Treatment for Mild Cognitive Impairment:
Systematic Review and Meta-analysis

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Methods (as per mini-protocol)

The protocol is registered with the International Prospective Registry of Systematic Reviews (PROSPERO #CRD42014015431)

Analytic Framework, Key Questions and Contextual Questions

Please see Figure 1 for Analytic Framework.

Key Questions

KQ1. Do pharmacological or non-pharmacologic interventions for Mild Cognitive Impairment (MCI) in community dwelling adults (≥65 years of age) improve: 1) cognition, 2) function, 3) behaviour, 4) global status, or 5) mortality?

a. How effective are the screening tools validated for Canadian populations (e.g. MoCA) in improving: 1) cognition, 2) function, 3) behaviour, 4) global status, or 5) mortality?

KQ2. What are the adverse events (AE) including serious (hospitalization or death) and psycho-social harms such as depression, lack of independence, etc. of pharmacological or non-pharmacologic interventions for MCI?

KQ3. What are the diagnostic properties of screening tools validated in a Canadian population of adults older than age 65?

a. What are the cut-offs for mild cognitive impairment in adults 65 years and over and how well they work (i.e. examine how well the screening tools differentiate between no cognitive impairment and mild cognitive impairment, and between mild and severe cognitive impairment).

Contextual Questions

CQ1. People's willingness to be screened for MCI and elements that factor into this decision process (I am willing because…; I am not willing because…)

CQ2. People's willingness to be diagnosed for MCI (i.e. interest in knowing the diagnosis if MCI was found (given available treatment options) and elements that are factored into this decision process (I am willing because…; I am not willing because…)

Search Strategy

Our search was based on the search conducted by the United States Preventive Services Task Force (USPSTF) for their 2013 systematic review entitled: Screening for Cognitive impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force.[1] We modified their strategy to narrow it to those with MCI. We searched Medline, EMBASE and the Cochrane Central

Register of Controlled Trials for the period of Dec 2012-Dec 2014. See Appendix A for full search strategy.

For the question on test properties (KQ3), a separate search, without date or language limits, was conducted in Medline, EMBASE and PsycINFO for test properties of the Montreal Cognitive Assessment (See Appendix B for full search strategy). In addition, a specific targeted search was also undertaken using Google Advanced, limited to Canada and with the search terms "(MoCA OR Montreal Cognitive Assessment) AND (cognitive OR cognition)."

For the contextual questions, we searched Medline and EMBASE from January 1, 2004 to December 8, 2014. The detailed search strategies can be found in Appendix C.

Study Selection

After removing all duplicates, citations found through our updated search, as well as citations from the USPSTF review[1] and a recent systematic review conducted by Tricco et al.[2], were uploaded to a web-based systematic review software program for screening.[3] The titles and abstracts of papers considered for the key questions and sub questions were reviewed in duplicate; articles marked for inclusion by either team member went on to full text relevance testing. Full text screening was done independently by two people with consensus required for inclusion or exclusion.

For citations located in the contextual questions search, title and abstract screening was done by two people. Full text screening and data extraction was done by one person. Results have been reported narratively.

Inclusion and Exclusion Criteria

Language
The published results of studies had to be available in either English or French.

Population
The population of interest for this review is community-dwelling older adults, average age 65 years or older diagnosed with MCI.

Excluded from this review are studies that focused on people institutionalized and people who reside in intermediate care facilities (i.e., rehabilitation centers or skilled nursing facilities).

Interventions
Pharmacologic interventions used to treat MCI for the purpose of preventing cognitive decline: approved drugs for use in Canada. Non-pharmacologic interventions aimed at patients MCI.

Study Design and Comparison Groups
Randomized controlled trials with placebo or usual care control groups.

Outcomes

Cognition: measured with Mini Mental Status Examination (MMSE) or Alzheimer's Disease Assessment Scale — cognition subscale (ADAS-CS).

Adverse Events: serious (i.e. hospitalization or death) and psycho-social harms (e.g. lack of independence, stress, depression, etc.).

For the outcome of Cognition, the intervention duration must be at least 6 months; there were no requirements for intervention duration for harms data.

Secondary outcomes
Function measured with Alzheimer's Disease Cooperative Study activities of daily living inventory (ADL); behaviour measured by Neuropsychiatric Inventory (NPI); global status measured by Clinician's Interview-based Impression of Change plus Caregiver (CGIC-MCI) and mortality.

Data Abstraction

Review team members extracted data about population, study design, intervention, analysis and results for outcomes of interest. One team member completed full abstraction, followed by a second team member who independently verified all extracted data and ratings. Conflicts were resolved through discussion or by a third member of the review team.

Assessing Risk of Bias

We used the Cochrane Risk of Bias tool to assess the quality of the included studies.[4] For the outcomes of cognition and serious adverse events we evaluated the quality of the body of evidence using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) method using GRADEPro software.[5, 6]

Strategy for data synthesis

For the continuous outcomes of benefit of treatment and management of mild cognitive impairment such as cognition, function, behavior, and global status, we utilized immediate post-treatment data and extracted data were meta-analyzed when appropriate. The DerSimonian and Laird random effects models with inverse variance (IV) method was utilized to generate the summary measures of effect in the form of mean difference (MD).[7] MD was calculated using change from baseline data [i.e., mean difference between pre-treatment (baseline) and post-treatment (final/end-point) values along with the standard deviation (SD) for both intervention

and control groups]. For studies that did not report SD, we calculated this value from the reported standard error (SE) of the mean, or from the 95% confidence intervals (CI) using equations provided in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions.[8] For studies that provided neither SD or SE for the follow-up data, we imputed the SD from either the baseline values or other included studies using recommended methods provided in Chapter 16.1.3.1 of the Cochrane Handbook for Systematic Reviews of Interventions.[9] The primary subgrouping in meta-analysis was based on intervention type. The Cochran's Q (α=0.05) was employed to detect statistical heterogeneity and I^2 statistic to quantify the magnitude of statistical heterogeneity between studies where I^2>50% represents moderate and I^2>75% represents substantial heterogeneity across studies.[10] Where meta-analysis was not possible the findings are provided in a narrative summary.

Results

Search Results

After removing duplicates, we uploaded 403 unique citations from our search, as well as 163 unique citations from the USPSTF review[1] and the Tricco et al. systematic review[2] to DistillerSR[3] for screening at title and abstract. We excluded 429 articles at title and abstract, leaving 137 to be reviewed at the full text level. At this level we identified 22 systematic reviews and excluded 98 studies. We identified no additional studies through a handsearch of the included studies lists of 22 relevant systematic reviews. We included 17studies. Please see PRISMA 2009 Flow Diagram – Treatment for details.[11]

In our search for test properties data, we uploaded 292 unique citations after removing duplicates to be screened at title and abstract. We excluded 267 articles at title and abstract, leaving 25 to be screened at full text. After exclusions at full text, we included 2 studies on test properties. The findings from these studies are reported narratively. Please see PRISMA 2009 Flow Diagram – Test Properties for details.[11]

Summary of Included Studies

We included 17 RCTs; 12 answered the question of benefits of treatment for MCI;[12-23] 11 answered the question on harms of treatment for MCI.[12, 13, 16, 20, 21, 23-28] Five studies examined the effects of pharmacological treatments on MCI.[12, 13, 20, 23, 24] Seven studies focus on dietary supplements/vitamins as treatment for MCI[18, 19, 22, 23, 26-28] and seven studies investigated behavioural interventions.[14-17, 21, 25, 26]

KQ1. Do pharmacological or non-pharmacologic interventions for Mild Cognitive Impairment (MCI) in community dwelling adults (>65 years of age)

improve: 1) cognition, 2) function, 3) behaviour, 4) global status, or 5) mortality?

Twelve RCTs were identified to answer the question on the effectiveness of treatment.[12-23] Studies reported on cognition, function, behavior and/or global status; no studies reported on mortality. See Table 1 for Characteristics of included studies.

Four pharmacological studies were identified: one study examined the effects of rivastigmine (3-12 mg/day);[12] one study examined the effects of galantamine (8-12 mg/BID);[13] and 2 studies examined donepezil (10mg/day).[20, 23] These studies were published between 2005-2009 and took place primarily in Canada and the US, though one study[12] took place across 14 different countries.

Five studies focused on behavioural interventions as treatment for MCI.[14-17, 21] Three of these behavioural studies focused on exercise interventions[14, 16, 21] while one comprised a holistic cognitive rehabilitiation program[15] and one centred on a multi-modal intervention with stimulation and cognitive training sessions.[17] The behavioural studies were published between 2009 and 2014 and took place in Japan, Greece, China and Argentina.

Four studies examined the benefits of dietary supplements or vitamins used to treat MCI.[18, 19, 22, 23] Two studies examined the effects of Vitamin E either 2000IU in combination with a multivitamin (including 15 IU Vitamin E) daily[23] or 300 mg in combination with 400 mg of Vitamin C daily.[19] One study examined a combination of 1.3 g of docosahexaenoic (DHA) and 0.45 mg of eicosapentaenoic acid (EPA) (fish oil)[18] and another examined Vitamin B (0.8 mg folic acid, 0.5 mg Vitamin B12 and 20 mg Vitamin B6) daily.[22] These studies were published between 2005 and 2014 and took place in the US and Canada, Malaysia, Iran and the UK.

See **Evidence Set 1** for GRADE Tables and Forest Plots.

KQ1a. How effective are the screening tools validated for Canadian populations (e.g. MoCA) in improving: 1) cognition, 2) function, 3) behaviour, 4) global status, or 5) mortality?

There were no included studies that met the inclusion criteria for the outcomes measured with screening tools validated in Canadian populations.

KQ2. What are the adverse events (AE) including serious (hospitalization or death) and psycho-social harms such as depression, lack of independence, etc. of pharmacological or non-pharmacologic interventions for MCI?

Adverse events of interest included serious adverse events (hospitalization or death) and psychosocial harms. The included studies did not have any data for death from treatment.

Serious Adverse Events

We identified 11 RCTs that answered the question on serious adverse events for treatments of MCI.[12, 13, 16, 20, 21, 23-28]

Five studies examined serious adverse events that occurred as a result of pharmacological treatments.[12, 13, 20, 23, 24] Three studies examined the effects of donepezil (10 mg/day);[20, 23, 24] one study examined rivastigamine (3-12 mg/day);[12] and one study examined galantamine (8-16mg/day).[13] These studies were published between 2004 and 2009. Two studies took place in the US; two took place in Canada as well as the US and Germany and one study took place across 14 countries.

See **Evidence Set 2** for GRADE Tables and Forest Plots.

Three studies reported no serious adverse events as a result of dietary supplements/vitamins on serious adverse events.[23, 27, 28] One study examined two daily doses of capsules containing: 720 mg of DHA, 286 mg of EPA, 16 mg of Vitamin E, 160 mg of soy phospholipids 160 mg, 95 mg of tryptophan and 5 mg of melatonin 5;[27] one study examined Vitamin E (2000 IU) in combination with a multivitamin (including 15 IU Vitamin E) daily[23] and one study examined lyophilized royal jelly (750 mg) in combination with Ginkgo Biloba (120 mg) and Panax ginseng (150 mg).[28] These studies were published between 2005 and 2013 and took place in Italy, Egypt, the US and Canada.

Four studies reported no serious adverse events as a result of participation in behavioural interventions.[16, 21, 25, 26] All four studies focused on exercise interventions. The studies were published between 2008 and 2014 and took place in Japan, China and the US.

Psychosocial Harms

One study provided data for depression (psychosocial harm) associated with rivastigmine (3-12 mg/day) treatment for MCI and found no significant differences as compared to control group using both dichotomous and continuous (Beck Depression Inventory) outcome measures [RR= 0.99 (95% CI 0.71, 1.38); MD = -0.30 (95% CI -0.97, 0.37)].[12]

KQ3.What are the diagnostic properties of screening tools validated in a Canadian population of adults older than age 65?

a. What are the cut-offs for mild cognitive impairment in adults 65 years and over and how well they work (i.e. examine how well the screening tools differentiate between no cognitive impairment and mild cognitive impairment, and between mild and severe cognitive impairment).

Two studies with a total sample size of 324 provided test properties data for MoCA as a screening tool for MCI.[29, 30] Across these two studies, using a recommended cutoff score of 26, MoCA showed a mean sensitivity of 85% (range: 80% to 90%) and a specificity of 58.5% (range: 30% to 87%). The gold standard for diagnosis of MCI differed across the two studies. One study used Montebello Rehabilitation Factor Scores (MRFS > 0.5)[29] and the other used evaluation by trained neurologists or geriatricians and a standardized mental status battery.[30]

One study with a total sample size of 277 (90 Controls, 94 MCI, 93 AD) also compared test properties data for MoCA as a screening tool for MCI vs. Alzheimer's disease (AD).[30] MoCA showed a sensitivity of 90% and 100% for MCI and mild AD respectively and a specificity of 87% for both. The positive and negative predictive values were 89% and 91% for MCI and 89% and 100% for mild AD.

Contextual questions

Five primary studies have been identified that answer the question of participants' willingness to be screened for or diagnosed with MCI.[31-35] All papers refer to cognitive screening or memory loss screening more generally, rather than screening for MCI specifically. We also conducted a grey literature search for Canadian specific data on willingness to be screened and diagnosed, but the search returned no results. Below, we have summarized the results from five studies from Israel, the US and the UK.

CQ1. Willingness to be screened

In a 2010 study conducted in the US, 119 ethnically diverse individuals (African American, Afro-Caribbean, European American and Hispanic American) underwent a structured interview in order to determine reasons for participating in cognitive screening and follow-up testing.[31] Participants stated they valued screening (89%) and that they would recommend screening to others (92%). Reasons for undergoing screening included: wanting to know more about their memory loss; personal or familial concerns about their memory (65%); or taking advantage of the screening opportunity (29%). The study found an increased level of concern or worry over memory in African American (73%) and European American (86%) participants compared to Afro Caribbean (48%) or Hispanic American (54%) participants. In terms of dealing with a positive screening result, 39% of participants agreed that they would seek follow-up care.

One non-comparative 2004 study in Israel examined screening practices of first-degree relatives of patients with Alzheimer's disease.[32] The study interviewed 93 participants with a mean age of 50.7 (SD 8.1) years, investigating whether these relatives would undergo a cognitive status examination within the next year or during the next five years. The study found no statistically significant differences in participants' willingness to be screened during the next year (31.9%) or during the next five years (42.1%). Common beliefs about cognitive status examinations revolved around helping to prepare an individual for the future. Participants responded that results of a cognitive status examination would "help me and my physician plan for future

treatments" (56.8%); help me make adjustments in my life (53.2%); help me to make important later-life decisions (49.5%); help me deal with the problem if there was one (54%); help me find the right treatment (61.8%); help me plan my life (51.7%); and make things easier for me (46.7%). Other responses and beliefs about cognitive status examinations included cost (performing an evaluation is very expensive – 29.5%); time (performing an evaluation is very time-consuming – 28% or it is a waste of time to go to a physician for a cognitive evaluation – 26.4%) and importance (other things are much more important to me – 35.9%).

In another 2004 study from Israel, 79 community-dwelling elderly persons underwent semi-structured interviews about their beliefs on memory problems.[33] This study examined both structural and psychosocial barriers that prevented individuals from undergoing a memory assessment. The most frequently reported structural barrier was cost, while the most frequently cited psychosocial barriers were fear of learning that one does have a memory problem and the associated stigma. As a result, the study reports that almost all of the participants would only seek medical help if their memory problems began to affect their daily functioning.

One additional American study from 2008 examined the differences between participants diagnosed with MCI in a primary research setting to those in a tertiary care memory disorder clinic.[34] Of the 48 subjects who received a diagnosis of MCI, 13 (27%) from the research setting refused follow-up testing. Of these 13, the study found that one individual had another diagnosis and felt additional medical evaluation was inappropriate while the other 12 participants stated that they did not accept the diagnosis of MCI and therefore did not require further medical attention.

CQ2. Willingness to be diagnosed

We found one recent UK study (2013) that examined patients and carers' views on communication with health professionals while undergoing diagnostic assessments.[35] Through interviews with 53 participants, the study focused on two themes: being kept informed (throughout the process) and being told outcomes of the assessment. Participants' considered being told the outcomes of their assessments (positive, uncertain, or negative) important.

Evidence Set 1

- ES Table 1.1. Overview of Key Results
- ES Table 1.2. GRADE Evidence Profile: Effect of Treatment for Mild Cognitive Impairment on Cognition
- ES Table 1.3. GRADE Summary of Findings Table: Treatment for Mild Cognitive Impairment (Cognition)
- Forest Plots 1.1-1.10

ES Table 1.1. Overview of Key Results

Forest Plot #	Outcome	Intervention	Number of Studies	Mean Difference (95% CI)
1.1	Cognition (ADAS-Cog)	Cholinesterase inhibitors (AChEIs)	4	-0.3343 [-0.7263, 0.0577]
1.2	Cognition (MMSE)	Cholinesterase inhibitors (AChEIs)	3	0.1682[-0.1330, 0.4694]
1.3	Cognition (ADAS-Cog)	Dietary supplements/vitamins	1	0.8500[-0.3161, 2.0161]
1.4	Cognition (MMSE)	Dietary supplements/vitamins	4	0.1959[-0.0403, 0.4321]
1.5	Cognition (ADAS-Cog)	Non-pharmacological interventions (exercise)	1	-0.6000[-1.4421, 0.2421]
1.6	Cognition (MMSE)	Non-pharmacological interventions (exercise or cognitive training/rehabilitation)	4	1.0072 [0.2475, 1.7668]
1.7	Behaviour (NPI)	Cholinesterase inhibitors (AChEIs)	2	0.1193[-0.9278, 1.1665]
1.8	Global Status (CGIC-MCI)	Cholinesterase inhibitors (AChEIs)	1	0.0000[-0.2772, 0.2772]
1.9	Function (ADL)	Cholinesterase inhibitors (AChEIs)	3	0.2041[-0.2832, 0.6914]
1.10	Function (ADL)	Dietary Supplements/vitamins	1	0.7600[-0.7707, 2.2907]

ES Table 1.2. GRADE Evidence Profile: Effect of treatment for Mild Cognitive Impairment on Cognition

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Control	Mean Difference(95% CI)		
Effect of AChEIs on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention ranged from 11 to 48 months; follow-up: immediate post)											
4	randomised trials[1]	serious[2]	no serious inconsistency[3]	no serious indirectness[4]	serious[5]	none[6]	2,078	2,110	-0.3343 (-0.7263 to 0.0577)	⊕⊕OO LOW	CRITICAL
Effect of donepezil on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention ranged from 11 to 36 months; follow-up: immediate post)											
2	randomised trials[7]	serious[8]	no serious inconsistency[9]	no serious indirectness[10]	serious[1]	none[6]	632	637	-0.5966 (-1.3473 to 0.1542)	⊕⊕OO LOW	CRITICAL
Effect of rivastigmine on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention: 48 months; follow-up: immediate post)											
1	randomised trials[12]	serious[13]	no serious inconsistency[14]	no serious indirectness[15]	serious[16]	none[6]	508	510	0 (-0.7987 to 0.7987)	⊕⊕OO LOW	CRITICAL
Effect of galantamine on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention: 24 months; follow-up: immediate post)											
1	randomised trials[17]	serious[18]	no serious inconsistency[14]	no serious indirectness[19]	serious[20]	none[6]	938	963	-0.2073 (-0.7951 to 0.3805)	⊕⊕OO LOW	CRITICAL
Effect of AChEIs on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention ranged from 11 to 48 months; follow-up: immediate post)											
3	randomised trials[21]	serious[22]	no serious inconsistency[23]	no serious indirectness[24]	serious[25]	none[6]	1,140	1,147	0.1682 (-0.1330 to 0.4694)	⊕⊕OO LOW	CRITICAL
Effect of donepezil on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention ranged from 11 to 36 months; follow-up: immediate post)											
2	randomised trials[7]	serious[8]	no serious inconsistency[26]	no serious indirectness[10]	serious[27]	none[6]	632	637	0.2376 (-0.1902 to 0.6653)	⊕⊕OO LOW	CRITICAL
Effect of rivastigmine on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention: 48 months; follow-up: immediate post)											
1	randomised trials[12]	serious[13]	no serious inconsistency[14]	no serious indirectness[15]	serious[28]	none[6]	508	510	0.1000 (-0.3242 to 0.5242)	⊕⊕OO LOW	CRITICAL
Effect of dietary supplements on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention: 36 months; follow-up: immediate post)											
1	randomised trials[29]	serious[30]	no serious inconsistency[14]	no serious indirectness[31]	serious[32]	none[6]	257	259	0.8500 (-0.3161 to 2.0161)	⊕⊕OO LOW	CRITICAL
Effect of dietary supplements on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention ranged from 12 to 36 months; follow-up: immediate post)											
4	randomised trials[33]	serious[34]	no serious inconsistency[35]	no serious indirectness[36]	serious[37]	none[6]	511	519	0.1959 (-0.0403 to 0.4321)	⊕⊕OO LOW	CRITICAL

Effect of non-pharma interventions on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention: 6 months; follow-up: immediate post)											
1	randomised trials[38]	no serious risk of bias[39]	no serious inconsistency[14]	no serious indirectness[40]	serious[41]	none[6]	47	45	-0.6000 (-1.4421 to 0.2421)	⊕⊕⊕O MODERATE	CRITICAL
Effect of non-pharma interventions on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention ranged from 6 to 12 months; follow-up: immediate post)											
5	randomised trials[42]	serious[43]	no serious inconsistency[44]	no serious indirectness[45]	no serious imprecision[46]	none[6]	221	187	1.0072 (0.2475 to 1.7668)	⊕⊕⊕O MODERATE	CRITICAL

ES Table 1.3. Summary of Findings: Treatment for Mild Cognitive Impairment (Cognition)

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Risk difference with Treatment (95% CI)
Effect of AChEIs on Cognition ADAS-Cog	4,188 (4 studies[1])	⊕⊕⊖⊖ **LOW**[2,3,4,5,6] due to risk of bias, imprecision	The mean effect of AChEIs on cognition in the intervention groups was **0.3343 lower** (0.7263 lower to 0.0577 higher)
Effect of donepezil on Cognition ADAS-Cog	1,269 (2 studies[7])	⊕⊕⊖⊖ **LOW**[6,8,9,10,11] due to risk of bias, imprecision	The mean effect of donepezil on cognition in the intervention groups was **0.5966 lower** (1.3473 lower to 0.1542 higher)
Effect of rivastigmine on Cognition ADAS-Cog	1,018 (1 study[12])	⊕⊕⊖⊖ **LOW**[6,13,14,15,16] due to risk of bias, imprecision	The mean effect of rivastigmine on cognition in the intervention groups was **0 higher** (0.7987 lower to 0.7987 higher)
Effect of galantamine on Cognition ADAS-Cog	1,901 (1 study[17])	⊕⊕⊖⊖ **LOW**[6,14,18,19,20] due to risk of bias, imprecision	The mean effect of galantamine on cognition in the intervention groups was **0.2073 lower** (0.7951 lower to 0.3805 higher)
Effect of AChEIs on Cognition MMSE	2,287 (3 studies[21])	⊕⊕⊖⊖ **LOW**[6,22,23,24,25] due to risk of bias, imprecision	The mean effect of AChEIs on cognition in the intervention groups was **0.1682 higher** (0.1330 lower to 0.4694 higher)
Effect of donepezil on Cognition MMSE	1,269 (2 studies[7])	⊕⊕⊖⊖ **LOW**[6,8,10,26,27] due to risk of bias, imprecision	The mean effect of donepezil on cognition in the intervention groups was **0.2376 higher** (0.1902 lower to 0.6653 higher)
Effect of rivastigmine on Cognition MMSE	1,018 (1 study[12])	⊕⊕⊖⊖ **LOW**[6,13,14,15,28] due to risk of bias, imprecision	The mean effect of rivastigmine on cognition in the intervention groups was **0.1000 higher** (0.3242 lower to 0.5242 higher)
Effect of dietary supplements on Cognition ADAS-Cog	516 (1 study[29])	⊕⊕⊖⊖ **LOW**[6,14,30,31,32] due to risk of bias, imprecision	The mean effect of dietary supplements on cognition in the intervention groups was **0.8500 higher** (0.3161 lower to 2.0161 higher)
Effect of dietary supplements on Cognition MMSE	1,030 (4 studies[33])	⊕⊕⊖⊖ **LOW**[6,34,35,36,37] due to risk of bias, imprecision	The mean effect of dietary supplements on cognition in the intervention groups was **0.1959 higher** (0.0403 lower to 0.4321 higher)
Effect of non-pharma interventions on Cognition	92 (1 study[38])	⊕⊕⊕⊖ **MODERATE**[6,14,39,40,41] due to imprecision	The mean effect of non-pharma interventions on cognition in the intervention groups was **0.6000 lower** (1.4421 lower to 0.2421 higher)

ADAS-Cog			
Effect of non-pharma interventions on Cognition MMSE	408 (5 studies[42])	⊕⊕⊕⊖ **MODERATE**[6,43,44,45,46] due to risk of bias	The mean effect of non-pharma interventions on cognition in the intervention groups was **1.0072 higher** (0.2475 to 1.7668 higher)

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 1) Doody et. al, 2009; 2) Petersen et. al, 2005; 3) Feldman et. al, 2007; 4) Winblad et. al, 2008.

[2] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 3 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (50%), and allocation concealment (50%); and high risk of bias associated with incomplete outcome reporting (25%) and other sources of bias (75%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] The statistical heterogeneity is minimal [Chi^2=4.63, df=4 (P=0.33); I^2=14%] and the confidence intervals overlap across most studies. This body of evidence was not downgraded for inconsistency.

[4] Four RCTs provided data for this outcome. All studies included mixed gender population. The mean age across studies ranged from 69 to 74 years. The intervention arm received donepezil (10 mg/day) in two studies, rivastigmine (3-12 mg/day) in one study and galantamine (16-24 mg/day) in one study. The control group across all studies received placebo. Two studies were conducted in US and Canada, one in US and one in 14 countries. All studies were published from 2005 to 2009. The length of intervention across four studies ranged from 11 to 48 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[5] The sample size is adequate i.e. > 300 (2,078 intervention arm, 2,110 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "0" [MD= -0.3343 (-0.7263, 0.0577)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[6] There were too few studies (n<10) to assess publication bias.

[7] 1) Doody et. al, 2009; 2) Petersen et. al 2005.

[8] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and one as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (50%), and allocation concealment (50%); and high risk associated with other sources of bias (50%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] The statistical heterogeneity is minimal [Chi^2=1.48, df=1 (P=0.22); I^2=33%] and the confidence intervals overlap across studies. This body of evidence was not downgraded for inconsistency.

[10] Two RCTs provided data for this outcome. Both studies included mixed gender samples. The mean age across studies ranged from 70 to 74 years. The intervention arm received donepezil (10 mg/day) and the control group received placebo. One study was conducted in US and one in US and Canada. One study was published in 2005 and one in 2009. The length of intervention across studies ranged from 11 to 36 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[11] The sample size is adequate i.e. > 300 (632 intervention arm, 637 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "0" [MD= -0.5966 (-1.3473, 0.1542)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[12] Feldman et. al, 2007

[13] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was high risk of bias associated with incomplete outcome reporting and other sources of bias (i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that the information is from a study with moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[14] The statistical heterogeneity across studies could not be assessed due to only one study providing data for this outcome.

[15] One RCT provided data for this outcome. The study included a mixed gender sample. The mean age was 70.6 years for the intervention group and 70.3 years for the control group. The intervention

arm received rivastigmine (3-12 mg/day). The control group received placebo. The study was conducted in 14 countries and published in 2007. The length of intervention was 48 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[16] The sample size is adequate i.e. > 300 (508 intervention arm, 510 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "0" [MD= 0.0 (-0.7987, 0.7987)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[17] Winblad et. al, 2008.

[18] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was a lack of certainty (unclear ratings) regarding sequence generation, and allocation concealment; and high risk of bias associated with incomplete outcome reporting and other sources of bias (i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[19] One RCT provided data for this outcome. The study included a mixed gender sample. The study included results from two trials with mean age as 69.2 years for the intervention group and 70.1 years for the control group in one trial and mean age of 70.6 years for the intervention group and 70.9 years for the control group in the 2nd trial. The intervention arm received galantamine (16-24 mg/day) in both trials. The control group received placebo. The study was conducted in the US and Canada and published in 2008. The length of intervention was 24 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[20] The sample size is adequate i.e. > 300 (938 intervention arm, 963 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "0" [MD= -0.2073 (-0.7951, 0.3805)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[21] 1) Doody et. al, 2009; 2) Petersen et. al, 2005; 3) Feldman et. al, 2007

[22] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 2 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (33%), and allocation concealment (33%); and high risk of bias associated with incomplete outcome reporting (33%) and other sources of bias (67%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[23] The statistical heterogeneity is minimal [Chi^2=0.79, df=2 (P=0.68); I^2=0%] and the confidence intervals overlap across most studies. This body of evidence was not downgraded for inconsistency.

[24] Three RCTs provided data for this outcome. All studies included mixed gender samples. The mean age across studies ranged from 69 to 74 years. The intervention arm received donepezil (10 mg/day) in two studies and rivastigmine (3-12 mg/day) in one study. The control group across all studies received placebo. One study was conducted in US and Canada, one in US and one in 14 countries. All studies were published from 2005 to 2009. The length of intervention across four studies ranged from 11 to 48 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[25] The sample size is adequate i.e. > 300 (1,140 intervention arm, 1,147 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "0" [MD= 0.1682 (-0.1330, 0.4694)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[26] The statistical heterogeneity is minimal [Chi^2=0.58, df=1 (P=0.44); I^2=0%] and the confidence intervals overlap across studies. This body of evidence was not downgraded for inconsistency.

[27] The sample size is adequate i.e. > 300 (632 intervention arm, 637 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "0" [MD= 0.2376 (-0.1902, 0.6653)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[28] The sample size is adequate i.e. > 300 (508 intervention arm, 510 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "0" [MD= 0.1 (-0.3242, 0.5242)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[29] Petersen et. al 2005.

[30] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was a lack of certainty (unclear ratings) regarding sequence generation, and allocation concealment. Given that the information is from a study with moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[31] One RCT provided data for this outcome. The study included mixed gender population. The mean age was 72.8 years for the intervention group and 72.9 years for the control group. The intervention arm received donepezil (10 mg/day). The control group received placebo. The study was conducted in US and Canada, and published in 2005. The length of intervention was 36 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

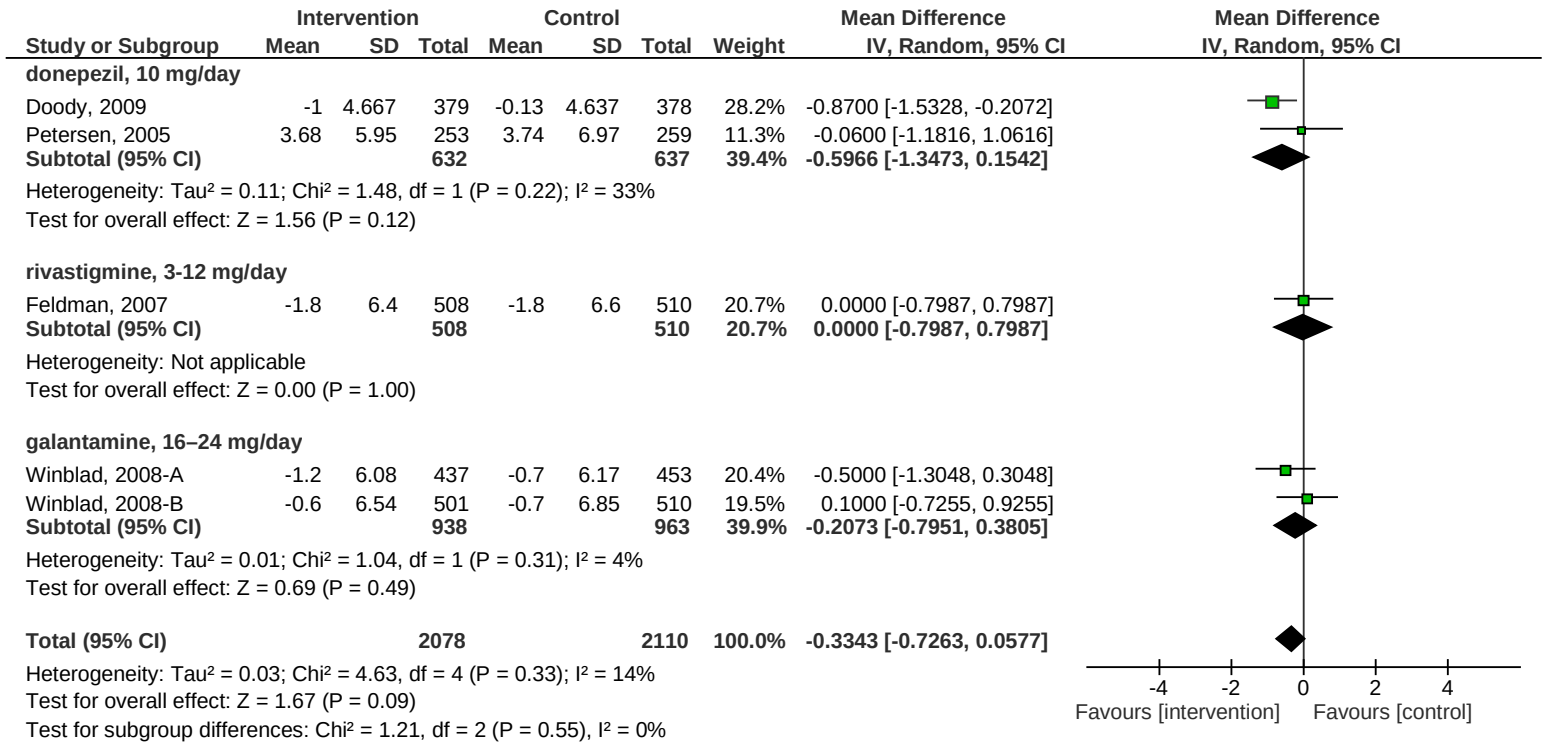
[32] The sample size is not adequate i.e. < 300 (257 intervention arm, 259 control arm) and the pooled effect estimate is not precise with a confidence interval that includes the null value "0" [MD= 0.8500 (-0.3161, 2.0161)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[33] 1) Petersen et. al, 2005; 2) de Jager et. al, 2012; 3) Lee et. al, 2013; 4) Naeini et. al, 2014.

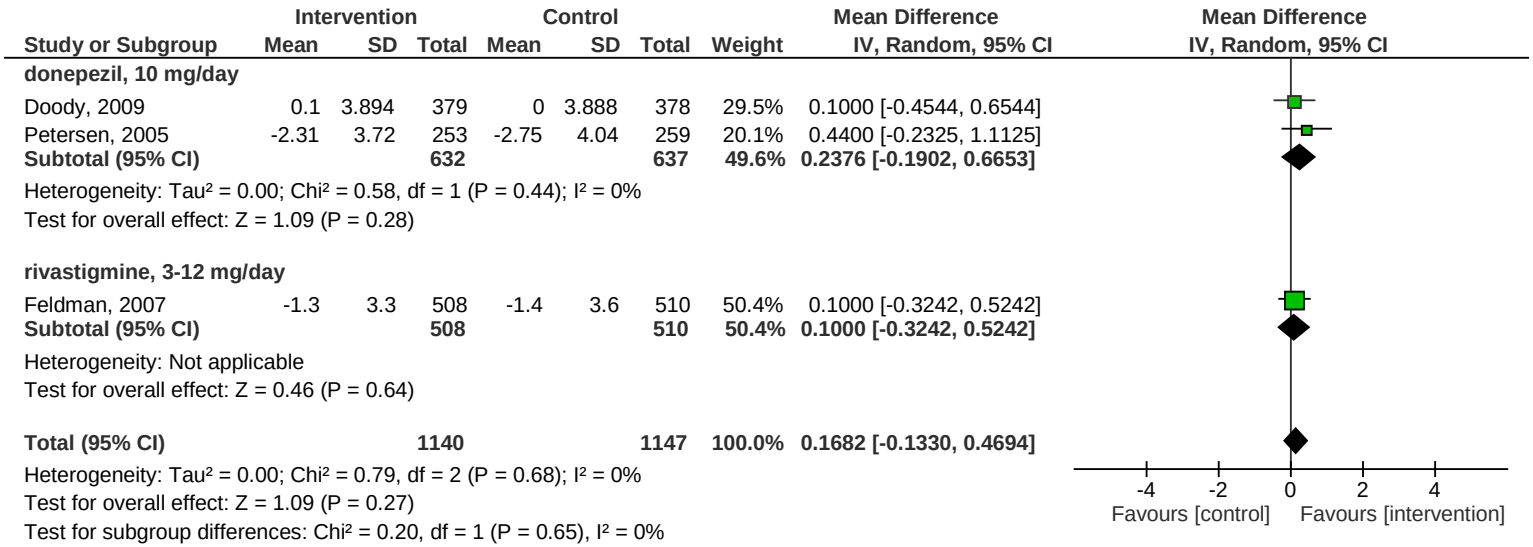
[34] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 3 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (50%), and allocation concealment (75%); and high risk associated with other sources of bias (25%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[35] The statistical heterogeneity is minimal [Chi2=1.36, df=3 (P=0.71); I2=0%] and the confidence intervals overlap across most studies. This body of evidence was not downgraded for inconsistency.
[36] Four RCTs provided data for this outcome. All studies included mixed gender population. The mean age across studies ranged from 66 to 77 years. The intervention arm received Vitamin E in one study, Vitamin E and folic acid in one study, DHA (fish oil) in one study and Vitamins E and C in one study. The control group across all studies received placebo. One study was conducted in US and Canada, one in UK, one in Malaysia and one in Iran. All studies were published from 2005 to 2014. The length of intervention across four studies ranged from 12 to 36 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.
[37] The sample size is adequate i.e. > 300 (511 intervention arm, 519 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "0" [MD= 0.1959 (-0.0403, 0.4321)]. This body of evidence was downgraded for serious concerns regarding imprecision.
[38] Suzuki et. al, 2013
[39] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as low risk. There were no serious concerns regarding risk of bias and this body of evidence was not downgraded for serious study limitations.
[40] One RCT provided data for this outcome. The study included mixed gender population. The mean age was 74.8 years for the intervention group and 75.8 years for the control group. The intervention arm received a multi-component exercise program: biweekly. The control group received minimal contact with two education classes about health promotion. The study was conducted in Japan and published in 2013. The length of intervention was 6 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[41] The sample size is not adequate i.e. < 300 (47 intervention arm, 45 control arm) and the pooled effect estimate is not precise with confidence interval including the null value "0" [MD= -0.6000 (-1.4421, 0.2421)]. This body of evidence was downgraded for serious concerns regarding imprecision.
[42] 1) Suzuki et. al, 2012; 2) Tsolaki. al, 2009; 3) Wei et. al, 2014; 4) Suzuki et. al, 2013: 5) Rojas et. al, 2013.
[43] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 4 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (80%), allocation concealment (80%), blinding (20%), incomplete outcome reporting (20%) and other sources of bias (20%); and high risk of bias associated with blinding (20%), incomplete outcome reporting (20%) and other sources of bias (40%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.
[44] The statistical heterogeneity is high [Chi^2=16.92, df=4 (P=0.002); I^2=76%] but the direction of the effect is consistent across studies and the confidence intervals overlap across most studies. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.
[45] Five RCTs provided data for this outcome. All studies included mixed gender population. The mean age across studies ranged from 65 to 77 years. The intervention arm received multi-component exercise programs in three studies and cognitive training and rehabilitation in two studies. The control group across studies either received no therapy, waitlist or minimal contact involving education about health promotion. Two studies were conducted in Japan, one in China, one in Greece and one in Argentina. All studies were published from 2009 to 2014. The length of intervention across four studies ranged from 6 to 12 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.
[46] The sample size is not adequate i.e. < 300 (221 intervention arm, 187 control arm) but the pooled effect estimate is precise with a narrow confidence interval [MD= 1.0072 (0.2475, 1.7668)]. This body of evidence was not downgraded for serious concerns regarding imprecision.

Forest Plot 1.1: Effect of cholinesterase inhibitors on Cognition assessed with ADAS-Cog



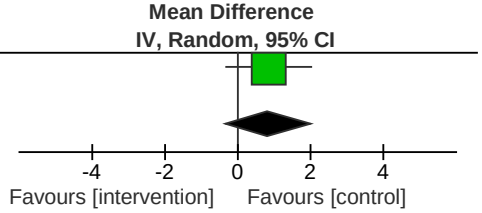
Forest Plot 1.2: Effect of cholinesterase inhibitors on Cognition assessed with MMSE



Forest Plot 1.3: Effect of Dietary supplements/Vitamins on Cognition assessed with ADAS-Cog

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Petersen, 2005	4.59	6.54	257	3.74	6.97	259	100.0%	0.8500 [-0.3161, 2.0161]
Total (95% CI)			**257**			**259**	**100.0%**	**0.8500 [-0.3161, 2.0161]**

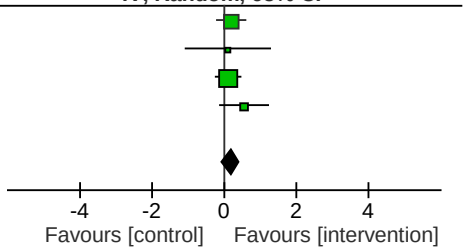
Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)



Forest Plot 1.4: Effect of Dietary supplements/ Vitamins on Cognition with MMSE

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
de Jager, 2012	-0.4	1.489	110	-0.595	1.515	113	35.9%	0.1950 [-0.1993, 0.5893]
Lee, 2013	0.2	1.769	17	0.1	1.761	18	4.1%	0.1000 [-1.0700, 1.2700]
Naeini, 2014	2.3	1.355	127	2.19	1.446	129	47.4%	0.1100 [-0.2332, 0.4532]
Petersen, 2005	-2.2	3.64	257	-2.75	4.04	259	12.7%	0.5500 [-0.1134, 1.2134]
Total (95% CI)			**511**			**519**	**100.0%**	**0.1959 [-0.0403, 0.4321]**

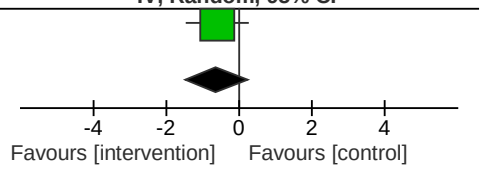
Heterogeneity: Tau² = 0.00; Chi² = 1.36, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)



Forest Plot 1.5: Effect of non-pharmacological interventions on Cognition assessed with ADAS-Cog

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Suzuki, 2013	-0.8	2.083	47	-0.2	2.038	45	100.0%	-0.6000 [-1.4421, 0.2421]
Total (95% CI)			**47**			**45**	**100.0%**	**-0.6000 [-1.4421, 0.2421]**

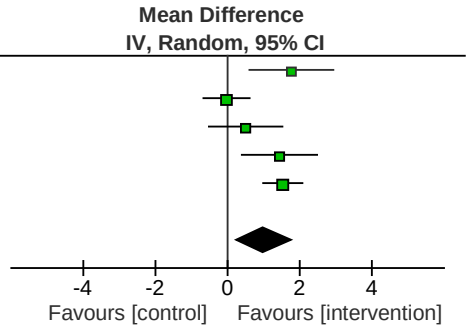
Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)



Forest Plot 1.6: Effect of non-pharmacological interventions on Cognition assessed with MMSE

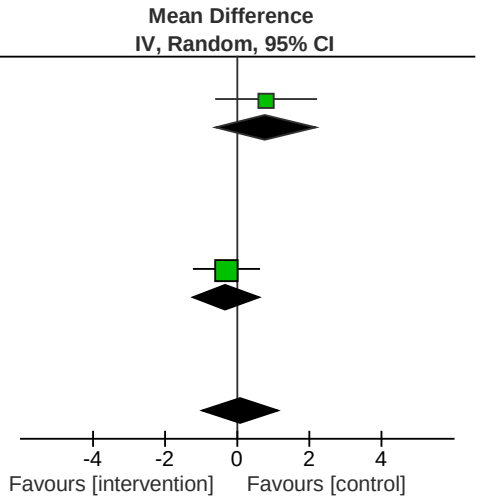
Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Rojas, 2013	0	1.562	15	-1.77	1.686	15	16.7%	1.7700 [0.6069, 2.9331]
Suzuki, 2012	-0.47	1.19	25	-0.44	1.114	25	22.9%	-0.0300 [-0.6690, 0.6090]
Suzuki, 2013	0.2	2.43	47	-0.3	2.547	45	18.3%	0.5000 [-0.5180, 1.5180]
Tsolaki, 2011	0.91	5.097	104	-0.53	1.553	72	18.0%	1.4400 [0.3968, 2.4832]
Wei, 2014	1.2	1.169	30	-0.33	0.966	30	24.0%	1.5300 [0.9873, 2.0727]
Total (95% CI)			**221**			**187**	**100.0%**	**1.0072 [0.2475, 1.7668]**

Heterogeneity: Tau² = 0.55; Chi² = 16.92, df = 4 (P = 0.002); I² = 76%
Test for overall effect: Z = 2.60 (P = 0.009)

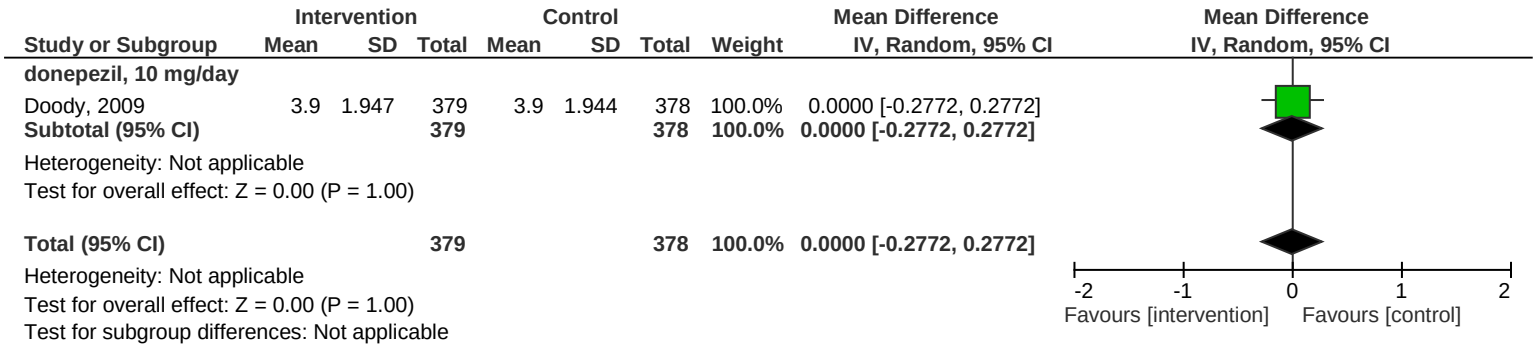


Forest Plot 1.7: Effect of cholinesterase inhibitors on Behaviour assessed with NPI

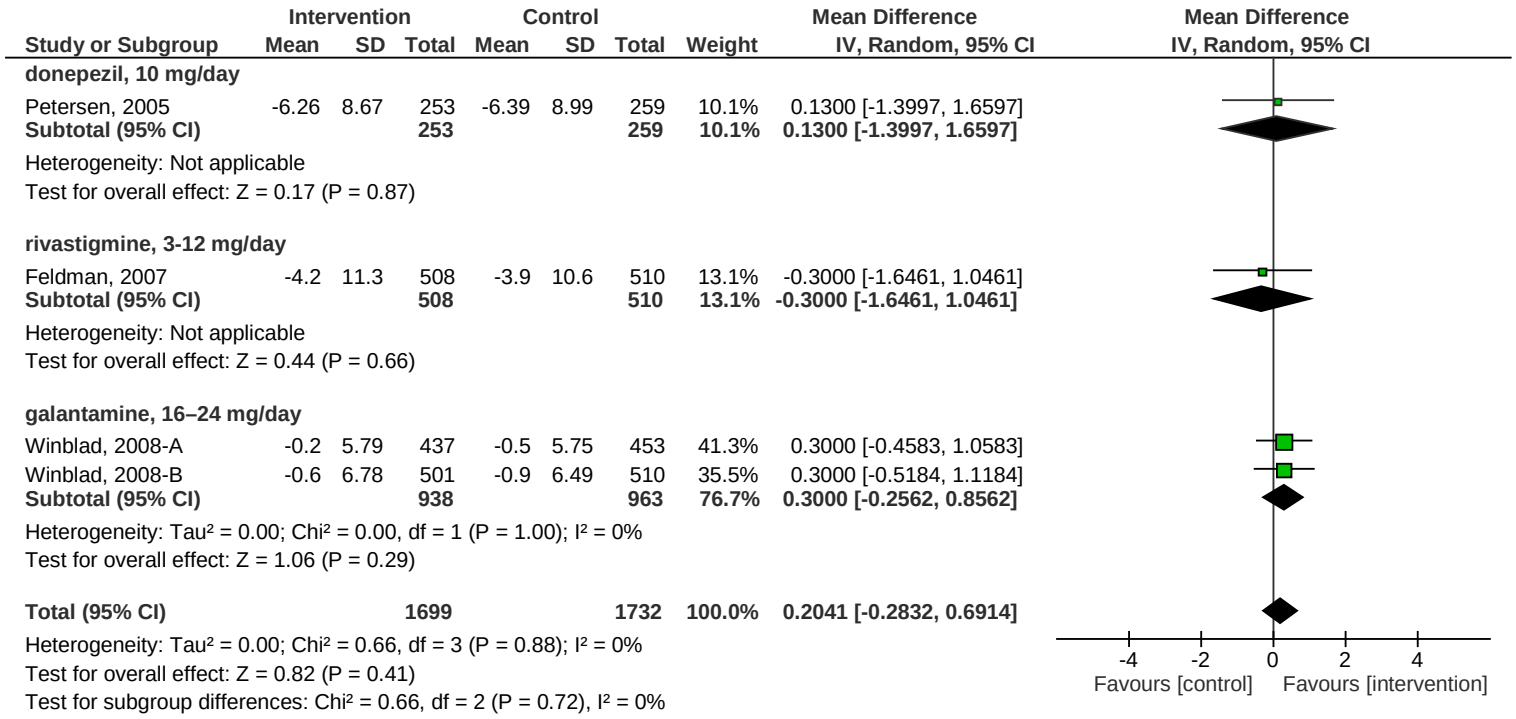
Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
donepezil, 10 mg/day								
Doody, 2009	1.8	9.734	379	1	9.721	378	38.1%	0.8000 [-0.5859, 2.1859]
Subtotal (95% CI)			**379**			**378**	**38.1%**	**0.8000 [-0.5859, 2.1859]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.13 (P = 0.26)								
rivastigmine, 3-12 mg/day								
Feldman, 2007	-2	7.6	508	-1.7	7.1	510	61.9%	-0.3000 [-1.2036, 0.6036]
Subtotal (95% CI)			**508**			**510**	**61.9%**	**-0.3000 [-1.2036, 0.6036]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.52)								
Total (95% CI)			**887**			**888**	**100.0%**	**0.1193 [-0.9278, 1.1665]**
Heterogeneity: Tau² = 0.25; Chi² = 1.70, df = 1 (P = 0.19); I² = 41%								
Test for overall effect: Z = 0.22 (P = 0.82)								
Test for subgroup differences: Chi² = 1.70, df = 1 (P = 0.19), I² = 41.1%								



Forest Plot 1.8: Effect of cholinesterase inhibitors on Global status assessed with CGIC-MCI



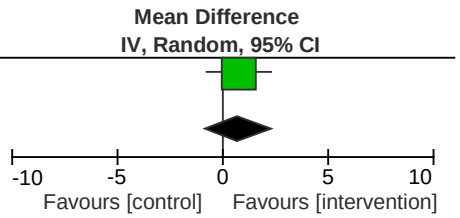
Forest Plot 1.9: Effect of cholinesterase inhibitors on Function assessed with ADL



Forest Plot 1.10: Effect of Dietary supplements/Vitamins on Function assessed with ADL

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Petersen, 2005	-5.63	8.75	257	-6.39	8.99	259	100.0%	0.76 [-0.77, 2.29]
Total (95% CI)			**257**			**259**	**100.0%**	**0.76 [-0.77, 2.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)



Evidence Set 2

- ES Table 2.1. GRADE Evidence Profile: Serious Adverse Events associated with AChEI for Mild Cognitive Impairment
- ES Table 2.2. GRADE Summary of Findings Table: Serious Adverse Events for MCI Treatment
- Forest Plot 2.1

ES Table 2.1. GRADE Evidence Profile: Serious Adverse Events associated with AChEIs for Mild Cognitive Impairment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Serious Adverse Events	Control	Relative (95% CI)	Absolute per 1000		
Serious AE's associated with AChEIs for MCI (assessed with: Number of Events) (length of intervention ranged from 6 to 48 months; follow-up: immediate post)												
5	randomised trials[1]	serious[2]	no serious inconsistency[3]	no serious indirectness[4]	serious[5]	none[6]	393/2308 (17.0277%)	401/2314 (17.3293%)	RR 0.9750 (0.8622 to 1.1027)	4 fewer (from 24 fewer to 18 more)	⊕⊕OO LOW	CRITICAL
Serious AE's associated with donepezil for MCI (assessed with: Number of Events) (length of intervention ranged from 6 to 36 months; follow-up: immediate post)												
3	randomised trials[7]	serious[8]	no serious inconsistency[9]	no serious indirectness[10]	serious[11]	none[6]	60/777 (7.7220%)	52/783 (6.6411%)	RR 1.1506 (0.8081 to 1.6381)	10 more (from 13 fewer to 42 more)	⊕⊕OO LOW	CRITICAL
Serious AE's associated with rivastigmine for MCI (assessed with: Number of Events) (length of intervention: 48 months; follow-up: immediate post)												
1	randomised trials[12]	serious[13]	no serious inconsistency[14]	no serious indirectness[15]	serious[16]	none[6]	141/505 (27.9208%)	155/509 (30.4519%)	RR 0.9169 (0.7567 to 1.1110)	25 fewer (from 74 fewer to 34 more)	⊕⊕OO LOW	CRITICAL
Serious AE's associated with galantamine for MCI (assessed with: Number of Events) (length of intervention: 24 months; follow-up: immediate post)												
1	randomised trials[17]	serious[18]	no serious inconsistency[14]	no serious indirectness[19]	serious[20]	none[6]	192/1026 (18.7135%)	194/1022 (19.9824%)	RR 0.9858 (0.8237 to 1.1799)	3 fewer (from 33 fewer to 34 more)	⊕⊕OO LOW	CRITICAL

ES Table 2.2. Summary of Findings: Serious Adverse Events for MCI treatment

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	**Risk difference with Serious Adverse Events** (95% CI)
Serious AE's associated with AChEIs for MCI	4622 (5 studies[1])	⊕⊕⊖⊖ **LOW**[2,3,4,5,6] due to risk of bias, imprecision	**RR 0.9750** (0.8622 to 1.1027)	**Study population**	
				173 per 1000	**4 fewer per 1000** (from 24 fewer to 18 more)
Serious AE's associated with donepezil for MCI	1560 (3 studies[7])	⊕⊕⊖⊖ **LOW**[6,8,9,10,11] due to risk of bias, imprecision	**RR 1.1506** (0.8081 to 1.6381)	**Study population**	
				66 per 1000	**10 more per 1000** (from 13 fewer to 42 more)
Serious AE's associated with rivastigmine for MCI	1014 (1 study[12])	⊕⊕⊖⊖ **LOW**[6,13,14,15,16] due to risk of bias, imprecision	**RR 0.9169** (0.7567 to 1.1110)	**Study population**	
				305 per 1000	**25 fewer per 1000** (from 74 fewer to 34 more)
Serious AE's associated with galantamine for MCI	2048 (1 study[17])	⊕⊕⊖⊖ **LOW**[6,14,18,19,20] due to risk of bias, imprecision	**RR 0.9858** (0.8237 to 1.1799)	**Study population**	
				190 per 1000	**3 fewer per 1000** (from 33 fewer to 34 more)

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 1) Doody et. al, 2009; 2) Petersen et. al, 2005; 3) Salloway et. al, 2004; 4) Feldman et. al, 2007; 5) Winblad et. al, 2008.
[2] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 4 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (60%), and allocation concealment (60%); and high risk of bias associated with incomplete outcome reporting (40%) and other sources of bias (80%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.
[3] The statistical heterogeneity is minimal [Chi^2=1.64, df=4 (P=0.80); I^2=0%] and the confidence intervals overlap across most studies. This body of evidence was not downgraded for inconsistency.
[4] Five RCTs provided data for this outcome. All studies included mixed gender samples. The mean age across studies ranged from 69 to 74 years. The intervention arm received donepezil (10 mg/day) in three studies, rivastigmine (3-12 mg/day) in one study and galantamine (16-24 mg/day) in one study. The control group across all studies received placebo. Two studies were conducted in US and Canada, two in US and one in 14 countries. All studies were published from 2004 to 2009. The length of intervention across four studies ranged from 6 to 48 months. There were no serious concerns regarding indirectness for this

body of evidence and it was not downgraded.

[5] The sample size is adequate i.e. > 300 (2308 intervention arm, 2314 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "1" [RR= 0.9750 (0.8622, 1.1027)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[6] There were too few studies (n<10) to assess publication bias.

[7] 1) Doody et. al, 2009; 2) Petersen et. al, 2005; 3) Salloway et. al, 2004.

[8] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and two studies as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (67%), and allocation concealment (67%); and high risk of bias associated with incomplete outcome reporting (33%), and other sources of bias (67%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm,). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] The statistical heterogeneity is minimal [Chi^2=0.39, df=2 (P=0.82); I^2=0%] and the confidence intervals overlap across studies. This body of evidence was not downgraded for inconsistency.

[10] Three RCTs provided data for this outcome. All studies included mixed gender population. The mean age across studies ranged from 70 to 74 years. The intervention arm received donepezil (10 mg/day) and the control group received placebo. Two studies were conducted in US and one in US and Canada. One study was published in 2004, one in 2005 and one in 2009. The length of intervention across studies ranged from 6 to 36 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[11] The sample size is adequate i.e. > 300 (777 intervention arm, 783 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "1" [RR= 1.1506 (0.8081, 1.6381)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[12] Feldman et. al, 2007

[13] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was high risk of bias associated with incomplete outcome reporting and other sources of bias (i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[14] The statistical heterogeneity across studies could not be assessed due to only one study providing data for this outcome.

[15] One RCT provided data for this outcome. The study included mixed gender population. The mean age was 70.6 years for the intervention group and 70.3 years for the control group. The intervention arm received rivastigmine (3-12 mg/day). The control group received placebo. The study was conducted in 14 countries and published in 2007. The length of intervention was 48 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[16] The sample size is adequate i.e. > 300 (505 intervention arm, 509 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "1" [RR= 0.9169 (0.7567, 1.1110)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[17] Winblad et. al, 2008.

[18] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was a lack of certainty (unclear ratings) regarding sequence generation, and allocation concealment; and high risk of bias associated with incomplete outcome reporting and other sources of bias (i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm,). Given that the information is from a study with moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[19] One RCT provided data for this outcome. The study included a mixed gender sample. The study included results from two trials with mean age as 69.2 years for the intervention group and 70.1 years for the control group in one trial and mean age as 70.6 years for the intervention group and 70.9 years for the control group in 2nd trial. The intervention arm received galantamine (16-24 mg/day) in both trials. The control group received placebo. The study was conducted in the US and Canada and published in 2008. The length of intervention was 24 months. There were no serious concerns regarding indirectness for this body of evidence and uit was not downgraded.

[20] The sample size is adequate i.e. > 300 (1026 intervention arm, 1022 control arm) but the pooled effect estimate is not precise and the confidence inte rval includes the null value "1" [RR= 0.9858 (0.8237, 1.1799)]. This body of evidence was downgraded for serious concerns regarding imprecision.

Forest Plot 2.1: Serious Adverse Events associated with the use of cholinesterase inhibitors for MCI

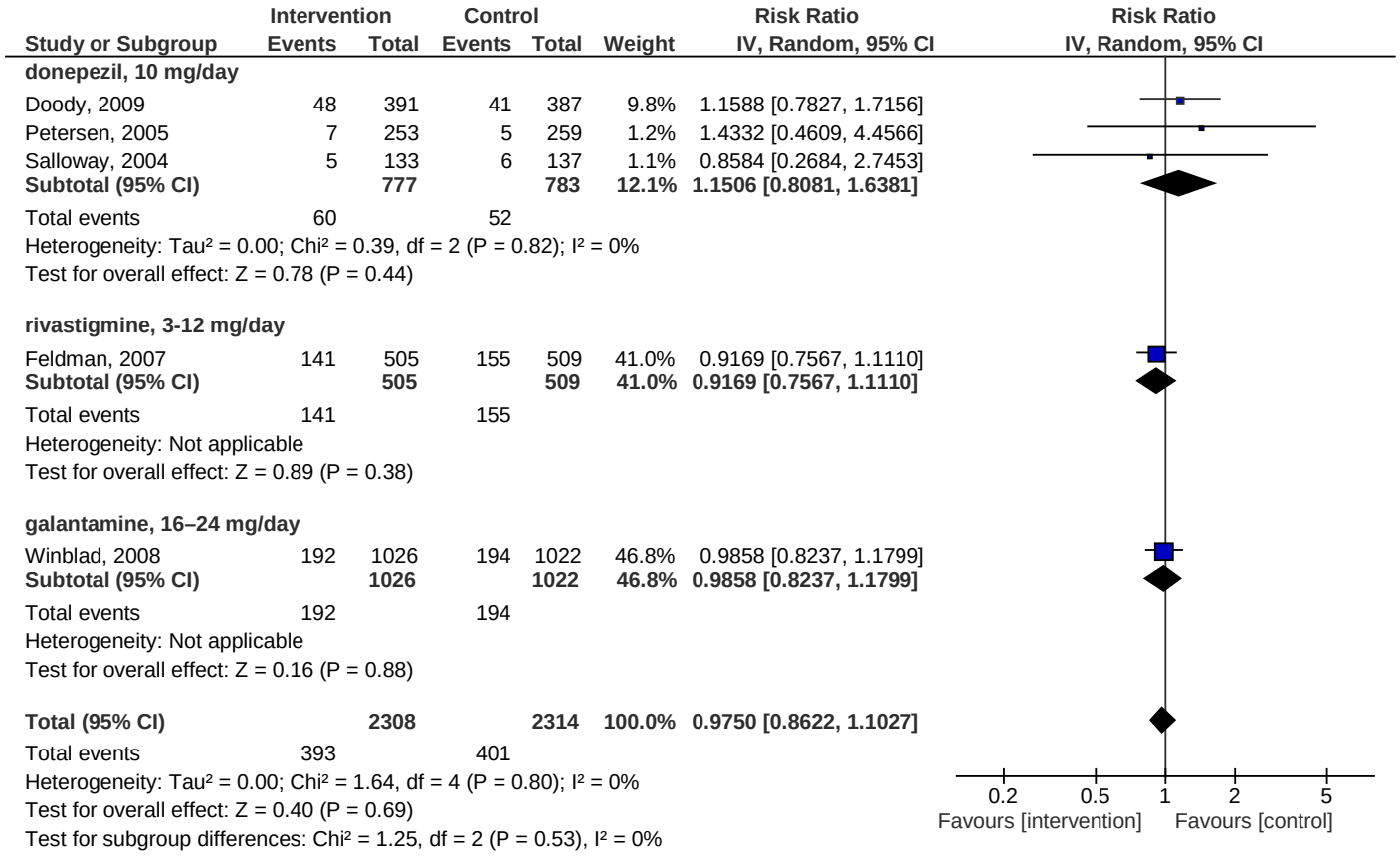
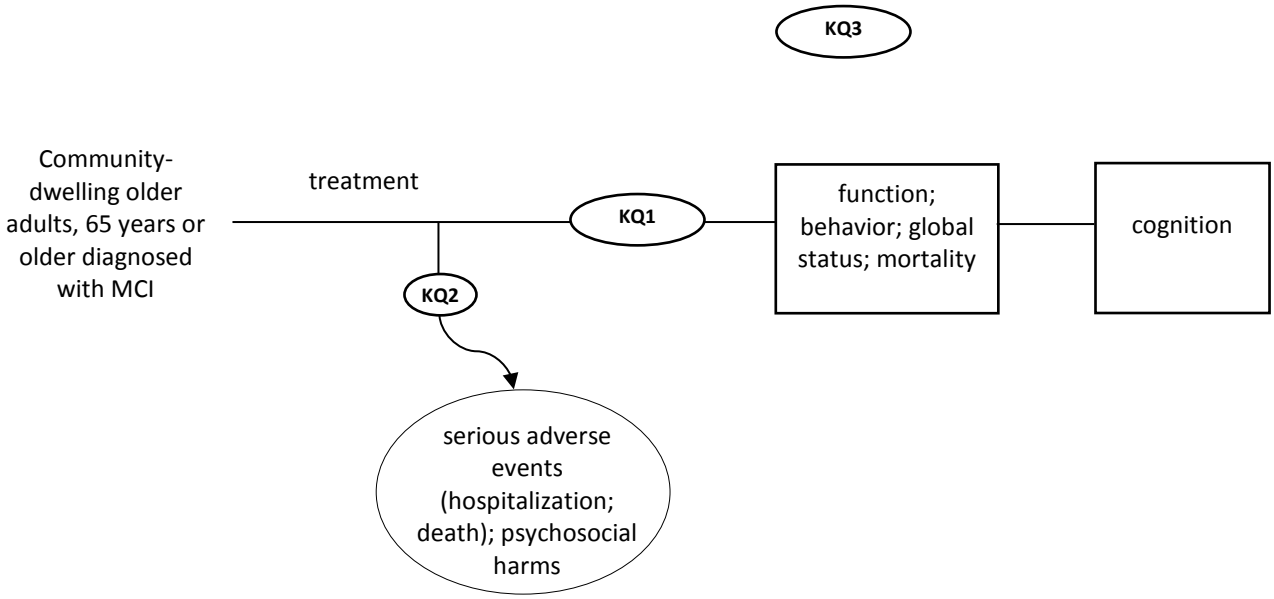
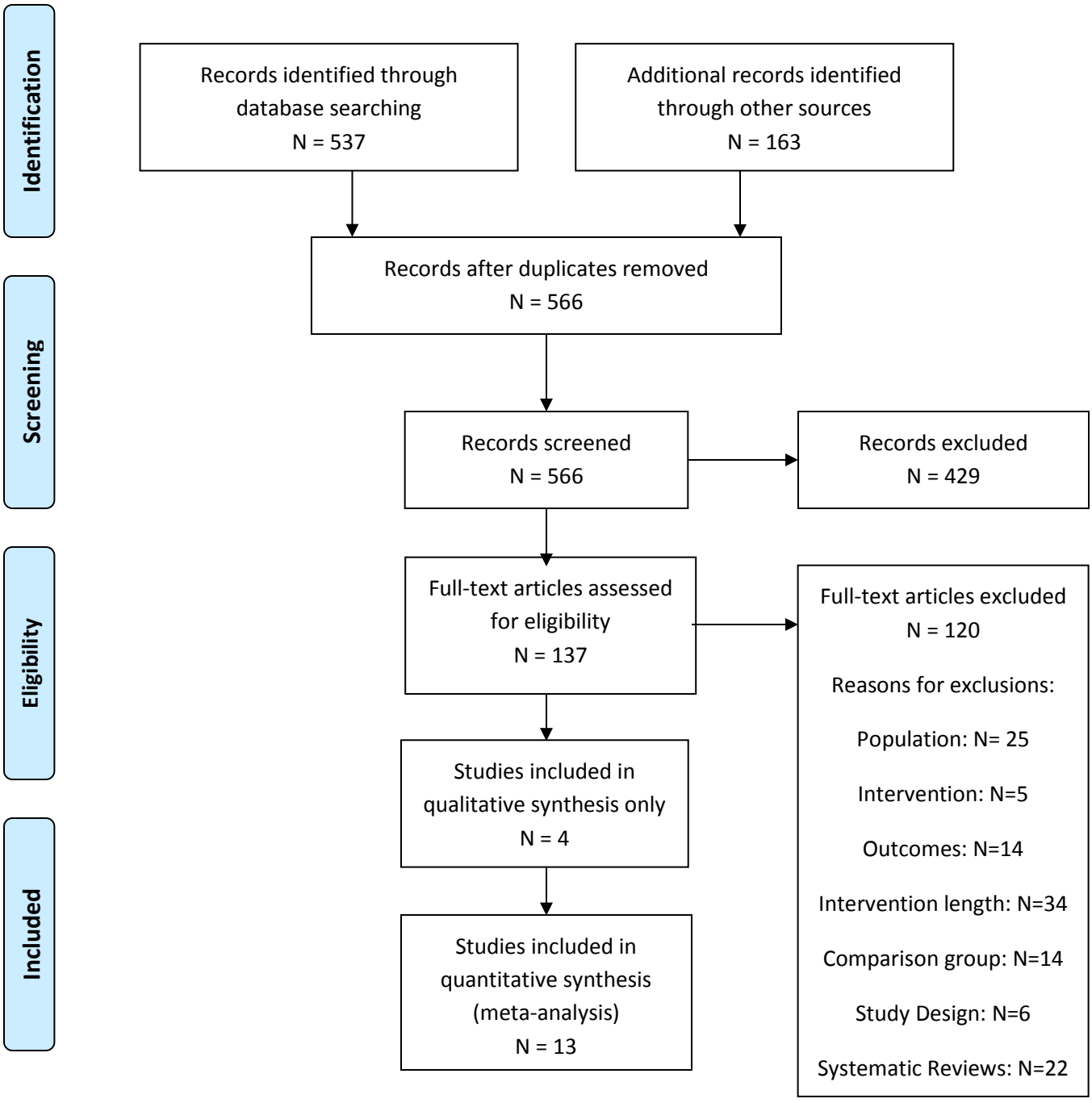


Figure 1. Analytic Framework for Mild Cognitive Impairment Evidence Review



PRISMA 2009 Flow Diagram – Treatment



PRISMA 2009 Flow Diagram – Test Properties

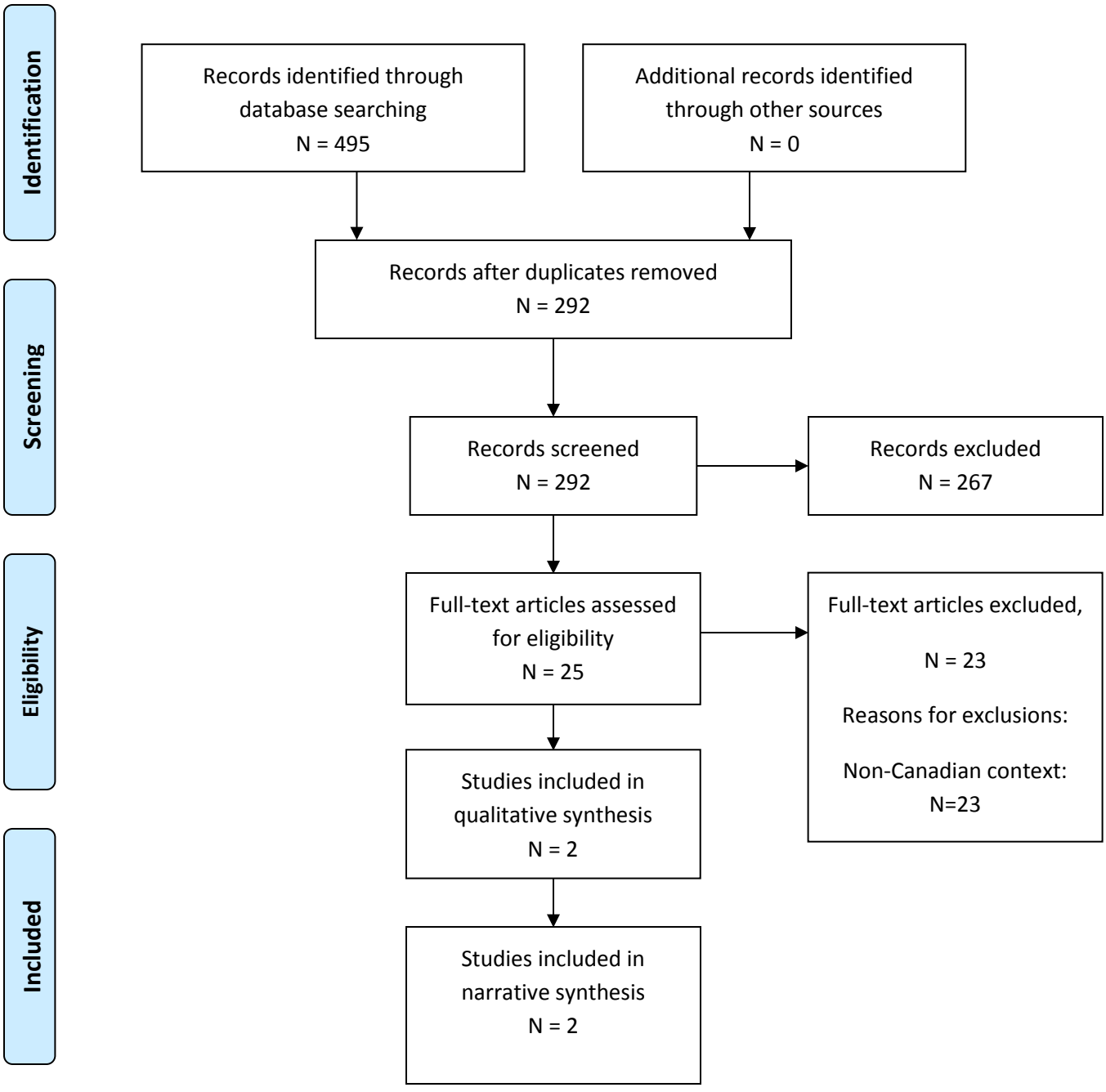


Table 1: Characteristics of Included Studies

Study/Location	de Jager 2012;[22] UK *Companion paper:* Smith 2010[36]
Objective	To determine the effect of B vitamins on cognitive and clinical decline
Methods	Design: RCT Recruitment: recruited through advertisements in the local newspaper or radio seeking elderly people with concerns about their memory Inclusion Criteria: age ≥70 years; study partner available as informant, and diagnosis of amnestic or non-amnestic MCI according to Petersen's criteria Exclusion Criteria: diagnosis of dementia or being treated with anti-dementia drugs; active cancer; major stroke within past 3 months; treatment with methotrexate, anti-cancer or anti-epileptic drugs, or taking folic acid >300 mg/d pyridoxine >3 mg/d or vitamin B12 >1.5 mg/d by mouth or any dose by injection
Participants	Sample: n=271 Intervention n=138; Control n=133 Mean Age (SD): Intervention: 76.8 (5.1) years; Control: 76.7 (4.8) years Gender [Female n(%)]: Intervention: 70 (63.6); Control: 73 (64.6) Loss to Follow-up Intervention n=23; Control n=20
Intervention	Description of Intervention: daily dose of TrioBe Plus W, containing 0.8mg folic acid, 0.5mg cyanocobalamin and 20mg pyridoxine HCl Description of Control: placebo Duration of Intervention: 24 months Length of Follow-up: immediate post

Study/Location	Doody 2009;[20] US
Objective	To investigate the effect of 48 weeks of donepezil treatment on amnestic MCI
Methods	Design: RCT Recruitment: not reported Inclusion Criteria: global Clinical Dementia Rating (CDR) score of 0.5 at screening with the Memory Box score of 0.5 or 1.0, with no more than two other box scores rated as high as 1.0, and no box score 1.0; Mini-Mental State

	Examination (MMSE) score 24 –28 inclusive (or 24 –30 before protocol amendment); Logical Memory II Delayed Paragraph Recall subtest of the Wechsler Memory Scale–Revised score 8 (16 or more years of education), 4 (8 –15 years of education), or 2 (0 –7 years of education); and Rosen modified Hachinski Ischemia scale score ; an informant; a CT scan or MRI study within 12 months of screening showing no clinical evidence of infection, infarction, other focal lesions, or clinically significant comorbid pathologies Exclusion Criteria: diagnosis of probable or possible vascular dementia; another form of dementia; a neurologic or psychiatric disorder; a sleep disorder that could affect cognitive performance; drug or alcohol abuse or dependence within the previous 5 years; uncontrolled hypertension regardless of antihypertensive medication; uncontrolled diabetes mellitus; any medical condition deemed incompatible with study participation; past treatment with a ChEI or memantine for 1 month or within 3 months of screening; anticholinergics, anticonvulsants, antiparkinsonian agents, stimulants, cholinergic agents, antipsychotics, or antidepressants or anxiolytics with anticholinergic or procholinergic effects
Participants	Sample: n= 821 Intervention n=409; Control n=412 Mean Age (SD): Intervention: 70.2 (9.71) years; Control: 69.8 (10.32) years Gender [Female (%)]: Intervention: 48.3%; Control: 42.6% Loss to Follow-up: Intervention: n=165; Control: n=114
Intervention	Description of Intervention: donepezil (5 mg/day for 6 weeks, 10 mg/day for 42 weeks) Description of Control: placebo Duration of Intervention: 48 weeks Length of Follow-up: immediate post

Study/Location	Feldman 2007;[12] Canada
Objective	To assess the effect of rivastigmine in patients with MCI on the time to clinical diagnosis of Alzheimer's disease (AD) and the rate of cognitive decline
Methods	Design: RCT Recruitment: referral to the research centres, through advertising, or from patients known to the investigators at the participating research centres Inclusion Criteria: entry score of less than 13 on the 17-item Hamilton rating

	scale for depression (HAM-D) with HAM-D item 1 (depressed mood) of 1 or lower Exclusion Criteria: patients who met the AD diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders IV or the AD criteria of the National Institute of Neurological and Communicative Disorders and Stroke-AD and Related Disorders Association; any primary neurodegenerative disease; any advanced, severe unstable medical condition that could interfere with assessment; uncontrolled seizure disorder; score of > 4 on the modified Hachinski ischaemic scale; documented history of transient ischaemic attack; any severe or unstable cardiovascular disease or asthmatic conditions; hypersensitivity to cholinesterase inhibitors; treatment with cholinergic drugs during 2 weeks prior to trial, or with rivastigmine during the previous 4 weeks; prior participation in a previous clinical study of rivastigmine
Participants	Sample: n=1018 Intervention n=508; Control n=510 Mean Age (SD): Intervention: 70.3 (7.4) years; Control: 70.6 (7.6) years Gender [Female n(%)]: Intervention: 270 (53.1%); Control: 262 (51.4%) Loss to Follow-up: Intervention: 196; Control: 164
Intervention	Description of Intervention: rivastigmine (3-12 mg daily) Description of Control: placebo Duration of Intervention: up to 48 months Length of Follow-up: immediate post

Study/Location	Lee 2013;[18] Malaysia
Objective	To investigate the effects of fish oil supplementation on cognitive function in elderly people with MCI
Methods	Design: RCT Recruitment: recruited from middle to low socioeconomic households in Cheras, Kuala Lumpur, Malaysia with help of the Housing Management Officer, and residential representatives, as well as using posters, banners, invitation letters, informational lectures and word-of-mouth invitation Inclusion Criteria: diagnosed with MCI residing in their own home; not currently living alone or on a waiting list for a nursing home. Exclusion Criteria: any type of newly diagnosed neurodegenerative disease,

	psychiatric disease or mental disorder; taking omega-3 preparations, vitamin supplements/drinks/injections with doses of vitamin B6, folate or vitamin B12, vitamin E and ginkgo biloba for the past year; suffering from alcohol abuse or from a concomitant disease, such as uncontrolled diabetes, cancer and kidney failure
Participants	Sample: n=36 Intervention n=18; Control n=18 Mean Age (SD): Intervention: 66.4 (5.1) years; Control: 63.5 (3.0) years Gender [Female n(%)]: Intervention: 14 (82.4%); Control: 13 (72.2%) Loss to Follow-up Intervention n= 1; Control n= 0
Intervention	Description of Intervention: three 1-g soft gelatine capsules each day, each containing 430 mg of DHA and 150 mg of EPA. The total dosage for the fish oil group was approximately 1.3 g DHA and 0.45 mg EPA daily Description of Control: placebo Duration of Intervention: 12 months Length of Follow-up: immediate post

Study/Location	Naeini 2014;[19] Iran
Objective	To investigate the effect of Vitamins E and C on cognitive performance among the elderly in Iran
Methods	Design: RCT Recruitment: retiree clubs Inclusion Criteria: not reported Exclusion Criteria: obvious disabling disease; alcohol intake; smoking; routine consumption of neurological or antioxidant drugs
Participants	Sample: n=256 Intervention: n=127; Control n=129 Mean Age (SD): Intervention 66.5 (0.39) years; Control: 66.3 (0.38) years Gender [Female n(%)]: Intervention: 64 (50.4%); Control: 72 (55.8%) Loss to Follow-up: n=40 overall
Intervention	Description of Intervention: 300 mg/d of vitamin E plus 400 mg/d vitamin C

	Description of Control: placebo Duration of Intervention: 12 months Length of Follow-up: immediate post

Study/Location	Petersen 2005; [23] US; Canada *Companion papers:* Lu 2009[37]
Objective	To determine if there is a benefit of using donepezil or vitamin E in patients with MCI
Methods	Design: RCT Recruitment: recruited from 69 Alzheimer's Disease Cooperative Study sites Inclusion Criteria: have amnestic MCI of a degenerative nature; impaired memory; a Logical Memory delayed-recall score approximately 1.5 to 2 SD below an education-adjusted norm; a Clinical Dementia Rating of 0.5; a score of 24 to 30 on the Mini–Mental State Examination; age 55-90 years
Participants	Sample: n=769 Intervention 1 (donepezil) n= 253; Intervention 2 (Vitamin E) n= 257; Control n= 259 Mean Age (SD): Intervention 1: 73.1 (7.1) years; Intervention 2:72.8 (7.3) years; Control: 72.9 (7.6) years Gender [Female n(%)]: Intervention 1: 112 (44%); Intervention 2: 119 (46%); Control: 121 (47%) Loss to Follow-up: not reported
Intervention	Description of Intervention: Intervention 1 (donepezil, placebo Vitamin E and multivitamin): initial dose of 5 mg daily; increased to 10 mg daily after 6 weeks Intervention 2 (Vitamin E, placebo donepezil, multivitamin): initial dose of Vitamin E of 1000 IU daily; increased to 2000 IU daily after 6 weeks Description of Control: placebo donepezil, placebo vitamin E, and multivitamin Duration of Intervention: 36 months Length of Follow-up: immediate post

Study/Location	Rojas 2013;[17] Argentina
Objective	To examine the efficacy of a six-month cognitive intervention program in patients with MCI and to assess patients' condition at one year follow-up
Methods	Design: RCT Recruitment: referral pool of 120 community-dwelling patients who had consulted the memory clinic of a public general hospital between January 2002 and April 2008 Inclusion Criteria: all MCI subtypes Exclusion Criteria: other neurologic diseases or major psychiatric diagnoses consistent with the Diagnostic and Statistical Manual of Mental Disorders criteria; drug or alcohol abuse or dependence in the past five years; treatment with cholinesterase inhibitors (donepezil, rivastigmine, or galantamine) or memantine
Participants	Sample: n=46 Intervention: n=24; Control: n=22 Mean Age (SD): Intervention: 72 (14.29) years; Control: 76.93 (7.05) years Gender [Female n(%)]: Intervention: 6 (25%); Control: 7 (32%) Loss to Follow-up: Intervention n=9; Control n=7
Intervention	Description of Intervention: multi-modal intervention program included cognitive stimulation training sessions and cognitive training delivered by two experienced neurophysiologists in 2 weekly group (4-5 participants) sessions of 120 minutes located in hospital-based outpatient memory clinics over 6 months Description of Control: no treatment Duration of Intervention: 6 months Length of Follow-up: 6 months

Study/Location	Suzuki 2012;[14] Japan
Objective	To examine the effects of a multicomponent exercise program on the cognitive function of older adults with aMCI
Methods	Design: RCT Recruitment: volunteer databases Inclusion Criteria: community dwelling adults ≥ 65 years; Petersen criteria for MCI

	Exclusion Criteria: a CDR = 0, 1, 2, and 3; a history of neurological, psychiatric, and cardiac disorders or other severe health issues; use of donepezil; loss of independence in basic activities of daily living (ADL); current participation in other research projects
Participants	Sample: n=50 Intervention: n=25; Control: n=25 Mean Age (SD): Intervention: 75.3 (7.5) years; Control: 76.8 (6.8) years Gender [Female n(%)]: Intervention: 12 (48%); Control: 11(44%) Loss to Follow-up: Intervention: n= 1; Control n= 2
Intervention	Description of Intervention: multicomponent exercise group under the supervision of physiotherapists for 90 min/d, 2 d/wk, for a total of 80 times over 12 months Description of Control: three education classes on health promotion (information on aging, healthy diet, oral care, brain image diagnosis, prevention of urinary incontinence, and health checks) Duration of Intervention: 12 months Length of Follow-up: immediate post

Study/Location	Suzuki 2013;[21] Japan
Objective	To examine the effect of multicomponent exercise program on memory function in older adults with MCI
Methods	Design: RCT Recruitment: recruited from two volunteer databases; selected by random sampling or at medical check-up in Obu, Japan Inclusion Criteria: community-dwelling individuals aged ≥ 65 years; meet Petersen criteria for MCI; objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests Exclusion Criteria: a CDR=0, or a CDR of 1–3; a history of neurological, psychiatric, or cardiac disorders or other severe health issues; use of donepezil; impairment in basic activities of daily living (ADL); participation in other research project
Participants	Sample: n=100

	Intervention: n= 50; Control: n= 50 Mean Age (SD): Intervention= 74.8 (7.4) years; Control= 75.8 (6.1) years Gender [Female n(%)]: Intervention n= 25 (50%); Control n=24 (48%) Loss to Follow-up Intervention: n= 3; Control n= 5
Intervention	Description of Intervention: six-month, multicomponent exercise program including biweekly 90-minute sessions involving aerobic exercise, muscle strength training, postural balance retraining, and dual-task training and focus on promoting exercise and behaviour change Description of Control: two education classes on health promotion: information regarding healthy diet, oral care, prevention of urinary incontinence, and health checks Duration of Intervention: 6 months Length of Follow-up immediate post

Study/Location	Tsolaki 2000;[15] Greece
Objective	This study aimed to examine the effectiveness of a holistic cognitive rehabilitation program on patients with MCI
Methods	Design: RCT Recruitment: outpatients of the memory and dementia clinic of the G Papanikolaou general hospital and day centres of the Greek Alzheimer Association between 2000 and 2008 Exclusion Criteria: stroke history or evidence of ischemic lesions; use of cholinesterase inhibitors; diagnosis of dementia; lack of insight into their deficits and visual/hearing impairment or reading/writing disability sufficient to interfere with training
Participants	Sample: n=196 Intervention n= 122; Control n= 79 Mean Age (SD): Intervention: 68.45(6.99) years; Control: 66.86 (8.79) years Gender [Female n(%)]: Intervention: 72 (59%); Control: 54 (68%) Loss to Follow-up: Intervention: n=18; Control: n=5
Intervention	Description of Intervention: Therapeutic Techniques of nPhTh: holistic approach including cognitive training, cognitive stimulation and psychotherapeutic techniques

	Description of Control: no therapy Duration of Intervention: 6 months Length of Follow-up: immediate post

Study/Location	Wei 2014;[16] China
Objective	To examine the effect of handball training on cognitive ability in elderly with MCI
Methods	Design: RCT Recruitment: not reported Inclusion Criteria: aged 60 to 75 years old; existing subjective or objective cognitive impairment; MMSE Score ≤26 points, the level of Global Deterioration Scale assessment is between 2 and 3; activity of daily living scale (ADL) Score ≤18 points; Hachinski ischemia index (HIS) ≤4 points; course of cognitive impairment>3 months; normal or corrected-to-normal hearing and vision Exclusion criteria: depression (self-rating depression scale standard <53); history of drug use, such as memory-improving drugs; body movement disorder
Participants	Sample: n=60 Intervention: n= 30; Control: n= 30 Mean Age (SD): Intervention: 66.73 (5.48); Control: 65.27 (4.63) Gender [Female n(%)]: Intervention: 9 (30%); Control: 11 (37%) Loss to Follow-up: not reported
Intervention	Description of Intervention: two groups (15 participants per group) exercised respectively under the supervision of the well-trained nurses for 30 min/day, 5days/week, for a total of 120 times over 6 months Description of Control: The control group maintained the original life entertainment, such as cards playing, etc. Duration of Intervention: 6 months Length of Follow-up immediate post

Study/Location	Winblad 2008;[13] Canada; US
Objective	To determine the safety of galantamine in patients with MCI, its impact on cognition and global functioning, and its potential to delay progression to dementia
Methods	Design: RCT; (two studies are included in this trial) Recruitment: seven centres in the US and Canada enrolled participants in both studies Inclusion Criteria: ≥50 years with gradual onset and slow progression of declining cognitive ability by history; CDR score of 0.5 and CDR memory score 0.5, and insufficient impairment of cognition and activities of daily living to meet diagnostic criteria for dementia; Delayed Recall score 10 on the New York University Paragraph Recall test; sufficient visual, hearing, and communication capabilities (glasses and hearing aids permitted); willingness to complete serial standard tests of cognitive function; ability to read, write, and fully understand the language of the cognitive scales used; consistent informant accompaniment to scheduled study visits Exclusion Criteria: neurodegenerative disorders or other conditions possibly resulting in cognitive impairment (e.g.,Parkinson disease, Pick's disease, Huntington chorea, cerebral trauma, stroke, hypoxic cerebral damage, vitamin deficiency states, CNS infections, AIDS, brain cancer, significant endocrine or renal disease, or mental retardation); current, clinically significant cardiovascular disease; a history of drug or alcohol abuse; participants with contraindications to the use of MRI
Participants	**Study 1:** Sample: n=990 Intervention: n= 494; Control: n= 496 Mean Age (SD): Intervention: 69.2 (9.07) years; Control: 70.1 (9.14) years Gender [Female n(%)]: Intervention: 258 (52%); Control: 273 (55%) Loss to Follow-up: Intervention: n=211; Control: n=154 **Study 2:** Sample: n=1058 Intervention: n=532; Control n=526 Mean Age (SD): Intervention: 70.6 (8.65) years; Control: 70.9 (8.72) years Gender [Female n(%)]: Intervention: 293 (55%); Control: 310 (59%)

	Loss to Follow-up: Intervention: n=215; Control: n=141
Intervention	Description of Intervention: galantamine was administered at 4 mg BID for 1 month, then 8 mg BID for 1 month. If well tolerated, the dose could be titrated to 12 mg BID, but could be lowered back to 8 mg BID after 1 month, if necessary; dose selected at month 3 (8 or 12 mg BID) was fixed for the remainder of the 24-month study Description of Control: placebo Duration of Intervention: 24 months Length of Follow-up immediate post

Table 2: Risk of Bias

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome data	Selective Reporting	Other	Overall
Doody[20]	L	L	L	L	L	H	L
Feldman[12]	L	L	L	H	L	H	U
Petersen[23]	U	U	L	L	L	L	U
Salloway[24]	U	U	L	H	L	H	U
Winblad[13]	U	U	L	L	L	H	U
Suzuki[14]	U	U	L	L	L	H	U
Tsai[25]	L	U	L	L	L	H	U
de Jager[22]	L	L	L	L	L	U	L
Tsolaki[15]	U	U	U	L	L	L	U
van Uffelen[26]	L	L	L	L	L	H	L
Wei[16]	U	U	H	U	L	U	U
Suzuki[21]	L	L	L	L	L	L	L
Rojas[17]	U	U	L	H	L	H	U
Lee[18]	L	U	L	L	L	H	U
Naeini[19]	U	U	L	L	L	L	U
Opizzi[27]	U	U	L	L	L	H	U
Salem[28]	L	L	L	L	L	H	L

Appendix A: Search Strategies for Treatment

Treatment (limited to MCI)

Medline-OVID

December 9, 2014

1. Dementia/
2. Alzheimer Disease/
3. Aphasia, Primary Progressive/
4. Dementia, Vascular/
5. Dementia, Multi-Infarct/
6. Frontotemporal Dementia/
7. Delirium, Dementia, Amnestic, Cognitive Disorders/
8. dementia.ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. Cognition Disorders/
11. cognitive impairment$.ti.
12. cognitive decline.ti.
13. cognitive loss.ti.
14. cognitive disorder$.ti.
15. 10 or 11 or 12 or 13 or 14
16. clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/
17. (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
18. control groups/ or double-blind method/ or single-blind method/
19. random$.ti,ab.
20. placebo*.ti,ab.
21. clinical trial$.ti,ab.
22. controlled trial$.ti,ab.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 9 and 23
25. 15 and 23
26. statin$.mp.
27. Hydroxymethylglutaryl-CoA Reductase Inhibitors/
28. lovastatin.mp.
29. simvastatin.mp.
30. cerivastatin.mp.
31. atorvastatin.mp.
32. rosuvastatin.mp.
33. pravastatin.mp.
34. fluvastatin.mp.
35. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 24 and 35
37. limit 36 to ed=20121201-20141209
38. 25 and 35
39. limit 38 to ed=20121201-20141209
40. Antihypertensive Agents/
41. Antihypertensive*.ti,ab.
42. Diuretics/
43. Diuretic*.ti,ab.
44. exp Adrenergic beta-Antagonists/
45. Adrenergic beta Antagonist*.ti,ab.
46. beta blocker*.ti,ab.
47. exp Adrenergic alpha-Antagonists/
48. Adrenergic alpha Antagonist*.ti,ab.
49. alpha blocker*.ti,ab.
50. Angiotensin-Converting Enzyme Inhibitors/
51. ace inhibitor*.ti,ab.
52. Angiotensin Converting Enzyme Inhibitor*.ti,ab.
53. Calcium Channel Blockers/
54. Calcium Channel Blocker*.ti,ab.

55. Vasodilator Agents/
56. Vasodilator*.ti,ab.
57. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58. 24 and 57
59. limit 58 to ed=20121201-20141209
60. 25 and 57
61. limit 60 to ed=20121201-20141209
62. Aspirin/
63. aspirin*.ti,ab.
64. 62 or 63
65. 24 and 64
66. limit 65 to ed=20121201-20141209
67. 25 and 64
68. limit 67 to ed=20121201-20141209
69. Anti-Inflammatory Agents, Non-Steroidal/
70. Nonsteroidal Anti Inflammatory Agent*.ti,ab.
71. Non steroidal Anti Inflammatory Agent*.ti,ab.
72. Nonsteroidal Antiinflammatory Agent*.ti,ab.
73. Non steroidal Antiinflammatory Agent*.ti,ab.
74. NSAID*.ti,ab.
75. Diclofenac/
76. Diclofenac.ti,ab.
77. Ibuprofen/
78. Ibuprofen.ti,ab.
79. Indomethacin/
80. Indomethacin.ti,ab.
81. Ketoprofen/
82. Ketoprofen.ti,ab.
83. Ketorolac/
84. Ketorolac.ti,ab.
85. Naproxen/
86. Naproxen.ti,ab.
87. Piroxicam/
88. Piroxicam.ti,ab.
89. Salicylates/
90. Salicylate*.ti,ab.
91. Sulindac/
92. Sulindac.ti,ab.
93. Cyclooxygenase Inhibitors/
94. Cyclooxygenase Inhibitor*.ti,ab.
95. Cyclooxygenase 2 Inhibitors/
96. Cyclooxygenase 2 Inhibitor*.ti,ab.
97. COX 2 Inhibitor*.ti,ab.
98. 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97

99. 24 and 98
100. limit 99 to ed=20121201-20141209
101. 25 and 98
102. limit 101 to ed=20121201-20141209
103. Gonadal Steroid Hormones/
104. Hormone Replacement Therapy/
105. Estrogen Replacement Therapy/
106. Estradiol/
107. Estrogens/
108. "Estrogens, Conjugated (USP)"/
109. Medroxyprogesterone Acetate/
110. Progesterone/
111. Progesterone Congeners/
112. Androgens/
113. Testosterone/
114. Dehydroepiandrosterone/
115. Dehydroepiandrosterone Sulfate/
116. Norethindrone/
117. Hormone Replacement Therapy.ti,ab.
118. estrogen*.ti,ab.
119. Estradiol.ti,ab.
120. Medroxyprogesterone.ti,ab.
121. Progesterone.ti,ab.
122. Androgens.ti,ab.
123. Testosterone.ti,ab.
124. Dehydroepiandrosterone.ti,ab.
125. Norethindrone.ti,ab.
126. 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125
127. 24 and 126
128. limit 127 to ed=20121201-20141209
129. 25 and 126
130. limit 129 to ed=20121201-20141209
131. Cholinesterase inhibitors/
132. Cholinesterase Inhibitor*.ti,ab.
133. Anticholinesterase*.ti,ab.
134. Galantamine/
135. Galantamine.ti,ab.
136. Tacrine/
137. Tacrine.ti,ab.
138. rivastigmine.ti,ab.
139. donepezil.ti,ab.
140. 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139
141. 24 and 140
142. limit 141 to ed=20121201-20141209
143. 25 and 140

144. limit 143 to ed=20121201-20141209
145. Memantine/
146. Memantine.ti,ab.
147. 145 or 146
148. 24 and 147
149. limit 148 to ed=20121201-20141209
150. 25 and 147
151. limit 150 to ed=20121201-20141209
152. folic acid/
153. folic acid.ti,ab.
154. folate.ti,ab.
155. Vitamin B Complex/
156. Thiamine/
157. Thiamine.ti,ab.
158. Thiamin.ti,ab.
159. Thiamine Monophosphate/
160. Thiamine Pyrophosphate/
161. Thiamine Triphosphate/
162. Vitamin B 1.ti,ab.
163. Vitamin B1.ti,ab.
164. Riboflavin/
165. Riboflavin.ti,ab.
166. Vitamin B 2.ti,ab.
167. Vitamin B2.ti,ab.
168. Vitamin B 6/
169. Vitamin B 6.ti,ab.
170. Vitamin B6.ti,ab.
171. Pyridoxine/
172. Pyridoxine.ti,ab.
173. Vitamin B 12/
174. Vitamin B 12.ti,ab.
175. Vitamin B12.ti,ab.
176. Cobamides/
177. Hydroxocobalamin/
178. Cobalamin.ti,ab.
179. Cyanocobalamin.ti,ab.
180. Cobamides.ti,ab.
181. Hydroxocobalamin.ti,ab.
182. 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181
183. 24 and 182
184. limit 183 to ed=20121201-20141209
185. 25 and 182
186. limit 185 to ed=20121201-20141209
187. Antioxidants/

188. Antioxidant*.ti,ab.
189. Vitamin E/
190. Vitamin E.ti,ab.
191. alpha-Tocopherol/
192. Tocopherols/
193. Tocopherol*.ti,ab.
194. Ascorbic acid/
195. Ascorbic acid.ti,ab.
196. Vitamin C.ti,ab.
197. ascorbate.ti,ab.
198. beta carotene/
199. beta carotene.ti,ab.
200. 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199
201. 24 and 200
202. limit 201 to ed=20121201-20141209
203. 25 and 200
204. limit 203 to ed=20121201-20141209
205. fatty acids, omega-3/ or alpha-linolenic acid/ or docosahexaenoic acids/ or neuroprostanes/ or eicosapentaenoic acid/
206. Omega 3.ti,ab.
207. n 3 Fatty Acid*.ti,ab.
208. Linolenic Acids/
209. Linolenic Acid*.ti,ab.
210. Fatty Acids, Essential/
211. Dietary Fats, Unsaturated/
212. Fish Oils/
213. fish oil*.ti,ab.
214. diet* fatty acid*.ti,ab.
215. Diet, Mediterranean/
216. Mediterranean diet*.ti,ab.
217. 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216
218. 24 and 217
219. limit 218 to ed=20121201-20141209
220. 25 and 217
221. limit 220 to ed=20121201-20141209
222. Exercise/
223. Exercise Therapy/
224. Physical Fitness/
225. Walking/
226. exercis*.ti,ab.
227. physical activity.ti,ab.
228. physical training.ti,ab.
229. strength training.ti,ab.
230. resistance training.ti,ab.
231. Resistance Training/
232. aerobic training.ti,ab.

233. cardiovascular training.ti,ab.
234. endurance training.ti,ab.
235. flexibility training.ti,ab.
236. Relaxation/
237. relaxation.ti,ab.
238. Tai Ji/
239. Tai Chi.ti,ab.
240. walking.ti,ab.
241. Yoga/
242. yoga.ti,ab.
243. Dancing/
244. (dancing or dance).ti,ab.
245. 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244
246. 24 and 245
247. limit 246 to ed=20121201-20141209
248. 25 and 245
249. limit 248 to ed=20121201-20141209
250. Caregivers/
251. caregiver*.ti,ab.
252. caregiving.ti,ab.
253. (carer or carers).ti,ab.
254. Self-Help Groups/
255. self help.ti,ab.
256. Respite Care/
257. care giver*.ti,ab.
258. Respite Care/
259. respite.ti,ab.
260. Family Therapy/
261. family therapy.ti,ab.
262. Social Support/
263. social support*.ti,ab.
264. Day Care/
265. (day care or daycare).ti,ab.
266. skills training.ti,ab.
267. Health Education/
268. health education.ti,ab.
269. education.fs.
270. education, continuing/ or education, medical, continuing/ or education, nursing, continuing/
271. 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270
272. 24 and 271
273. limit 272 to ed=20121201-20141209
274. Counseling/
275. Directive Counseling/
276. Cognitive Therapy/

277. cognitive therapy.ti,ab.
278. psychotherapy/ or psychotherapy, brief/
279. Behavior Therapy/
280. psychotherap*.ti,ab.
281. counsel*.ti,ab.
282. 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281
283. 24 and 282
284. limit 283 to ed=20121201-20141209
285. 25 and 282
286. limit 285 to ed=20121201-20141209
287. (cognitive* adj3 engage*).ti,ab.
288. (creative* adj3 engage*).ti,ab.
289. (cognitive* adj3 stimulat*).ti,ab.
290. cognitive training.ti,ab.
291. cognitive intervention*.ti,ab.
292. group reminiscence.ti,ab.
293. reality orientation.ti,ab.
294. Reality Therapy/
295. reality therapy.ti,ab.
296. cognitive exercis*.ti,ab.
297. 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296
298. 24 and 297
299. limit 298 to ed=20121201-20141209
300. 25 and 297
301. limit 300 to ed=20121201-20141209
302. Case Management/
303. Patient Care Management/
304. care manage*.ti,ab.
305. case manage*.ti,ab.
306. 302 or 303 or 304 or 305
307. 24 and 306
308. limit 307 to ed=20121201-20141209
309. 25 and 306
310. limit 309 to ed=20121201-20141209
311. ((multicomponent or multi component or multidisciplinary or multi disciplinary or multimodal or multi modal) adj3 (treatment* or program* or intervention*)).ti,ab.
312. 24 and 311
313. limit 312 to ed=20121201-20141209
314. 25 and 311
315. limit 314 to ed=20121201-20141209
316. 37 or 39 or 59 or 61 or 66 or 68 or 100 or 102 or 128 or 130 or 142 or 144 or 149 or 151 or 184 or 186 or 202 or 204 or 219 or 221 or 247 or 249 or 273 or 284 or 286 or 299 or 301 or 308 or 310 or 313 or 315
317. limit 316 to (english or french)
318. limit 317 to humans
319. limit 317 to animals

320. 319 not 318
321. 317 not 320
322. remove duplicates from 321
323. Mild Cognitive Impairment/
324. ((mild or slight) adj2 (cognitive or cognition) adj2 (disorder* or defect* or deficit* or disabilit* or dysfunction or impair*)).tw.
325. 323 or 324
326. 322 and 325

EMBASE-OVID

December 09, 2014

1. Dementia/
2. Alzheimer Disease/
3. Aphasia, Primary Progressive/
4. multiinfarct dementia/
5. frontotemporal dementia/
6. dementia.ti.
7. cognitive defect/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. cognitive impairment$.ti.
10. cognitive decline.ti.
11. cognitive loss.ti.
12. cognitive disorder$.ti.
13. 9 or 10 or 11 or 12
14. "controlled clinical trial (topic)"/ or "clinical trial (topic)"/ or "randomized controlled trial (topic)"/
15. control group/
16. double blind procedure/
17. controlled clinical trial/ or clinical trial/ or randomized controlled trial/
18. random$.ti,ab.
19. placebo*.ti,ab.
20. clinical trial$.ti,ab.
21. controlled trial$.ti,ab.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 8 and 22
24. 13 and 22
25. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
26. lovastatin.mp.
27. simvastatin.mp.
28. cerivastatin.mp.
29. atorvastatin.mp.
30. rosuvastatin.mp.
31. pravastatin.mp.
32. fluvastatin.mp.
33. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34. 23 and 33
35. limit 34 to em=201248-201450
36. 24 and 33
37. limit 36 to em=201248-201450
38. exp antihypertensive agent/
39. Antihypertensive*.ti,ab.
40. exp diuretic agent/
41. Diuretic*.ti,ab.
42. exp beta adrenergic receptor blocking agent/
43. Adrenergic alpha Antagonist*.ti,ab.
44. alpha blocker*.ti,ab.
45. dipeptidyl carboxypeptidase inhibitor/
46. ace inhibitor*.ti,ab.
47. Angiotensin Converting Enzyme Inhibitor*.ti,ab.
48. exp calcium channel blocking agent/
49. Calcium Channel Blocker*.ti,ab.
50. exp vasodilator agent/
51. Vasodilator*.ti,ab.
52. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 23 and 52
54. limit 53 to em=201248-201450
55. 24 and 52
56. limit 55 to em=201248-201450
57. acetylsalicylic acid/
58. aspirin*.ti,ab.
59. 57 or 58
60. 23 and 59
61. limit 60 to em=201248-201450
62. 24 and 59
63. limit 62 to em=201248-201450
64. exp nonsteroid antiinflammatory agent/
65. Nonsteroidal Anti Inflammatory Agent*.ti,ab.
66. Non steroidal Anti Inflammatory Agent*.ti,ab.
67. Nonsteroidal Antiinflammatory Agent*.ti,ab.
68. Non steroidal Antiinflammatory Agent*.ti,ab.
69. NSAID*.ti,ab.
70. diclofenac/
71. Diclofenac.ti,ab.
72. ibuprofen/
73. Ibuprofen.ti,ab.
74. indometacin/
75. Indomethacin.ti,ab.
76. ketoprofen/
77. Ketoprofen.ti,ab.
78. ketorolac/
79. Ketorolac.ti,ab.

80. Naproxen/
81. Naproxen.ti,ab.
82. Piroxicam/
83. Piroxicam.ti,ab.
84. exp salicylic acid derivative/
85. Salicylate*.ti,ab.
86. sulindac/
87. Sulindac.ti,ab.
88. exp cyclooxygenase 2 inhibitor/
89. Cyclooxygenase 2 Inhibitor*.ti,ab.
90. exp prostaglandin synthase inhibitor/
91. Cyclooxygenase Inhibitor*.ti,ab.
92. COX 2 Inhibitor*.ti,ab.
93. 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92
94. 23 and 93
95. limit 94 to em=201248-201450
96. 24 and 93
97. limit 96 to em=201248-201450
98. exp sex hormone/
99. exp hormone substitution/
100. estradiol/
101. exp estrogen/
102. exp conjugated estrogen/
103. medroxyprogesterone acetate/
104. progesterone/
105. progesterone derivative/
106. exp androgen/
107. testosterone/
108. prasterone/
109. prasterone sulfate/
110. norethisterone/
111. Hormone Replacement Therapy.ti,ab.
112. estrogen*.ti,ab.
113. Estradiol.ti,ab.
114. Medroxyprogesterone.ti,ab.
115. Progesterone.ti,ab.
116. Androgens.ti,ab.
117. Testosterone.ti,ab.
118. Dehydroepiandrosterone.ti,ab.
119. Norethindrone.ti,ab.
120. 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119
121. 23 and 120
122. limit 121 to em=201248-201450
123. 24 and 120

124. limit 123 to em=201248-201450
125. exp cholinesterase inhibitor/
126. Cholinesterase Inhibitor*.ti,ab.
127. Anticholinesterase*.ti,ab.
128. galantamine/
129. Galantamine.ti,ab.
130. tacrine/
131. Tacrine.ti,ab.
132. rivastigmine.ti,ab.
133. donepezil.ti,ab.
134. 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133
135. 23 and 134
136. limit 135 to em=201248-201450
137. 24 and 136
138. limit 137 to em=201248-201450
139. memantine/
140. Memantine.ti,ab.
141. 139 or 140
142. 23 and 141
143. limit 142 to em=201248-201450
144. 24 and 141
145. limit 144 to em=201248-201450
146. folic acid/
147. folic acid.ti,ab.
148. folate.ti,ab.
149. vitamin B complex/
150. thiamine phosphate/
151. cocarboxylase/
152. thiamine triphosphate/
153. Vitamin B 1.ti,ab.
154. Vitamin B1.ti,ab.
155. exp riboflavin/
156. Riboflavin.ti,ab.
157. Vitamin B 2.ti,ab.
158. Vitamin B2.ti,ab.
159. Vitamin B6.ti,ab.
160. Vitamin B 6.ti,ab.
161. pyridoxine/
162. Pyridoxine.ti,ab.
163. cyanocobalamin/
164. Vitamin B 12.ti,ab.
165. Vitamin B12.ti,ab.
166. cobamamide/
167. hydroxocobalamin/
168. Cobalamin.ti,ab.
169. Cyanocobalamin.ti,ab.

170. Cobamides.ti,ab.
171. Hydroxocobalamin.ti,ab.
172. 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171
173. 23 and 172
174. limit 173 to em=201248-201450
175. 24 and 172
176. limit 175 to em=201248-201450
177. exp antioxidant/
178. Antioxidant*.ti,ab.
179. Vitamin E.ti,ab.
180. alpha tocopherol/
181. exp tocopherol/
182. Tocopherol*.ti,ab.
183. exp ascorbic acid/
184. Ascorbic acid.ti,ab.
185. Vitamin C.ti,ab.
186. ascorbate.ti,ab.
187. beta carotene/
188. beta carotene.ti,ab.
189. 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188
190. 23 and 189
191. limit 190 to em=201248-201450
192. 24 and 189
193. limit 192 to em=201248-201450
194. omega 3 fatty acid/
195. linolenic acid/
196. docosahexaenoic acid/
197. neuroprostane/
198. icosapentaenoic acid/
199. Omega 3.ti,ab.
200. n 3 Fatty Acid*.ti,ab.
201. linolenic acid/
202. Linolenic Acid*.ti,ab.
203. exp essential fatty acid/
204. exp unsaturated fatty acid/
205. fish oil/
206. fish oil*.ti,ab.
207. diet* fatty acid*.ti,ab.
208. Mediterranean diet/
209. Mediterranean diet*.ti,ab.
210. 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209
211. 23 and 210
212. limit 211 to em=201248-201450
213. 24 and 210

214. limit 213 to em=201248-201450
215. exp exercise/
216. exp kinesiotherapy/
217. fitness/
218. walking/
219. exercis*.ti,ab.
220. physical activity.ti,ab.
221. physical training.ti,ab.
222. resistance training/
223. strength training.ti,ab.
224. resistance training.ti,ab.
225. aerobic training.ti,ab.
226. cardiovascular training.ti,ab.
227. endurance training.ti,ab.
228. flexibility training.ti,ab.
229. relaxation.ti,ab.
230. Tai Chi/
231. Tai Chi.ti,ab.
232. yoga/
233. yoga.ti,ab.
234. dancing/
235. (dancing or dance).ti,ab.
236. recreation/
237. 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236
238. 23 and 237
239. limit 238 to em=201248-201450
240. 24 and 237
241. limit 240 to em=201248-201450
242. caregiver/
243. caregiver*.ti,ab.
244. caregiving.ti,ab.
245. (carer or carers).ti,ab.
246. self help/
247. self help.ti,ab.
248. respite care/
249. care giver*.ti,ab.
250. respite.ti,ab.
251. family therapy/
252. family therapy.ti,ab.
253. social support/
254. social support*.ti,ab.
255. day care/
256. (day care or daycare).ti,ab.
257. skills training.ti,ab.
258. health education/

259. health education.ti,ab.
260. education.fs.
261. continuing education/
262. 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261
263. 23 and 262
264. limit 263 to em=201248-201450
265. 24 and 262
266. limit 265 to em=201248-201450
267. counseling/ or directive counseling/ or patient counseling/
268. cognitive therapy/
269. cognitive therapy.ti,ab.
270. exp psychotherapy/
271. behavior therapy/
272. psychotherap*.ti,ab.
273. counsel*.ti,ab.
274. 267 or 268 or 269 or 270 or 271 or 272 or 273
275. 23 and 274
276. limit 275 to em=201248-201450
277. 24 and 274
278. limit 277 to em=201248-201450
279. (cognitive* adj3 engage*).ti,ab.
280. (creative* adj3 engage*).ti,ab.
281. (cognitive* adj3 stimulat*).ti,ab.
282. cognitive training.ti,ab.
283. cognitive intervention*.ti,ab.
284. group reminiscence.ti,ab.
285. reality orientation.ti,ab.
286. reality therapy/
287. cognitive exercis*.ti,ab.
288. 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287
289. 23 and 288
290. limit 289 to em=201248-201450
291. 24 and 288
292. limit 291 to em=201248-201450
293. case management/
294. care manage*.ti,ab.
295. case manage*.ti,ab.
296. 293 or 294 or 295
297. 23 and 296
298. limit 297 to em=201248-201450
299. 24 and 296
300. limit 299 to em=201248-201450
301. ((multicomponent or multi component or multidisciplinary or multi disciplinary or multimodal or multi modal) adj3 (treatment* or program* or intervention*)).ti,ab.
302. 23 and 301

303. limit 302 to em=201248-201450
304. 24 and 301
305. limit 304 to em=201248-201450
306. 35 or 37 or 54 or 56 or 61 or 63 or 95 or 97 or 122 or 124 or 136 or 138 or 143 or 145 or 174 or 176 or 191 or 193 or 212 or 214 or 239 or 241 or 264 or 266 or 276 or 278 or 290 or 292 or 298 or 300 or 303 or 305
307. mild cognitive impairment/
308. ((mild or slight) adj2 (cognitive or cognition) adj2 (disorder* or defect* or deficit* or disabilit* or dysfunction or impair*)).tw.
309. mild dementia*.tw.
310. 307 or 308 or 309
311. 306 and 310
312. mild cognitive impairment/dm, dt, rh, th [Disease Management, Drug Therapy, Rehabilitation, Therapy]
313. 22 and 312
314. limit 313 to em=201248-201450
315. 311 or 314
316. limit 315 to (english or french)
317. limit 316 to conference abstract
318. 316 not 317

Cochrane Central-OVID

December 17 2014
1. Mild Cognitive Impairment/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
2. mild cognitive impairment.tw.
3. ((mild or slight) adj2 (cognitive or cognition) adj2 (disorder* or defect* or deficit* or disabilit* or dysfunction or impair*)).tw.
4. mild dementia*.tw.
5. 2 or 3 or 4
6. (treatment* or program* or intervention* or therap*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. 5 and 6
8. 1 or 7
9. limit 8 to (english or french)
10. limit 9 to yr="2012 -Current"

Appendix B: Search Strategies for Test Properties

Medline-OVID

January 5, 2015

1. Montreal Cognitive Assessment.tw.
2. exp "Sensitivity and Specificity"/
3. exp "reproducibility of results"/
4. exp *Cognition Disorders/di [Diagnosis]
5. 2 or 3 or 4
6. 1 and 5

EMBASE-OVID

January 5 2015

1. Montreal Cognitive Assessment.tw.
2. diagnostic accuracy/
3. "sensitivity and specificity"/
4. measurement precision/ or reproducibility/
5. mild cognitive impairment/di [Diagnosis]
6. "psychometry"/
7. 2 or 3 or 4 or 5 or 6
8. 1 and 7

PsycINFO-OVID

January 5, 2015

1. Montreal Cognitive Assessment.tw.
2. psychometrics/
3. test reliability/ or test validity/
4. 2 or 3
5. 1 and 4

Appendix C: Search Strategies for Contextual Questions

Medline-Ovid

1. "patient acceptance of health care"/
2. patient compliance/
3. exp patient participation/
4. patient satisfaction/
5. patient preference/
6. "treatment refusal"/
7. consumer satisfaction/
8. ((parent? or guardian*) adj3 (acceptance or preference? or satisfaction or experience?)).tw.
9. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
10. (patient? adj3 (acceptance or perference? or satisfaction or experience?)).tw.
11. willingness to pay.tw.
12. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
13. Choice Behavior/
14. standard gamble.ti.
15. standard gamble.tw.
16. time trade off.tw.
17. choice model?ing.mp.
18. survey preferences.mp.
19. preference?.tw.
20. or/1-19
21. Cognition Disorders/
22. cognitive impairment$.ti.
23. cognitive decline.ti.
24. cognitive loss.ti.
25. cognitive disorder$.ti.
26. 21 or 22 or 23 or 24 or 25
27. screen$.ti,ab.
28. Mass Screening/
29. 27 or 28
30. 26 and 29
31. *Cognition Disorders/di [Diagnosis]
32. 30 or 31
33. Dementia/
34. Alzheimer Disease/
35. Aphasia, Primary Progressive/
36. Dementia, Vascular/
37. Dementia, Multi-Infarct/
38. Frontotemporal Dementia/
39. Delirium, Dementia, Amnestic, Cognitive Disorders/
40. dementia.ti.
41. or/33-40
42. screen$.ti,ab.

43. mass screening/
44. 42 or 43
45. 41 and 44
46. *Dementia/di [Diagnosis]
47. *Alzheimer Disease/di [Diagnosis]
48. *Delirium, Dementia, Amnestic, Cognitive Disorders/di [Diagnosis]
49. or/46-48
50. 45 or 49
51. 20 and 50
52. limit 51 to (english or french)
53. limit 52 to yr="2004 - 2015"

EMBASE-Ovid

1. patient attitude/
2. exp patient compliance/
3. patient participation/
4. patient preference/
5. patient satisfaction/
6. refusal to participate/
7. treatment refusal/
8. decision making/ or patient decision making/
9. decision making/
10. consumer attitude/
11. ((parent? or guardian*) adj3 (acceptance or preference? or satisfaction or experience?)).tw.
12. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
13. (patient? adj3 (acceptance or perference? or satisfaction or experience?)).tw.
14. (patient? adj3 (acceptance or perference? or satisfaction)).tw.
15. willingness to pay.tw.
16. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
17. standard gamble.tw.
18. time trade off.tw.
19. choice model?ing.mp.
20. preference?.tw.
21. or/1-20
22. exp *dementia/
23. cognitive defect/
24. cognitive impairment$.ti.
25. cognitive decline.ti.
26. cognitive loss.ti.
27. cognitive disorder$.ti.
28. or/22-27
29. screening/ or mass screening/ or screening test/
30. screen*.ti,ab.
31. 29 or 30
32. 28 and 31

33. 21 and 32
34. limit 33 to (english or french)
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