



Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia*

Draft review available for public comment from October 4, 2016, to October 31, 2016.

Research Review Citation: Kane RL, Butler M, Fink HA, Brasure M, Davila H, Desai P, Jutkowitz E, McCreedy E, Nelson VA, McCarten JR, Calvert C, Ratner E, Hemmy LS, Barclay T. Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia. Comparative Effectiveness Review No. 188. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-00008-I.) AHRQ Publication No. 17-EHC008-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017.
www.effectivehealthcare.ahrq.gov/reports/final.cfm. doi:
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Comments to Research Review

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The table below includes the original comments by peer reviewers and the public, as well as the authors' response for each comment that was submitted for the draft research review. Comments are not edited for spelling, grammar, or other content errors. Each public comment is listed with the name and affiliation of the commentator, if this information is provided. Peer reviewers are listed by number. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the AHRQ.

Research Review Section	Reviewer, Affiliation	Comment	Response
Abstract	Public Reviewer Andrea Bozoki, Michigan State University	Two minor quibbles here. First, referring to "Vitamin B" as it does in the summary of findings, must be an editing mistake as there are numerous individual vitamins in this class, so the preferred term is "B vitamins." However, even using the preferred term is misleading because only a few of the 12 individual B vitamins have been tested with any regularity. A more accurate summary statement would name them: "B6 and B12" (the authors could add B9 if they wish).	Thank you, we have changed this to either "B vitamins" collectively or named each B vitamin specifically studied.
Abstract	Public Reviewer Andrea Bozoki, Michigan State University	Second, a small error in the table of contents which I wouldn't have noticed except that I am especially curious about the results of various nutraceutical studies so I went to it first, and found that the subheading "Logic of..." reiterated physical activity interventions instead of being updated to "nutraceutical interventions." This suggests that a more thorough editorial review of the TOC might be in order.	Thank you, we have corrected this error and have given the report a thorough editing.
Intro- duction	Peer Reviewer #1	Please clarify the goals of this document. If it was to look at factors that predict MCI and CATD, then many of the studies reviewed are irrelevant, because they don't look some general measure of "dementia" as the outcome, or they look at "cognitive aging," which is one of the goals but not very well defined. If I've got this wrong, please put clear text in the beginning of the document.	Thank you for the question. As the Title notes, the report is on prevention interventions, and as such does not focus on risk factors. We have revised the Scope section to state this explicitly.
Intro- duction	Peer Reviewer #1	I found the goals of this study difficult to understand. The "Key Questions" were in my view often not concordant with the studies that were reviewed. For example, if one of the key questions is to understand what interventions may diminish the risk of CATD, why are studies included that only include a change in the MMSE as an outcome, or only studies where the outcome is "dementia?" The goals and the studies included need to be better aligned, or some additional explanation is needed.	Thank you for the question. The Key Questions include three subquestions examining three outcomes: cognitive decline, MCI and dementia (CATD).

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Research Review Section	Reviewer, Affiliation	Comment	Response
Intro-duction	Peer Reviewer #1	Also, if there are a lot of problems with intermediate outcomes in cognitive interventions, and I agree with this sentiment, why were studies with these outcomes included? There are some intermediate outcomes, such as white matter lesions, that are not particularly known to be related to CATD or MCI (in fact, it's not at all certain what they mean), so again, why include them?	Thank you for the question. The scope for this report, arrived at through a consensus process with the NIA and IOM, included intermediate biomarker and cognitive outcomes. We agree that the links between the intermediate biomarkers and the final outcomes of decline, MCI, and dementia are not clear. This is in part what motivated include Key Question 3 to look for what the studies provide to support such linkages.
Intro-duction	Peer Reviewer #1	Again, it was frustrating not to have the specific methods for searches and summarization for review.	The Methods chapter summarizes the methods used for the review. The specific search algorithms are available in Appendix A.
Intro-duction	Peer Reviewer #2	The introduction is quite complete. It is very informative. It includes a reasonable background literature description, it provides definitions for relevant terminology, it states the key questions and outlines the analytic framework.	Thank you for the comment.
Intro-duction	Peer Reviewer #3	The rationale for the study is clear and the target population (normal cognition and MCI) is described well. Issues related to changing concepts and definitions for cognitive disorders are discussed appropriately. In my opinion, the DSM-5 shift to major neurocognitive disorder further muddies the water, but the team seems to have not choice other that to describe the change. There are some parts of the introduction that seem repetitive (pg 16 of 230: lines 24-30) and I'm not certain that Table 1.1 is helpful (certainly some of these etiologies for MND aren't relevant to the report). In contrast, the section "Underlying Theories" is useful as is the focus on describing studies theoretical rational for why a particular intervention may be beneficial (e.g., physical activity).	Thank you for the comment. As a topic, cognitive decline and dementia can be confusing, so some repetition seemed useful to help readers with less exposure to the topic.

Research Review Section	Reviewer, Affiliation	Comment	Response
Intro-duction	Public Reviewer Dan Blazer, Duke University	this looks good to me. Minor comment. Could reference IOM cognitive aging report on p. 15 in intro section as they do on p. 16	Thank you for the comment. The IOM report is now referenced in both the “Age-Related Cognitive Decline and Mild Cognitive Impairment – Definitions and Diagnostics” and the following “Distinguishing between Mild Cognitive Impairment and Dementia” sections.
Methods	Peer Reviewer #1	Did you include only studies that had IRB approval?	IRB approval was not an eligibility criterion.
Methods	Peer Reviewer #2	Research strategy is described with clarity and seems logical. So is data abstraction, management and synthesis. Inclusion and exclusion criteria are justifiable. Classification and categorization of data is outlined. The definitions and diagnostic criteria for the outcome measures are appropriate. Classification of neuropsychological tests into cognitive domains is done according to current literature. The report describes well the approach regarding grading strength of evidence taking into account limitations, directness, consistency and reporting bias. The definition of directness is a bit unclear and requires some better explanation, possibly with examples. Many aspects of risk of bias have been considered including selection-randomization, attrition, detection (blinding, timing, instrument quality), performance (ITT analyses, adjustments, cross-overs etc), reporting etc.	We have expanded the explanation of directness as follows: “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 our 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 then lowers 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.”
Methods	Peer Reviewer #3	Overall, the methods are strong. The key questions are clear, stated explicitly, and clinically relevant. The attention to reliable change indices and focus on studies with low to moderate ROB are methodological strengths. I found it helpful that you reported scoring ranges for scales (e.g., Tabl 4!.4)	Thank you for the comment.

Research Review Section	Reviewer, Affiliation	Comment	Response
Methods	Peer Reviewer #3	Justify the eligibility criteria to restrict KQ3 to large prospective cohorts ≥ 500 (why the threshold of 500?)	The eligibility criteria are explained in Table 2.1. Only studies that were eligible for KQ1 or KQ2 were eligible for KQ3. The sample size threshold is only for observational studies; RCTs of any size were eligible. We clarified the text: “For KQ1-2: RCTs of any size and large prospective quasi-experimental cohort studies with comparator arms ($n \geq 250$ per arm).”
Methods	Peer Reviewer #3	Clarify the approach to GRADING the SOE. Page 26 of 230, lines 16-17 states that limitations in study design were based on study design and ROB. The grade approach begins by assigning RCTs as High ROE and non-randomized studies as Low ROE, then using ROB to downgrade. Did you follow this approach and if yes, revise this description to improve clarity.	We assessed strength of evidence according to AHRQ methodology (as noted by the references), not GRADE. The two approaches differ slightly. We do, however, note the problems of applying SOE criteria to studies showing no difference. We also further clarified in the Assessment of Methodological Risk of Bias of Individual Studies section how study limitations are assessed: “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).” Tables the provide specifics of the assessments are provided in the Appendix sections for each intervention class.
Methods	Peer Reviewer #3	State more clearly how you examined results for publication bias when considering observational studies.	Thank you for the suggestion. We did not identify any observational studies to include, so publication bias for this class of studies was not a concern. The reviewer does, however, correctly note that identifying publication bias for observational studies is difficult to accomplish.

Research Review Section	Reviewer, Affiliation	Comment	Response
Methods	Public Reviewer Dan Blazer, Duke University	I think the methods are discussed reasonably well, but as I mentioned in a memo to Clair, many studies were excluded because of inadequate study design yet I am not certain we have a clear definition of what constitutes inadequate study design. For example, what is the difference between high risk of bias and inadequate study design. A quick review suggested that many well-known studies were excluded because of inadequate study design.	<p>As noted in the methods section, eligible study designs included randomized controlled trials and large quasi-experimental cohort studies. A study would be considered quasi-experimental if there was a comparator arm and appropriate techniques to address selection bias were used. A list of well-known observational studies that did not reach the study design threshold were included in Appendix E.</p> <p>Studies that passed all inclusion criteria, including study design, were then subjected to risk of bias assessment. Eligible studies assessed as high risk of bias were not analyzed because we had little confidence in their results resulting from the way the study was conducted.</p>
Methods	Public Reviewer M.A. Quiroga, Universidad Complutense de Madrid	It seems that either the inclusionary criteria or the databases that were searched, somehow, did not include any of the vast research related to music therapy, Rhythmic Auditory Stimulation (RAS)/Neurological Music Therapy that has demonstrated the efficacy of music therapy in the treatment of neurocognitive disorders. This is troublesome since the efficacy of music therapy for cognitive stimulation, reality orientation, reminiscence and life review has been effectively demonstrated in that research. This has to call into question the methodological rigor of this review.	Thank you for the comment. This review focused on interventions to preventive cognitive decline and dementias, not treatments for dementia or other cognitive disorders.

Research Review Section	Reviewer, Affiliation	Comment	Response
Methods	Public Reviewer Fredric Wolinsky, University of Iowa	The methods used are flawed in several respects. First, the attrition rate that is deemed acceptable is not defined based on the length of follow-up.	That is correct, we did not establish specific acceptable attrition rates based on length of followup. While longer term studies do typically have higher attrition rates, high attrition for any study length limits our confidence in the results. Methods to address attrition are available and should be utilized in original research. Studies with moderate attrition that addressed attrition appropriately in their analysis were not assessed high risk of bias.
Methods	Public Reviewer Fredric Wolinsky, University of Iowa	Second, the approach to assessing quality does not follow Equator guidelines.	The assessment of risk of bias (similar to study quality) is based on EPC standard practices, as is the assessment of strength of evidence. The Equator Network (http://www.equator-network.org/) provides guidelines for reporting studies. These guidelines, while related, are not tools for assessing risk of bias of an individual study.
Methods	Public Reviewer Fredric Wolinsky, University of Iowa	Third, statements about several studies that are cited, such as ACTIVE (its methodology, attrition analyses, and booster training randomization) are incorrect and reflect a poor read of the articles cited.	We have revised some elements of the description of the ACTIVE trial. In Chapter 4A Results: Cognitive Training.
Methods	Public Reviewer Fredric Wolinsky, University of Iowa	Fourth, transfer to everyday activities over a year or more has been shown, but those papers are not included in the review, even though they meet the criteria for inclusion.	Transfer to everyday activities such as IADLs are noted in Table 4A.5
Methods	Public Reviewer Fredric Wolinsky, University of Iowa	Fifth, there is no metaanalysis of the available trial data provided.	Meta-analysis was deemed infeasible because of the wide variety of comparisons, outcomes, and measures used for assessing cognition. Few comparable studies addressed dementia incidence.

Research Review Section	Reviewer, Affiliation	Comment	Response
Methods	Public Reviewer Harry Rice Global Organization for EPA and DHA Omega-3s (GOED)	The current report excluded randomized controlled trials (RCTs) and observational studies with less than 250 subjects. Systematic reviews and subsequent meta-analyses are meant to facilitate an evaluation of the totality of the available evidence. The AHRQ Methods Guide for Effectiveness 1075 Hollywood Ave, Salt Lake City, Utah 84105, United States Tel: +1 (801) 746-1413 Fax: +1 (801) 474-2571 www.goedomega3.com Page2 and Comparative Effectiveness Reviews (ECER Guide)1 notes that excluding studies based on small sample size introduces bias and "... may exclude valuable information." Thus said, GOED recommends smaller (<250 subjects) studies be included provided they meet the other inclusion criteria.	Randomized controlled trials of any size were eligible. We clarified the text: "For KQ1-2: RCTs of any size and large prospective quasi-experimental cohort studies with comparator arms (n≥250 per arm)."
Methods	Public Reviewer Harry Rice Global Organization for EPA and DHA Omega-3s (GOED)	Given that you "identified eligible studies published prior to 2009 using the previous AHRQ review, including the excluded study bibliography", the timeframe (January 2009 – March 2016) of the current literature search should have been adequate to capture all of the relevant studies; however, we identified studies that were not noted in either the text of the present report or any of its appendices. What follows is a list of nonexhaustive studies not identified by AHRQ for the current draft report. This list includes articles regardless of whether the reported results are positive (i.e. EPA/DHA benefit) or neutral (i.e. no EPA/DHA benefit). [See supplemental materials for list of 24 articles]	Thank you for the list of suggested articles. We screened all studies that any reviewer suggested were incorrectly excluded. The vast majority of these were not eligible. The most frequent reason was inadequate follow up time (i.e. less than 6 months) or study design issues (non-experimental design). Three suggested citations did meet eligibility criteria and were incorporated into our review.

Research Review Section	Reviewer, Affiliation	Comment	Response
Methods	Public Reviewer Harry Rice Global Organization for EPA and DHA Omega-3s (GOED)	The electronic search strategy was limited to English language publications. The AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (ECER Guide) ² notes on page 142 that restricting to English language publications should be avoided as it increases the risk of selection bias. The ECER Guide goes on to note that of EPC reviews conducted prior to 2014, 71% likely suffered from selection bias due, at least in part, to English language restrictions.	Our search strategy was in English and used English language databases. However, the search strategy did not limit results to English language studies. Therefore, articles published in other languages but indexed in Medline, Embase, PsycInfo, or the Cochrane library would be identified. We did not include studies that were not available in English, but did not see evidence that many non-English studies were available.
Methods	Public Reviewer Henry Mahncke, Posit Science	There are a surprising number of peer-reviewed publications in the field of computerized cognitive training that are well known to experts and can be found in PubMed that are simply missing from the review (both the main body and the appendix). Their absence raises significant concerns about the literature search process. Each of these missing publications derives from a randomized controlled trial with cognitive function measures, and virtually all document transfer of improvement to generalized measures of cognitive function. Here are the first twenty missing publications that I identified by a quick check through a publicly available database of RCTs in computerized cognitive training ^{1–20} . There are quite likely more, but time for this response is limited. [List of articles and full letter available in Supplemental Material.]	We screened all studies that any reviewer suggested were incorrectly excluded. The vast majority of these were not eligible. The most frequent reason was inadequate follow up time (i.e. less than 6 months). Any studies that met eligibility criteria were incorporated into our review. [See the report's Appendix D for reasons for exclusions for any reference supplied by the reviewer.]
Methods	Public Reviewer Henry Mahncke, Posit Science	<i>the missing papers should be added to the review process and fully reviewed.</i> In particular, the full set of results from ACTIVE and IHAMS documenting transfer to IADLs, health measures, depressive symptoms, and driving measures should be included.	Thank you for the comment. We did include information on IADLs. Health and depression were judged to be out of scope. We note driving but do not include it as cognitive performance per se. We included any article derived from the ACTIVE study that met inclusion criteria (including a followup of at least 6 months). However, for context, we did comment on 2 studies of only 6 weeks duration that addressed IADLs.

Source: <https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2417>
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Research Review Section	Reviewer, Affiliation	Comment	Response
Methods	Public Reviewer Henry Mahncke, Posit Science	These missing publications raise concerns about the review's publication search and/or review process. The review is missing 7 key publications from an overall total of 12 publications from ACTIVE and IHAMS covering <i>a priori</i> outcome measures, for an effective search rate of 42% or a missing publication rate of 58%. As a result, the review's summary of ACTIVE is factually incorrect (in addition, please also see commentary regarding booster training and attrition below). The argument that "diffusion to other domains was rare" in ACTIVE cannot be sustained with a full review of the results from ACTIVE.	Thank you for the comment. As part of our handsearch process, described in the methods section, we reviewed all ACTIVE and IHAM publications and addressed those that were salient to the goals of this review.

Research Review Section	Reviewer, Affiliation	Comment	Response
Methods	Public Reviewer Henry Mahncke, Posit Science	<p>Second, <i>the requirement of that studies have a duration of 6 months should be eliminated</i>, the review should fully consider those papers, and consider evidence for benefits immediately post-training, as well as at the 6 month (and longer) periods.</p> <p>In the current review, studies are required to have a "minimum follow-up of 6 months for intermediate outcomes." I am not able to locate anywhere in the review where this requirement is justified. One possibility is that the criterion was chosen because the review felt that interventions must have benefit over 6 months to have the opportunity to significantly affect cognitive decline. A second possibility is that the criterion was chosen as a proxy for the evaluation of the endurance of training effects after the completion of training. However, both of these goals are ill-served by this requirement. For an intervention to have effects over time, it must first have effects at all, and a review would benefit from including all studies evaluating such effects, regardless of their duration.</p> <p>As a result of this decision, the review identifies exactly 6 trials to review in normal aging (discussed in 9 publications), only four trials of which involve computer-based cognitive training. In the database that I maintain of computerized cognitive training publications, a quick count shows 99 published papers that analyze results from RCTs (including healthy adults and MCI, excluding non-randomized trials, case studies, reviews, and meta-analyses). Thus this choice eliminates <i>some 90% of studies</i> of cognitive training conducted in the past twenty years from consideration. [Examples provided in Supplemental Material.]</p>	<p>Thank you for the comment. While there is no gold standard for study duration of a chronic condition, six months has been widely used. The intent is to identify sustained effects.</p> <p>The primary goal of this review is to identify interventions that reduce incidence of dementia. Short-term studies provide little confidence that the interventions will reduce incidence. We do acknowledge an indirect causal chain argument.</p>

Research Review Section	Reviewer, Affiliation	Comment	Response
Results - Search	Peer Reviewer #2	The report results include an informative literature flow diagram. Much detail is presented in the results section but this is somehow understandable for a review of this type. Study characteristics are clearly described and key messages are clear and explicit. Study selection and exclusion seem appropriate. It is understandable that set publication dates of literature should be defined. But if more recent large studies (ie. MAPT – if published in an article form; PREDIVA Lancet. 2016 Aug 20;388(10046):797-805; Henderson Neurology 2016; 87; 699-708 etc) were included it would be ideal.	Thank you for the suggestion. We updated the search during the peer review process. The search date in the report has been amended to September, 2016. The two articles mentioned here were identified in the update search and included in the review.
Results - Search	Peer Reviewer #3	Consider showing the number of eligible studies by KQ in Figure 3.1	Thank you for the suggestion. However, given the extensive overlap of articles used for both KQ1 and KQ2, the result would have been potentially more confusing to readers.
Results - Search	Peer Reviewer #3	Consider organizing Table 3.1 to show intervention type by those with the most to least studies.	Thank you for the suggestion. The team discussed the possibility but determined that number of contributing articles was not the most salient characteristic for organizing the report.
Results - Search	Public Reviewer Fredric Wolinsky, University of Iowa	The number of papers not included that represent reliable and valid work of considerable quality is enormous. And as noted above, many of the omitted papers actually meet the report author's guidelines for inclusion. Thus, this is a very selective review that reaches an erroneous conclusion because of the substantial omission of high quality randomized controlled trials.	We respectfully disagree. The established inclusion criteria were applied to all publications identified using the search algorithm supplied in Appendix A. We also screened all studies that any reviewer suggested were incorrectly excluded. The vast majority of these were not eligible. The most frequent reason was inadequate follow up time (i.e. less than 6 months). [See supplemental materials for reasons for exclusions for any reference supplied by a reviewer.] Any studies that met eligibility criteria were incorporated into our review. Including these studies did not substantially change results or conclusions.

Research Review Section	Reviewer, Affiliation	Comment	Response
Results – Cognitive Training	Peer Reviewer #3	Page 30 Of 230: consider explaining WHY the ACTIVE trial is an exemplar and a model for subsequent work. This relates back to the methods approach of which studies to emphasize (weight more strongly) in qualitative synthesis.	We do provide reasons why we emphasize the ACTIVE trial. In the ACTIVE Trial section in Chapter 4A, we note that it received wide attention, and serves as a model for subsequent work.
Results – Cognitive Training	Peer Reviewer #3	Table 4A.4: Presumably the results in BOLD represent statistically and clinically significant results. Make this clear.	That is correct; the bold font is intended to highlight the statistically significant results. We also used an asterisk and footnote to denote statistical significance, a p-value of less than 0.01.
Results – Cognitive Training	Peer Reviewer #3	Table 4A.8: Table is misnamed. It gives details on individual studies but really doesn't synthesize or summarize the evidence.	The reviewer is correct; the table does not synthesize the studies. This was not the intent of the table. The table instead summarizes the studies by providing specific salient characteristics of the included studies to give the reader a reasonably quick but complete overview of the studies.
Results – Cognitive Training	Public Reviewer M.A. Quiroga, Universidad Complutense de Madrid	First of all, I would like to signal that "Key Messages" provided at the beginning of the chapter, do not properly summarize analyzed results but incline the weight to the non-effect side when in fact, there are medium effect sizes even in the 10-year outcomes; and for the cognitive measures, effect size for Speed of Processing in the 10-year outcomes is .66.	We respectfully disagree. The 10-year outcomes have serious attrition problems and sample bias that make effect size less salient.

Research Review Section	Reviewer, Affiliation	Comment	Response
Results – Cognitive Training	Public Reviewer M.A. Quiroga, Universidad Complutense de Madrid	Second, authors of this report point as a critical cue the absence of transfer results from the trained domain to another. Why are researchers demanding to cognitive training more than what they demand to physical training? If you train physical strength, results do not extend to speed, albeit these areas are correlated. This is the case for processing speed, reasoning and memory. Even being correlated, correlations among them are not perfect, indicating different response patterns among participants. This is important because, at the mean level, training in processing could not extend to other cognitive domains, but this could not be the case for all the participants. Individual differences analyses need to be run (for example K-means cluster).	The conceptual basis for transfer is quite different for cognitive training than for physical exercise. Cognitive training is specifically directed at the cognitive performance, while the physical exercise is not. Physical exercise, as hypothesized, may impact cognitive performance, but the mechanism is less direct.
Results – Cognitive Training	Public Reviewer M.A. Quiroga, Universidad Complutense de Madrid	Third, I would like to point to the fact that we should expect that cognitive training results were related to the status the trained concept has, in the theoretical model describing abilities and intelligence. By now, the CHC model (Cattell.Horn-Carroll) is the one getting a higher consensus in the field. In this model, processing speed show the lower percentage of shared variance with inductive reasoning in adults (see for example McGrew, 2009 for a review of the CHC model), thus its training will influence other intellectual domains proportionately to their correlations.	Thank you for the information. The review focused empirical evidence rather than theoretical models.
Results – Cognitive Training	Public Reviewer M.A. Quiroga, Universidad Complutense de Madrid	Finally, I want to point that an effect size of .66 after 10 year, is an impressive result. Our elders will benefit if we continue doing research in this field. We need more research funds; not to stop a very promising line of research.	The 10-year outcomes have serious attrition problems and sample bias that make effect size less salient. We agree that an effect size of 0.66 after 10 years is relatively large in magnitude, but it needs to be interpreted in the context of attrition bias.

Research Review Section	Reviewer, Affiliation	Comment	Response
Results – Cognitive Training	Public Reviewer Fredric Wolinsky, University of Iowa	All of my comments above refer to the cognitive training component and are repeated here. The methods used are flawed in several respects. First, the attrition rate that is deemed acceptable is not defined based on the length of follow-up. Second, the approach to assessing quality does not follow Equator guidelines. Third, statements about several studies that are cited, such as ACTIVE (its methodology, attrition analyses, and booster training randomization) are incorrect and reflect a poor read of the articles cited. Fourth, transfer to everyday activities over a year or more has been shown, but those papers are not included in the review, even though they meet the criteria for inclusion. Fifth, there is no metaanalysis of the available trial data provided. The number of papers not included that represent reliable and valid work of considerable quality is enormous. And as noted above, many of the omitted papers actually meet the report author's guidelines for inclusion. Thus, this is a very selective review that reaches an erroneous conclusion because of the substantial omission of high quality randomized controlled trials. Ultimately, the conclusions that are reached are ludicrous.	<p>We respectfully disagree. We summarize our comments made earlier. The correlation of attrition and duration of follow-up is a recognized problem, but efforts need to be made to keep the cohort as intact as possible. Much of the loss was not for non-preventable reasons.</p> <p>We used AHRQ EPC methods for risk of bias assessment; EQUATOR provides guideline for reporting studies, not assessing risk of bias.</p> <p>We have revised our description of the booster assignment but it does not alter the bias conclusion. Table – addresses IADLs. We now discuss driving, but note its non-direct relationship to dementia. We could not perform meta-analyses because the cognitive measures were too diverse; they did not even allow some crude standardization. We have, however, used Cohen's D.</p>
Results – Cognitive Training	Public Reviewer Jerri Edwards, University of South Florida	When evaluating the results of the ACTIVE study, the effects of booster training should be taken into account. [See supplemental material for the full letter provided by the reviewer.]	The booster/dosage question is indeed important, but the research design must allow the effect to be isolated.

Research Review Section	Reviewer, Affiliation	Comment	Response
Results – Cognitive Training	Public Reviewer Jerri Edwards, University of South Florida	Only participants who completed booster training received between 9 and 13 sessions of adaptive cognitive speed of processing training. According to the Model of Adult Plasticity (Lovden, Backman, Lindenberger, Schaefer, & Schmiedek, 2010), cognitive training programs that are adaptive in difficulty will be most effective. By comparing effect sizes across six randomized clinical trials of cognitive speed of processing training (detailed below), it is evident that adaptive training produces larger training gains, in support of Lovden et al. Thus, in the ACTIVE study, the effects of cognitive speed of processing training overall were reduced because of the less effective method of nonadaptive training. [See supplemental material for the full letter provided by the reviewer.]	We have expanded our discussion of the adaptive training. However, that distinction makes the transfer case even more tenuous. There is a risk of training to the test.
Results – Cognitive Training	Public Reviewer Jerri Edwards, University of South Florida	In ACTIVE, cognitive speed of processing participants who received booster training after one year demonstrated improved everyday functional performance with a net effect size of $d=0.92$ at 1 year and a net effect size of $d=0.35$ at two years, demonstrating improved everyday functional performance on primary outcomes (Ball, Ross, Roth, & Edwards, 2013). These boosted participants maintained significant improvements on this everyday speed composite after 5 years (Willis et al., 2006). These functional performance improvements are important to note in the review as functional impairment is by definition a feature of dementia. Thus, interventions that successfully improve everyday function, or delay the onset of functional impairment, should delay the onset of dementia. Forthcoming work from ACTIVE supports this conclusion. [See supplemental material for the full letter provided by the reviewer.]	Although the Edwards studies had too short of followups for inclusion, we have now briefly discussed the Edwards studies, including the reported effects on timed IADLs

Research Review Section	Reviewer, Affiliation	Comment	Response
Results – Cognitive Training	Public Reviewer Jerri Edwards, University of South Florida	Minor Comments By 10 years, that gain, while still significant, had fallen 24 points. The metric is actually 24 milliseconds. Speed of processing is measured by display speed threshold in milliseconds (not points)	Thank you, we have corrected this.
Results – Cognitive Training	Public Reviewer Jerri Edwards, University of South Florida	Table 4A.4.- The possible range of speed of processing outcome is 48-1500. 0 is an illegal value.	Thank you, we have corrected this.
Results – Cognitive Training	Public Reviewer Henry Mahncke, Posit Science	The review states that "much of the sample loss [in ACTIVE] was unexplained." This is factually incorrect. As shown in the CONSORT table in the 10-year follow-up publication ²⁹ only 5.1% of participants are lost due to "family refuses access" or "lost to follow-up" - quite an accomplishment for a 10-year study. Twenty-three percent are lost due to death, which is outside the control of the study, another 21.3% are due to the subject's decision to withdraw, which would be unethical for investigators to interfere with, and 9.8% are due to the site's decision to drop the participant, which are typically due to participant behavioral issues and compliance with study requirements. [See supplemental material for the full letter provided by the reviewer.]	Thank you for the comment. We have provided a table in Appendix F showing our calculations for the ACTIVE trial based on what was reported. The rate of attrition at 10 years was 55-60%; 22-26% was due to death.
Results – Cognitive Training	Public Reviewer Henry Mahncke, Posit Science	The review misstates how booster training was assigned in ACTIVE, and as a result, ignores important conclusions from the booster training analysis. [See supplemental material for the full letter provided by the reviewer.]	Thank you for the comment. Randomization to booster was limited to a self-selected subset of adherents, which limits what can be inferred from the data.
Results – Cognitive Training	Public Reviewer Henry Mahncke, Posit Science	Thus, the interpretation in the review that with regard to cognitive training "diffusion to other domains was rare" is simply in conflict with the vast majority of the actual published literature.	We respectfully disagree. We believe our findings are appropriate based on the studies which met inclusion criteria. Further, as noted in the Discussion section of the report, our findings are consistent with a review published by See, Psychological Science in the Public Interest 2016 17(3)103-186r

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Research Review Section	Reviewer, Affiliation	Comment	Response
Results – Cognitive Training	Public Reviewer Henry Mahncke, Posit Science	Table 4A.1.: There is an extra phrase "but not at 10 years" in the "reasoning" row and "conclusion" column that inadvertently alters the conclusion.	Thank you, we have corrected this.
Results – Cognitive Training	Public Reviewer Henry Mahncke, Posit Science	Table 4A.2 Key ACTIVE Studies: The text for the "testing outcomes" and "primary outcomes" rows are reversed between the "Willis 2006" and "Unverzagt 2010" columns.	Thank you, we have corrected this.
Results – Physical Activity	Peer Reviewer #3	Table 4B.1: This is a fascinating table but the detail is exhausting. Consider deleting the table (or moving to appendices) and summarizing the main message in a short paragraph.	Thank you for the suggestion. We agree and have removed the table and replaced it with a more succinct paragraph summarizing the logic provided for physical activities.
Results – Physical Activity	Peer Reviewer #3	Table 4B.3: This table is designs to give summary information. However, without information on the number of studies consider, study design, or number of patients enrolled it requires a leap of faith to accept the SOE ratings. This is an instance where a bit more detail in the summary would be helpful.	We understand the reviewer's concern. As report writers, we work to balance report readability with the necessary detail to understand the report findings. In that regard, all results chapters include conclusion tables which are followed by narrative and tables describing individual study results that contribute to summary assessments. We also provide signposts to appropriate appendixes with further detail for the more interested readers.
Results – Physical Activity	Peer Reviewer #3	Page 52 of 230, lines 42-46: Is this an example of a ceiling effect? That is, studies to improve cognition or slow cognitive decline that are conducted in those who are normal at baseline, may have great difficulty showing positive effects due to high baseline function and limited followup. If yes, is this a problem that may affect many studies and require discussion?	Physical activity studies aim to improve cognition or reduce the rate of cognitive decline. Instrument-specific ceiling effects are a possibility. Because we do see statistical differences with some interventions on some instruments, we do not believe this to be a significant limitation.
Results – Physical Activity	Peer Reviewer #3	Tables (e.g., Table 4B.4) Major headers (e.g. Multicomponent Physical Activity) may be clearer if the cells are merged, rather than having a series of empty cells across the table.	Thank you for the comment; our report needs to comply with accessibility regulations which only allow certain cells to be merged.

Research Review Section	Reviewer, Affiliation	Comment	Response
Results – Nutraceuticals	Peer Reviewer #1	Page 69, Line 4: Be careful with the term “nutraceuticals;” I personally don’t like that term. Most are not standardized drugs in the same way that a chemical drug might be, and the many have no known nutritional value. These are really unproven dietary supplements	Thank you for the comment. We have left the term, as it is commonly used in the literature despite, as the reviewer notes, the lack of specificity.
Results – Nutraceuticals	Public Reviewer Harry Rice Global Organization for EPA and DHA Omega-3s (GOED)	The use of measurements of EPA and DHA status, like the Omega-3 Index, while not validated biomarkers, are well established correlates for many outcome measurements, like cognition. We recommend the inclusion of cognition studies with a measurement of EPA and DHA. Low EPA and DHA status has been shown to correlate with cognitive deficits. Minimally, this type of research should be acknowledged in “Suggestions for Future Research”. Below is a non-exhaustive list of studies which include a measurement of EPA and DHA and associated cognitive status. [See supplemental material for list of 7 articles.]	Thank you for the comment. Since we did not delve in great detail into the type of research that might be recommended for each intervention type, we have let the reviewer’s letter serve as the suggestion for future research.
Results - Diet			No comments received for this section.
Results - Multimodal	Peer Reviewer #1	Page 103, Line 16: the FINGER study note is an example of not having the outcomes that are among the key questions. [See General Comments section]	It is true the FINGER study did not have diagnostic incidence outcomes. However, the cognitive performance outcomes were part of the Key Questions.

Research Review Section	Reviewer, Affiliation	Comment	Response
Results - Multimodal	Public Reviewer Michelle Carlson, John Hopkins University	<p>The review of multimodal intervention trials was incomplete, particularly with regard to those targeting "social engagement" for which authors identified only two studies, placed in the "Other Intervention" category. For example, results from the SYNAPSE trial (Park et al., 2014) were not considered. If included, they would likely have been viewed as being at high risk of bias along with many other multimodal trials. Of the three published studies observing cognitive and brain benefits following participation in the multimodal Experience Corps program (Carlson et al., 2008; Carlson et al., 2009; Carlson et al., 2015), only the first of these studies was identified in the review and deemed as being at high risk of bias (Carlson et al., 2008). Unfortunately, results from the most recent neuroimaging intention to- treat (ITT) trial (N=111) were not identified or considered. As a result, the aggregate pattern of beneficial effects that have replicated over three separate study samples and three different modalities- cognitive, fMRI, and structural MRI- was not given adequate consideration. Briefly, results from the Baltimore Experience Corps Trial's Brain Health Study revealed program-specific increases in cortical and hippocampal volumes by the second year that were greater in men than in women. These results suggest that multimodal activity embedded within a social health promotion program forestalled and possibly reversed age-related declines in annual rates of atrophy. These findings are the first from a RCT of a multimodal activity intervention to show age-related brain plasticity in the hippocampus, a region important to memory formation and risk for Alzheimer's disease.</p>	<p>Thank you for the comment. Carlson 2009 was identified in our search and screened out because no outcomes of interest were reported. Eligible studies assessed as high risk of bias (Carlson 2008) were not analyzed because we had little confidence in their results resulting from the way the study was conducted.</p> <p>While our search did not identify Park 2014, we did screen it upon request and it was excluded for inadequate follow-up time. Post-intervention outcomes appear to be measure after the 3 month intervention (our review required 6).</p> <p>Carlson 2015 does appear to be eligible, but would be assessed as high risk of bias due to the high attrition rate and lack of appropriate methodology to account for the missing data and the selective analysis (by sex only).</p>

Research Review Section	Reviewer, Affiliation	Comment	Response
Results - Multimodal	Public Reviewer Michelle Carlson, John Hopkins University	Additional References: Carlson MC, Kuo JH, Chuang YF, Varma VR, Harris GC, Albert MA, Erickson KI, Kramer AF, Parisi JM, Xue QL, Tan EJ, Tanner EK, Gross A, Seeman TW, Gruenewald TL, McGill S, Rebok GW, Fried LP. Impact of a multi-modal intervention on brain volume: the Baltimore experience corps trial brain health study. <i>Alzheimer s & Dementia</i> . 2015 Nov;11(11):1340-8. doi: 10.1016/j.jalz.2014.12.005. Epub 2015 Mar 31. Carlson MC, Erickson KI, Kramer AF, Voss MW, Bolea N, Mielke M, McGill S, Rebok GW, Seeman T, & Fried LP. Evidence for Neurocognitive Plasticity in At-risk Older Adults: The Experience Corps Program. <i>Journals of Gerontology: Biological Sciences and Medical Sciences</i> . 2009; 64(12):1275-82. PMID: 19692672. Park DC, Lodi-Smith J, Drew L, Haber S, Hebrank A, Bischof GN, et al. The impact of sustained engagement on cognitive function in older adults: the Synapse Project. <i>Psychol Sci</i> 2014;25:103 12.	Thank you for the comment. Carlson 2009 was identified in our search and screened out because no outcomes of interest were reported. Eligible studies assessed as high risk of bias (Carlson 2008) were not analyzed because we had little confidence in their results resulting from the way the study was conducted. While our search did not identify Park 2014, we did screen it upon request and it was excluded for inadequate follow-up time. Post-intervention outcomes appear to be measure after the 3 month intervention (our review required 6). Carlson 2015 does appear to be eligible, but would be assessed as high risk of bias due to the high attrition rate and lack of appropriate methodology to account for the missing data and the selective analysis (by sex only).
Results - Hormone	Peer Reviewer #1	Soy and soy protein are included in this section, but in fact soy is not a hormone by any stretch of the imagination. That needs to be corrected. In fact, there is a general issue of combining other hormones and hormone therapies into one section. The real hormones are very different from each other, and other than the name, they don't have that much in common. For example, see Page 126, Lines 6-11.	Thank you for the comment. We have left soy and soy protein in the chapter since women often view the use of soy's phytoestrogens as an alternative to hormone therapy.
Results - Vitamins	Peer Reviewer #1	Other than what is noted above about B vitamins, one problem with this section on Vitamins is that multivitamins have many compounds in them, nutritional and otherwise, and they are not the same as each other. This needs to be clarified in the relevant text.	Thank you. We have explicitly stated which specific vitamins and minerals comprised the multivitamins analyzed
Results - Vitamins	Peer Reviewer #1	There is a reference to "Chapter 14," but none was sent to me. Where is it?	Thank you for noting this. This was typo carried over from an earlier version of the report. The correct chapter, Chapter 4K, is now noted.

Research Review Section	Reviewer, Affiliation	Comment	Response
Results - Vitamins	Public Reviewer Dan Blazer, Duke University	The description of studies of Vitamin B need to be more specific, namely in text and tables separate B12, B6, etc. At some points they do but in others it is not clear.	Thank you. We have revised this to name each B vitamin explicitly throughout Chapter 4G and Appendix L.
Results – Antihypertension	Peer Reviewer #1	Page 145, Line 17: There is a mistake in this bullet.	Thank you. The bullet has been revised.
Results – Antihypertension	Peer Reviewer #1	Page 159, Line 15. If the study didn't have the needed outcomes, why was it mentioned in this section.	We believe the reviewer is referring to our statement about the Williamson study that compared intensive versus standard antihypertensive medication treatment: “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.” In our revised report, we deleted this reference to the MRI results, but retained the text on the cognitive performance test outcomes, for which attrition was less than 20 percent.
Results – Lipid Lowering Drugs	Peer Reviewer #1	Page 162, Line 34. Why are you reviewing a report that only has intermediate outcomes?	Thank you for the question. The scope for this report, arrived at through a consensus process with the NIA and IOM, included intermediate cognitive outcomes.
Results - NSAIDs			No comments received for this section.
Results – Anti-dementia			No comments received for this section.
Results – Diabetes Management			No comments received for this section.
Results – Other Interventions			No comments received for this section.

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Research Review Section	Reviewer, Affiliation	Comment	Response
Results – Biomarker/ Cognitive Performance Agreement			No comments received for this section.
Discussion	Peer Reviewer #1	Page 197, Line 21. This contention about Vitamin B12 may be incorrect. This is used orally in very high doses because of can override the lack of absorption.	Thank you for the suggestion. We have revised the Discussion section to note “For B ₁₂ these higher doses could overcome malabsorption problems.”
Discussion	Peer Reviewer #2	Implications of the major findings are clearly stated. Limitations of examined studies are presented in a systematic way in the results section. A separate section on limitations of this review itself is included. Most important literature is included in the discussion.	Thank you for the comments.
Discussion	Peer Reviewer #2	The inclusion of prospective cohorts - observational studies that use tools to simulate quasi-experimental design is not clearly justified. Which and how many of these studies are actually included in the analyses? Examples should be provided.	Thank you, we have revised Types of Studies section to read: “Prospective cohort studies: studies that categorized but do not assign an intervention; these frequently rely on self-reported outcomes of the intervention’s impact. (Unfortunately, no studies that used analytic tools to simulate quasi-experimental design and address selection bias in order to test causality were identified in the searches.)”
Discussion	Peer Reviewer #2	It is generally accepted that the burden of evidence lies at the intervention side. On the other side, although implied, it should be more clearly stated that absence of evidence does not necessarily mean evidence of absence.	Thank you, we have revised the Limitations section to read: “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.”

Research Review Section	Reviewer, Affiliation	Comment	Response
Discussion	Peer Reviewer #3	Overall the major findings and implications are stated clearly. The summary figures (e.g., 5.1) are a gallant effort to show the key findings pictorially but I'm not sure the juice is worth the squeeze. Anything that requires a paragraph to explain and an entire table to give the key is of questionable value, particularly when it is just another way of saying most studies show no effect (and not weighting by ROB).	Thank you for the comment.
Discussion	Peer Reviewer #3	Minor quibble: page 197 of 230, lines 40-41: Grade no longer incorporates whether results are likely to be overturned in future research as part of the SOE definition.	Thank you for the comment. We used the AHRQ EPC's criteria for assessing the strength of evidence.
Conclusion	Peer Reviewer #3	I liked that you broke out the conclusion and future research as separate chapters.	Thank you for the comment.
Suggested Research	Peer Reviewer #1	Page 206, Line 28. You should refer to the NIH Toolbox, which has standard measures.	Thank you for the suggestion. We have added mention of the NIH Toolbox in the Measures section.
Suggested Research	Peer Reviewer #2	The future research section is quite extensive and taps on many methodological issues of the field. At the same time, suggestions for future research seem quite restrictive. It is understandable to recommend against research that has been shown non effective. But it is not prudent to do the same for areas with observational studies and lack of interventional studies (i.e. nutrition).	Thank you for the comment. Our suggestions are based on the literature that was examined for this review. We did not comment on areas that lacked interventional studies.
Suggested Research	Public Reviewer Harry Rice, Global Organization for EPA and DHA Omega-3s (GOED)	GOED believes it is a disservice not to recognize the potential cognitive benefits of EPA and DHA by not suggesting future research for these fatty acids.	Thank you for the comment. We will let the reviewer's submitted letter, made available here as supplemental material, speak to future research suggestions specific to this one potential intervention.
Figures/ Tables	Peer Reviewer #1	In general, I found the study tables tough to read; they might be made more user friendly.	Thank you for the comment. The Results Summary tables, in particular, have undergone some revision to hopefully improve their readability.

Research Review Section	Reviewer, Affiliation	Comment	Response
Figures/ Tables	Peer Reviewer #2	Many tables and figures have been included; they all present data in detail and seem useful as references but are somehow not easy to grasp and absorb without very careful inspection. A more visually friendly graphical presentation of results would be ideal.	Thank you for the comment. It is indeed difficult to reach ideal graphical presentations that balance summary level and detail.
Figures/ Tables	Peer Reviewer #2	The use of symbols in page 172 and on should be better explained. For example do they refer to cognitive tests or dementia/MCI? If the latter then how in Table 5.1 there are more symbols than number of studies?	Thank you for the comment. We have tried to provide explanations to assist with understanding the graphics.
References			No comments received for this section.
Appendix			No comments received for this section.
General	Peer Reviewer #1	This is a rough draft and has typos, and needs some organization in places, but these can be corrected. It certainly needs more scientific as well as copy editing.	Thank you, the report has undergone a thorough editing before publication.
General	Peer Reviewer #1	Page and chapter numbers unclear and need better organization.	Thank you, the report has undergone a thorough editing before publication.
General	Peer Reviewer #1	Appendices were not provided, so a detailed review of methodology was not possible.	Thank you for the comment.
General	Peer Reviewer #1	I may have missed it, but despite the use of the word "Prevention" in the title, there are many important dimensions of prevention related to cognitive performance that are not considered, many related to public health. For example, this might include protecting workers from agricultural pesticides, keeping lead out of the drinking water, the long term effects of psychotropic drugs used to treat mental illnesses or using condoms to prevent transmission of HIV.	Thank you for the suggestions. We focused the report on prevention interventions, and as such does not focus on risk factors. We have revised the Scope section to state this explicitly.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Peer Reviewer #1	You have sections in the various chapters on the “logic of the intervention.” I thought about this a lot, and I don’t have an easy answer for this, but I’m worried about them because they are often gratuitous and not well explained in research proposals or papers. Some general biological notions such as “stress,” or “oxidation” or “inflammation” are not well characterized and basically, they are largely irrelevant to the trials because these trials per se don’t provide mechanistic answers anyway. I’d urge you to be careful with this. Some analysis of the “logic” themes might be of interest some time, but not now. Otherwise, you should impanel a group of basic scientists who can interpret these for you.	Thank you for the comment. We have discussed this dilemma as well and decided to leave the sections in at this very high level for the benefit of readers with less exposure to particular interventions or dementia in general, while also keeping the sections brief and high level. We certainly hope that users of the material with more experienced or nuanced views would rely on the greater knowledge available elsewhere.
General	Peer Reviewer #1	Some studies have many cognitive test outcomes, and it appears that some were “cherry-picking” the results. Did you check each study for multiple outcomes? (Bonferroni)	Most were not significant even without Bonferroni corrections. We did check studies for selective outcome reporting (noting when the reported outcomes did not match outcomes listed in protocols or methods sections).
General	Peer Reviewer #1	Some of the discussions of the studies seem to trip a bit over directionality of findings (e.g, either “favorable” or not significant). The obvious assumption is that unless other specified, that you’re talking about “good” outcomes, but that isn’t always clear. Is a significant “bad” outcome of a cognitive test in a study an adverse event?	Thank you for the question. We note in the Results Summary tables in each results section if the control group performed better than the intervention group (“bad” outcome of a cognitive test).
General	Peer Reviewer #1	One important area not discussed much as far as I can see is the impact of co-morbidity on intervention outcomes. Most older people have comorbid conditions, including mental illnesses other than depression, and many trial participants are likely to have them; few are totally “healthy.” Why were they not considered? I understand that it possible that the bias evaluation might include the issue, but that needs to be discussed, in my view.	This comment raises a valid point. Unfortunately, most studies provided little information on co-morbidities and none used them in their analysis. We have added a recommendation about addressing them in the discussion: Subsequent studies should take greater cognizance of comorbidities and address them as confounders in their analyses.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Peer Reviewer #1	You refer in several places to “vitamin B,” but in fact, that is a really a group of vitamins (as you note in some of the interventions); that needs to be changed as it looks naïve.	Thank you, we have changed this to either “B vitamins” collectively or named each B vitamin specifically studied.
General	Peer Reviewer #1	If cleaned up, this review can be important for assessing the state of the art in intervening for preventing advancing cognitive impairment and its clinical manifestations, and the work that went into it was appreciated.	Thank you for the comment.
General	Peer Reviewer #1	See my general comments. There are still a number of issues that need to be clarified, as well as making the document more user-friendly. When that is done, it will be much more relevant both to research and decisions in clinical practice.	Thank you for the comment.
General	Peer Reviewer #2	This is a very useful and clinically meaningful report. The target population and audience to whom it is addressed could be more explicitly defined. The central theme of this review is the efficacy of interventions targeting modifiable factors that may affect rates of cognitive decline and conversion to dementia and MCI. Specific key questions around this main theme are clearly appropriate and stated with clarity and in an explicit way.	Thank you for the comment. The target user for the report is noted in the report preface.
General	Peer Reviewer #2	The report is in general well-structured and organized. Main points are clearly presented. A more visually friendly graphical presentation of results would be ideal. Clearly both the report and conclusions deriving from it are very relevant not only to policy but also to practice decisions. They do not necessarily contribute new information but they provide an important global picture, thus increasing understanding in the field.	Thank you for the comment.
General	Peer Reviewer #3	This is a comprehensive report that examines a broad range of potential interventions that potentially could slow cognitive decline. The report is well organized and generally written clearly. However, due in part to its length, key messages can sometimes be obscured.	Thank you for the comment. We have tried to make the key messages more prominent by including an Executive Summary in the final version.

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Research Review Section	Reviewer, Affiliation	Comment	Response
General	Peer Reviewer #3	Data are synthesized qualitatively, which seems appropriate, but this sometimes leads to long sections discussing studies individually and simple “vote counting” for the synthesis. With the notable exception of the ACTIVE study, there isn’t a clear approach to weighting larger, higher quality studies more strongly in the syntheses. The report would be strengthened by a clearer delineation of the approach to qualitative synthesis and a stronger link between the methodological approach and results reporting.	Thank you for the comments. Since we included only low or medium risk of bias studies in the analysis, the analysis is by default weighted by the higher quality studies. Most findings that reached a level of at least low strength of evidence (in fact, the vast majority were low strength of evidence) were based on only one or two contributing studies, so a more specific weighting method would imply more precision than we in fact could apply.
General	Peer Reviewer #3	For all key messages, state explicitly which group(s) [i.e. normal cognition vs MCI] they apply to and where possible, the “dose” of the intervention and timeframe for the outcomes.	Thank you for the suggestion. We have revised the key messages to provide more information where appropriate.
General	Peer Reviewer #3	The general organization of the results sections is effective, but the results are lengthy and somewhat overwhelming. Where possible, use more summary and less detail (or put the detail in appendices).	Thank you for the suggestion. We approached each results section as stand-alone chapters and included some level of detail thought important to readers who would focus on those specific interventions.
General	Peer Reviewer #3	The report is well organized. The executive summary and subsequent journal version will be key to dissemination as few individuals will have the time and patient to wade through such a lengthy report. The key implications relate more to future research than any actionable clinical/health policy recommendations.	Thank you for the comment.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public Reviewer Andrea Bozoki, Michigan State University	My major concern with this paper is the conflation of studies aimed at producing an acute improvement with studies whose aim is to allay or prevent decline over time. For reasons of expediency, the vast majority of studies in the area of age-related cognitive decline have taken a short-term approach; studies with long term follow up are rare, and studies whose primary aim is actually prevention are even rarer. This is not made clear anywhere in the review; indeed the review does not categorize or group studies based on duration of the intervention or of follow-up. Please note that the very title of the paper is misleading in this respect, as most clinicians and scientists would not interpret the word "prevent" (or "delay" for that matter) as referring to short-term (1 year) follow-up periods at all, as the biological meaning of those words implies a structural or functional change in the brain that is simply not possible to demonstrate non-invasively with follow-up periods that brief. I recognize that it would require a major overhaul of the paper's structure to systematically address this concern, but I believe it would yield a more useful framework for researchers hoping to find evidence to support or refute a potential target for further studies. It is quite likely that the set of interventions that can allay (prevention seems a very aspirational goal) cognitive decline is quite distinct from those that can yield short-term gains in cognitive function.	We tried hard to avoid acute improvement studies, hence the six month rule. The basic premise, used in many studies of chronic diseases, is that effects need to be sustained. Six months may be arbitrary but it seems much more reasonable than six weeks. We have made some allusions to shorter studies to offer a more nuanced outlook.
General	Public Reviewer Dan Blazer, Duke University	to reinforce what I wrote before. I think the report could benefit from a more clear statement of why studies were excluded. They do a good job with their description of how bias was rated. We must also recognize that this review will go against some well "established" views in the field, such as the benefit of aerobic exercise. will make for some very interesting discussions.	As we noted previously, studies that passed all inclusion criteria, including study design, were then subjected to risk of bias assessment. Eligible studies assessed as high risk of bias were not analyzed because we had little confidence in their results resulting from the way the study was conducted.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public #5	<p>I am a physical therapist, experienced in both basic science and clinical research in the area of neuroscience. I am a professor at UCSF and see elderly patients and individuals post neurological trauma and chronic neurological and musculoskeletal diseases. I work in a health and wellness setting. The evidence in support of exercise as the best medical treatment to maintain cognitive skills, physical independence, community participation and quality of life despite aging or chronic disease. The evidence in support of continued learning and physical exercise to maintain the health of our nervous system and our musculoskeletal system is impressive. The evidence is also strong that physical immobility, depression, excessive medications and lack of social engagement is the formula to imbalance, falls, loss of independence and dementia. At a time when we have a growing population of elders, it is surprising that you would have such a negative review of the effectiveness of exercise and cognitive training to maintain the plasticity of the brain over the life span. It is particularly important to apply the concepts of neural plasticity to keep our elders at the top of their game. While I believe there was some good intent in the purpose of this review of the literature, there were some limitations that should be addressed before sharing the conclusions.</p>	<p>Thank you for the comments. While we value clinical insights, this review was based on published trials.</p>
General	Public #5	<p>First, I was surprised that there were a limited number of experts in neuroscience included as consultants in this review. Neuroscience experts in basic, clinical and epidemiological research should be included as well as those experienced in the care of elderly individuals with and without disease.</p>	<p>Thank you for the comments. We agree, and team members did include neuropsychologists and geriatricians.</p>

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public #5	<p>Second, I am surprised that the reviewers fail to realize that randomized controlled trials have serious limitations from a clinical perspective. There is no such thing as an average patient who is aging or has a chronic neurological or musculoskeletal condition. Learning activities must be to each individual to engage that individual to be motivated, compliant with recommended activity programs and expect to experience measurable gains in performance. When a standardized behavioral intervention is required rather than simply taking a prescription drug, the program must be sensitive to each individual. More innovative designs such as those with delayed starts or those which include multifactorial, progressive behavioral interventions that include and confirm education, nutrition, life style changes, sleep and specific behavioral training paradigms targeting fall prevention, physical abilities, sensory processing, attention, memory and cognition while monitoring falls, health care utilization, community participation, quality of life, physical independence (e.g. need for help with self care and community activities).</p>	<p>Thank you for the comments. We are very aware of the limitations of RCTs, especially with regard to subgroup analysis. We comment on this in the discussion section. Likewise, steps to promote adherence and tailor interventions are necessary. However, RCTs do provide a study design that can address questions of causality beyond association. We would have accepted other innovative study designs mentioned had they been identified in the searches and conducted in a robust manner.</p>
General	Public #5	<p>Third, the report does not consider the brain as an organ. There is a significant body of literature relating to specific forms of intensive engagement (brain training) to the physical status of the brain as an organ.</p>	<p>Thank you, we did look at studies that addressed intermediate outcomes such as brain volume or other structural changes if the study duration was at least 6 months.</p>
General	Public #5	<p>Fourth, the report confuses healthy exercises that combine cognitive training and brain games rather than brain exercises to improve physical/functional brain health. Throwing them into the same basket with the implication that they are the same thing is (always has been) just plain wrong. Scientists that understand different aspects of the relationship between perceptual or cognitive ability and the physical and functional health of the brain.</p>	<p>Thank you for the comment. We were subject to what was available in the literature and how the studies were presented. The investigators chose the exercises. We sought to identify which ones worked best for whom. In many cases, the studies did not provide enough basis for this analysis. Nor did the study investigators necessarily note this more nuanced approach.</p>

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public #5	Fifth, the conclusions dismiss the fundamental translational research about brain science. This suggests that agencies such as NIA, NINDS and the other half-dozen government agencies who support studies related to adult brain health is useless. This suggests money was wasted and nothing was proven. Perhaps we should close the doors of these wasteful agencies or perhaps withdraw grant support for the 99 out of 100 scientists in our field who fail to meet the standards espoused here as requisite for taking their science seriously.	Thank you for the comment.
General	Public #5	Sixth, criteria for inclusion of studies are in several important respects arbitrary and unsupportable. To cite one example, if a study is shorter than 6 months, the reviewers argue that the study cannot be regarded as proving anything. The fact that individuals may not be able to stick with an effective intervention over time is a great frustration. That does not mean the intervention is not effective. It simply means the individual might prefer to drink sodas, eat candy, sit and watch TV and take pills rather than engage in positive nutrition, attentive, energy consuming activities designed to improve physical, sensory, cognitive and mental status. The reviewers seem to throw out the evidence that shows convincingly that training in the right forms has substantial far-transfer benefits.	Thank you for the comment. While there is no gold standard for study duration of a chronic condition, six months has been widely used. The intent is to identify sustained effects. If volunteers for an experimental study are not motivated to adhere to an intervention for the time period hypothesized to be necessary for good outcomes, the net result is still a lack of effect.
General	Public #5	Seventh, this review specifically excluded input from individuals from the commercial side who have been dedicated to discover technology to allow home training to deliver help maintain the independence of our older citizens. Most NIH policy-setting activities involve academic researchers, advocacy organizations, policy groups, patients themselves, and industry representatives. Everyone should have input into the process, so that the outcome is respected by everyone.	Thank you for the suggestion. The make-up of the advisory panel was determined by the purpose of and funding for the report. The report itself is not a policy-setting activity, but an information source. The purpose of the process as established was to support the independence of reviewers and the robust methods as established by the AHRQ EPC program.

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Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public #5	<p>Eighth, this report appears to be designed to minimize the opportunity to help our increasing number of elders have access to current effective clinical education and activity programs to support maintaining independence. Rather, this report minimizes the opportunities for individuals to pursue healthy activities to maintain physical and cognitive health. Rather, the report seems to support what the CDC considers the most important, negative health condition of physical immobility. Thus, more of our elders will be forced to accept declining physical independence, unnecessary injuries from falls and ultimately the dependency on others. This dependency unnecessarily increases the costs of health care for society and our elders. Now, instead of enjoying life in one's own home, these elders will need board and care or skilled nursing facility services because they can no longer care for themselves because of physical weakness, sensory losses, risks of falling, depression and dementia. Young families will not be able to assume the responsibility for their elder parents because they are trying to work and raise their own young families.</p>	<p>Thank you for the suggestion. The make-up of the advisory panel was determined by the purpose of and funding for the report. The report itself is not a policy-setting activity, but an information source. The purpose of the process as established was to support the independence of reviewers in examining the available evidence using the robust methods as established by the AHRQ EPC program.</p>
General	Public #5	<p>Ninth, this report provides almost no help for people in need. Really, doing nothing for our elders is the equivalent of doing harm. Every person who could benefit from the good and valid science on plasticity will have minimal if practical guidance on how to benefit from applying the principles of plasticity to maintaining health, wellness, productivity and independence.</p>	<p>Thank you for the comment. We hope this report will help people make more informed decisions about what steps to take. Unfortunately we do not yet have strong evidence for interventions.</p>

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public #5	Tenth, the literature review of computerized brain training opportunities is lacking. The reviewers conclude that "transfer to other domains was rare" despite that fact that there are more than a hundred published papers showing such transfer in healthy aging and MCI alone. Some of these studies are listed at a public reference library for computerized cognitive training publications that is hosted by a company called Positscience at https://www.zotero.org/groups/cognitive_training_data/ .	Thank you, the report did include a full table (Table 4A.5) on IADL outcomes. We have also provided brief commentary on several other 6-week studies on IADL outcomes to provide context.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public #5	<p>In Summary Please rethink how you are interpreting the findings from this review. There are minimal risks of exercise and cognitive training. We know we need to improve information on dosage and strategies of neurological retraining paradigms to maximize recovery of function and maintenance of function with aging. Physical activities, community participation, social engagement and cognitive training are all better approaches to managing aging and chronic disease and impairments than prescription drugs. I remember almost 20 years ago the Surgeon General said that if individuals would increase their exercise levels (cardiac, strengthening, flexibility and balance), individuals would need fewer medications for high blood pressure, heart disease, diabetes etc. In addition, it would reduce the risks of cancer and chronic kidney disease. This is even more true today. The guidelines from the Center of Disease control now recommend that everyone, young and old need between 120 and 300 minutes of exercise a week to stay healthy. Unfortunately, the CDC does not address what individuals need to do to maintain attention, cognition and memory despite aging. It will be necessary to add appropriate nutrition, getting adequate sleep, managing stress, avoiding smoking, being productive and having fun and feeling positive about oneself. In the future, I believe the CDC will encourage individuals to endeavor in cognitive training during physical training with increased emphasis on doing several tasks simultaneously. The publication of this review in its current state may cause more harm than good. All clinicians and researchers need to continue to develop programs to maximize plasticity and minimize the deterioration of aging. This endeavor to support ongoing learning behaviors and physical activities throughout one's life is not like playing football where 100% of players will suffer a concussion injury. Interestingly, individuals</p>	Thank you for the comment.

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Research Review Section	Reviewer, Affiliation	Comment	Response
General (continued)	Public #5 (continued)	still strive to play football, successful football players especially in the NFL earn a lot of money to play and the world loves to watch the game despite the violence of the sport and the serious injuries. Unfortunately, with aging, society is watching these professional football players become depressed, poverty stricken, physically and cognitively impaired with a high rate of dependence, criminal offenses and suicide. The reviewers preparing this document to share need to carefully consider the limitations of their review and the negative influence it will have on society in terms of decreasing health, wellness and independence of our elderly and those with chronic disease or impairments. This report is very likely to increase costs of health care to maintain dependency of our aging population with chronic disease. This is a terrible outcome given the projected proportion of elderly in society.	
General	Public Reviewer Harry Rice, Global Organization for EPA and DHA Omega-3s (GOED)	The Agency for Healthcare Research and Quality (AHRQ) is to be commended for its efforts in compiling and analyzing vast amounts of data.	Thank you for the comment.
General	Public Reviewer Harry Rice, Global Organization for EPA and DHA Omega-3s (GOED)	The page numbering in the Contents is incorrect. For example, the Contents indicates that Chapter 4C. Results: Nutraceutical Interventions begins on page 56, but it really begins on page 50.	Thank you, the report has undergone a thorough editing before publication.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public Reviewer Michael Merzenich, University of Florida	<p>The National Institutes of Aging had a great notion when they fostered a review (“Interventions to Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer’s- Type Dementia”) designed to help medical professionals guide our older citizens to the adoption of life strategies (diet, exercise, cognitive training, meditation, et alia) that positively support their brain health and older-age wellbeing.</p> <p>Alas, this is another instance in which the best of intentions can go substantially awry. [See supplemental materials for the reviewer’s full letter.]</p> <p>I could make quite a number of critical comments about the overall document—which offers limited valid help for any medical professional, legislator or citizen for defining what they should be doing to best sustain their brain health and personal vitality in the latter decades of life—but I’m going to limit my remarks to the “cognitive training” part of this report. [See supplemental materials for the reviewer’s full letter.]</p>	Thank you for the comments.
General	Public Reviewer Michael Merzenich, University of Florida	First, rather astonishingly, it almost completely lacks any consideration of the brain as an organ. Since its real subject is organic brain health, this would seem to me to be a rather significant oversight. [See supplemental materials for the reviewer’s full letter.]	Thank you for the comment. We respectfully suggest that such a complex topic as dementia is benefits from many approaches. We do consider the brain as an organ through the inclusion of several of intermediate outcomes.
General	Public Reviewer Michael Merzenich, University of Florida	Second, the report once again fails to distinguish brain health exercises from “cognitive training” or “brain games”—indeed, appears blind to the fact that the former category actually exists. [See supplemental materials for the reviewer’s full letter.]	Thank you for the comment. Brain health is a concept open to different interpretations. If the commentator means “delays dysfunction”, we have tried to address that. What is training and what are games is again a subject for the beholder. We tried to define the intervention trials without labeling them.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public Reviewer Michael Merzenich, University of Florida	Third, the NIA adopted what in my view was a peculiar strategy for assuring objectivity, by engaging ARC to organize a review process that specifically excluded expert-scientist involvement. [See supplemental materials for the reviewer's full letter.]	The underlying goal was to bring objectivity to bear. We have benefitted from feedback from many people like yourself.
General	Public Reviewer Michael Merzenich, University of Florida	Fourth, the report comes to a major, damning conclusion about fundamental and American and international translational research related to brain science. [See supplemental materials for the reviewer's full letter.]	Thank you for the comment. Our task was to weigh the evidence impartially.
General	Public Reviewer Michael Merzenich, University of Florida	Fifth, criteria for inclusion of studies are in several important respects arbitrary and unsupportable. To cite one example, if a study is shorter than 6 months, the reviewers argue that it cannot be regarded as proving anything. [See supplemental materials for the reviewer's full letter.]	Dementia is a chronic disease. Hence, any substantial effects need to be sustained. Short followups may be helpful to propose effects but they do not establish them. Obviously long followups raise design issues around attrition.
General	Public Reviewer Michael Merzenich, University of Florida	Sixth, why did this review specifically exclude input from individuals who are dedicated, from the commercial side, to delivering help to our older citizens? [See supplemental materials for the reviewer's full letter.]	The make-up of the advisory panel was determined by the purpose of and funding for the report. The report itself is not a policy-setting activity, but an information source. The purpose of the process as established was to support the independence of reviewers in examining the available evidence using the robust methods as established by the AHRQ EPC program.
General	Public Reviewer Michael Merzenich, University of Florida	Seventh, this report provides almost no help for people in need. [See supplemental materials for the reviewer's full letter.]	Thank you for your concern. We certainly want to help people, but the first step is to assess the quality of the evidence. One can argue that unproven interventions that cause no harm are worth trying but they do typically cost money.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public Reviewer Michael Merzenich, University of Florida	Eighth, the literature review of computerized brain training in this report is severely lacking. The reviewers inexplicably missed quite a few papers, and they conclude that "diffusion [transfer] to other domains was rare"—despite that fact that there are more than a hundred published papers showing such transfer in healthy aging and MCI alone. [See supplemental materials for the reviewer's full letter.]	We respectfully disagree. The established inclusion criteria were applied to all publications identified using the search algorithm supplied in Appendix A. We also screened all studies that any reviewer suggested were incorrectly excluded. The vast majority of these were not eligible. The most frequent reason was inadequate follow up time (i.e. less than 6 months). [See supplemental materials for reasons for exclusions for any reference supplied by a reviewer.] Any studies that met eligibility criteria were incorporated into our review.
General	Public Reviewer Michael Merzenich, University of Florida	Ninth, why HAVE a 'open comment' period, when almost no one in our field is aware that this review has been written—much less "open", for a brief post-draft-publication period, "for comment". Where and when did you inform people about this? [See supplemental materials for the reviewer's full letter.]	Thank you for the comment. AHRQ's process for soliciting public comments for EPC reports has been used for 8 years.
General	Public Reviewer Michael Merzenich, University of Florida	As I understand your process going forward, you'll now convey this report draft and this feedback to the NAM. [See supplemental materials for the reviewer's full letter.]	That is correct. This report is designed to stand on its own merits as well as providing input to the NAM committee.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public Reviewer Ball, Marsiske, Rebok, & Willis, ACTIVE study investigators	We are four of the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Study Principal Investigators (Ball, Marsiske, Rebok, Willis). With this brief comment, we wish to express our thanks to the National Institute on Aging and the Agency for Healthcare Research and Quality for commissioning and overseeing the systematic review on “Interventions to Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia”. We thank the National Academies of Sciences, Engineering, and Medicine (the National Academies) for convening an expert committee to make recommendations, and we thank the Minnesota Evidence-based Practice Center (EPC) for their voluminous review of the relevant prevention and intervention literature. In this comment, our goal is to highlight a few features of the ACTIVE study that we believe deserve emphasis and also to finish with a few “reframing ideas” that hopefully will inform future scholarship on cognitive interventions with older adults. [See supplemental materials for the reviewer’s full letter.]	Thank you for your interest.
General	Public Reviewer Ball, Marsiske, Rebok, & Willis, ACTIVE study investigators	There are several areas of the systematic review (AHRQ, 2016) that may benefit from broader conceptualization. First, we suggest that the reviewers may have held a fairly restricted view of the meaning of “transfer” (in the report, described as “diffusion” and “spillover”). [See supplemental materials for the reviewer’s full letter.]	We have taken your comments into account and tried to expand the review to acknowledge work that did not meet selection criteria.

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public Reviewer Ball, Marsiske, Rebok, & Willis, ACTIVE study investigators	<p><i>Expanding the period of expected transfer to ‘legacy’ transfer.</i> In populations with delayed-onset outcomes, transfer may not be immediate. ...In support of the idea that training may have delayed “legacy” effects, and as expected in our initial conceptual model (Jobe et al., 2001), self-reported IADL limitation data at A5 and A10 suggested that members of trained groups did not improve on IADLS, but rather, declined at slower rates than untrained controls (Rebok et al, 2014; Willis et al., 2006. In situations where participants are at ceiling, it is impossible to see improvement at initial training; transfer may be observed at the point where decline becomes normative. [See supplemental materials for the reviewer’s full letter.]</p>	<p>We have specifically acknowledged IADL effects and the issues involved in merging short term effects with longer terms study results that reflect attrition. We have left the speculation and theorizing to others.</p>
General	Public Reviewer Ball, Marsiske, Rebok, & Willis, ACTIVE study investigators	<p><i>Attending to dosage.</i> In comparing different intervention modalities, it is important to pay attention to relative dosing and participant burden. [See supplemental materials for the reviewer’s full letter.]</p>	<p>The dosage question is indeed important. Unfortunately the boosters in ACTIVE were not provided to all randomized participants.</p>

Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public Reviewer Ball, Marsiske, Rebok, & Willis, ACTIVE study investigators	<p><i>Training effectiveness with cognitively impaired individuals.</i> One of the calls of the systematic review was for more interventions focused on risk cohorts – people at risk of imminent decline. In ACTIVE, while we did not initially seek to enroll cognitively impaired individuals, we did not exclude individuals who performed at low normal levels at baseline. In post-hoc analyses, using algorithmic classification of cognitive impairment (defined, largely, by being 1-1.5 standard deviations below average on multiple measures of an ability; Cook et al, 2013), we compared the training-related improvement of individuals who were cognitively low versus those who were not (Unverzagt et al, 2007). Looking specifically at those who were initially low in memory, we found that these individuals, while not profiting from memory training, evinced no difference in the magnitude of 2-year training gain and maintenance in the reasoning and speed of processing groups. Thus, our interventions continued to be effective for improvement in cognition (e.g. speed, reasoning for low-memory individuals. In contrast, low-memory individuals experienced substantially less improvement in memory training. [See supplemental materials for the reviewer’s full letter.]</p>	<p>Although the Cook and Unverzagt studies did not meet inclusion criteria, we have now briefly discussed the studies in the ACTIVE Trial section of Chapter 4A to provide further context.</p>
General	Public Reviewer Ball, Marsiske, Rebok, & Willis, ACTIVE study investigators	<p><i>Attrition leads to a positively selected subset of participants, but this positive selection largely operates at the population level, not the sample.</i> The increasing selectivity of the ACTIVE study (e.g., Rebok et al., 2014) due to attrition, which is true for most longitudinal studies of older adults (Chatfield, Brayne & Matthews, 2005), in part reflects death and illness that is occurring in the population at large. Thus, at least some of the selective sample loss represents a real aging phenomenon, and not solely a methodological artifact of longitudinal studies. [See supplemental materials for the reviewer’s full letter.]</p>	<p>We now provide a table of attrition for ACTIVE in Appendix F. At 10 years, death accounted for more like 25% of attrition.</p>

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General	Public Reviewer Ball, Marsiske, Rebok, & Willis, ACTIVE study investigators	<p><i>The impact of selective attrition, if any, can be assessed and statistically adjusted for.</i> Modern methods of handling missing data, in particular propensity score weighted analyses (in which participants who share features with participants who dropped out are weighted more highly in computation of estimates; e.g., used by Wolinsky et al., 2009 in ACTIVE) and missing data pattern mixture analyses (in which separate estimates are obtained for different groups with different dropout patterns, and then final estimates represent the weighted combination of different group patterns; Hedeker & Gibbons, 1997; used by Thomas and Marsiske, 2015 in ACTIVE) have not revealed substantial differences in rate of change patterns when selective attrition is accounted for. Moreover, when followup analyses are based on archival records (State motor vehicle records, Medicare claims databases), investigators are able to follow everyone until driving cessation/death, even if participants stop attending followup visits. Taken together, attrition may not be as destructive to drawing long-term conclusions as the current review suggests. [See supplemental materials for the reviewer's full letter.]</p>	Adjusting for attrition is usually more effective than adjusting for initial selection bias but it is imperfect. Last value forward works for benefits but not declines.
General	Public Reviewer Ball, Marsiske, Rebok, & Willis, ACTIVE study investigators	<p>Our commentary is aimed not at refuting or challenging the main conclusions of the systematic review. Instead, our intent with this comment is to (a) highlight key features and findings of the ACTIVE study for those who are unfamiliar with the study, (b) suggest that there may be some additional evidence, contained in studies not cited by the systematic review, that responds to some of the key questions to emerge from the review, and (c) to offer some alternative (and less pessimistic?) ways of considering several key methodological critiques of ACTIVE. [See supplemental materials for the reviewer's full letter.]</p>	We appreciate the spirit of these comments and have endeavored to offer a balanced perspective on the ACTIVE trial.

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General	Public Reviewer Henry Mahncke, Posit Science	I should note that this report finds insufficient or low evidence of efficacy for such widely recommended interventions as physical exercise, diet, mental stimulation, sleep, and socialization - each of which is currently recommended by the NIA* and the AARP†. This seems on its face, very odd. [See supplemental materials for the reviewer's full letter.]	Thank you for your concern. Unfortunately, based on this review, we do not believe the strength of current evidence supports extensive or enthusiastic recommendations.
General	Public Reviewer Henry Mahncke, Posit Science	First, the review suffers from very significant process problems in that 1) the reviewers actively chose to decline input from experts in the field of cognitive training during the review planning and initial data analysis process [See supplemental materials for the reviewer's full letter.]	Thank you for the comment. The make-up of the advisory panel was determined by the purpose of and funding for the report. The purpose of the process as established was to support the independence of reviewers and the robust methods as established by the AHRQ EPC program.
General	Public Reviewer Henry Mahncke, Posit Science	There was little or no notification that the draft review was complete and that a very time-limited comment period had begun, such that domain experts had very limited opportunity to contribute significant comments. [See supplemental materials for the reviewer's full letter.]	Thank you for the comment. AHRQ's process for soliciting public comments for EPC reports has been used since before 2006.
General	Public Reviewer Henry Mahncke, Posit Science	First, the strong conclusion from the review is that there has been little to no value to American taxpayers of NIA funded and organized research into how to maintain cognitive function in aging. Of course, I disagree with this conclusion - not only as it applies to brain training but also as it applies to other widely recommended interventions including exercise, diet, sleep, and socialization. I believe that NIA funded and organized research has driven important, actionable advances in this field, through ACTIVE, IHAMS, and many other studies. However, others may see this review as a verdict on the NIA's effectiveness over the past twenty years. [See supplemental materials for the reviewer's full letter.]	We respectfully disagree. This is not our conclusion. Science builds on the shoulders of others. However, more and better work remains to be done.
General	Public Reviewer Henry Mahncke, Posit Science	Second, this review will accelerate an existing trend to its final conclusion: lack of investment in science by venture investors and brain training companies. [See supplemental materials for the reviewer's full letter.]	Thank you for your concern. We cannot speak to the issues of venture capital for commercial ventures.

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Research Review Section	Reviewer, Affiliation	Comment	Response
General	Public Reviewer Henry Mahncke, Posit Science	Finally, the intent of the review is "to make recommendations that inform public health strategies and messaging on preventive interventions." The only conclusion possible from the draft review is that there are no such recommendations (I note that all other interventions are rated as even less supported by evidence than cognitive training). [See supplemental materials for the reviewer's full letter.]	Thank you for your concern. Unfortunately, we do not believe the strength of current evidence supports extensive or enthusiastic recommendations.
General	Public Reviewer Henry Mahncke, Posit Science	Finally, and most importantly, the <i>recommendations should incorporate a patient-centered approach</i> . Right now, there are a tremendous number of seniors who want to invest time and effort taking proactive steps to maintain their cognitive health. Those seniors deserve to know what is the best advice, given the evidence at this time, that the NIA and AHRQ can provide them - not at some point in the future when more research has been done - but <i>right now</i> . [See supplemental materials for the reviewer's full letter.]	Thank you for your concern. We appreciate the need for a patient-centered approach. This would include what outcomes are most salient.