Evidence-based Practice Center Systematic Review Protocol

Project Title: Interventions for Preventing Cognitive Decline, Mild Cognitive Impairment, and Alzheimer's Disease

I. Background and Objectives for the Systematic Review

Neurocognitive disorders, typically referred to as dementia and cognitive impairment related to Alzheimer's disease, are a growing concern. Prevalence of dementia and cognitive impairment among U.S. adults over 70 are approximately 14 and 22 percent, respectively.[1, 2] The World Health Organization (WHO) estimated that 35.6 million individuals suffered from dementia in 2010. With approximately 7.7 million new cases diagnosed each year, WHO projected global prevalence of 115.4 million by 2050.[3] Dementia negatively impacts individuals' functioning and quality of life, creates burden and stress on the entire family, and is a major predictor of institutionalization. Additionally, dementia-related expenses exceed those for other diseases, including heart disease and cancer, and are often paid directly by the family.[4] Given the enormous burdens associated with dementia, identifying interventions with potential to prevent or delay its onset is an urgent public health priority.

The terminology used to discuss dementia and cognitive impairment is inconsistent and changing. Several criteria are available to diagnose dementia. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) described criteria in 1983.[5] These Alzheimer's disease criteria describe a gradual onset of cognitive impairment with continuing decline, not due to another condition. While the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-4) used the dementia terminology, the 5th edition (DSM-5) calls these types of conditions "neurocognitive disorders" and separates them into major and mild. Specific etiologies of neurocognitive disorders include Alzheimer's disease and many other less common conditions (e.g., frontotemporal lobar degeneration, Lewy body disease, traumatic brain injury, etc.).[6] Diagnosis of a neurocognitive disorder due to Alzheimer's disease requires cognitive decline 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. Because DSM-5 was very recently published, most of the literature discussing clinical cognitive diagnoses uses terminology from DSM-4. Other criteria discuss the neuropathic assessment of Alzheimer's disease.[7]

Peterson's criteria is typically used to diagnose mild cognitive impairment (MCI), which is 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 [8]Age related cognitive decline or cognitive aging is the process of normal changes that occur as individuals age and is highly variable.[9]

Causes of Alzheimer's disease are unclear and causal relationships are difficult to establish. A number of reviews have assessed the evidence linking risk factors and protective factors to Alzheimer's disease and MCI, including a 2015 Institute of

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Medicine report on cognitive aging[9] and a 2010 Agency for Healthcare Research and Quality (AHRQ) systematic review.[10] Several risk factors are correlated with incident Alzheimer's disease, 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 Alzheimer's disease, 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 have been developed to address chronic disease status, modifiable risk factors as well as protective factors (Table 1). Examples include treatment and control of chronic medical or mental health conditions (i.e., cardiovascular disease, obesity, depression), physical activity programs, smoking cessation, cognitively stimulating activities, social engagement, anti-inflammatory medications, and supplements. More comprehensive intervention programs address multiple risk factors simultaneously with multidomain interventions with components addressing nutrition, physical activity, cognitive training, social activity, and/or vascular risk factor management.[11]

Table 1. Interventions aimed at preventing cognitive decline, MCI, and/or Alzheimer's disease

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 D)

Interventions cannot change nonmodifiable risk factors. However age, sex, race/ethnicity, and family history are relevant to intervention effectiveness because they can modify the effect of interventions. 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.[9]

Prevention 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

Alzheimer's disease and other dementias. Important to note is that individuals diagnosed with MCI (which is characterized by progressive symptoms or impairment of episodic memory, known as amnestic MCI) are more likely to progress to Alzheimer's disease. One small study showed that nearly half of individuals diagnosed with MCI developed dementia within three years.[12] Cognitive decline is measured with validated neurocognitive tests. Biomarkers are measured using lab tests and imaging (e.g., total brain and hippocampal volumes; white matter hyperintensity volume; 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, phospho-Tau, and amyloid beta).

As the preceding paragraphs imply, studying dementia interventions is complex. The etiology may involve more than one risk factor and interventions may have several components. Because dementia may result from cumulative and possibly synergistic insults, the 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.

The review will ask a set of KQs that address the effects of interventions for delaying or slowing age-related cognitive decline and preventing, delaying or slowing MCI and Alzheimer's disease.

Challenges Discovered from Preliminary Literature Scan

Preliminary assessment of the literature identified several potential challenges. The most basic, the search strategy is difficult to design given the wide range of interventions. Our strategy will incorporate terms for interventions previously identified in the literature.

A large portion of the studies evaluating the effectiveness of interventions in preventing incidence of MCI or Alzheimer's disease are of relatively short duration and followup. This is concerning since expected latency period to reach clinical MCI and Alzheimer's disease and even intermediate cognitive outcomes may be quite long in younger adult populations. Consequently, short-term studies may be inadequate to test effectiveness of interventions to prevent these outcomes. Studies with longer durations and followup may experience different rates of mortality and loss to followup between intervention and comparison subjects that result in biases in missing data and confound interpretation about the effectiveness of the interventions. The Look AHEAD Study is one example where such a bias was found in an average 8-year followup.[13] We will address this challenge with separate analysis of studies by the average age of the subjects enrolled and study duration.

Evidence synthesis with intermediate outcomes introduces two important, related challenges. One is understanding the relationship between the intermediate outcomes and the clinical outcomes of MCI and dementia. We will include a Key Question (KQ) examining the association between the intermediate and the onset of MCI or dementia. Without a clear understanding of the knowledge based underlying the presence or absence of such linkages, it is difficult to interpret findings from short-term studies using intermediate outcomes.

The more difficult related challenge is how to distinguish between normal age-related cognitive decline, diagnosed exclusively by cognitive tests for cognitive impairment, from early cognitive manifestations of MCI and dementia, diagnosed using specific biomarkers and neurocognitive tests for cognitive and functional impairment. The degree of increase in biomarker protein levels in a patient's blood or cerebrospinal fluid (CSF), or decline in cognitive test results, in brain matter volume, or brain cell activity that is considered abnormal is not clear, and the distinction between intermediate and disease incidence outcomes is lost. Assessing cognitive decline will require careful attention to the nature of the way the outcome is expressed. We will distinguish changes in mean performance between treatment and control groups from proportions of persons showing a change of a given size. In some instances the outcome may be expressed as the proportion of persons who perform some level (typically 1.5 standard deviation) below the demographically adjusted mean. The latter will be treated as impairment directly relevant to dementia or MCI. In some instances the other measures of decline could apply to either dementia or age-related cognitive decline. This is an area of rapidly evolving literature and lack of consensus.

We will rely on direct measures of cognitive performance rather than patient or family reports, because the latter can be unreliable.

The presence of functional impairment depends on social factors independent of the underlying disease, including the functional demands faced by an individual and the source of information about functional performance (e.g., self, caregiver, and employer). We are unable to determine a clear a priori operational definition to address this challenge and will need to understand what is provided in the literature before we can fully map a process. We will search for literature describing minimal important differences or other established thresholds for intermediate neurocognitive outcomes instruments and biomarkers. These thresholds are likely different at different ages, adding to the complexity. Normal age-related cognitive decline, which is measured with cognitive testing can start in young adulthood (e.g., processing speed peaks in young adulthood and begins to decline in the third decade of life). One option would be to define a threshold of change in cognitive function (e.g., 0.5 standard deviation decline from baseline). Another option would be to empirically compare definitions used in the literature with approaches suggested by guideline groups or content expert publications.

The Institute of Medicine (IOM) committee has recognized the potential problems involved in using a cognitive decline definition for dementia and MCI.[9] 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 *MCI* 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." One would expect a

potentially substantial time gap between the intervention and the incident event. Furthermore, the cognitive disorder must be based on objective cognitive tests. Based on current criteria, diagnosing dementia depends on identifying both cognitive and functional impairment. Unfortunately, recognizing whether functional impairment is present depends on social factors independent of the underlying disease, including the functional demands faced by an individual and the source of information about 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 the work force."

Oversimplification of the models testing intervention effectiveness is another challenge we identified in our preliminary assessment of the literature. Research to date has examined fairly simple models testing intervention effects on populations with normal cognition. Williams et al., suggest that intervention effectiveness is likely more complex due to effect modification from nonmodifiable risk factors.[10] For example, brain exercises may be differentially effective for those with more or less formal education or jobs with different levels of intellectual engagement. Certain vitamins may be more effective for those whose levels are low at baseline. Additionally, we anticipate that age of participants enrolled in studies will vary widely. We will therefore group studies in the most appropriate way possible and analyze data for specific subgroups when possible.

A major challenge for this review will be to delineate which intervention studies aimed at managing underlying disease better are most salient to dementia. In some instances cognitive status may be included as an outcome in an intervention study designed to address a clinical problem (e.g., sleep problems) but it is not the major target. Some drug interventions to control heart disease or diabetes, for example, may involve a second order analysis of effects on cognition. The volume of all such studies would be overwhelming but some large trials may shed important light on the potential for interventions. The challenge is to determine the most effective decision rules for inclusion that balance comprehensiveness and feasibility to ensure that reliable evidence is examined to answer the questions.

We will examine the treatment of diseases such as cardiovascular disease, cerebrovascular disease, hypertension, and diabetes at several levels. We will ascertain whether the treatment was effective in controlling the disease. When possible, we will separately examine subgroups of treatments such as drug classes or non-pharmacological treatment to look for specific effects. We will include studies designed to address the effect of improving sleep on cognitive decline. We will require at least six months of treatment. We will assess the effects by the duration of followup, especially the lag between the end of treatment and the measurement of cognitive effect. We will examine how treatment for depression affects the cognitive decline. We will attempt to assess subgroups defined by drug classes and non-pharmacological treatment.

When sufficient trial data are not available, we will analyze high quality observational studies of interventions that do not only report risk factors. The methods section gives further detail on the full search strategy.

We acknowledge the potential for paradoxical attrition effects, wherein successful treatments may lead to higher survival and hence increase the morbidity in treatment groups. We will pay close attention to this phenomenon.

II. The Key Questions

The review will ask a set of KQs that address the effects of interventions for delaying or slowing age-related cognitive decline and preventing, delaying or slowing MCI and clinical Alzheimer's-type dementia.

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

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

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

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

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

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

The KQs are further specified by the populations, interventions, comparators, outcomes, timing, and settings (PICOTS) laid out in Table 2.

Table 2. Preliminary Populations, Interventions, Comparators, Outcomes, Timing, and Settings (PICOTS)

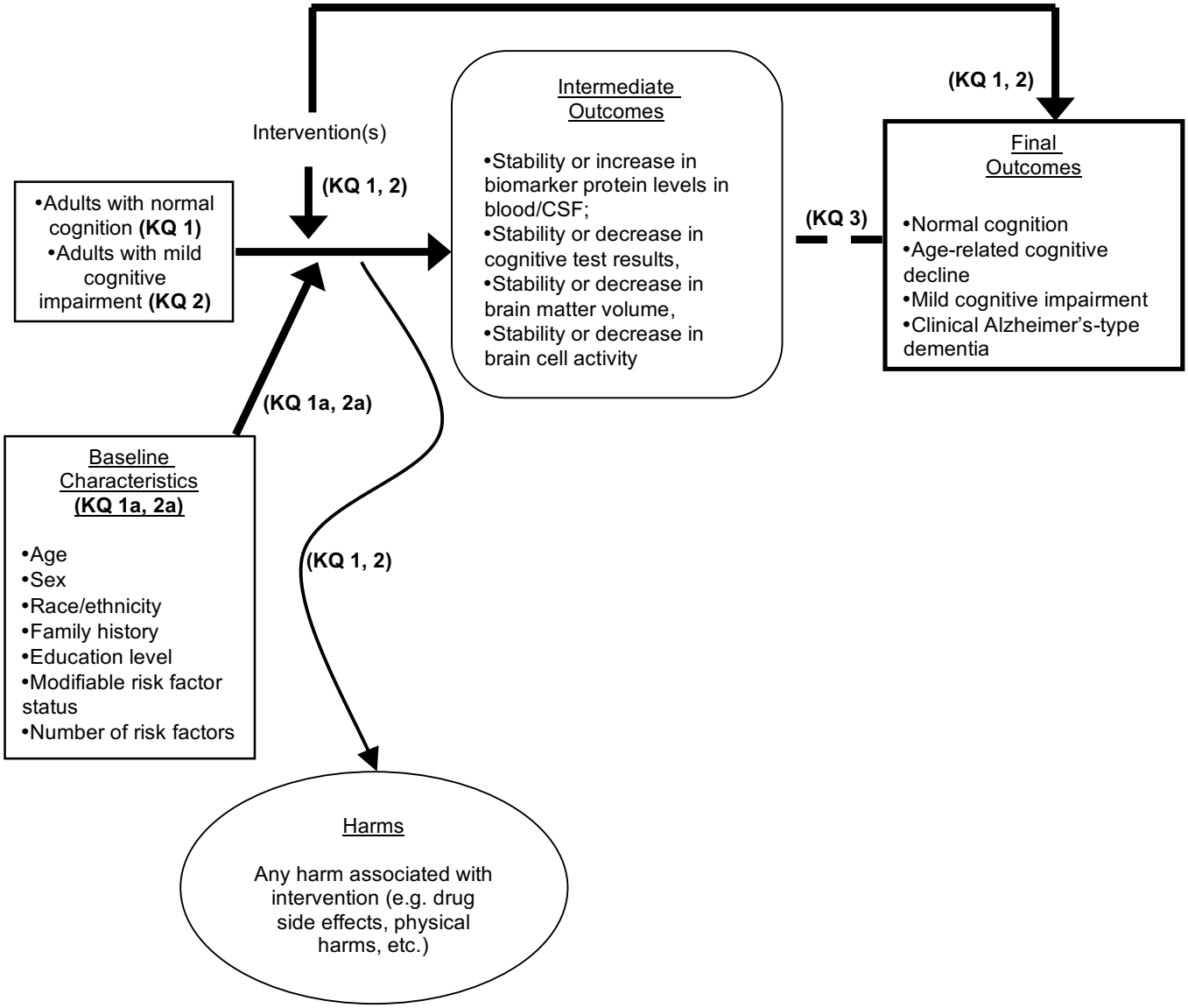
PICOTS	KQ 1	KQ 2	KQ3
Population	Adults with normal cognition	Adults with MCI	Adults with normal cognition or MCI
Intervention	Interventions aimed at preventing, delaying, or slowing the development of age-related cognitive decline, incident MCI or AD	Interventions aimed at preventing, delaying, or slowing the development AD	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 AD Intermediate outcomes: Biomarker protein level(s) Cognitive test results Brain matter volume Brain cell activity level As determined by: •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 AD Intermediate outcomes: Biomarker protein level(s) Cognitive test results Brain matter volume Brain cell activity level As determined by: •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 AD
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

AD = Alzheimer's-type dementia, MCI = mild cognitive impairment

III. Conceptual and Analytic Frameworks

Figure 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 AD.

Figure 1. Analytic framework for interventions to prevent cognitive decline, mild cognitive impairment and Alzheimer's disease



IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included in the review based on the PICOTS framework outlined above and the study-specific inclusion criteria described in Table 3.

Table 3. 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 intermediate outcomes and incidence of MCI of clinical Alzheimer's-type dementia.
Study Design	For KQ1-2: RCTs and large prospective cohort studies with comparator arms ($n \geq 250$ per arm). For KQ3: large prospective cohort studies ($n \geq 500$)
Outcomes	Cognitive decline measured with validated instruments, biomarkers associated with Alzheimer's disease, and incident MCI or Alzheimer's disease
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

RCTs= Randomized controlled trials

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We will search Ovid Medline, Ovid PsycInfo, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials, nonrandomized controlled trials, and observational studies published and indexed in bibliographic databases since 2008 for KQ1 and 2. Using 2008 will capture any literature published since the previous AHRQ review, allowing some overlap of time given the time lags that occur between publications and indexing and posting the article to a database. We will identify eligible studies published prior to 2009 using the previous AHRQ review, including the excluded study bibliography.[10] Our search strategy will include relevant medical subject headings and natural language terms for concepts of dementia, MCI, cognitive decline, and the various intervention types. These concepts were combined with filters to select study designs. The search strategy for KQ3 will first identify intermediate outcomes in KQ1 and KQ2. For those studies, we will include both intervention studies and other clinical studies that have compared intermediate outcomes to the final outcomes. This search will be restricted to literature published since 1996 to capture the latest scientific developments. We will supplement our search strategies with backward and forward citation searches of other recent relevant systematic reviews. To confirm that our search has identified all high quality, longitudinal observational studies, the search results will be compared against a list of these studies provided by the IOM Committee. We will update searches while the draft report is under public/peer review.

We will review bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. Search results will be downloaded to EndNote. Titles and abstracts will be reviewed by two independent investigators to identify studies meeting PICOTS framework and inclusion/exclusion criteria. Two investigators will independently perform full-text screening to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator. We will document the inclusion and exclusion status of citations undergoing full-text screening. Throughout the screening process, team members will meet regularly to discuss training material and issues as they arise to ensure consistency in application of inclusion criteria.

We will conduct additional grey literature searching to identify relevant completed and ongoing studies. We will search ClinicalTrials.gov for ongoing studies. Grey literature search results will be used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and inform future research needs. We will also track ongoing trials that have yet to publish results (e.g., PreDIVA, SPRINT-MIND, and Exercise MCI Trial[14]) emphasizing their contributions to a potential research agenda.

C. Data Abstraction and Data Management

Studies meeting inclusion criteria will be distributed among investigators for data extraction. Extraction of basic study information will inform risk of bias assessment. These fields will include author, year of publication; population, intervention, comparison, outcomes, timing, and setting. Additional data will be extracted from studies assessed as having low to moderate risk of bias. These fields include subject inclusion and exclusion criteria, intervention and comparison characteristics (components, timing, frequency, and duration), follow-up duration, participant baseline demographics, comorbidities; descriptions and results of included outcomes and adverse effects, and study funding source. Relevant data will be extracted into Microsoft Excel. Evidence tables will be reviewed and verified for accuracy by a second investigator. Data will be extracted to evidence and outcomes tables by one investigator and reviewed and verified for accuracy by a second investigator.

D. Assessment of Methodological Risk of Bias of Individual Studies

Risk of bias of eligible studies will be assessed using instruments specific to study design. We will develop instruments based upon AHRQ guidance.[15] Relevant items will include participant selection, method of randomization, attrition, blinding, allocation concealment, and appropriateness of analytic methods. Two investigators will independently assess risk of bias for all eligible studies. Investigators will consult to reconcile discrepancies in overall risk of bias. Overall risk of bias assessments for each study will be classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations.

E. Data Synthesis

We will summarize the results in evidence tables and synthesize evidence for each unique population, comparison, and outcome or harm. The evidence tables will be organized by interventions and timing of outcomes in order to address the challenges of

interpreting intermediate outcomes. Subgroups, where possible, will be examined in separate tables. As noted above, we will separately analyze studies by the average age of the subjects enrolled and study duration.

We will use minimal important differences to assess the efficacy and comparative effectiveness of outcomes with well-established minimal important differences, but many outcomes will not have such minimal important differences established. For outcomes measured with instruments that lack established thresholds to measure improvement, we will calculate standard effect sizes and require a small effect size ($d \geq 0.2$) to conclude efficacy or comparative effectiveness.

If certain comparisons can be pooled, we will meta-analyze the data using a random effects model. We will calculate risk ratios and absolute risk differences with the corresponding 95 percent confidence intervals for binary primary outcomes. Weighted mean differences and/or standardized mean differences with the corresponding 95 percent confidence intervals will be calculated for continuous outcomes. We will assess the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[16] We will assess statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic.[16]

F. Grading the Strength of Evidence for Major Comparisons and Outcomes

The overall strength of evidence for select outcomes for KQ1 and 2 within each comparison will be 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.[17] Based on study design and risk of bias, study limitations will be rated as low, medium, or high. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study) based on whether intervention effects are similar in direction and magnitude, and statistical significance of all studies. Directness will be rated as either direct or indirect based on the need for indirect comparisons when inference requires observations across studies. That is, more than one step is needed to reach the conclusion. Precision will be 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, reporting bias will be evaluated by 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 an assessment of the grey literature to assess potentially unpublished studies. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association.

Based on these factors, the overall strength of evidence for each outcome will be 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 randomized controlled trials with a low risk of bias, with consistent, direct, and precise domains. We will assess strength of evidence for key final health outcomes measured with validated scales.

G. Assessing Applicability

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, the population from which the study participants are enrolled, diagnostic assessment processes, narrow eligibility criteria, and patient and intervention characteristics different than those described by population studies.[18] These applicability issues are present in the synthesis frameworks and sensitivity analyses described in more detail in the data synthesis section.

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Explain what the change hopes to accomplish.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Because of the overall design from our National Institute on Aging sponsor, this project is following a unique model. The role of the Key Informants was filled by the Institute of Medicine (IOM) committee that will use the report to help develop its own report on the state of knowledge on the efficacy, comparative effectiveness, and harms of interventions to protect cognitive health and prevent cognitive decline and dementia. Because the IOM panel would not see the draft key questions, PICOTS, and analytic framework until the key questions were posted for public comment, a panel of content experts from federal agencies acted as a proxy Key Informants. The content experts were drawn from the National Institute on Aging, the Veterans Administration, The National Institute of National Institute of Neurological Disorders and Stroke, and the Center for Disease Control and Prevention. There was not a separate, independent Key Informant panel.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Because of the overall design from our NIA sponsor, this project is following a unique model. The role of the Technical Experts will be filled by the IOM committee that will use the report to help develop its own report on the state of knowledge on the efficacy, comparative effectiveness and harms of interventions to protect cognitive health and prevent cognitive decline and dementia. There will not be a separate, independent Technical Expert Panel.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

The topic for this project was nominated by the National Institute on Aging and funded under Contract No. HHSA290201500008I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.