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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, frontotemporal 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.[1 2] While several different definitions exist for MCI, amnestic Mild Cognitive Impairment (aMCI) as defined by Petersen *et al*[3 4] 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*[3] 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.[5] 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*,[3] and could include single or multidomain aMCI subtypes (amendments to criteria were allowed as long as they were stated and Petersen *et al*[3] 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

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

Figure 1 Petersen criteria for amnestic Mild Cognitive Impairment.

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*[3] criteria or had inadequate details to support the use of Petersen *et al*[3] 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[6–17] (including: donepezil,

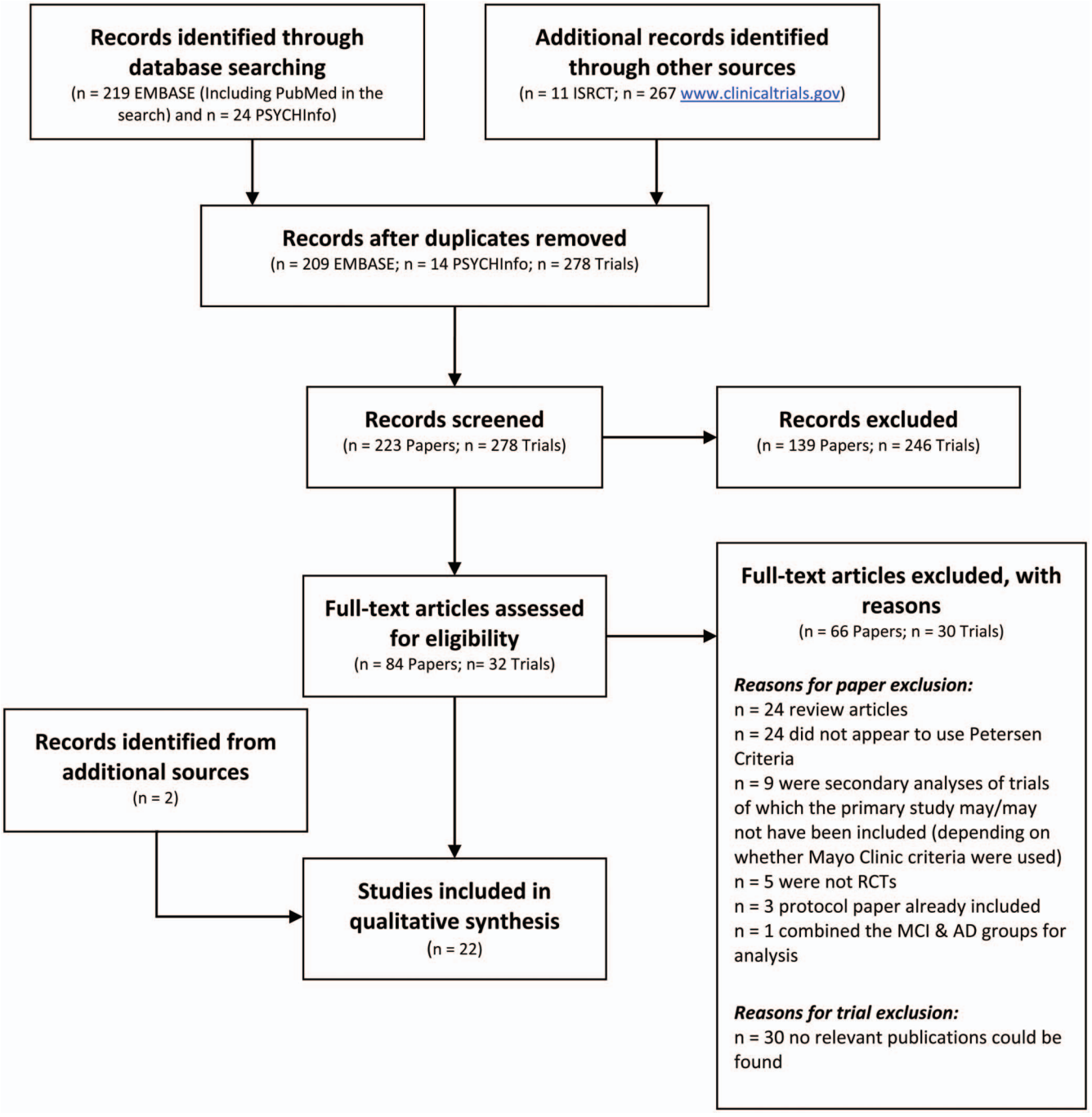

Figure 2 PRISMA (2009) flow diagram of article selection.

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,[18] physical activity[19 20] (eg, aerobic exercise), cognitive training/rehabilitation programmes[21–25] (eg, memory training, strategy learning) and combined therapies including cholinesterase inhibitor use combined with a cognitive training programme,[26] and physical activity combined with vitamin B supplementation.[27] 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,[9] 5–6%/year,[11] 24% over 1 year,[16] 11.9% over a 24-week trial[17] and 15% over 4 years.[12] Most results were negative.

Operationalising MCI component criterion

Two studies[16 19] did not report details of the operationalisation protocol for defining MCI.

Criterion 1: memory complaint

Five studies[7 8 16 18 19] reported no details on how memory complaint was obtained. The memory complaint was obtained from the subject in four[15 21 22 27] studies, whereas 11 studies[6 9–11 13 14 17 20 23 24 26] utilised subject report and informant corroboration. One study[25] gave unclear details on who had reported the complaint. In one study,[12] 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[10 22 27] used specific scales rather than a single question to assess memory complaint. Smith *et al*[10] used four items from the Cambridge Examination for Mental Disorders.[28] Rapp *et al*[22] used the Memory Functioning Questionnaire,[29] which is a 64-item questionnaire assessing memory problems and the use of mnemonics. Van Uffelen *et al*[27] used a positive response to a single item 'Do you have memory complaints?' or answering 'sometimes' at least twice on the cognition scale of Strawbridge.[30]

Criterion 2: general cognitive function

This criterion was the one most consistently measured and was typically operationalised using the Mini Mental State Examination (MMSE)[31] score either alone[6–8 10 11 22] or in combination with other measures including: a structured interview with the patient and informant,[24] the Dementia Rating Scale-II[32] (DRS-II),[23] the Mattis DRS[33] (total score),[14] the Telephone Interview for Cognitive Status[34] (TICS),[27] the Clinic Dementia Rating[35] (CDR) score[9 26] or the Alzheimer's Disease Assessment Scale-Cognitive Subscale[36], in addition to the Clinician Interview-Based Impression of Change[37] (CIBIC).[17] One study used only the CDR score of 0.5.[12]

The cut-off chosen for the MMSE varied from 23 to 26. Most studies used a cut-off value of ≥24,[6 9–11 22 26 27] but ≥26,[7] ≥23,[25] or a score adjusted for age/education,[8 23] were also used. In one study,[6] the protocol was modified during recruitment and the cut-off was adjusted from 24–30 to 24–28. One study[20] used a 12-Item shortened MMSE with a cut-off score of ≥7. Three studies[14 17 24] specified the use of the MMSE but did not report a cut-off score. Six studies did not specify operationalisation of this criterion.[13 15 16 18 19 21]

Criterion 3: object memory decline

Five studies did not specify operationalisation of this criterion.[7 8 16 19 26] Numerous different tests were used 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,[11] 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[14 21 24] reported the inclusion of single or multidomain aMCI. One study[10] reported the use of combined amnestic and non-amnestic (single and multidomain) cases.

In terms of non-memory performance, one study[22] reported that this was tested and required to be unimpaired (defined using a cut-off >10th percentile). Another[13] reported that performance was required to be relatively normal in non-memory domains. In one study,[15] 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.[38]

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

Seven studies did not specify operationalisation of this criterion.[6 8 13 15 16 18 19] In 11 studies,[7 9 11 12 17 21 23–27] 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.[25] 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

assessment in some studies[10 11 21 26 27] including: the Functional Autonomy Measurement System[39] (SMAFQ), the Blessed Dementia Rating Scale (BDRS)-CERAD[40] version, the Groningen Activity Restriction Scale[41] and selected items from the Lawton[42] and Katz[43] scales or items from the Cambridge Behavioural Inventory[44] (CBI). In only two studies did it appear that no evidence of any functional impairment was allowed; one,[10] based on five items, related to ADLs from the CBI, and another[20] specified no decline in ADLs without their measurement being specified.

Criterion 5: dementia diagnosis

Three studies did not specify operationalisation of this criterion.[7 14 19] Fourteen[6 8–11 13 15 17 18 20 21 24–26] studies used the Diagnostic and Statistical Manual (DSM-III-R/IV-TR/-IV),[45 46] National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[47] criteria or National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINCDS-AIREN)[48] criteria. Two studies used the CDR score,[12 16] and one each used a self-report of a diagnosis,[22] clinical judgement[23] or the TICS combined with a MMSE score <24.[27]

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[19 21] administered the DRS, seven[6 8–12 26] the CDR, one[11] the BDRS,[40] one[17] the CIBIC, and one[25] the Global Deterioration Scale[49] (GDS). One study[10 50] also had informants complete both the Informant Questionnaire on Cognitive Decline in the Elderly[51] (IQCODE-Short form) and EuroQol[52] (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*[3] 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[53]), dementia and its subtypes (such as Alzheimer's disease, Lewy Body dementia, frontotemporal dementia and vascular dementia), pre-MCI[54] and other predementia states such as VCIND.[55] 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[56] and progression.[57] Similarly, for dementia, different criteria have been found to affect prevalence.[58 59] 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,[60] 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

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.[57 61] 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).[62 63] 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[9] (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.[64] 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 (predementia) Alzheimer's disease (AD) argues for the use of aMCI criteria in combination with biomarkers to improve case selection for clinical trials.[2 65] Suggestions for possible biomarkers have included hippocampal or whole brain atrophy, CSF Aβ42 levels, PiB imaging, genetic screening (APOE e4 status) or behavioural deficits,[66–68] 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.[65 69] 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 AD'; an early symptomatic stage where a patient shows evidence of memory impairment and positive ratings on pathophysiological and topographical markers of AD.[65] Clinical trial research may therefore shift some focus to asymptomatic at-risk states (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.[70 71] 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[56] 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).[57] 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[72] and subtypes should be adopted in RCTs, or whether no distinction should be made between MCI and AD during recruitment[2] 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;76:280–6.
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, Liberati A, Tetzlaff 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* 2009;72:1555–61.
7. Koontz J, 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 Dementias* 2005;20:295–302.
8. Mowla A, Mosavinasab 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, Thomas 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, Gauthier S, 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* 2006;18:178–85.
15. Kotani S, Sakaguchi E, Warashina S, *et al*. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. *Neurosci Res* 2006;56:159–64.
16. Forlenza OV, Diniz BS, Radanovic M, *et al*. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. *Br J Psychiatry* 2011;198:351–6.
17. Sherwin BB, Chertkow H, Schipper H, *et al*. A randomized controlled trial of estrogen treatment in men with mild cognitive impairment. *Neurobiol Aging* 2011;32:1808–17.
18. 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;69:29–38.
19. Baker LD, Frank LL, Foster-Schubert K, *et al*. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 2010;67:71–9.
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 randomised controlled study. *Neuropsychol Rehabil* 2010;20:377–405.
22. Rapp S, Brenes G, 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 randomised controlled trial. *Neuropsychol Rehabil* 2008;18:65–88.
24. Kinsella GJ, Mullaly E, Rand E, *et al*. Early intervention for mild cognitive impairment: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2009;80:730–6.
25. 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.
26. 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.
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:10.1186/1471-2318-1185-1118
28. Roth M, Tym E, Mountjoy CQ, *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:S9–16.
31. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
32. Jurica PJ, Leitten CL, Mattis S. *Dementia rating scale-2: professional manual*. Lutz: Psychological Assessment Resources, 2001.
33. Mattis S. *Dementia rating scale: orofessional manual*. Odessa, FL: Psychological Assessment Resources, 1988.
34. Brandt J, Spencer M, Folstein M. The telephone interview for cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol* 1988;1:111–17.
35. Hughes CP, Berg L, Danziger WL, *et al*. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566–72.
36. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984;141:1356–64.
37. 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:S22–32.
38. 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;20:310–19.
39. Hebert R, Carrier R, Bilodeau A. The Functional Autonomy Measurement System (SMAF): description and validation of an instrument for the measurement of handicaps. *Age Ageing* 1988;17:293–302.
40. 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* 1988;24:641–52.
41. 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.
42. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–86.
43. Katz S, Downs TD, Cash HR, *et al*. Progress in development of the index of ADL. *Gerontologist* 1970;10:20–30.
44. 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.
45. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (Third Edition, revised) (DSM-III-R)*. Washington, DC: APA, 1987.
46. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (Fourth Edition) (Text Revision: DMS-IV-TR)*. Arlington, VA: American Psychiatric Publishing Inc, 2000.
47. 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.
48. 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.
49. 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.
50. 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.
51. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. *Int Psychogeriatr* 2004;16:275–93.
52. 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 Geriatric 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 Geriatric Psychiatry* 2007;15:1034–45.
60. Lonie JA, Tierney 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, Sherzai 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. Sperling 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 (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
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-I, 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 (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
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, DSRS, 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 Out-patients (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]	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)	M=68.1 (SD=6.3) [MCI]; M=57.5 (SD=12.4) [Organic]; M=67.0 (SD=6.3) [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)	55-75	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)	55-90	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)	M=75.1 (SD=7.0)	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)	63-78	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 (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
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 E_2 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 sub-types)	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 (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
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+	916:1132	Unknown	Unknown	Cognitive: CDR, ADAS-cog adapted for MCI, DSST; Non-cognitive: ADCS-ADL adapted to MCI

Table 1b Methods used to map aMCI in included studies

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	Unknown	Unknown	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	Impaired on at least one of three memory tests: CERAD Neuropsychological Battery Immediate-recall, Delayed-recall &/or Recognition	1.5SD (Age/education adjusted)	MMSE≥23	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	CAMCOG	Unknown
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-5D (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 total≤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 score≤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 score≤5 & percentage savings score≤100	1SD	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 Score≤10	CDR	Insufficient impairment in ADL to meet diagnostic criteria for dementia	N/A	CDR≥1

KEY (Supplementary Tables 1a and 1b)

Aβ 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** Cerebral Spinal 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; **DRS-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 Leaning Test; **HVLT-R** Hopkins Verbal Leaning 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 la 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; **SRM** Spatial Recognition Memory; **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) neuropsychological test-battery[10]	[11-14]
– 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] (see[24] for the specific subtests)	[25]
– 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]

Table References

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:10.1186/471-2318-5-18
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. *Repeatable 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