]					
		NS [White Matter Lesion Volume]					
NSAIDs		**None Reported**					
Antidementia Drugs		**None Reported**					
Diabetes Treatment							
Glycemic Control vs Placebo							

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
ACCORD-MIND Trial Seaquist 2013[13] Launer, 2011[14] 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 [Stroop Test]	NS [RAVLT]	1 of 6 favor I 1 of 6 favor C	NS [Mortality]
		C>I [Abnormal white matter]		NS [DSST]			
Other Drugs							
Forlenza 2011[15] Lithium titrated to serum levels 0.25-0.5 mmol/l vs placebo n=41 12 months	NS [Conversion to Probable AD]	**I>C [Amyloid-beta]**				2 of 3 favor I	NS [Ischemic stroke, death due to sepsis;
		NS [Total tau]					neither deemed due
		I>C [Phosphorylated tau]					to treatment]

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; AVLT=Auditory Verbal Learning Test; BCT=brief cognitive test; BVRT=Benton Visual Retention Test; C=control; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); I=intervention; g=grams; LC-n3-FA=long-chair omega-3 fatty acid; MCI=mild cognitive impairment; mg=milligrams; MMSE=Mini-Mental Status Examination; MNP=multidomain neuropsychological performance; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; n=sample size; NS=no statistically significant difference; NR=not reported; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation; TMT=Trail Making Test (Part A and/or B)

Appendix Table S2. Relationship between biomarkers and cognitive performance and incidence outcomes in adults with MCI

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]

Cognitive Training							
Buschert, 2012[16] **Forster, 2011**[17] Group-based formal mnemonic memory training & informal cognitive & social engagement activities vs. exercises of isolated, sustained attention n=24 (MCI) 15 & 28 months	**I>C [Conversion to CATD]**	**I>C [FDG-PET Reuptake]**	NS BCT [MMSE]	NS [TMT A]	**I>C [RBANS-Immediate Memory]**	3 of 7 favor I	NR
			I>C MNP [ADAS-Cog]	NS [TMT B]	NS [RBANS-Delayed Recall]		
Physical Activity							
Suzuki, 2013[18] **Suzuki, 2012**[19] Multicomponent physical activity vs. attention control n=100 (MCI) n=50 (aMCI)* [19] 6 months		NS [MTA-ERC]	BCT NS [MMSE] *[I>C for subgroup with aMCI (n=50) at 6 months, but NS for aMCI subgroup at 12 months]		NS [WMS-LM I] *[I>C for subgroup with aMCI (n=50) at 6 months, but NS for aMCI subgroup at 12 months]	0 of 6 (no differences)	NS [Falls & hospitalzation for illness]
		NS [WBS]	MNP NS [ADAS-Cog]		NS [WMS-LM II]		
Nutraceuticals		**None Reported**					
Diet Interventions		**None Reported**					
Multimodal Interventions		**None Reported**					
Other Health / Lifestyle Interventions		**None Reported**					

Hormone Therapies		**None Reported**					
Vitamins		**None Reported**					
Antihypertensive Treatment		**None Reported**					
Lipid Lowering Treatment		**None Reported**					
NSAIDs		**None Reported**					
Antidementia Drugs		**None Reported**					
Diabetes Treatment		**None Reported**					
Other Drugs		**None Reported**					

3MS=Modified Mini Mental Status Examination; AD=Alzheimer's disease; AVLT=Auditory Verbal Learning Test; BCT=brief cognitive test; BVRT=Benton Visual Retention Test; C=control; CVLT=California Verbal Learning Test; DS=Digit Span (Forward and/or Backward); I=intervention; g=grams; LC-n3-FA=long-chair omega-3 fatty acid; MCI=mild cognitive impairment; mg=milligrams; MMSE=Mini-Mental Status Examination; MNP=multidomain neuropsychological performance; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; n=sample size; NS=no statistically significant difference; NR=not reported; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation; TMT=Trail Making Test (Part A and/or B)

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