Diagnosing Mild Cognitive Impairment (MCI) in clinical trials: a systematic review

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ABSTRACT

Objective: To describe how criteria for amnestic Mild Cognitive Impairment (aMCI) have been operationalised in randomised controlled clinical trials (RCTs).

Design: Systematic review.

Information sources: EMBASE, PubMed and PSYCHInfo were searched from their inception to February 2012. Electronic clinical trial registries were also searched (February 2012).

Study selection: RCTs were included where participant selection was made using Petersen et al-defined aMCI. There was no restriction on intervention type or the outcome tested.

Data extraction: For each trial, we extracted information on study design, demographics, exclusion criteria and the operationalisation strategy for the five aMCI diagnostic criteria including: (1) memory complaint, (2) normal general cognitive function, (3) memory impairment, (4) no functional impairment and (5) no dementia.

Results: 223 articles and 278 registered trials were reviewed, of which 22 met inclusion criteria. Various methods were applied for operationalising aMCI criteria resulting in variability in participant selection. Memory complaint and assessment of general cognitive function were the most consistently measured criteria. There was large heterogeneity in the neuropsychological methods used to determine memory impairment. It was not possible to assess the impact of these differences on case selection accuracy for dementia prediction. Further limitations include selective and unclear reporting of how each of the criteria was measured.

Conclusions: The results highlight the urgent need for a standardised approach to map aMCI. Lack of uniformity in clinical diagnosis, however, is not exclusively a problem for MCI but also for other clinical states such as dementia including Alzheimer’s disease, Lewy Body, frontaltemporal or vascular dementia. Defining a uniform approach to MCI classification, or indeed for any classification concept within the field of dementia, should be a priority if further trials are to be undertaken in the older aged population based on these concepts.

ARTICLE SUMMARY

Article focus

- Accurate identification of individuals at risk of dementia or with predementia is important for clinical trial enrolment.
- Diagnosis of predementia is usually made using the amnestic form of Mild Cognitive Impairment (aMCI). While specific criteria for implementation exist, there is no operationalisation protocol.
- Research Question: How have criteria for aMCI been operationalised in randomised controlled clinical trials?

Key messages

- Various methods have been applied for operationalising aMCI criteria in randomised controlled clinical trials resulting in variability in participant selection.
- The results highlight the urgent need for a standardised approach to map aMCI.
- Lack of specific methods for clinical diagnosis is not a problem unique to the field of MCI. Across studies there continues to be inconsistency in the instruments and methodology used to diagnose Alzheimer’s disease and Vascular Dementia, including its prodromal stage, Vascular Cognitive Impairment no Dementia. Revision of diagnostic criteria should be a research priority.

Strengths and limitations of this study

- The review focuses on predementia defined using aMCI. However, not all clinical trials on predementia cognitive states have used this definition of MCI.
- We chose to focus on aMCI as this is one of the commonly applied definitions in clinical and research practice.

INTRODUCTION

As new preventative strategies for dementia are developed, methods to select persons accurately for clinical trial involvement will be needed. In this perspective, Mild Cognitive Impairment (MCI), an intermediate state between normal ageing and dementia, has
become a focus for trials to prevent or delay progression to Alzheimer’s disease. The expectation is that positive results are more likely to be achieved with earlier treatment initiation. While several different definitions exist for MCI, amnestic Mild Cognitive Impairment (aMCI) as defined by Petersen et al is often used in clinical and research practice. However, despite being commonly applied, no standardised method for the operationalisation of each of the five component criteria (figure 1) necessary for an aMCI diagnosis exists, resulting in heterogeneity in diagnostic methods and case ascertainment across studies. Indeed, there are numerous possibilities for the measurement of the five criteria as highlighted in figure 1. The lack of an established diagnostic methodology for identifying cases for clinical trial enrolment is problematic as study-specific participant selection raises questions regarding the nature of the sample selected, while also making cross study comparison and generalisability of findings difficult.

We undertook a systematic review to explore the methods used to classify aMCI cases, defined using Petersen et al criteria, in randomised controlled clinical trials (RCTs). The focus was on inclusion criteria and variation in the operationalisation of each of the five aMCI component criteria as outlined in figure 1.

METHODS
This review has been undertaken with adherence to the PRISMA statement. The review protocol is available on request.

Search strategy
EMBASE (including MEDLINE) and PSYCHInfo were searched using the following keywords and using Medical Subject Heading terms: (‘mild cognitive impairment’ OR MCI) AND (‘randomised controlled trial’ OR ‘randomised controlled trial’ OR RCT). Articles were searched from inception to 6 June 2011, with the search updated on 21 February 2012. Web-based searches, using the term ‘mild cognitive impairment’, were also undertaken in the ISRCTR trial registry (http://www.controlled-trials.com) and on www.clinicaltrials.gov (17 February 2012). Only studies that were published in English were included. Two investigators (BS and TM) independently searched publications using the following inclusion criteria: (1) the study was a RCT; (2) the trial had been completed (was not ongoing or terminated) and results published; (3) the authors report selecting participants using the definition of aMCI as reported in Petersen et al, and could include single or multidomain aMCI subtypes (amendments to criteria were allowed as long as they were stated and Petersen et al was referenced) and (4) the MCI group was analysed separately to the dementia or control groups. The protocol paper or the first publication reporting the primary outcome was selected in case of multiple publications using the same study sample. Titles and abstracts were searched first, followed by the full text of any identified articles. Reviews were also retained and the reference lists of these and each included paper were interrogated. Disagreements were resolved by consensus. Data quality was not assessed as all included studies were RCTs.

Data extraction
Data on the lead author, date of publication, study design (country, site, sampling framework, duration and intervention), demographics (age and gender distributions), trial exclusion criteria, dementia progression rates, outcomes tested and the methods used to operationalise each of the five component criteria for the diagnosis of aMCI were abstracted by two investigators (EP and TM) and checked by a third (MS).

RESULTS
A total of 223 articles were identified from the literature search. From the electronic search, 11 trials were identified from the ISRCTR trial registry and 267 from http://www.clinicaltrials.gov. Based on the title-abstract

**Figure 1** Petersen criteria for amnestic Mild Cognitive Impairment.

1. Subjective memory complaint (preferably corroborated by an informant)  
   **Operationalisation Issues** Participant, informant, single question, questionnaire

2. Normal general cognitive function  
   **Operationalisation Issues** Test selection, use of a cut-off score, adjustments for age, education or prior ability

3. Objective memory impairment  
   **Operationalisation Issues** Test selection, use of a cut-off score, adjustments for age, education or prior ability

4. Preserved activities of daily living (ADL)  
   **Operationalisation Issues** Type of impairment such as instrumental or basic activities of living, degree of difficulty (if any) allowed

5. No dementia  
   **Operationalisation Issues** Impact of diagnostic criteria on caseness
search, 84 articles were identified for full text review. In total, 22 articles met inclusion criteria and were retained for this review. Figure 2 shows the selection process using the PRISMA (2009) Flow Diagram. As shown in Figure 2, articles were mainly excluded as the sample did not appear to be defined using the Petersen et al criteria or had inadequate details to support the use of Petersen et al criteria (eg, only stated an objective cognitive deficit), or the article was a review. Online supplementary table S1A summarises the general characteristics, demographics and outcomes tested in each included article. Online supplementary table S1B summarises the operationalisation protocol used for identifying aMCI cases in each trial.

Trial exclusion criteria varied, but were mainly related to cerebrovascular and cardiovascular disease or health and psychiatric-related conditions that could be associated with cognitive decline. There were also differences in the population sampled (clinic vs community), site (single vs multicentre), duration (eg, 90 days to 4 years) and sample demographics (eg, age range: 50–90 years). Interventions included pharmacological agents and supplementation (including: donepezil,
galantamine, rofecoxib, fluoxetine, lithium treatment, oestrogen treatment (E$_2$), vitamin supplementation (E and B) and supplementation with ω-3 polyunsaturated fatty acids, arachidonic and docosahexaenoic acids), insulin therapy, physical activity, aerobic exercise, cognitive training/rehabilitation programmes (eg, memory training, strategy learning) and combined therapies including cholinesterase inhibitor use combined with a cognitive training programme and physical activity combined with vitamin B supplementation. Outcomes varied extensively across studies and included assessment of cognitive function (in all studies either as a primary or secondary outcome, with no neuropsychological assessment applied consistently) in addition to non-cognitive measures (eg, vascular health such as blood pressure, quality of life, depression, cerebrospinal fluid (CSF) biomarkers of Alzheimer’s disease pathology and neuroimaging). Only five studies reported dementia progression rates, all of which varied: 16%/year, 5–6%/year, 24% over 1 year, 11.9% over a 24-week trial and 15% over 4 years. Most results were negative.

**Operationalising MCI component criterion**

Two studies did not report details of the operationalisation protocol for defining MCI.

**Criterion 1: memory complaint**

Five studies reported no details on how memory complaint was obtained. The memory complaint was obtained from the subject in four studies, whereas 11 studies utilised subject report and informant corroboration. One study gave unclear details on who had reported the complaint. In one study, this criterion was operationalised using a history of gradual onset and slow progressive decline in cognitive function, but how this was reported, for example, the subject or informant, was not stated. Three studies used specific scales rather than a single question to assess memory complaint. Smith et al. used four items from the Cambridge Examinations for Mental Disorders. Rapp et al. used the Memory Functioning Questionnaire, which is a 64-item questionnaire assessing memory problems and the use of mnemonics. Van Uffelen et al. used a positive response to a single item ‘Do you have memory complaints?’ or answering ‘sometimes’ at least twice on the occlusion scale of Strawbridge.

**Criterion 2: general cognitive function**

This was the criterion most consistently measured and was typically operationalised using the Mini Mental State Examination (MMSE) score either alone or in combination with other measures including: a structured interview with the patient and informant, the Dementia Rating Scale-II (DRS-II), the Mattis DRS (total score), the Telephone Interview for Cognitive Status (TICS), the Clinic Dementia Rating (CDR) score or the Alzheimer’s Disease Assessment Scale-Cognitive Subscale, in addition to the Clinician Interview-Based Impression of Change (CIBIC). One study used only the CDR score of 0.5.

The cut-off chosen for the MMSE varied from 23 to 26. Most studies used a cut-off value of ≥24, but ≥26, ≥23, or a score adjusted for age/education were also used. In one study, the protocol was modified during recruitment and the cut-off was adjusted from 24–30 to 24–28. One study used a 12-Item shortened MMSE with a cut-off score of ≥7. Three studies specified the use of the MMSE but did not report a cut-off score. Six studies did not specify operationalisation of this criterion.

**Criterion 3: object memory decline**

Five studies did not specify operationalisation of this criterion. Five studies used different tests to assess cognition as shown in online supplementary table S2. In addition to inconsistency in test selection, there was no consistency in impairment severity (eg, 1SD, 1.5SDs or 2SDs below the mean). Further, it was not always stated whether cut-off scores for impairment were adjusted for age, education or premorbid ability. In one study, severity was adjusted from 1.5SDs below the mean (used in the first 6 months) to 1SD below the mean during the course of screening. Based on the nature of the objective deficit, three studies reported the inclusion of single or multidomain aMCI. One study reported the use of combined amnestic and non-amnestic (single and multidomain) cases.

In terms of non-memory performance, one study reported that this was tested and required to be unimpaired (defined using a cut-off >10th percentile). Another reported that performance was required to be relatively normal in non-memory domains. In one study, division of cases was unclear; the objective deficit in this study was defined as impairment on a total score comprising five domains (immediate and delayed memory, visuospatial/construction, language and attention) assessed using the Repeatable Battery for the Assessment of Neuropsychological Status.

**Criterion 4: Activities of Daily Living (ADL)/Instrumental Activities of Daily Living (IADL)**

Seven studies did not specify operationalisation of this criterion. In 11 studies, minimal or non-significant functional impairment was allowed. One study required that in MCI cases that had an MMSE score between 23 and 25, cognitive impairments did not significantly interfere with daily activities or social functioning, determined by a caregiver report. This restriction was not required in MCI cases with a MMSE score ≥26.

Functional impairment tended to be assessed by a self-report or informant report of the difficulty with ADLs or Basic ADLs. Specific scales were used for functional...
assessments in some studies including the Functional Autonomy Measurement System (SMAFQ), the Blessed Dementia Rating Scale (BDRS)-CERAD, the Groningen Activity Restriction Scale, and selected items from the Lawton and Katz scales or items from the Cambridge Behavioural Inventory (CBI). In only two studies did it appear that no evidence of any functional impairment was allowed; one based on five items, related to ADLs from the CBI, and another specified no decline in ADLs without their measurement being specified.

Criterion 5: dementia diagnosis

Three studies did not specify operationalisation of this criterion. Fourteen studies used the Diagnostic and Statistical Manual (DSM-III-R/IV-TR/-IV), National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria or National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINCDS-AIREN) criteria. Two studies used the CDR score, and one each used a self-report of a diagnosis, clinical judgement or the TICS combined with a MMSE score <24.

Additional measures

In some studies, additional measures, generally related to the assessment of global functioning (such as the CDR sum of boxes score) or dementia severity (eg, from none, mild, moderate and severe), were made in parallel to the mapping of the five aMCI criteria. For example, two studies administered the DRS, seven the CDR, one the BDRS, one the CIBIC, and one the Global Deterioration Scale (GDS). One study also had informants complete both the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-Short form) and EuroQol (EQ-5D), a measure of health status.

DISCUSSION

This review highlights the lack of consistency in MCI case ascertainment in currently completed RCTs. How MCI was diagnosed was not always reported or clear, and varying operationalisation protocols make it impossible to determine similarity across the samples recruited in the different trials. A priority for clinical trial research is to agree on a uniform set of criteria to operationalise MCI. The recruitment protocols identified in this review could provide the basis for future work to determine best practice (eg, in terms of testing classification accuracy of the different methods used), in order to inform the development of a consistent recruitment methodology for MCI clinical trials.

The review highlights the continuing challenge of operationalising the current Petersen et al definition of aMCI. Without a standard operationalisation protocol for defining aMCI cases clinical trial recruitment will continue to be variable. Indeed, within the field of dementia, there is a lack of consistency in operationalisation protocols not only for aMCI, but its associated disorders (eg, Cognitive Impairment No Dementia, dementia and its subtypes (such as Alzheimer’s disease, Lewy Body dementia, frontotemporal dementia and vascular dementia), pre-MCI and other predementia states such as VCIND. For some dementias and their related conditions, it may however be difficult and unrealistic to have one set of operational criteria, precise assessment instruments or cut-off values. For example, a single set of criteria may not be possible for defining symptom fluctuations (eg, as seen in Lewy Body dementia), capturing variability in symptom profiles (eg, the different type of aphasic deficit presented in frontotemporal dementia) or reflecting differences in neuropathological profiles (eg, for vascular dementia and VCIND, the type and location of vascular damage may result in variable symptom profiles). Different diagnostic criteria for MCI affect prevalence and progression. Similarly, for dementia, different criteria have been found to affect prevalence. Inconsistency in case classification for any health condition, whether it is within the field of dementia or any other disease category, can have an impact on research and trial recruitment and outcomes.

With regard to aMCI, consensus needs to be reached on five core issues relating to the measurement of each of the component criteria. First, whether memory complaint should be self-reported and/or informant reported and how it should be assessed (eg, single or multiple items). Second, how global cognitive function should be assessed with possible measures including the MMSE, CDR and GDS, and what the best cut-off score is (within and across cultures). Third, which neuropsychological test(s) should be used to assess memory, what should be the severity of cognitive impairment (1SD, 1.5SD) and whether covariate adjustment is needed. In addition, there is the question of whether both memory and non-memory domains should be tested. The possible tests identified in this review are outlined in online supplementary table S2. Fourth, how functional performance should be assessed (the type of questions), the nature of the task (eg, instrumental ADLs, basic ADLs), reporting (eg, patient, informant or clinician) and what is the maximum level of impairment (eg, none, mild, moderate or severe difficulty or significant difficulty in some areas but not in others). Fifth, how should dementia be defined for exclusion with examples used including: the DSM or NINCDS-ADRDA criteria, the CDR sum of boxes score ≥1 or via screening instruments (eg, the Telephone Screening Instrument). It should be noted that aMCI is not always operationalised as originally specified (eg, permissible significant functional impairment in some studies), and consensus needs to be reached on whether all five criteria are necessary. Further, whether modifications (if any) to criteria can be made and the

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implications of making modifications, for example, in terms of dementia predictability and effect on generalisability, needs to be established.

Decision also needs to be reached on the best treatment target. The impairment captured in aMCI is not always progressive, with a proportion of cases reverting to normal or remaining stable at follow-up, particularly when mapped in population-based studies. Indeed, symptoms of MCI are not always a consequence of Alzheimer’s pathology, but rather can have multiple aetiologies such as depression or vascular disease, each with different outcomes (eg, dementia progression, improvement with treatment for the underlying health symptoms). Better methods are needed to determine the underlying cause of disease in this patient group to accurately identify those individuals whose MCI is associated with Alzheimer’s disease. One possibility could be defining aMCI as in the Alzheimer’s Disease Cooperative Study trial (based on a subjective memory complaint, MMSE score, impaired performance on the Logical Memory II Subscale, no functional impairment and a CDR score of 0.5) as strict implementation of this methodology has been found to result in a consistent rate of dementia progression (approximately 16%/year) across studies, including the multicentre Alzheimer’s Disease Neuroimaging Initiative. Further research is needed to test this method of operationalisation across cohorts (clinical and population based; across countries) and calculate prevalence and longitudinal course in order to determine the generalisability of these findings. Such results could have important implications in terms of identifying a standard protocol for all future aMCI clinical trials.

A recent task force on designing trials in early (prodromal) Alzheimer’s disease (AD) argues for the use of aMCI criteria in combination with biomarkers to improve case selection for clinical trials. Suggestions for possible biomarkers have included hippocampal or whole brain atrophy, CSF Aβ42 levels, PiB imaging, genetic screening (APOE e4 status) or behavioural deficits as each has been associated with dementia. Further, how dementia and AD are defined is currently undergoing revision, with the aim of improved stratification of patients. Where MCI now sits in the ever changing ‘lexicon’ of AD (ie, given there is currently no concrete border between preclinical and clinical disease) will have implications for who is targeted for clinical trial recruitment. For example, MCI, as defined by Petersen et al criteria, may no longer be considered at-risk, but as already AD and encompassed in the new-term ‘prodromal/pre-dementia’; an early symptomatic stage where a patient shows evidence of memory impairment and positive ratings on pathophysiological and topographical markers of AD. Clinical trial research may therefore shift some focus to asymptomatic at-risk stages (eg, pre-MCI) where individuals are biomarker positive for AD but are otherwise healthy. However, like aMCI efforts are needed to standardise criteria and develop an operational protocol for any new stage of disease (eg, prodromal AD and pre-MCI) and to undertake validation across settings including oldest-old age groups and populations (vs clinical samples).

The review should be viewed in light of some limitations. First, we chose to focus on Petersen et al defined aMCI, as this is one of the commonly applied definitions in clinical and research practice. However, not all trials on preclinical cognitive states have used this definition of MCI, with some studies defining intermediate cognitive states using simply a MMSE score or using criteria that have made refinements to the original aMCI criteria. The main change has been in the acceptable level of functional impairment: from none to allowing minor problems, particularly in complex activities such as, for example, account keeping. Different definitions of MCI have different prevalence estimates and also vary in their risk of dementia progression (eg, more extensive patterns of cognitive changes have been associated with greater progression of MCI to dementia). Subtypes have also been defined depending on the neuropsychological profile including amnestic and non-amnestic single or multidomain MCI, and multidomain combined MCI that includes both memory and non-memory deficits. Which, if any, of the many different criteria and subtypes should be adopted in RCTs, or whether no distinction should be made between MCI and AD during recruitment requires further discussion.

CONCLUSION

Much work needs to be done on the characterisation of individuals at risk of dementia for clinical trial recruitment. Within this framework, attention is being focused on redefining the earliest stages of disease and generating new definitions of what constitutes ‘prodromal/pre-dementia’ and ‘at-risk’. Standardisation in the definition and development of an operational protocol will result in improvements in diagnosis and clinical trial methodology.

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REFERENCES

1. Petersen RC. Mild cognitive impairment clinical trials. Nat Rev Drug Discov 2003;2:646–53.
2. Aisen PS, Andrieu S, Sampaio C, et al. Report of the task force on designing clinical trials in early (predementia) AD. Neurology 2011;76:280–8.

3. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.

4. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–92.

5. Moher D, Liberman A, Thraulf J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

6. Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology 2005;65:155–61.

7. Koontz JJ, Baskys A. Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo-controlled study. Am J Alzheimers Dis Other Neuropsychiatry 2005;20:295–302.

8. Mowla M, Makguchi M, Pani A. Does fluoxetine have any effect on the cognition of patients with mild cognitive impairment? A double-blind, placebo-controlled, clinical trial. J Clin Psychopharmacol 2007;27:67–70.

9. Petersen RC, Thagmos RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379–88.

10. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by b vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One 2010;5:1–10.

11. Thal LJ, Ferris SH, Kirby L, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 2005;30:1204–15.

12. Winblad B, Gautier C, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008;70:2024–35.

13. Chiu CC, Su KP, Cheng TC, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer’s disease and mild cognitive impairment: a preliminary randomized, double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1538–44.

14. Chen X, Magnotta VA, Duff K, et al. Donepezil effects on cerebral blood flow in older adults with mild cognitive deficits. J Neuropsychiatry Clin Neurosci 2010;22:175–85.

15. Kotani S, Sakaguchi E, Warashina S, et al. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res 2006;56:59–69.

16. Forlenza OV, Diniz BS, Radanovic M, et al. Disease-modifying properties of memantine: a double blind trial for the treatment of mild cognitive impairment: randomised controlled trial. Br J Psychiatry 2011;198:351–6.

17. Sherwin BB, Cherkov K, Schipper H, et al. A randomized controlled trial of estrogen treatment in men with mild cognitive impairment. Neurobiol Aging 2009;30:179–87.

18. Craft S, Baker LD,Monte J, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012;69:29–38.

19. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 2010;67:1–9.

20. Scherder EJ, Van Paasschen J, Deijen JB, et al. Physical activity and executive functions in the elderly with mild cognitive impairment. Aging Ment Health 2005;9:272–80.

21. Jean L, Simard M, Wiederkehr S, et al. Efficacy of a cognitive training programme for mild cognitive impairment: results of a randomized controlled study. Neuropsychol Rehabil 2010;20:377–405.

22. Petersen RC, Brechman T, Marsh AP. Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. Aging Mental Health 2002:6:5–11.

23. Troyer AK, Murphy KJ, Anderson ND, et al. Changing everyday memory behaviour in amnestic mild cognitive impairment: a randomized controlled trial. J Neurol Neurosurg Psychiatry 2009;80:730–6.

24. Buschert VC, Friese U, Teipel SJ, et al. Effects of a newly developed cognitive intervention in amnestic mild cognitive impairment and mild Alzheimer’s disease: a pilot study. J Alzheimers Dis 2011;25:679–94.

25. Rozzini L, Costardi D, Chilovi V, et al. Efficacy of cognitive rehabilitation in patients with mild cognitive impairment treated with cholinesterase inhibitors. Int J Geriatric Psychiatry 2007;22:356–60.

26. Van Uffelen JGZ, Hopman-Rock M, Chin A, et al. Protocol for Project FACT: a randomised controlled trial on the effect of a walking program and vitamin B supplementation on the rate of cognitive decline and psychosocial wellbeing in older adults with mild cognitive impairment [ISRCTN19227688]. BMC Geriatrics 2005;5. doi:10.1186/1471-2318-11-118.

27. Van Uffelen JGZ, Hopman-Rock M, Chin A, et al. Protocol for Project FACT: a randomised controlled trial on the effect of a walking program and vitamin B supplementation on the rate of cognitive decline and psychosocial wellbeing in older adults with mild cognitive impairment [ISRCTN19227688]. BMC Geriatrics 2005;5. doi:10.1186/1471-2318-11-118.

28. Roth M, Tym E, Mountjoy CO, et al. CAMDEX: the cambridge examination for mental disorders of the elderly. Cambridge: Cambridge University Press, 1988.

29. Gilewski MJ, Zelinski EM. Memory Functioning Questionnaire (MFQ). Psychopharmacol Bull 1988:24:665–70.

30. Strawbridge WJ, Shema SJ, Balfour JL, et al. Antecedents of frailty over three decades in an older cohort. J Gerontol Series B, Psychol Sci Soc Sci 1998;53:59–66.

31. Forlenza OV, Diniz BS, Radanovic M, et al. The telephone interview for cognitive status. Neuropsychiatry Neuropsychol Behav Neurol 1998;1:111–17.

32. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–72.

33. Rosen WG, Mohs RC, Davis KL, A new rating scale for Alzheimer’s disease. Am J Psychiatry 1984;141:1356–64.

34. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer’s disease cooperative study-clinical global impression of change. The Alzheimer’s Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11:292–302.

35. Randolph C, Tierney MC, Mohr E, et al. The Repeatability Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validation. J Clin Exp Neuropsychol 1998;20:310–19.

36. Hebert R, Carrier R, Billodeau A. The Functional Autonomy Measurement System (SMAF): description and validation of an instrument for the measurement of handicaps. Age Ageing 1988;17:293–302.

37. Morris JC, Mohs RC, Rogers H, et al. Consortium to establish a registry for Alzheimer’s disease (CERAD) clinical and neuropsychological assessment of Alzheimer’s disease. Psychopharmacol Bull 1989:24:641–52.

38. Kempen GI, Miedema I, Ormel J, et al. The assessment of disability with the Groningen activity restriction scale, Conceptual framework and psychometric properties. Soc Sci Med 1996;43:1601–10.

39. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:189–96.

40. Katz S, Downs TD, Cash HR, et al. Progress in development of the index of ADL. Gerontologist 1970;10:20–30.

41. Wedderburn C, Wear H, Brown J, et al. The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. J Neurol Neurosurg Psychiatry 2008;79:500–3.

42. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (Third Edition, revised) (DSM-III-R). Washington, DC: APA, 1987.

43. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (Fourth Edition) (Text Revision: DMS-IV-TR). Arlington, VA: American Psychiatric Publishing Inc, 2000.

44. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer’s disease: report of the NINCDS-ADRDA Work Group Under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease. Neurology 1984:34:939–44.

45. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993:43:250–60.

46. Reisberg B, Ferris SH, de Leon MJ, et al. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136–9.

47. de Jager CA, Oulhaj A, Jacoby R, et al. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatric Psychiatry 2012;26:592–600.

48. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. Int Psychogeriatr 2004;16:275–93.

49. EuroQol Group. EuroQol-A new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
53. Ebly EM, Hogan DB, Parhad IM. Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging. Arch Neurol 1995;52:612–19.

54. Duara R, Loewenstein DA, Greig MT, et al. Pre-MCI and MCI: neuropsychological, clinical, and imaging features and progression rates. Am J Geriatr Psychiatry 2011;19:951–60.

55. Stephan BC, Matthews FE, Khaw KT, et al. Beyond mild cognitive impairment: vascular cognitive impairment, no dementia (VCIND). Alzheimer’s Res Ther 2009;1:4.

56. Stephan BC, Matthews FE, McKeith IG, et al. Early cognitive change in the general population: how do different definitions work? J Am Geriatr Soc 2007;55:1534–40.

57. Matthews FE, Stephan BC, McKeith IG, et al. Two-year progression from mild cognitive impairment to dementia: to what extent do different definitions agree? J Am Geriatr Soc 2008;56:1424–33.

58. Erkinjuntti T, Ostbye T, Steenhuis R, et al. The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med 1997;337:1667–74.

59. Wancata J, Borjesson-Hanson A, Ostling S, et al. Diagnostic criteria influence dementia prevalence. Am J Geriatr Psychiatry 2007;15:1034–45.

60. Lonie JA, Tiemey KM, Ebmeier KP. Screening for mild cognitive impairment: a systematic review. Int J Geriatr Psychiatry 2009;24:902–15.

61. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia—meta-analysis of 41 robust inception cohort studies. Acta Psychiatrica Scandinavica 2009;119:252–65.

62. DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2003;2:15–21.

63. Panza F, Capurso C, D’Introno A, et al. Heterogeneity of mild cognitive impairment and other predementia syndromes in progression to dementia. Neurobiol Aging 2007;28:1631–2.

64. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer’s Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 2010;74:201–9.

65. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer’s disease: a new lexicon. Lancet Neurol 2010;9:1118–27.

66. Whitehair DC, Zerba A, Emond J, et al. Influence of apolipoprotein e (epsilon)4 on rates of cognitive and functional decline in mild cognitive impairment. Alzheimer’s Dementia 2010;6:412–19.

67. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade. Lancet Neurol 2010;9:119–28.

68. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. Lancet 2006;367:1262–70.

69. Sperring RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:280–92.

70. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–6.

71. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:270–9.

72. Matthews FE, Stephan BC, Bond J, et al. Operationalization of mild cognitive impairment: a graphical approach. PLoS Med 2007;4:1615–19.
**Table 1a Characteristics of included studies**

| Reference         | Sample (Country)                      | Intervention                                                                 | Number of Subjects Randomised | Age Range | Gender (M:F) | Mean Baseline MMSE (MCI cases) | Single or Multi Domain Amnestic MCI | Outcomes Tested                                                                 |
|-------------------|---------------------------------------|------------------------------------------------------------------------------|-------------------------------|-----------|--------------|--------------------------------|------------------------------------|----------------------------------------------------------------------------------|
| Baker 2010        | Memory Clinic (USA)                    | Exercise vs. Stretching. Duration: 6 months                                  | 19 MCI (Aerobic), 10 MCI (Stretching) | 55-85     | 15:14        | 27.4                           | Unknown                           | Cognitive: TMT A&B, Stroop, Task Switching, Verbal Fluency, SDMT, Story Recall, List learning, Delayed-Match-to-Sample; Non-Cognitive: Cardio respiratory fitness (VO2peak, treadmill grade, time to exhaustion), blood pressure, adiposity, hyperinsulinemic-euglycemic clamp, blood/plasma: insulin, IGF-1, cortisol levels, BDNF, platelet factor 4, Aβ40, Aβ42, lipids |
| Buschert 2011 & Forster 2011 | Dementia Research Section & University Based Memory Clinic (Germany) | Multicomponent cognitive intervention vs. Active control. NOTE: Intervention varied for the MCI & AD groups. Duration: 6 months | 24 aMCI (12 intervention, 12 control), 15 Mild AD (8 intervention, 7 control) | 50+       | 19:20        | 27.4 (1.6)                       | Either                             | Cognitive: ADAS-Cog, MMSE, TMT A&B, RBANS Story Memory & Recall; Non-cognitive: MADRS, QoL-AD, FDG-PET |
| Chen 2006         | Community volunteers (USA)             | Donepezil (titrated to 10mg daily over 6 weeks & continued for 6 months) vs. Placebo. Duration: 6 months | 4 MCI (Treatment) vs. 7 MCI (Placebo) | M=74.8 (SD=7.4) [Treatment]; M=68.4 (SD=4.0) [Placebo] | 4:7          | 29.8 (0.5) [Treatment]; 29.6 (0.8) [Placebo] | Either                             | Cognitive: MMSE, HVLT-R; Non-cognitive: Global & regional cerebral blood flow (gCBF, rCBF) on PET during the verbal recall task |
| Chiu 2008         | Newspaper recruited (1 site; Taiwan)   | Omega-3 PUFAs (3 capsules twice daily, 1080mg EPA+720mg DHA) vs. Placebo (Olive oil). Duration: 24 weeks | 10 AD/14 MCI (Omega-3); 13 AD/9 MCI (Placebo) | 55-90     | Unknown (for MCI cases)        | Unknown                           | Unknown                           | Cognitive: ADAS-Cog (Cognitive items only), MMSE; Non-cognitive: HDRS (At baseline & week 24 only), CIBIC-plus, erythrocyte membrane fatty acid compositions, fatty acids (e.g., total n3 PUFAs, DHA, EPA, plasma amino acid levels) |
| Reference          | Sample (Country)                  | Intervention                                                                 | Number of Subjects Randomised | Age Range | Gender (M:F) | Mean Baseline MMSE (MCI cases) | Single or Multi Domain Amnestic MCI | Outcomes Tested                                                                                                                                 |
|-------------------|-----------------------------------|-------------------------------------------------------------------------------|-------------------------------|-----------|--------------|-------------------------------|-------------------------------------|-------------------------------------------------------------------------------------|
| Craft 2012        | Clinical Research Unit of a Veterans Affairs medical center (USA) | Intranasal insulin (10 or 20 IU twice/day for a total dose of 20 or 40 IU/day) vs. Placebo (Saline twice a day). Duration: 4 months | 64 MCI [n=21 Placebo, n=20 20-IU, n=23 40-IU] vs. 40 Probable AD (CDR=0.5-1 & MMSE>15) [n=9 Placebo, n=16 20-IU, n=15 40-IU] | 55+       | 59:45        | Unknown                       | Unknown                             | Cognitive: Story Recall-Delayed, DRS5, ADAS-Cog; Non-cognitive: ADCS-ADL, Plasma biological markers, glucose metabolism, CSF (AB42, AB40, tau protein to AB42 ratio, P181-tau) & FDG-PET cerebral metabolic rate of glucose (CMRG1c) utilisation (Subsample) |
| Doody 2009        | Multicentre (USA)                 | Donepezil (5 mg/day for 6 weeks followed by 10 mg/day) vs. Placebo. Duration: 48 weeks | 409 MCI (Treatment), 412 MCI (Placebo) | 45-90     | 424:354      | 27.5                          | Unknown                             | Cognitive: Modified ADAS-Cog, CDR-SB, SDMT, MMSE, Digit Span Backwards; Non-Cognitive: NPI, PDQ [Self and respondent versions], The AD Cooperative Study CGIC-MCI, PGA |
| Forlenza 2011     | Community Dwelling Outpatients (1 site; Brazil) | Low dose lithium (150mg titrated to target serum levels of 0.25-0.5 mmol/l) vs. Placebo. Duration: 1 year | 24 MCI (Lithium) vs. 21 MCI (Placebo) | 60+       | Unknown      | Unknown                       | Unknown                             | Cognitive: CDR, ADAS-Cog, CERAD Delayed Recall Test, Sequence of Letters & Numbers, TMT A&B; Non-cognitive: CSF concentrations (AB42, total tau, P-tau) |
| Jean 2010         | Unknown (Canada)                  | Errorless learning + spatial retrieval vs. Errorful learning. All groups given information about memory (n=6 sessions). Duration: 10 weeks | 11 MCI (Training), 11 MCI (Controls) | 50+       | 9:13         | 29.5                          | Either (12 single; 10 multi-domain)                                             | Cognitive: Face-Name Associations (Training Measure), DRS-2, MMSE, MMQ, RBMT, CVLT-II; Non-cognitive: Anxiety & fatigue, Self-Esteem Scale, NPI, SMAP |
| Kinsella 2009     | Memory Clinic (2 sites; Australia) | Memory intervention vs. Waitlist control. Duration: 5 weeks | 22 (Intervention), 22 (Waitlist) | M=78.9 (SD=5.7) (Intervention); M=74.7 (SD=6.1) (Waitlist) | 19:25 | 25.9 (2.8) [Intervention]; 26.8 (1.8) [Waitlist] | Unknown                       | Either                                                                 | Cognitive: RMBT (Reminding Task-Modified), Envelope Task; Non-cognitive: MMQ [Ability Scale, Strategy & Contentment sub-scales], Strategy Knowledge Repertoire |
| Koontz 2005       | Outpatients (1 site; USA)         | Galantamine (Dose escalation: 8, 15, 24 mg/d) vs. Placebo. Duration: 16 weeks | 8 MCI (Treatment), 11 MCI (Control) | 51-87     | 19:0         | Unknown                       | Unknown                             | Cognitive: CANTAB (DMS, PAL, PRM, SRM, IED, SOC), CVLT; Non-cognitive: FAQ         |
| Reference (First Author, Year) | Sample (Country) | Intervention | Number of Subjects Randomised | Age Range | Gender (M:F) | Mean Baseline MMSE (MCI cases) | Single or Multi Domain Amnestic MCI | Outcomes Tested |
|--------------------------------|-----------------|--------------|------------------------------|-----------|--------------|-------------------------------|-----------------------------------|----------------|
| Kotani 2006                   | Out patients Minami-gaoka Hospital (Japan) | PUFA [ARA & DHA: 240mg/day of each: 6 capsules/day] vs. Placebo (Olive oil: MCI Placebo group only). Duration: 90 days | 12 (MCI Treatment), 9 (MCI Placebo), 10 (Organic brain lesions), 8 (Early AD) | 19:20 | Unknown | Either | Cognitive: RBANS [Form A baseline & Forms A or B randomly used at follow-up]; Non-cognitive: Serum chemistry |
| Mowla 2007                    | Referrals for memory problems (Iran) | Fluoxetine (10 mg/d baseline, increase by 20mg/d in 1-2 weeks) vs. Placebo. Duration: 8 weeks | 33 MCI (Treatment), 25 MCI (Control) | 56.8% (Women) | 23.9 | Unknown | Cognitive: WMS-III Immediate & Delayed score, Digit Span (forward/backward), WMS-III Family Pictures, MMSE; Non-cognitive: HAM-D, CGI |
| Petersen 2005                 | AD Cooperative Sites (69 sites; USA & Canada) | Vitamin E (2000 IU) vs. Donepezil (5mg/d initially to 10mg after 6 weeks) vs. Placebo. Duration: 3 years | 253 (Donepezil), 257 (Vitamin E), 259 (Placebo) | 417:352 | 27.3 | Unknown | Cognitive: Dementia diagnosis, MMSE, CDR, GDS, ADAS-Cog (11 & 13 item), New York University Paragraph Recall Test, SDMT, Category Fluency Test, Number Cancellation Test, BNT, Digits Backwards Test, CDT, Maze Tracing Task; Non-cognitive: ADCS-MCI ADL |
| Rapp 2002                     | Community dwelling (USA) | Cognitive & behavioural treatment (6 weekly group meetings) vs. Control (No memory education or training). Duration: 6 weeks | 9 MCI (Treatment), 10 MCI (Control) | 8:11 | 27.6 | Unknown | Cognitive: Word List Recall, Grocery List Task, Names & Faces Task, Wechsler Paragraph Recall Test (Immediate & Delayed); Non-cognitive: MFQ, Memory Controllability Inventory, Profile of Mood States |
| Rozzini 2007                  | Independent living (2 sites; Italy) | ChEIs vs. ChEIs + TNP vs. Not treated. Duration: 3 blocks of sessions every 2 months (Consisting of 20 individual sessions/block) | 22 (ChEIs), 15 (ChEIs + TNP), 22 (Control) | Unknown | 26.4 | Unknown | Cognitive: Short Story Recall, Category & Letter Fluency, Raven’s Coloured Matrices, Rey’s figure (Copy & Delayed), MMSE; Non-cognitive: NPI, GDS-15 Items |
| Reference | Sample (Country) | Intervention | Number of Subjects Randomised | Age Range | Gender (M:F) | Mean Baseline MMSE (MCI cases) | Single or Multi Domain Amnestic MCI | Outcomes Tested |
|-----------|-----------------|--------------|-------------------------------|-----------|-------------|-------------------------------|-----------------------------------|----------------|
| Scherder 2005 | Residents of a combined home for the elderly/nursing home (1 site; Netherlands) | Walking Group vs. Hand & Face Exercises vs. Control. Duration: 6 weeks (30 mins/day; 3 times/week) | 15 MCI (Walking), 13 MCI (Hand & Face Exercises), 15 MCI (Control) | M=86 | 5:38 | Used a 12-Item short MMSE version [Range 0-12]. M=9.7 (SD=1.9) [Walking]; M=9.2 (SD=1.3) [Hand/Face]; M=9.9 (SD=1.4) [Control] | Unknown | Cognitive: Category Naming (Animals, Occupations), TMT A&B, Digit Span (WMS-R), Visual Memory Span (WMS-R), Verbal Learning & Memory Test: List A (Direct Recall, Delayed Recall, Recognition), RBMT (Face & Picture Recognition); Non-cognitive: N/A |
| Sherwin 2011 | Memory clinic | Estrogen (1mg/day micronised E2 orally) vs. Placebo. Duration: 24 weeks (12 weeks treatment & 12 weeks cross-over) | 22 MCI (Treatment-placebo; GROUP A; 16 analysed) vs. 21 (Placebo-treatment; GROUP B; 12 analysed) | 55-95 | 43:0 | 27.0 (2.0) [GROUP A]; 27.8 (2.3) [GROUP B] | Unknown | Cognitive: Buschke Selective Reminding task, WMS-R: Logical Memory I & II, PAL, Visual Reproduction subtest, Block Design, Waterline Task, Mental Rotation Tasks, Digit Span (Forwards & Backwards), Digit Symbol, Similarities Subtest; Non-cognitive: NPI, hormone levels |
| Smith 2010 & de Jager 2011 | Single centre (via local newspaper & radio seeking elderly people with memory concerns) (1 site; UK) | Supplementary B vitamins (folic acid 0.8mg/d, vitamin B12 0.5mg/d + vitamin B6 20mg/d) vs. Placebo. Duration: 2 years | 113 (85 completed MRI protocol) (Treatment), 110 (83 completed MRI protocol) (Placebo) | 70+ | 66:102 | 28.3 | Amnestic or non-amnestic (single or multi-domain on either subtypes) | Cognitive: MMSE, HVLT, CANTAB (PAL, CLOX), TMT A&B, CERAD Category Fluency (Fruits, Vegetables), SDMT, Map Search, TICS-M & clinical outcome measures including the CDR & IQ-CODE; Non-cognitive: MRI rate of atrophy, total level of homocystein, Geriatric Depression Scale |
| Thal 2005 | Multicentre (46 sites; USA) | Rofecoxib 25mg once daily vs. Placebo once daily. Duration: up to 4 years | 725 (Rofecoxib), 732 (Placebo) | 65+ | 31% women (Placebo), 34% women (Rofecoxib) | 27.3 | Unknown | Cognitive: AD based on CDR≥1 on 2 visits 2 months apart, or clinical appraisal despite CDR=0.5, SRT-Summed, SRT-Delayed, ADAS-Cog, CDR-SB; Non-cognitive: BDRS |
| Reference (First Author, Year) | Sample (Country) | Intervention | Number of Subjects Randomised | Age Range | Gender (M:F) | Mean Baseline MMSE (MCI cases) | Single or Multi Domain Amnestic MCI | Outcomes Tested |
|--------------------------------|------------------|--------------|------------------------------|-----------|-------------|-------------------------------|---------------------------------|----------------|
| Troyer 2008                    | Physician referrals & newspaper advertisements (Canada) | 10 2-hour sessions over 6 months. Sessions grouped into: 1) info regarding a lifestyle factor that can affect memory (e.g., nutrition), 2) focused memory intervention training, 3) review of information or intervention &/or 4) outcome testing. Participants given weekly home assignments. Duration: 2 years | 24 (Intervention), 24 (Control) | M=75.4 | 32:36 | 27.8 | Unknown | Cognitive: Memory Toolbox Questionnaire, Self-reported strategy use during memory testing & at home, MMQ [Subscales: Strategy, Contentment, Ability], Impact Rating Scale, Lifestyle Importance Questionnaire & Study created memory tests including: Name, number & wordlist recall; Non-cognitive: Hospital Anxiety & Depression Scale |
| Van Uffelen 2007, 2008 & 2009  | Community dwelling (Netherlands) | Pharmacological + Activity. Two conditions: 1) twice-weekly group based moderate intensity walking programme vs. a low-intensity placebo activity programme & 2) daily vitamin pill containing 5mg folic acid, 0.4mg vitamin B12, 50mg vitamin B6 vs. placebo pill. Duration: 1 year | 152 total including: 77 (Walking), 75 (Low intensity), 78 (Vitamin), 74 (Placebo) | 70-80 | 44% women | Median=29 (all 4 groups) | Unknown | Cognitive: MMSE, AVLT, Verbal Fluency Test (Letter), DSST, Abridged Stroop Color Word Test, IQ-CODE; Non-Cognitive: SF-12, D-Qol, Euro-Qol, Geriatric Depression Scale, accelerometer, cardiovascular endurance (Groningen Fitness test), BMI, BP, blood vitamin levels + plasma concentrations, LASA physical activity questionnaire. In a subsample: Heart rate & measurement of subjective intensity (Borg Scale) (measured at start & during exercise programs and after 6 & 12 months) & the Physical Activity Readiness Questionnaire |
| Reference | Sample (Country) | Intervention | Number of Subjects Randomised | Age Range | Gender (M:F) | Mean Baseline MMSE (MCI cases) | Single or Multi Domain | Outcomes Tested |
|-----------|-----------------|--------------|------------------------------|-----------|-------------|-------------------------------|------------------------|------------------|
| Winblad 2008 | Multicentre (177 centres). Two studies (one with the addition of MRI) (International: 16 countries) | Galantamine (4mg BID for 1 month then 8mg BID for 1 month (plus 12mg BID if well tolerated)) vs. Placebo. Duration: 24 months (Each study) | Study 1 (494 Galantamine, 496 Control); Study 2 (532 Galantamine, 526 Control) | 50+ | Unknown | 916:1132 | Unknown | Cognitive: CDR, ADAS-cog adapted for MCI, DSST; Non-cognitive: ADCS-ADL adapted to MCI |
| Reference (First Author, Year) | Role of Clinical Judgement | CRD or other Global score | Memory Complaint | Objective Deficit | Cut-off | Global Cognitive Function | ADL | Other | Dementia Diagnostic Criteria |
|--------------------------------|-----------------------------|---------------------------|-----------------|------------------|---------|--------------------------|-----|-------|----------------------------|
| Baker 2010                    | Unknown                     | DRS                       | Unknown         | Impaired on at least one of three memory tests: CERAD Neuropsychological Battery Immediate-recall, Delayed-recall &/or Recognition | 1.5SD (Age/education adjusted) | Unknown | Unknown | N/A | Unknown |
| Buschert 2011 & Forster 2011  | Comprehensive clinical & neurological assessment to support diagnosis of MCI or mild AD | For MCI GDS=3; for mild AD GDS=4 | Memory complaint | MMSE≥23 | N/A | No impairment in daily activities or social functioning in MCI cases with MMSE scores between 23-25 | N/A | DSM-IV/NINCDS-ADRDA criteria for AD |
| Chen 2006                     | Reviewed all available medical records, current medications & undertook patient examination (for health related inclusion) | N/A | Self-perception of memory loss | Impaired on a least one of: Mattis Dementia Rating Scale: Memory subscale, Logical Memory (WMS-III) or Brief Visuospatial Memory Test-Revised | 1SD (Age adjusted based on pre-morbid function) | MMSE & Mattis Dementia Rating Scale total score (within normal limits) | No self-reported difficulties with ADL | Barona IQ, estimate, MMSE, HVLT-R | Unknown |
| Chiu 2008                     | Completed medical, psychiatric & neuropsychological assessment | N/A | Self or informant | Logical Memory Delayed Recall (WMS-III), Relatively normal performance in non-memory domains | 1.5SD (Age/education adjusted) | Unknown | No impairment (scale not specified) | CT scan or HIS (used to exclude vascular dementia) | DSM-IV |
| Craft 2012                    | Diagnosis of aMCI by expert consensus based on all available data: cognitive testing, medical history, physical examination, clinical laboratory screening | N/A | Unknown | Delayed story-recall score | 1.5SD (Age/education adjusted for pre-morbid ability [Shipley Vocabulary Test]) | Unknown | Unknown | Unknown | NINCDS-ADRDA criteria for AD |
| Doody 2009                    | Unknown                     | CDR=0.5 (Memory Box 0.5 or 1; no more than two other Box scores rated as high as 1) | Change from previous functioning corroborated by an informant | CDR Memory Box Score 0.5 or 1, WMS Logical Memory II delayed paragraph recall score | Education adjusted paragraph recall score: ≤8 (16+ years), ≤4 (8-15 years), ≤2 (0-7 years) | MMSE 24-28 (24-30 before protocol amendment) | Unknown | Rosen modified HIS<4, CT scan | Probable/Possible Vascular dementia (NINCDS/ADRDA, DSM-IV) or other form of dementia |
| Reference (First Author, Year) | Role of Clinical Judgement | CRD or other Global score | Memory Complaint | Objective Deficit | Cut-off | Global Cognitive Function | ADL | Other | Dementia Diagnostic Criteria |
|-------------------------------|-----------------------------|---------------------------|------------------|------------------|--------|--------------------------|-----|-------|-----------------------------|
| Forlenza 2011                 | Unknown                     | CDR (cut-off not specified) | Unknown          | Unknown          | Unknown | Unknown                   | Unknown | Unknown | CAMCOG                      |
| Jean 2010                    | Neuropsychologist judgement used to properly identify aMCI cases | DRS-2 Score ≥7 | Difficulty in recall of face-name associations in everyday life | CVLT-II (primarily used for diagnosis of aMCI), Animal Naming, TMT A&B, CDT | 1.5SD (on the CVLT-II) | Unknown | Absence or few problems (SMAF; IADL items score 0 to -8) | N/A | Possible/probable AD (DSM-IV-TR or NINCDS/ADRDA), or any other form of dementia |
| Kinsella 2009                | Unknown                     | N/A                       | Complaint by patient &/or informant | HVLT-R, RAVLT, Wechsler Logical Prose Passages, Word List Learning or Verbal Paired Associates | 1.5SD (Age/education adjusted) | Relatively normal on structured interview (with patient & informant) & on the MMSE | No impairment in personal ADL (clinical interview with the patient & family), IADL could be minimally impaired | WTAR | NINCDS-ADRDA criteria for AD |
| Koontz 2005                  | Unknown                     | N/A                       | Memory complaints | Unknown          | Age adjusted | MMSE≥26 | Normal or close to normal | N/A | Unknown |
| Kotani 2006                  | Unknown                     | N/A                       | Complaint of amnesia | Total score on 12 indexes (Form A RBANS; Japanese version) derived from five domains: Immediate & delayed memory, visuospatial/construction, language, attention | 1.5SD | Unknown | Unknown | N/A | NINCDS-ADRDA & NINDS-AIREN |
| Mowla 2007                   | Unknown                     | CDR=0.5                   | Unknown          | Unknown          | Unknown | MMSE (Age/education adjusted) | Unknown | N/A | DSM-IV |
| Petersen 2005                | Reviewed clinical & psychometric data to diagnose AD | CDR=0.5 (& at least 0.5 in the memory domain) | Memory complaint corroborated by informant | Paragraph Recall Logical Memory II WMS-R (Immediate & delayed recall score) | 1.5-2SD (Education adjusted) | Clinical judgement based on CDR, MMSE≥24 (ADAS-Cog also available) | Clinical interview with patient & informant (None or minimal) | Modified HIS≤4 & HDRS≤12 | NINCDS-ADRDA criteria for AD |
| Reference (First Author, Year) | Role of Clinical Judgement | CRD or other Global score | Memory Complaint | Objective Deficit | Cut-off | Global Cognitive Function | ADL | Other | Dementia Diagnostic Criteria |
|-------------------------------|---------------------------|--------------------------|------------------|------------------|---------|--------------------------|-----|-------|----------------------------|
| Rapp 2002                     | Unknown                   | N/A                      | Self-report (MFQ) | CERAD Battery (Verbal fluency, naming, constructional praxis, attention & concentration, executive function, memory) | ≤10th percentile (Scores on non-memory tests normal: >10th percentile) | MMSE>24 | Self-report of ADL/IADL impairment verified by an informant | N/A | Self-report of a diagnosis |
| Rozzini 2007                  | Clinical interview to determine normal general cognitive function, physical functioning & dementia status | CDR=0.5 (Memory box score 0.5 or 1) | Memory complaint corroborated by informant | Unknown | Unknown | Clinical judgement based on CDR=0.5 (Memory box score 0.5 or 1) & MMSE≥24 | No or minimal ADL (including IADL & BADL) determined by clinical interview with patient & informant (reference Lawton & Katz) | Geriatric Depression Scale<5 | NINCDS-ADRDA criteria for AD |
| Scherder 2005                 | Unknown                   | N/A                      | Subjective complaint supported by nursing assistant | Memory items of the MMSE | Unknown | 12-Item MMSE (Cut-off score≥7) | No decline in ADLs | N/A | NINCDS-ADRDA criteria for AD |
| Sherwin 2011                  | Expert evaluation to determine MCI | N/A                      | Patient or caregiver report of memory problems | Logical Memory 2 subtest (WMS-R) and/or RAVLT-Delayed recall score | 1SD (Age adjusted) | MMSE & ADAS-Cog | Generally intact ADLs determined according to age | CIBIC | NINCDS-ADRDA criteria for AD |
| Smith 2010 & de Jager 2011    | Unknown                   | Informant completed IQ-CODE (short form), EQ-SD (Health Questionnaire) & informant CDR (subject also completed the CDR) [CDR=0.5]. Note: CDR was not used for MCI classification | Subjective concern (based on CAMDEX), that did not interfere with ADL; informant corroborated | TICS-M & CERAD Category Fluency (Animals) | 1.5SD. More specifically: 17-29 (/39) on TICS-M, or TICS-M>29 but fluency<19 or TICS-M word recall ≤10/20, or TIC-M<17 but fluency≥19 or word recall≥10/20 | MMSE>24 | Normal ADL (5 questions relating to ADLs based on the CBI) | Geriatric Depression Scale | DSM-IV |
| Reference (First Author, Year) | Role of Clinical Judgement | CRD or other Global score | Memory Complaint | Objective Deficit | Cut-off | Global Cognitive Function | ADL | Other | Dementia Diagnostic Criteria |
|--------------------------------|---------------------------|--------------------------|-----------------|------------------|---------|---------------------------|-----|-------|-----------------------------|
| Thal 2005                      | In some cases the patient was determined by an investigator to have developed dementia despite their CDR results | CDR=0.5 (With memory domain score ≥0.5) & BDRS≤3.5 (no part 1 item score >0.5) | Patient report of memory problem or informant report of decline (past year) | AVLT totals<37 | 1.5SD (AVLT, age-adjusted) for the first 6 months and then 1SD used | MMSE≥24 | BDRS-CERAD. Informant based rating of patient’s ability to perform ADLs (household tasks/self-care). Required to have BDRS scores≤3.5, with no Part 1 item>0.5 (these were excluded due to possible dementia) | Modified HIS>4, HDS 17-item version>13 | NINCDS-ADRDA criteria for AD |
| Troyer 2008                    | Clinical evaluation & consensus used to classify aMCI | N/A | New memory complaint (informant corroborated) | HVLT, WMS-Revised Verbal Paired Associates, Brief Visuospatial Memory Test and Rey-Osterreith Complex Figure Recall | Age, education & intellectual function adjusted (1-1.5SD) | MMSE & DRS-II (Age/education adjusted) | No significant impairment in daily functioning determined by interview with clinician (self & where possible informant interview) | BNT, Digit Span, Rey-Osterreith Complex Figure Copy, TMT B (used for descriptive only) | Consideration of all MCI criteria & hinged on having no significant functional impairment |
| Van Uffelen 2007, 2008 & 2009  | Unknown                   | N/A | Strawbridge cognition scale (answer ‘yes’ to ‘do you have memory complaints’, or at least twice answering ‘sometimes’) | 10 Word Learning Test delayed recall scores≤5 & percentage savings scores≥100 | 15D | TICS≥19 & MMSE≥24 | No report of ADL disability on the GARS, except item ‘taking care of hands & feet’ | N/A | Absence of dementia given the following cut-offs: TICS≥19+MMSE≥24 |
| Winblad 2008                  | Unknown                   | CDR=0.5 (CDR memory score≥0.5) | A history of gradual onset & slow progression of declining cognitive ability | New York University Paragraph Recall Test | Delayed Recall Scores<10 | CDR | Insufficient impairment in ADL to meet diagnostic criteria for dementia | N/A | CDR≥1 |
KEY (Supplementary Tables 1a and 1b)

AB Amyloid beta; AD Alzheimer’s Disease; ADAS-Cog Alzheimer’s Disease Assessment Scale Cognitive Subscale; ADCS-ADL Alzheimer’s Disease Cooperative Study-Activities of Daily Living Inventory; ADL Activities of Daily Living; ARA Arachidonic acid; AVLT Auditory Verbal Learning Test; BADL Basic Activities of Daily Living; BDNF Brain-derived neurotrophic factor; BDRS Blessed Dementia Rating Scale; BDRS-CERAD Blessed Dementia Rating Scale-CERAD version; BMI Body Mass Index; BNT Boston Naming Test; BP Blood Pressure; CAMCOG Cambridge Cognitive Examination; CAMDEX Cambridge Mental Disorders of the Elderly Examination; CANTAB Cambridge Neuropsychological Test Automated Battery; CBI Cambridge Behavioural Inventory; CDR Clinical Dementia Rating Scale; CDR-SB Clinical Dementia Rating Scale Sum of Boxes; CDT Clock Drawing Test; CERAD Consortium to Establish a Registry for Alzheimer’s Disease; CGI Clinical Global Impression; CGIC-MCI Clinical Global Impression of Change Scale Scores Designed for Patients with Mild Cognitive Impairment; ChEis Cholinesterase Inhibitors; CIBIC Clinician Interview-Based Impression of Change; CIBIC-plus Clinician’s Interview-Based Impression of Change Scale (including the care-giver supplied information); CLOX Clock Drawing Test (CANTAB); CSF Cerebrospinal Fluid; CVLT California Verbal Learning Test; CVLT-II California Verbal Learning Test-II; DHA Docosahexaenoic acid; DMS Delayed Matching to Sample; DRS Dementia Rating Scale; DR-S-2 Dementia Rating Scale-2; DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSRS Dementia Severity Rating Score; DSST Digit Symbol Substitution Test; D-QoL Dementia Quality of Life; EPA Eicosapentaenoic acid; Euro-Qol Euro Quality of Life; FAQ Functional Activities Questionnaire; FDG-PET Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography; GARS Groningen Activity Restriction Scale; GDS Global Deterioration Scale; GDS-15 15-item Geriatric Depression Scale; HAM-D Hamilton Rating Scale for Depression; HDRS Hamilton Depression Rating Scale; HIS Hachinski Ischemia Scale; HVLT Hopkins Verbal Learning Test; HVLT-R Hopkins Verbal Learning Test Revised; IADL Instrumental Activities of Daily Living; IED Intra-Extra Dimensional Set Shift; IGF-I Insulin-like growth factor 1; IQ-CODE Informant Questionnaire on Cognitive Decline in the Elderly; LASA Longitudinal Aging Study Amsterdam; M Mean; MADRS Montgomery Asberg Depression Rating Scale; MFQ Memory Functioning Questionnaire; MMQ Multifactorial Memory Questionnaire; MMSE Mini Mental State Examination; N/A Not applicable; NINCDS-ADRDA National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association; NINDS-AIREN National Institute of Neurological Disorders and Stroke and Association Internationale pour le Recherché et l’Enseignement en Neurosciences; NPI Neuropsychiatric Inventory; PAL Paired Associates Learning Test; PDQ Perceived Deficits Questionnaire; PGA Patient Global Assessment; PRM Pattern Recognition Memory; P-tau Phosphorylated tau; PUFAs Polyunsaturated fatty acids; RAVLT Rey Auditory Verbal Learning Task; RBANS Repeatable Battery for the Assessment of Neuropsychological Status; RBMT Rivermead Behavioural Memory Test; SD Standard Deviation; SDMT Symbol Digit Modalities Test; SF-12 Psychological Wellbeing Short Form 12; SMAP Functional Autonomy Management System; SOC Stockings of Cambridge; SRT Selective Reminding Test; TICS Telephone Interview for Cognitive Status; TICS-M Telephone interview of cognitive status (modified); TMT A&B Trail Making Test (Parts A and B); TNP NeuroPsychological training; QoL-AD Quality of Life Alzheimer’s Disease Scale; WMS-III Wechsler Memory Scale-III; WMS-R Wechsler Memory Scale-Revised; WTAR Wechsler Test of Adult Reading
**Supplementary Table 2** Tasks used to assess the MCI criteria of “objective cognitive decline” (alphabetic order)

| Task                                                                 | References Used |
|----------------------------------------------------------------------|-----------------|
| Brief Visuospatial Memory Test[1] (BVMT)                            | [2]             |
| California Verbal Learning Test 2nd Edition (CVLT-II)[3]            | [4]             |
| Clinical Dementia Rating (CDR)[5] Memory Box Score                  | [6-8]           |
| - 0.5-1                                                             |                 |
| - ≥0.5                                                              |                 |
| Clock Drawing Test (CDT)[9]                                         | [4]             |
| Consortium to Establish a Registry for Alzheimer’s Disease (CERAD)  | [11-14]         |
| neuropsychological test-battery[10]                                 |                 |
| - Memory (immediate and delayed)                                     |                 |
| - Verbal/category fluency                                           |                 |
| - Naming                                                            |                 |
| - Constructional praxis                                             |                 |
| - Attention & concentration                                         |                 |
| - Recognition                                                       |                 |
| - Executive function                                                |                 |
| - 10 Word list test                                                 |                 |
| Delayed Story Recall                                                | [15]            |
| - 44 information bits to recall immediately and after 20 minutes delay |               |
| Hopkins Verbal Learning Test Revised (Brief Visuospatial Memory Test–Revised)[16 17] | [2 18 19]        |
| Mattis Dementia Rating Scale (DRS)                                  | [18]            |
| - Memory subscale[20]                                               |                 |
| Mini Mental State Examination (MMSE) 12-Item short form[21]         | [22]            |
| - Memory items                                                      |                 |
| Repeatable battery for assessment of neuropsychological status (RBANS)[23] [Japanese version] | [25]        |
| (see[24] for the specific subtests)                                |                 |
| - Immediate and delayed memory                                      |                 |
| - Visuospatial/construction, language and attention                 |                 |
| Rey Auditory Verbal Learning Test (RAVLT)[26]                      | [8 19 27]       |
| Rey-Osterreith Complex Figure Recall[28]                            | [2]             |
| Semantic and Phonemic Verbal Fluency                                | [4]             |
| - Animal naming[9]                                                  |                 |
| Trail Making Test (TMT) of the Delis-Kaplan Executive Function System (D-KEFS)[29] | [4]        |
| Wechsler Memory Scale-Revised (WMS-R)[30]                          | [2 27]          |
| - Logical Memory II Subtest                                         |                 |
| - Verbal Paired Associates                                          |                 |
| Wechsler Memory Scale—III[31]                                      | [6 18 19 32 33] |
| - Logical Prose Passages                                           |                 |
| - Word List Learning                                                |                 |
| - Verbal Paired Associates                                          |                 |
| - Logical Memory (II) Immediate recall and delayed paragraph recall |                 |
| New York University (NYU) Paragraph recall test                    | [7]             |
| - Delayed recall score                                              |                 |
| Telephone interview of cognitive status-modified (TICS-M)[34]       | [13]            |
1. Benedict RHB. *Brief Visuospatial Memory Test - Revised* Lutz, FL: Psychological Assessment Resources, 1997.
2. Troyer AK, Murphy KJ, Anderson ND, et al. Changing everyday memory behaviour in amnestic mild cognitive impairment: A randomised controlled trial. Neuropsychological Rehabilitation 2008;18(1):65-88
3. Delis D, Kramer J, Kaplan E, et al. *California Verbal Learning Test: Adult version manual*. San Antonio, TX: The Psychological Corporation, 1987.
4. Jean L, Simard M, Wiederkehr S, et al. Efficacy of a cognitive training programme for mild cognitive impairment: Results of a randomised controlled study. Neuropsychological Rehabilitation 2010;20(3):377-405
5. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566-72
6. Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: A 48-week randomized, placebo-controlled trial. Neurology 2009;72(18):1555-61
7. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008;70(22):2024-35
8. Thal LJ, Ferris SH, Kirby L, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 2005;30(6):1204-15
9. Strauss E, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. New York, NY: Oxford University Press, 2006.
10. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer’s disease. Neurology 1989;39(9):1159-65
11. Buschert VC, Friese U, Teipel SJ, et al. Effects of a newly developed cognitive intervention in amnestic mild cognitive impairment and mild Alzheimer’s disease: a pilot study. J Alzheimers Dis 2011;25(4):679-94
12. Rapp S, Brenes G, Marsh AP. Memory enhancement training for older adults with mild cognitive impairment: A preliminary study. Aging and Mental Health 2002;6(1):5-11
13. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by b vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. PLoS ONE 2010;5(9):1-10
14. Van Uffelen JGZ, Hopman-Rock M, Chin A Paw MJM, et al. Protocol for Project FACT: A randomised controlled trial on the effect of a walking program and vitamin B supplementation on the rate of cognitive decline and psychosocial wellbeing in older adults with mild cognitive impairment [ISRCTN19227688]. BMC Geriatrics 2005;5(18):doi:10.1186/1471-2318-5-18
15. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012;69(1):29-38
16. Benedict RHB, Schretlen D, Groninger L, et al. Hopkins Verbal Learning Test Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. The Clinical Neuropsychologist (Neuropsychology, Development and Cognition: Sec 1998;12(1):43-55
17. Brandt J, Benedict RHB. *Hopkins verbal learning test—revised*. Lutz: Psychological Assessment Resources, 2001.
18. Chen X, Magnotta VA, Duff K, et al. Donepezil effects on cerebral blood flow in older adults with mild cognitive deficits. J Neuropsychiatry Clin Neurosci 2006;18(2):178-85
19. Kinsella GJ, Mullaly E, Rand E, et al. Early intervention for mild cognitive impairment: a randomised controlled trial. Journal of Neurology, Neurosurgery & Psychiatry 2009;80(7):730-36
20. Lucas JA, Ivnik RJ, Smith GE, et al. Normative data for the Mattis Dementia Rating Scale. J Clin Exp Neuropsychol 1998;20(4):536-47
21. Braekhus A, Laake K, Engedal K. The Mini-Mental State Examination: identifying the most efficient variables for detecting cognitive impairment in the elderly. J Am Geriatr Soc 1992;40(11):1139-45
22. Scherder EJ, Van Paasschen J, Deijen JB, et al. Physical activity and executive functions in the elderly with mild cognitive impairment. Aging Ment Health 2005;9(3):272-80
23. Randolph C. *Repeatably Battery for the Assessment of Neuropsychological Status (RBANS).* San Antonio: Harcourt, TX: The Psychological Corporation, 1998.
24. Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 1998;20(3):310-9
25. Kotani S, Sakaguchi E, Warashina S, et al. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res 2006;56(2):159-64
26. Schmidt M. *Rey Auditory and verbal learning test: a handbook.* Los Angeles: Western Psychological Services, 1996.
27. Sherwin BB, Chertkow H, Schipper H, et al. A randomized controlled trial of estrogen treatment in men with mild cognitive impairment. Neurobiol Aging 2011;32(10):1808-17
28. Spreen O, Strauss EA. *Compendium of neuropsychological tests. Administration, norms and commentary (2nd ed.).* New York: Oxford University Press, 1998.
29. Delis DC, Kaplan E, Kramer JH. *The Delis-Kaplan Executive Function System.* San Antonio, TX: The Psychological Corporation, 2001.
30. Wechsler D. *Wechsler Memory Scale-Revised.* San Antonio, TX: The Psychological Corporation, 1987.
31. Wechsler D. *Wechsler Memory Scale—III.* San Antonio, TX: Psychological Corp, 1997.
32. Chiu CC, Su KP, Cheng TC, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer’s disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(6):1538-44
33. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352(23):2379-88
34. de Jager CA, Budge MM, Clarke R. Utility of TICS-M for the assessment of cognitive function in older adults. Int J Geriatr Psychiatry 2003;18(4):318-24