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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001909
Article Type:	Research
Date Submitted by the Author:	15-Aug-2012
Complete List of Authors:	Stephan, Blossom; Newcastle University, Institute of Health and Society Minett, Thais; Cambridge University, Department of Public Health and Primary Care Pagett, Emma; Cambridge University, Department of Public Health and Primary Care Siervo, Mario; Newcastle University, Institute of Ageing Brayne, Carol; University of Cambridge, Public Health and Primary Care McKeith, Ian; Newcastle University, Institute of Ageing
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Geriatric medicine
Keywords:	Dementia < NEUROLOGY, MENTAL HEALTH, NEUROLOGY

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Diagnosing Mild Cognitive Impairment (MCI) in Clinical Trials: A Systematic Review

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Article Type Systematic Review

Word Count 2,724 (Excluding the Abstract and References)
Summary 98
References 65
Figures 2
Supplementary Material 2 Tables

Keywords Mild Cognitive Impairment (MCI), Randomised Controlled Trials, Operationalisation, Systematic Review

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ABSTRACT

Objective To describe how criteria for amnestic Mild Cognitive Impairment (MCI) 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 (1999) 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 criterion including: (1) subjective memory complain, (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 operationalizing 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.

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Conclusion The results highlight the urgent need for a standardised approach to mapping aMCI. Defining a uniform approach to aMCI classicisation should be a priority if further trials are to be undertaken in the older aged population based on this concept.

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ARTICLE SUMMARY

Article focus

- Accurate identification of individuals with preclinical dementia is important for clinical trial enrolment.
- Diagnosis of preclinical cases 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 operationalizing aMCI criteria in randomised controlled clinical trials resulting in variability in participant selection.
- The results highlight the urgent need for a standardised approach to mapping aMCI.

Strengths and limitations

- The review focus on preclinical dementia defined using aMCI. However, not all clinical trials on preclinical cognitive states have however 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.

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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, Petersen et al[3 4] defined amnestic Mild Cognitive Impairment (aMCI) is often used in clinical and research practice. However, despite being commonly applied, no standardised method for the operationalization 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 highlight in Figure 1. The lack of an established diagnostic methodology for identifying aMCI cases in clinical trials is problematic as study specific participant selection raises questions regarding the nature of the sample selected, whilst also making cross study comparison and generalizability of findings difficult.

We undertook a systematic review to explore the methods used to classify aMCI cases, defined using Petersen et al[3], in randomised controlled clinical trials (RCTs). The focus was on inclusion criteria and variation in the operationalization of each of the five MCI component criteria as outlined in Figure 1.

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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 (MeSH) terms: ("mild cognitive impairment" OR MCI) AND ("randomised controlled trial" OR "randomized 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 on-going or terminated) and results published; (3) the authors report selecting participants using the definition of aMCI as reported in Petersen et al (1999), and could include single or multi-domain amnestic MCI subtypes (amendments to criteria were allowed as long as stated and Petersen et al (1999) 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

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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, intervention), demographics (age and gender distributions), trial exclusion criteria, dementia progression rates and the methods used to operationalized each of the five component criterion 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 www.clinicaltrials.gov. Based on the title-abstract 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 criteria or had inadequate details to support the use of Petersen criteria (e.g., only stated an objective cognitive deficit), or the article was a review.

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Supplementary Table 1 summarises the methodology, demographics, outcomes and operationalization protocol used for identifying aMCI cases in each included article. Trial exclusion criteria varied, but 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. multi-centre), duration (e.g., 90 days to 4 years), and sample demographics (e.g., age range: 50-90 years). Interventions included pharmacological agents and supplementation[6-17] (including: donepezil, galantamine, rofecoxib, fluoxetine, lithium treatment, estrogen treatment [E_2], vitamin supplementation (E and B), and supplementation with omega-3 poly unsaturated fatty acids, arachidonic and docosahexaenoic acids), insulin therapy[18], physical activity[19 20] (e.g., aerobic exercise), cognitive training/rehabilitation programmes[21-25] (e.g., memory training, strategy learning) and combined therapies including cholinesterase inhibitor (ChEI) use combined with a cognitive training program[26], and physical activity combined with vitamin B supplementation[27]. Only five studies reported dementia progression rates all of which varied: 16%/year[9], 5-6%/year[11], 24% over one year[16], 11.9% over a 24-weeks trial[17] and 15% over four years[12]. Most results were negative.

Operationalizing MCI Component Criterion

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

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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 while eleven 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 reported the complaint. In one study[12] this criterion was operationalized using a history of gradual onset and slow progressive decline in cognitive function, but how this was reported, for example from 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 (CAMDEX)[28]. Rapp et al[22] used the Memory Functioning Questionnaire (MFQ)[29] which is a 64-item questionnaire assessing memory problems and 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 most consistently measured and was typically operationalized 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 Dementia Rating Scale (DRS) [33] (total score) [14], the Telephone Interview for Cognitive Status [34] (TICS) [27], the Clinic Dementia Rating [35] (CDR) score [9 26] or

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the Alzheimer's disease Assessment Scale-Cognitive Subscale[36] (ADAS-Cog) in addition with 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 operationalization of this criterion[13 15 16 18 19 21].

Criterion 3: Object Memory Decline

Five studies did not specify operationalization of this criterion[7 8 16 19 26]. Numerous different tests were used to assess cognition as shown in Supplementary Table 2. In addition to inconsistency in test selection there was no consistency in impairment severity (e.g., 1 standard deviation (SD), 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 pre-morbid 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 inclusion of single amnestic or multi-domain

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amnestic MCI. One study [10] reported the use of combined amnestic and non-amnestic (single and multi-domain) 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 & delayed memory, visuospatial/construction, language & attention) assessed using the Repeatable battery for the assessment of neuropsychological status (RBANS)[38].

Criterion 4: ADL/IADL

Seven studies did not specify operationalization of this criterion[6 8 13 16 19]. In twelve studies[7 9 11 12 15 17 18 21 23-27], minimal or non-significant functional impairment was allowed. One study required that in MCI cases that had a 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 self or informant report of 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

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System[39] (SMAFQ), the Blessed Dementia Rating Scale-CERAD[40] version, the Groningen Activity Restriction Scale[41] (GARS) 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 5 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 operationalization 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 (e.g., from none, mild, moderate and severe) were made in parallel to the mapping of the five

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Mayo Clinic criterions. For example, two studies[19 21] administered the Dementia Rating Scale (DRS), seven[6 8-12 26] the CDR, one[11] the Blessed Dementia Rating Scale[40] (BDRS), 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 operationalization protocols make it impossible to determine similarity across the samples recruited in the different trials. No recruitment protocol for the selection of MCI cases for future clinical trials can be recommended until classification accuracy of current methods is tested.

The review highlights the classification problem associated with the current Petersen et al (1999) definition of aMCI. Without a standard operationalization protocol for defining aMCI trial recruitment will continue to be variable. 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 and/or information reported and how it should be assessed (e.g., single or multiple items). Second, how global cognitive function should be assessed with possible measures including the MMSE, CDR and Global Deterioration Scale, and what the best cut-off score is (within

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and across cultures). Third, which neuropsychological test(s) should be used to assess memory[53], what should be the severity of cognitive impairment (1SD, 1.5SD) and whether covariate adjustment is needed. In addition, is the question of whether both memory and non-memory domains should be tested. Possible tests identified in this review are outlined in Supplementary Table 2. Fourth, how functional performance should be assessed (the type of questions), the nature of the task (e.g., instrumental ADLs, basic ADLs), reporting (patient, informant, clinician) and what is the maximum level of impairment (e.g., none, mild, moderate or severe difficulty or significant difficulty in some areas but not in others). Fifth, how dementia should 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 (e.g., the Telephone Screening Instrument). It should be noted that aMCI is not always operationalised as originally specified (e.g., permissible significant functional impairment in some studies) and consensus needs to be reached on whether all five criterion 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 generalizability, needs to be established.

Decision also needs to be reached on whether aMCI is the best treatment target. The impairment captured in aMCI is not always progressive. When mapped in population based studies (and to a lesser extent in the clinic) aMCI is unstable, with a proportion of cases reverting to normal or remaining stable at follow-up[54 55]. This raises questions of utility, especially whether the criteria are sensitive and specific enough

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for classifying individuals at high risk of dementia progression[56]. A recent task force on designing trials in early (pre-dementia) AD argues for the use of aMCI criteria in combination with biomarkers to improve case selection for clinical trials[2 57]. Suggestions for possible biomarkers have included hippocampal or whole brain atrophy, CSF Aβ42 levels, PiB imaging, genetic screening (APOE e4 status) or behavioural deficits[58-60], as each has been associated with dementia. Further, how dementia and AD are defined is currently undergoing revision[57 61]. Where MCI now sits in the ever changing "lexicon" of AD (i.e., 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 criteria may no longer be considered at-risk, but as already AD, with the term "MCI" being replaced by a new definition of early "prodromal AD" (e.g., evidence of memory impairment and positive ratings on pathophysiological and topographical markers of AD)[57].

The review should be viewed in light of some limitations. First, we choose to focus on Petersen 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[62 63]. 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

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have different prevalence estimates[64] and also vary in their risk of dementia progression (e.g., more extensive patterns of cognitive changes have been associated with greater progression of MCI to dementia)[54]. Subtypes have also been defined depending on the neuropsychological profile including amnestic and non-amnestic single or multi-domain MCI, and multi-domain combined MCI that includes both memory and non-memory deficits. Which, if any, of the many different criteria[65] and sub-types of preclinical decline 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 definition and development of an operational protocol will result in improvements in diagnosis and clinical trial methodology.

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Additional Files Attached

Figure 1 Petersen criteria for amnestic MCI (aMCI)

Figure 2 PRISMA (2009) flow diagram of article selection

Supplementary Table 1 Characteristics of included studies

Supplementary Table 2 Tasks used to assess the MCI criteria of "objective cognitive decline" (alphabetic order)

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Acknowledgements

Author Contributions

ICMJE authorship met by all authors. BS and TM designed the review. BS, TM, EP and MS contributed to review article selection, data extraction and writing the results section. BS, TM and MS wrote the first draft of the paper. CM and IM made substantial contribution to the intellectual content. All authors contributed to the final version and approve its submission.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors were personally salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

Competing Interests

No author has a conflict of interest to declare.

Data Sharing Statement

The manuscript is a systematic review. The review protocol is available on request from the corresponding author.

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Figure 1 Petersen criteria for amnestic MCI (aMCI)

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

Petersen criteria for amnestic MCI (aMCI)
102x66mm (300 x 300 DPI)

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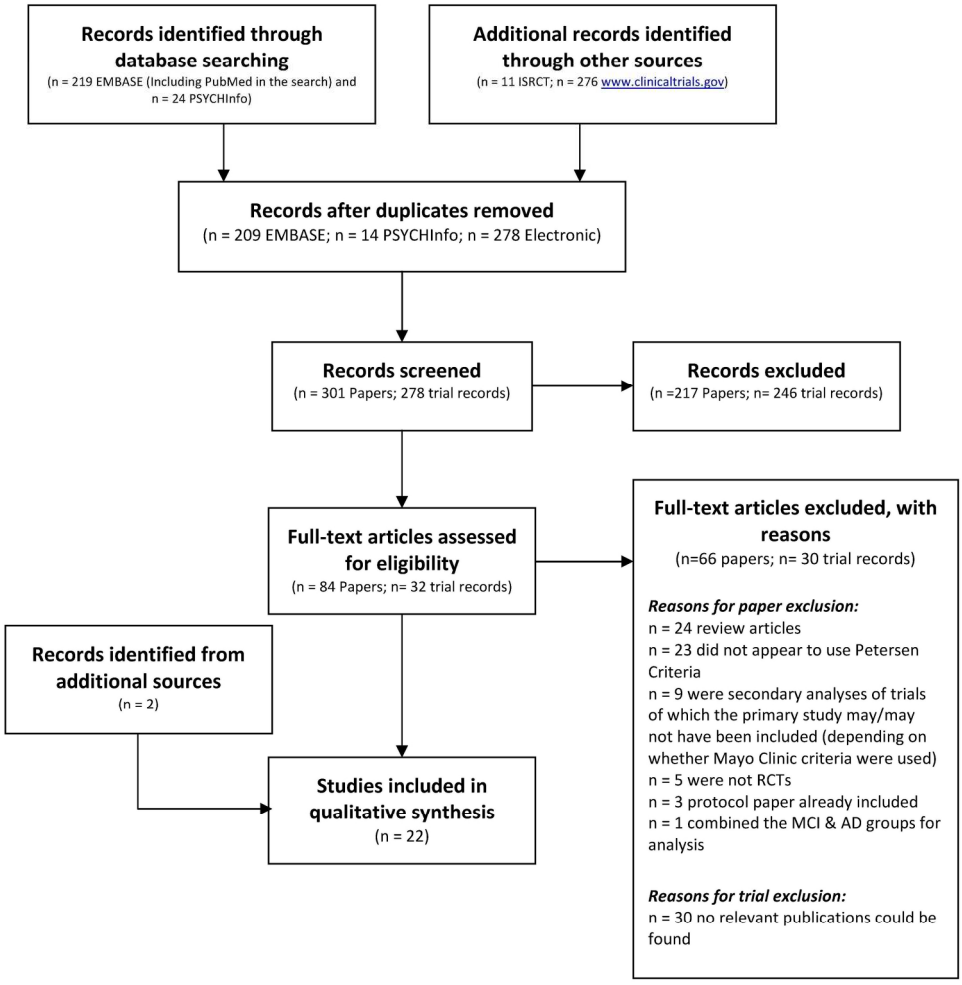

Figure 2. PRISMA (2009) flow diagram of article selection
191x205mm (300 x 300 DPI)

Supplementary Table 1 Characteristics of included studies **(First 9 Columns)**

Reference	Sample (Country)	Intervention	Number of Subjects Randomised	Age Range	Gender (M:F)	Mean Baseline MMSE (MCI cases)	Single or Multi Domain Amnestic MCI	Role of Clinical Judgement
Baker 2010	Memory Clinic (USA)	Exercise vs. Stretching. Duration: 6 months	19 MCI (Aerobic), 10 MCI (Stretching)	55-85	15:14	27.4	NS	Unknown
Buschert 2011 & Forster 2011	Dementia Research Section & University Based Memory Clinic (Germany)	Multicomponent cognitive intervention vs. Active control. NOTE: The 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	Comprehensive clinical and neurological assessment to support the diagnosis of MCI or mild AD
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	Reviewed all available medical records, current medications and undertook patient examination (for health related inclusion)
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 (Omage-3); 13 AD/9 MCI (Placebo)	55-90	NS (for MCI cases)	NS	NS	Completed medical, psychiatric and neuropsychological assessment
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	NS	NS	Diagnosis of aMCI by expert consensus based on all available data: cognitive testing, medical history, physical examination, clinical laboratory screening

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Reference	Sample (Country)	Intervention	Number of Subjects Randomised	Age Range	Gender (M:F)	Mean Baseline MMSE (MCI cases)	Single or Multi Domain Amnestic MCI	Role of Clinical Judgement
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	NS	Unknown
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+	NS	NS	NS	NS
Jean 2010	Unknown (Canada)	Errorless learning (EL) + spatial retrieval vs. Errorful learning (EF). 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)	Neuropsychologist judgement used to properly identify aMCI cases
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	Unknown
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	NS	Unknown
Kotani 2006	Out patients Minami-gaoka Hospital (Japan)	PUFA [Arachidonic acid (ARA) & docosahexaenoic acid (DHA): 240mg/day of each: 6 capsules/day] vs. Placebo (Olive oil: MCI Placebo group only). Duration: 90 days	12 (MCI Treatment) vs. 9 (MCI Placebo) vs. 10 (Organic brain lesions) vs. 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	NS	Either	Unknown

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Reference	Sample (Country)	Intervention	Number of Subjects Randomised	Age Range	Gender (M:F)	Mean Baseline MMSE (MCI cases)	Single or Multi Domain Amnestic MCI	Role of Clinical Judgement
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	NS	Unknown
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	NS	Reviewed clinical and psychometric data to diagnose AD
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	NS	Unknown
Rozzini 2007	Independent living (2 sites; Italy)	ChEIs vs. ChEIs + Neuropsychological training (TNP) vs. Not treated. Duration: 3 blocks of sessions every 2 months (Consisting of 20 individual sessions/block)	22 (ChEIs), 15 (ChEIs + Cognitive rehabilitation), 22 (Control)	63-78	Unknown	26.4	NS	Clinical interview to determine normal general cognitive function, physical functioning and dementia status
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]	NS	NS

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Reference	Sample (Country)	Intervention	Number of Subjects Randomised	Age Range	Gender (M:F)	Mean Baseline MMSE (MCI cases)	Single or Multi Domain Amnestic MCI	Role of Clinical Judgement
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]	NS	Expert evaluation to determine MCI
Smith 2010 & de Jager 2011	Single centre (via local newspaper and 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)	Unknown
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	NS	In some cases the patient was determined by an investigator to have developed dementia despite their CDR results
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 function (e.g., nutrition), 2) focused memory intervention training, 3) review of information or intervention &/or 4) outcome testing. Participants given weekly assignments to complete at home. Duration: 2 years	24 (Intervention), 24 (Control)	M=75.4	32:36	27.8	NS	Clinical evaluation & consensus used to classify aMCI

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Reference	Sample (Country)	Intervention	Number of Subjects Randomised	Age Range	Gender (M:F)	Mean Baseline MMSE (MCI cases)	Single or Multi Domain Amnestic MCI	Role of Clinical Judgement
Van Uffelen 2007, 2008 & 2009	Community dwelling (Netherlands)	Pharmacological + Activity. Two conditions: 1) a 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 (in all 4 groups)	NS	Unknown
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	NS	Unknown

Table 1 Continued …

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Table 1 Characteristics of included studies **(Last 8 Columns)**

Reference	CRD or other Global score	Memory Complaint	Objective Deficit	Cut-off	Global Cognitive Function	ADL	Other	Dementia Diagnostic Criteria
Baker 2010	Dementia Rating Scale (DRS)	NS	NS	NS	NS	NS	N/A	NS
Buschert 2011 & Forster 2011	Global Deterioration Scale (GDS) (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 where their MMSE score was 23-25	N/A	DSM-IV/NINCDS-ADRDA criteria for AD
Chen 2006	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, Hopkins Verbal Leaning Test Revised (HVLT-R)	NS
Chiu 2008	N/A	Self or informant	Logical Memory delayed recall (WMS-III). Relatively normal performance in non-memory domains	1.5SD (Age/education adjusted)	NS	No impairment (scale not specified)	CT scan or Hachinski's Ischemic Scale (used to exclude vascular dementia)	DSM-IV
Craft 2012	N/A	NS	Delayed story-recall score	1.5SD (Age/education adjusted of pre-morbid ability [Shipley Vocabulary Test])	NS	NS	N/A	NINCDS-ADRDA criteria for AD

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Reference	CRD or other Global score	Memory Complaint	Objective Deficit	Cut-off	Global Cognitive Function	ADL	Other	Dementia Diagnostic Criteria
Doody 2009	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)	NS	Rosen modified Hachinski Ischemia scale score≤4, CT scan	Probable/Possible Vascular dementia (NINCDS/ADRDA, DSM-IV) or other form of dementia
Forlenza 2011	CDR (cut-off not specified)	NS	NS	NS	NS	NS	Cambridge Cognitive Examination (CAMCOG)	NS
Jean 2010	Dementia Rating Scale-2nd Edition (DRS-2) Score ≥7	Difficulty in recall of face-name associations in everyday life	California Verbal Learning Test Second Edition (CVLT-II; primarily used for diagnosis of aMCI), Animal Naming, Trail Making Test (TMT) A & B, Clock Drawing Test	1.5SD (on the CVLT-II)	NS	Absence or few problems (Functional Autonomy Measurement System (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	N/A	Complaint by patient and/or informant	HVLT-R, Rey Auditory Verbal Learning Task (RAVLT/, Wechsler Logical Prose Passages, Word List Learning or Verbal Paired Associates	1.5SD (Age/education adjusted)	Relatively normal on structured interview with the patient and informant and on the MMSE	No impairment in personal ADL as determined by clinical interview with the patient & their family (IADL could be minimally impaired)	Wechsler Test of Adult Reading (WTAR)	NINCDS-ADRDA criteria for AD
Koontz 2005	N/A	Memory complaints	NS	Age adjusted	MMSE≥26	Normal or close to normal	N/A	NS
Kotani 2006	N/A	Complaint of amnesia	Total score on 12 indexes (Form A of the Repeatable Battery for the Assessment of Neuropsychological Status [RBANS; Japanese version]) derived from five domains: immediate & delayed memory, visuospatial/construction, language & attention)	1.5SD	NS	NS	N/A	NINCDS-ADRDA & NINDS-AIREN

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Reference	CRD or other Global score	Memory Complaint	Objective Deficit	Cut-off	Global Cognitive Function	ADL	Other	Dementia Diagnostic Criteria
Mowla 2007	CDR=0.5	NS	NS	NS	MMSE (age & education adjusted)	NS	N/A	DSM-IV
Petersen 2005	CDR=0.5 (and at least 0.5 in the memory domain)	Memory complaint corroborated by an 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 the patient & informant (none or minimal)	Modified Hachinski Ischemia scale score≤4 & Hamilton Depression Rating Scale≤12	NINCDS-ADRDA criteria for AD
Rapp 2002	N/A	Self-reported (Memory Functioning Questionnaire, 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	CDR=0.5 (Memory box score 0.5 or 1)	Memory complaint corroborated by an informant	NS	NS	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 and Katz)	Geriatric Depression Scale (GDS)<5	NINCDS-ADRDA criteria for AD
Scherder 2005	N/A	Subjective complaint supported by a nursing assistant	Memory items of the MMSE	NS	12-Item MMSE (Cut-off score≥7)	No decline in ADLs	N/A	NINCDS-ADRDA criteria for AD
Sherwin 2011	N/A	Patient or caregiver report of memory problems	Logical Memory 2 subtest of the Wechsler Memory Scale-Revised (WMS-R) and/or RAVLT-Delayed recall score	1SD (Age adjusted)	MMSE & ADAS-Cog	Generally intact ADLs determined according to age	The Clinician Interview-Based Impression of Change (CIBIC)	NINCDS-ADRDA criteria for AD

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Reference	CRD or other Global score	Memory Complaint	Objective Deficit	Cut-off	Global Cognitive Function	ADL	Other	Dementia Diagnostic Criteria
Smith 2010 & de Jager 2011	Informant completed the IQCODE (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 that was corroborated by an informant	Telephone Interview of Cognitive Status-Modified (TICS-M) and 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 Cambridge Behavioural Inventory: CBI)	GDS	DSM-IV
Thal 2005	CDR=0.5 (With memory domain score ≥0.5) & Blessed Dementia Rating Scale (BDRS)≤3.5 (no part 1 item score >0.5)	Patient report of memory problem or informant report of decline in the past year	Auditory Verbal Learning Test (AVLT) total score≤37	1.5SD (on the AVLT, age-adjusted) for the first 6 months and then 1SD was used	MMSE≥24	BDRS-CERAD. Informant based rating of patient's ability to perform ADLs (household tasks/self-care). Patients who scored >3.5 with any of the household-tasks part score >0.5 were excluded due to the possibility of dementia	Modified Hachinski Score>4, HDS (17-Item) version>13	NINCDS-ADRDA criteria for AD
Troyer 2008	N/A	New memory complaint corroborated by an informant	Hopkins Verbal Learning Test, WMS-Revised Verbal Paired Associates, Brief Visuospatial Memory Test and Rey-Osterreith Complex Figure Recall	Age, education & intellectual function adjusted (1-1.5SD)	MMSE & the Dementia Rating Scale-II (Age and education adjusted)	No significant impairment in daily functioning determined by interview with the clinician (self & where possible informant interview)	Boston Naming Task, Digit Span, Rey-Osterreith Complex Figure Copy, TMT B (used for descriptive only)	Consideration of all MCI criteria and hinged on criterion of no significant functional impairment

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Reference	CRD or other Global score	Memory Complaint	Objective Deficit	Cut-off	Global Cognitive Function	ADL	Other	Dementia Diagnostic Criteria
Van Uffelen 2007, 2008 & 2009	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	Telephone Interview for Cognitive Status (TICS)≥19 and MMSE≥24	No report of disability in ADL on Groningen Activity Restriction Scale (GARS), except item 'taking care of hands and feet'	N/A	Absence of dementia given the following cut-offs: TICS≥19+MMSE≥24
Winblad 2008	CDR=0.5 (CDR memory score≥0.5)	A history of gradual onset and 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

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Supplementary Table 1 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]

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Diagnosing Mild Cognitive Impairment (MCI) in Clinical Trials: A Systematic Review

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001909.R1
Article Type:	Research
Date Submitted by the Author:	05-Nov-2012
Complete List of Authors:	Stephan, Blossom; Newcastle University, Institute of Health and Society Minett, Thais; Cambridge University, Department of Public Health and Primary Care Pagett, Emma; Cambridge University, Department of Public Health and Primary Care Siervo, Mario; Newcastle University, Institute of Ageing Brayne, Carol; University of Cambridge, Public Health and Primary Care McKeith, Ian; Newcastle University, Institute of Ageing
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Geriatric medicine
Keywords:	Dementia < NEUROLOGY, MENTAL HEALTH, NEUROLOGY

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Manuscripts

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Diagnosing Mild Cognitive Impairment (MCI) in Clinical Trials: A Systematic Review

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Article Type Systematic Review

Word Count 3,075 (Excluding the Abstract and References)
Summary 98
References 72
Figures 2
Supplementary Material 2 Tables

Keywords Mild Cognitive Impairment (MCI), Randomised Controlled Trials, Operationalisation, 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 (1999) 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 criterion including: (1) memory complain, (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.

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Conclusion The results highlight the urgent need for a standardised approach to mapping 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 and 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.

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ARTICLE SUMMARY

Article focus

- Accurate identification of individuals with preclinical dementia is important for clinical trial enrolment.
- Diagnosis of preclinical cases 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 mapping 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 (VCIND). Revision of diagnostic criteria including standardisation of methods and instruments for operationalisation of each dementia subtype and for the different disease stages (e.g., prodromal, preclinical and clinical) should be a research priority.

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Strengths and limitations

- The review focuses on preclinical dementia defined using aMCI. However, not all clinical trials on preclinical 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.

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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, Petersen et al[3, 4] defined amnestic Mild Cognitive Impairment (aMCI) 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 highlight 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, whilst also making cross study comparison and generalizability 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.

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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 (MeSH) terms: ("mild cognitive impairment" OR MCI) AND ("randomised controlled trial" OR "randomized 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 on-going or terminated) and results published; (3) the authors report selecting participants using the definition of aMCI as reported in Petersen et al (1999), and could include single or multi-domain amnestic MCI subtypes (amendments to criteria were allowed as long as stated and Petersen et al (1999) 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

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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, intervention), demographics (age and gender distributions), trial exclusion criteria, dementia progression rates, outcomes tested and the methods used to operationalised each of the five component criterion 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 www.clinicaltrials.gov. Based on the title-abstract 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 1999 criteria or had inadequate details to support the use of Petersen et al 1999 criteria (e.g., only stated an objective cognitive deficit), or the article was a review. Supplementary Table 1a summarises the general characteristics, demographics and outcomes tested in each included

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article. Supplementary Table 1b summarises the operationalisation protocol used for identifying aMCI cases in each trial.

Trial exclusion criteria varied, but 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. multi-centre), duration (e.g., 90 days to 4 years), and sample demographics (e.g., age range: 50-90 years). Interventions included pharmacological agents and supplementation[6-17] (including: donepezil, galantamine, rofecoxib, fluoxetine, lithium treatment, estrogen treatment [E_2], vitamin supplementation (E and B), and supplementation with omega-3 poly unsaturated fatty acids, arachidonic and docosahexaenoic acids), insulin therapy[18], physical activity[19, 20] (e.g., aerobic exercise), cognitive training/rehabilitation programmes[21-25] (e.g., memory training, strategy learning) and combined therapies including cholinesterase inhibitor (ChEI) use combined with a cognitive training program[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 (e.g., 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

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varied: 16%/year[9], 5-6%/year[11], 24% over one year[16], 11.9% over a 24-weeks trial[17] and 15% over four years[12]. Most results were negative.

Operationalizing MCI Component Criterion

Two studies[16, 19] did not report details of the operationalization 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 while eleven 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 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 from 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 (CAMDEX)[28]. Rapp et al[22] used the Memory Functioning Questionnaire (MFQ)[29] which is a 64-item questionnaire assessing memory problems and 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].

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Criterion 2: General Cognitive Function

This criterion was the 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 Dementia Rating Scale (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] (ADAS-Cog) in addition with 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 Supplementary Table 2. In addition to inconsistency in test selection there was no consistency in impairment

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severity (e.g., 1 standard deviation (SD), 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 pre-morbid 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 inclusion of single amnestic or multi-domain amnestic MCI. One study[10] reported the use of combined amnestic and non-amnestic (single and multi-domain) 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 & delayed memory, visuospatial/construction, language & attention) assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[38].

Criterion 4: ADL/IADL

Seven studies did not specify operationalisation of this criterion[6, 8, 13, 16, 19]. In twelve studies[7, 9, 11, 12, 15, 17, 18, 21, 23-27], minimal or non-significant functional impairment was allowed. One study required that in MCI cases that had a MMSE score between 23 and 25, cognitive impairments did not significantly interfere with daily activities or

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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 self or informant report of 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-CERAD[40] version, the Groningen Activity Restriction Scale[41] (GARS) 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 5 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 operationalization 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].

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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 (e.g., 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 Dementia Rating Scale (DRS), seven[6, 8-12, 26] the CDR, one[11] the Blessed Dementia Rating Scale[40] (BDRS), 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. No recruitment protocol for the selection of MCI cases for future clinical trials can be recommended until classification accuracy of current methods is tested.

The review highlights the continuing challenge of classifying and operationalising the current Petersen et al (1999) definition of aMCI. Without a standard operationalisation protocol for defining aMCI trial recruitment will continue to be variable. Indeed, within the field of dementia there is a lack of consistency in

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operationalisation protocols not only for aMCI, but its associated disorders (e.g., Cognitive Impairment no Dementia[53]), dementia and its sub-types (such as Alzheimer's Disease and vascular dementia), pre-MCI[54] and other preclinical states such as VCIND[55]. 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 can have impactions for research and trial recruitment and outcomes.

With regard to MCI, 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 and/or information reported and how it should be assessed (e.g., single or multiple items). Second, how global cognitive function should be assessed with possible measures including the MMSE, CDR and Global Deterioration Scale, 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, is the question of whether both memory and non-memory domains should be tested. Possible tests identified in this review are outlined in Supplementary Table 2. Fourth, how functional performance should be assessed (the type of questions), the nature of the task (e.g., instrumental ADLs, basic ADLs), reporting (e.g., patient, informant or clinician) and what is the maximum level of impairment (e.g., none, mild, moderate or severe difficulty or significant difficulty in some areas but not in others). Fifth, how dementia should be defined for exclusion

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with examples used including: the DSM or NINCDS-ADRDA criteria, the CDR sum of boxes score ≥1 or via screening instruments (e.g., the Telephone Screening Instrument). It should be noted that aMCI is not always operationalised as originally specified (e.g., permissible significant functional impairment in some studies) and consensus needs to be reached on whether all five criterion 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 generalizability, 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 (e.g., 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 implementation of this methodology has been found to result in a consistent rate of dementia progression (approximately

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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 generalisability of these findings.

A recent task force on designing trials in early (pre-dementia) 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 (i.e., 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 criteria may no longer be considered at-risk, but as already AD, and encompassed in the new term "prodromal AD"; an early symptomatic stage pre-dementia 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 (e.g., 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

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disease (e.g., prodromal AD and pre-MCI) and 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 choose to focus on Petersen 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 (e.g., 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 multi-domain MCI, and multi-domain combined MCI that includes both memory and non-memory deficits. Which, if any, of the many different criteria[72] and sub-types of preclinical decline should be adopted in RCTs or whether no distinction should be made between MCI and AD during recruitment[2], requires further discussion.

Conclusion

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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 definition and development of an operational protocol will result in improvements in diagnosis and clinical trial methodology.

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Additional Files Attached

Figure 1 Petersen criteria for amnestic MCI (aMCI)

Figure 2 PRISMA (2009) flow diagram of article selection

Supplementary Table 1a Characteristics of included studies

Supplementary Table 1b Methods used to map aMCI in included studies

Supplementary Table 2 Tasks used to assess the MCI criteria of "objective cognitive decline" (alphabetic order)

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Acknowledgements

Author Contributions

ICMJE authorship met by all authors. BS and TM designed the review. BS, TM, EP and MS contributed to review article selection, data extraction and writing the results section. BS, TM and MS wrote the first draft of the paper. CB and IM made substantial contribution to the intellectual content. All authors contributed to the final version and approve its submission.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors were personally salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

Competing Interests

No author has a conflict of interest to declare.

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Diagnosing Mild Cognitive Impairment (MCI) in Clinical Trials: A Systematic Review

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Article Type Systematic Review

Word Count 3,075 (Excluding the Abstract and References)
Summary 98
References 72
Figures 2
Supplementary Material 2 Tables

Keywords Mild Cognitive Impairment (MCI), Randomised Controlled Trials, Operationalisation, 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 (1999) 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 criterion including: (1) memory complain, (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.

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Conclusion The results highlight the urgent need for a standardised approach to mapping 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 and 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.

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ARTICLE SUMMARY

Article focus

- Accurate identification of individuals with preclinical dementia is important for clinical trial enrolment.
- Diagnosis of preclinical cases 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 mapping 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 (VCIND). Revision of diagnostic criteria including standardisation of methods and instruments for operationalisation of each dementia subtype and for the different disease stages (e.g., prodromal, preclinical and clinical) should be a research priority.

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Strengths and limitations

- The review focuses on preclinical dementia defined using aMCI. However, not all clinical trials on preclinical 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.

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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, Petersen et al[3, 4] defined amnestic Mild Cognitive Impairment (aMCI) 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 highlight 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, whilst also making cross study comparison and generalizability 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.

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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 (MeSH) terms: ("mild cognitive impairment" OR MCI) AND ("randomised controlled trial" OR "randomized 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 on-going or terminated) and results published; (3) the authors report selecting participants using the definition of aMCI as reported in Petersen et al (1999), and could include single or multi-domain amnestic MCI subtypes (amendments to criteria were allowed as long as stated and Petersen et al (1999) 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

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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, intervention), demographics (age and gender distributions), trial exclusion criteria, dementia progression rates, outcomes tested and the methods used to operationalised each of the five component criterion 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 www.clinicaltrials.gov. Based on the title-abstract 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 1999 criteria or had inadequate details to support the use of Petersen et al 1999 criteria (e.g., only stated an objective cognitive deficit), or the article was a review. Supplementary Table 1a summarises the general characteristics, demographics and outcomes tested in each included

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article. Supplementary Table 1b summarises the operationalisation protocol used for identifying aMCI cases in each trial.

Trial exclusion criteria varied, but 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. multi-centre), duration (e.g., 90 days to 4 years), and sample demographics (e.g., age range: 50-90 years). Interventions included pharmacological agents and supplementation[6-17] (including: donepezil, galantamine, rofecoxib, fluoxetine, lithium treatment, estrogen treatment [E_2], vitamin supplementation (E and B), and supplementation with omega-3 poly unsaturated fatty acids, arachidonic and docosahexaenoic acids), insulin therapy[18], physical activity[19, 20] (e.g., aerobic exercise), cognitive training/rehabilitation programmes[21-25] (e.g., memory training, strategy learning) and combined therapies including cholinesterase inhibitor (ChEI) use combined with a cognitive training program[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 (e.g., 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

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varied: 16%/year[9], 5-6%/year[11], 24% over one year[16], 11.9% over a 24-weeks trial[17] and 15% over four years[12]. Most results were negative.

Operationalizing MCI Component Criterion

Two studies[16, 19] did not report details of the operationalization 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 while eleven 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 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 from 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 (CAMDEX)[28]. Rapp et al[22] used the Memory Functioning Questionnaire (MFQ)[29] which is a 64-item questionnaire assessing memory problems and 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].

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Criterion 2: General Cognitive Function

This criterion was the 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 Dementia Rating Scale (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] (ADAS-Cog) in addition with 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 Supplementary Table 2. In addition to inconsistency in test selection there was no consistency in impairment

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severity (e.g., 1 standard deviation (SD), 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 pre-morbid 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 inclusion of single amnestic or multi-domain amnestic MCI. One study[10] reported the use of combined amnestic and non-amnestic (single and multi-domain) 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 & delayed memory, visuospatial/construction, language & attention) assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[38].

Criterion 4: ADL/IADL

Seven studies did not specify operationalisation of this criterion[6, 8, 13, 16, 19]. In twelve studies[7, 9, 11, 12, 15, 17, 18, 21, 23-27], minimal or non-significant functional impairment was allowed. One study required that in MCI cases that had a MMSE score between 23 and 25, cognitive impairments did not significantly interfere with daily activities or

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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 self or informant report of 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-CERAD[40] version, the Groningen Activity Restriction Scale[41] (GARS) 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 5 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 operationalization 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].

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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 (e.g., 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 Dementia Rating Scale (DRS), seven[6, 8-12, 26] the CDR, one[11] the Blessed Dementia Rating Scale[40] (BDRS), 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. No recruitment protocol for the selection of MCI cases for future clinical trials can be recommended until classification accuracy of current methods is tested.

The review highlights the continuing challenge of classifying and operationalising the current Petersen et al (1999) definition of aMCI. Without a standard operationalisation protocol for defining aMCI trial recruitment will continue to be variable. Indeed, within the field of dementia there is a lack of consistency in

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operationalisation protocols not only for aMCI, but its associated disorders (e.g., Cognitive Impairment no Dementia[53]), dementia and its sub-types (such as Alzheimer's Disease and vascular dementia), pre-MCI[54] and other preclinical states such as VCIND[55]. 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 can have impactions for research and trial recruitment and outcomes.

With regard to MCI, 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 and/or information reported and how it should be assessed (e.g., single or multiple items). Second, how global cognitive function should be assessed with possible measures including the MMSE, CDR and Global Deterioration Scale, 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, is the question of whether both memory and non-memory domains should be tested. Possible tests identified in this review are outlined in Supplementary Table 2. Fourth, how functional performance should be assessed (the type of questions), the nature of the task (e.g., instrumental ADLs, basic ADLs), reporting (e.g., patient, informant or clinician) and what is the maximum level of impairment (e.g., none, mild, moderate or severe difficulty or significant difficulty in some areas but not in others). Fifth, how dementia should be defined for exclusion

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with examples used including: the DSM or NINCDS-ADRDA criteria, the CDR sum of boxes score ≥1 or via screening instruments (e.g., the Telephone Screening Instrument). It should be noted that aMCI is not always operationalised as originally specified (e.g., permissible significant functional impairment in some studies) and consensus needs to be reached on whether all five criterion 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 generalizability, 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 (e.g., 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 implementation of this methodology has been found to result in a consistent rate of dementia progression (approximately

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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 generalisability of these findings.

A recent task force on designing trials in early (pre-dementia) 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 (i.e., 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 criteria may no longer be considered at-risk, but as already AD, and encompassed in the new term "prodromal AD"; an early symptomatic stage pre-dementia 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 (e.g., 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

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disease (e.g., prodromal AD and pre-MCI) and 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 choose to focus on Petersen 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 (e.g., 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 multi-domain MCI, and multi-domain combined MCI that includes both memory and non-memory deficits. Which, if any, of the many different criteria[72] and sub-types of preclinical decline should be adopted in RCTs or whether no distinction should be made between MCI and AD during recruitment[2], requires further discussion.

Conclusion

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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 definition and development of an operational protocol will result in improvements in diagnosis and clinical trial methodology.

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Additional Files Attached

Figure 1 Petersen criteria for amnestic MCI (aMCI)

Figure 2 PRISMA (2009) flow diagram of article selection

Supplementary Table 1a Characteristics of included studies

Supplementary Table 1b Methods used to map aMCI in included studies

Supplementary Table 2 Tasks used to assess the MCI criteria of "objective cognitive decline" (alphabetic order)

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Acknowledgements

Author Contributions

ICMJE authorship met by all authors. BS and TM designed the review. BS, TM, EP and MS contributed to review article selection, data extraction and writing the results section. BS, TM and MS wrote the first draft of the paper. CB and IM made substantial contribution to the intellectual content. All authors contributed to the final version and approve its submission.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors were personally salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

Competing Interests

No author has a conflict of interest to declare.

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Figure 1 Petersen criteria for amnestic MCI (aMCI)

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

Petersen criteria for amnestic MCI (aMCI)
102x66mm (300 x 300 DPI)

eview only

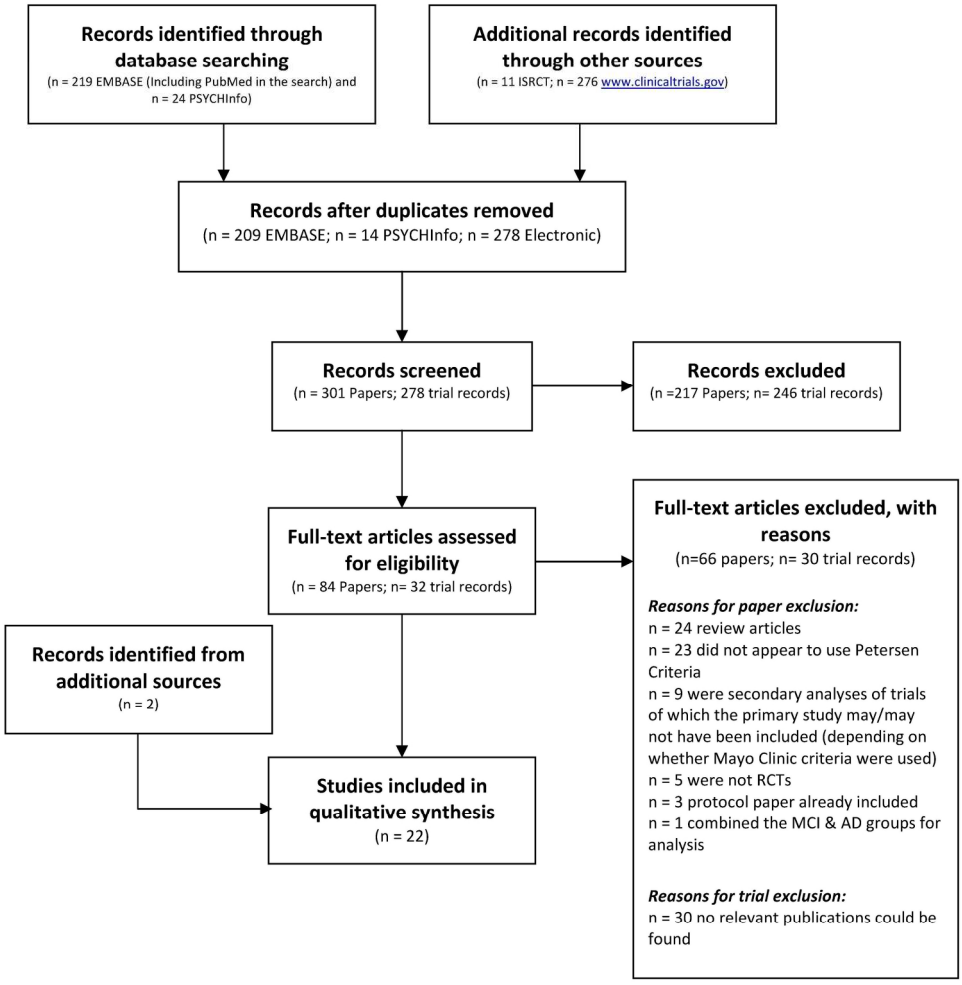

Figure 2. PRISMA (2009) flow diagram of article selection
191x205mm (300 x 300 DPI)

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)

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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]

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Diagnosing Mild Cognitive Impairment (MCI) in Clinical Trials: A Systematic Review

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001909.R2
Article Type:	Research
Date Submitted by the Author:	07-Jan-2013
Complete List of Authors:	Stephan, Blossom; Newcastle University, Institute of Health and Society Minett, Thais; Cambridge University, Department of Public Health and Primary Care Pagett, Emma; Cambridge University, Department of Public Health and Primary Care Siervo, Mario; Newcastle University, Institute of Ageing Brayne, Carol; University of Cambridge, Public Health and Primary Care McKeith, Ian; Newcastle University, Institute of Ageing
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Geriatric medicine
Keywords:	Dementia < NEUROLOGY, MENTAL HEALTH, NEUROLOGY

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Manuscripts

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Diagnosing Mild Cognitive Impairment (MCI) in Clinical Trials: A Systematic Review

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Article Type Systematic Review

Word Count 3,245 (Excluding the Abstract and References)
Summary 98
References 72
Figures 2
Supplementary Material 2 Tables

Keywords Mild Cognitive Impairment (MCI), Randomised Controlled Trials, Operationalisation, 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 (1999) 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 criterion including: (1) memory complain, (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.

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Conclusion The results highlight the urgent need for a standardised approach to mapping 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.

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ARTICLE SUMMARY

Article focus

- Accurate identification of individuals at risk of dementia or with pre-dementia is important for clinical trial enrolment.
- Diagnosis of pre-dementia 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 mapping 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 (VCIND). Revision of diagnostic criteria should be a research priority.

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Strengths and limitations

- The review focuses on pre-dementia defined using aMCI. However, not all clinical trials on pre-dementia 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.

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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, Petersen et al[3, 4] defined amnestic Mild Cognitive Impairment (aMCI) 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 highlight 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, whilst also making cross study comparison and generalizability 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.

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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 (MeSH) terms: ("mild cognitive impairment" OR MCI) AND ("randomised controlled trial" OR "randomized 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 on-going or terminated) and results published; (3) the authors report selecting participants using the definition of aMCI as reported in Petersen et al (1999), and could include single or multi-domain amnestic MCI subtypes (amendments to criteria were allowed as long as stated and Petersen et al (1999) 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

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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, intervention), demographics (age and gender distributions), trial exclusion criteria, dementia progression rates, outcomes tested and the methods used to operationalised each of the five component criterion 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 www.clinicaltrials.gov. Based on the title-abstract 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 1999 criteria or had inadequate details to support the use of Petersen et al 1999 criteria (e.g., only stated an objective cognitive deficit), or the article was a review. Supplementary Table 1a summarises the general characteristics, demographics and outcomes tested in each included

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article. Supplementary Table 1b summarises the operationalisation protocol used for identifying aMCI cases in each trial.

Trial exclusion criteria varied, but 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. multi-centre), duration (e.g., 90 days to 4 years), and sample demographics (e.g., age range: 50-90 years). Interventions included pharmacological agents and supplementation[6-17] (including: donepezil, galantamine, rofecoxib, fluoxetine, lithium treatment, estrogen treatment [E_2], vitamin supplementation (E and B), and supplementation with omega-3 poly unsaturated fatty acids, arachidonic and docosahexaenoic acids), insulin therapy[18], physical activity[19, 20] (e.g., aerobic exercise), cognitive training/rehabilitation programmes[21-25] (e.g., memory training, strategy learning) and combined therapies including cholinesterase inhibitor (ChEI) use combined with a cognitive training program[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 (e.g., 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

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varied: 16%/year[9], 5-6%/year[11], 24% over one year[16], 11.9% over a 24-weeks trial[17] and 15% over four years[12]. Most results were negative.

Operationalizing MCI Component Criterion

Two studies[16, 19] did not report details of the operationalization 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 while eleven 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 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 from 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 (CAMDEX)[28]. Rapp et al[22] used the Memory Functioning Questionnaire (MFQ)[29] which is a 64-item questionnaire assessing memory problems and 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].

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Criterion 2: General Cognitive Function

This criterion was the 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 Dementia Rating Scale (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] (ADAS-Cog) in addition with 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 Supplementary Table 2. In addition to inconsistency in test selection there was no consistency in impairment

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severity (e.g., 1 standard deviation (SD), 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 pre-morbid 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 inclusion of single amnestic or multi-domain amnestic MCI. One study[10] reported the use of combined amnestic and non-amnestic (single and multi-domain) 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 & delayed memory, visuospatial/construction, language & attention) assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[38].

Criterion 4: ADL/IADL

Seven studies did not specify operationalisation of this criterion[6, 8, 13, 16, 19]. In twelve studies[7, 9, 11, 12, 15, 17, 18, 21, 23-27], minimal or non-significant functional impairment was allowed. One study required that in MCI cases that had a MMSE score between 23 and 25, cognitive impairments did not significantly interfere with daily activities or

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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 self or informant report of 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-CERAD[40] version, the Groningen Activity Restriction Scale[41] (GARS) 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 5 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 operationalization 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].

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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 (e.g., 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 Dementia Rating Scale (DRS), seven[6, 8-12, 26] the CDR, one[11] the Blessed Dementia Rating Scale[40] (BDRS), 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 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 (e.g., 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.

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The review highlights the continuing challenge of operationalising the current Petersen et al (1999) definition of aMCI. Without a standard operationalisation protocol for defining aMCI 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 (e.g., Cognitive Impairment no Dementia[53]), dementia and its sub-types (such as Alzheimer's Disease, Lewy Body dementia, frontotemporal dementia and vascular dementia), pre-MCI[54] and other pre-dementia 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 (e.g., as seen in Lewy Body dementia), capturing variability in symptom profiles (e.g., the different type of aphasic deficit presented in frontotemporal dementia) or reflecting differences in neuropathological profiles (e.g., 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 impactions for 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

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complaint should be self and/or information reported and how it should be assessed (e.g., single or multiple items). Second, how global cognitive function should be assessed with possible measures including the MMSE, CDR and Global Deterioration Scale, 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, is the question of whether both memory and non-memory domains should be tested. Possible tests identified in this review are outlined in Supplementary Table 2. Fourth, how functional performance should be assessed (the type of questions), the nature of the task (e.g., instrumental ADLs, basic ADLs), reporting (e.g., patient, informant or clinician) and what is the maximum level of impairment (e.g., none, mild, moderate or severe difficulty or significant difficulty in some areas but not in others). Fifth, how dementia should 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 (e.g., the Telephone Screening Instrument). It should be noted that aMCI is not always operationalised as originally specified (e.g., permissible significant functional impairment in some studies) and consensus needs to be reached on whether all five criterion 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 generalizability, needs to be established.

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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 (e.g., 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 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 (pre-dementia) AD argues for the use of aMCI criteria in combination with biomarkers to improve case selection for clinical

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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 (i.e., 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 pre-dementia 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 (e.g., 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 (e.g., prodromal AD and pre-MCI) and 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 choose 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

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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 (e.g., 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 multi-domain MCI, and multi-domain combined MCI that includes both memory and non-memory deficits. Which, if any, of the many different criteria[72] and sub-types 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 definition and development of an operational protocol will result in improvements in diagnosis and clinical trial methodology.

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Additional Files Attached

Figure 1 Petersen criteria for amnestic MCI (aMCI)

Figure 2 PRISMA (2009) flow diagram of article selection

Supplementary Table 1a Characteristics of included studies

Supplementary Table 1b Methods used to map aMCI in included studies

Supplementary Table 2 Tasks used to assess the MCI criteria of "objective cognitive decline" (alphabetic order)

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Acknowledgements

Author Contributions

ICMJE authorship met by all authors. BS and TM designed the review. BS, TM, EP and MS contributed to review article selection, data extraction and writing the results section. BS, TM and MS wrote the first draft of the paper. CB and IM made substantial contribution to the intellectual content. All authors contributed to the final version and approve its submission.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors were personally salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

Competing Interests

No author has a conflict of interest to declare.

Data Sharing Statement

The manuscript is a systematic review. The review protocol is available on request from the corresponding author.

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Diagnosing Mild Cognitive Impairment (MCI) in Clinical Trials: A Systematic Review

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Article Type Systematic Review

Word Count 3,245 (Excluding the Abstract and References)
Summary 98
References 72
Figures 2
Supplementary Material 2 Tables

Keywords Mild Cognitive Impairment (MCI), Randomised Controlled Trials, Operationalisation, 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 (1999) 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 criterion including: (1) memory complain, (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.

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Conclusion The results highlight the urgent need for a standardised approach to mapping 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.

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ARTICLE SUMMARY

Article focus

- Accurate identification of individuals at risk of dementia or with pre-dementia is important for clinical trial enrolment.
- Diagnosis of pre-dementia 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 mapping 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 (VCIND). Revision of diagnostic criteria should be a research priority.

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Strengths and limitations

- The review focuses on pre-dementia defined using aMCI. However, not all clinical trials on pre-dementia 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.

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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, Petersen et al[3, 4] defined amnestic Mild Cognitive Impairment (aMCI) 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 highlight 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, whilst also making cross study comparison and generalizability 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.

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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 (MeSH) terms: ("mild cognitive impairment" OR MCI) AND ("randomised controlled trial" OR "randomized 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 on-going or terminated) and results published; (3) the authors report selecting participants using the definition of aMCI as reported in Petersen et al (1999), and could include single or multi-domain amnestic MCI subtypes (amendments to criteria were allowed as long as stated and Petersen et al (1999) 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

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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, intervention), demographics (age and gender distributions), trial exclusion criteria, dementia progression rates, outcomes tested and the methods used to operationalised each of the five component criterion 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 www.clinicaltrials.gov. Based on the title-abstract 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 1999 criteria or had inadequate details to support the use of Petersen et al 1999 criteria (e.g., only stated an objective cognitive deficit), or the article was a review. Supplementary Table 1a summarises the general characteristics, demographics and outcomes tested in each included

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article. Supplementary Table 1b summarises the operationalisation protocol used for identifying aMCI cases in each trial.

Trial exclusion criteria varied, but 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. multi-centre), duration (e.g., 90 days to 4 years), and sample demographics (e.g., age range: 50-90 years). Interventions included pharmacological agents and supplementation[6-17] (including: donepezil, galantamine, rofecoxib, fluoxetine, lithium treatment, estrogen treatment [E_2], vitamin supplementation (E and B), and supplementation with omega-3 poly unsaturated fatty acids, arachidonic and docosahexaenoic acids), insulin therapy[18], physical activity[19, 20] (e.g., aerobic exercise), cognitive training/rehabilitation programmes[21-25] (e.g., memory training, strategy learning) and combined therapies including cholinesterase inhibitor (ChEI) use combined with a cognitive training program[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 (e.g., 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

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varied: 16%/year[9], 5-6%/year[11], 24% over one year[16], 11.9% over a 24-weeks trial[17] and 15% over four years[12]. Most results were negative.

Operationalizing MCI Component Criterion

Two studies[16, 19] did not report details of the operationalization 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 while eleven 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 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 from 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 (CAMDEX)[28]. Rapp et al[22] used the Memory Functioning Questionnaire (MFQ)[29] which is a 64-item questionnaire assessing memory problems and 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].

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Criterion 2: General Cognitive Function

This criterion was the 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 Dementia Rating Scale (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] (ADAS-Cog) in addition with 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 Supplementary Table 2. In addition to inconsistency in test selection there was no consistency in impairment

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severity (e.g., 1 standard deviation (SD), 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 pre-morbid 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 inclusion of single amnestic or multi-domain amnestic MCI. One study[10] reported the use of combined amnestic and non-amnestic (single and multi-domain) 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 & delayed memory, visuospatial/construction, language & attention) assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[38].

Criterion 4: ADL/IADL

Seven studies did not specify operationalisation of this criterion[6, 8, 13, 16, 19]. In twelve studies[7, 9, 11, 12, 15, 17, 18, 21, 23-27], minimal or non-significant functional impairment was allowed. One study required that in MCI cases that had a MMSE score between 23 and 25, cognitive impairments did not significantly interfere with daily activities or

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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 self or informant report of 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-CERAD[40] version, the Groningen Activity Restriction Scale[41] (GARS) 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 5 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 operationalization 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].

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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 (e.g., 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 Dementia Rating Scale (DRS), seven[6, 8-12, 26] the CDR, one[11] the Blessed Dementia Rating Scale[40] (BDRS), 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 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 (e.g., 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.

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The review highlights the continuing challenge of operationalising the current Petersen et al (1999) definition of aMCI. Without a standard operationalisation protocol for defining aMCI 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 (e.g., Cognitive Impairment no Dementia[53]), dementia and its sub-types (such as Alzheimer's Disease, Lewy Body dementia, frontotemporal dementia and vascular dementia), pre-MCI[54] and other pre-dementia 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 (e.g., as seen in Lewy Body dementia), capturing variability in symptom profiles (e.g., the different type of aphasic deficit presented in frontotemporal dementia) or reflecting differences in neuropathological profiles (e.g., 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 impactions for 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

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complaint should be self and/or information reported and how it should be assessed (e.g., single or multiple items). Second, how global cognitive function should be assessed with possible measures including the MMSE, CDR and Global Deterioration Scale, 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, is the question of whether both memory and non-memory domains should be tested. Possible tests identified in this review are outlined in Supplementary Table 2. Fourth, how functional performance should be assessed (the type of questions), the nature of the task (e.g., instrumental ADLs, basic ADLs), reporting (e.g., patient, informant or clinician) and what is the maximum level of impairment (e.g., none, mild, moderate or severe difficulty or significant difficulty in some areas but not in others). Fifth, how dementia should 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 (e.g., the Telephone Screening Instrument). It should be noted that aMCI is not always operationalised as originally specified (e.g., permissible significant functional impairment in some studies) and consensus needs to be reached on whether all five criterion 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 generalizability, needs to be established.

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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 (e.g., 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 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 (pre-dementia) AD argues for the use of aMCI criteria in combination with biomarkers to improve case selection for clinical

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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 (i.e., 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 pre-dementia 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 (e.g., 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 (e.g., prodromal AD and pre-MCI) and 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 choose 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

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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 (e.g., 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 multi-domain MCI, and multi-domain combined MCI that includes both memory and non-memory deficits. Which, if any, of the many different criteria[72] and sub-types 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 definition and development of an operational protocol will result in improvements in diagnosis and clinical trial methodology.

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Additional Files Attached

Figure 1 Petersen criteria for amnestic MCI (aMCI)

Figure 2 PRISMA (2009) flow diagram of article selection

Supplementary Table 1a Characteristics of included studies

Supplementary Table 1b Methods used to map aMCI in included studies

Supplementary Table 2 Tasks used to assess the MCI criteria of "objective cognitive decline" (alphabetic order)

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Acknowledgements

Author Contributions

ICMJE authorship met by all authors. BS and TM designed the review. BS, TM, EP and MS contributed to review article selection, data extraction and writing the results section. BS, TM and MS wrote the first draft of the paper. CB and IM made substantial contribution to the intellectual content. All authors contributed to the final version and approve its submission.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors were personally salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

Competing Interests

No author has a conflict of interest to declare.

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Figure 1 Petersen criteria for amnestic MCI (aMCI)

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

Petersen criteria for amnestic MCI (aMCI)
102x66mm (300 x 300 DPI)

eview only

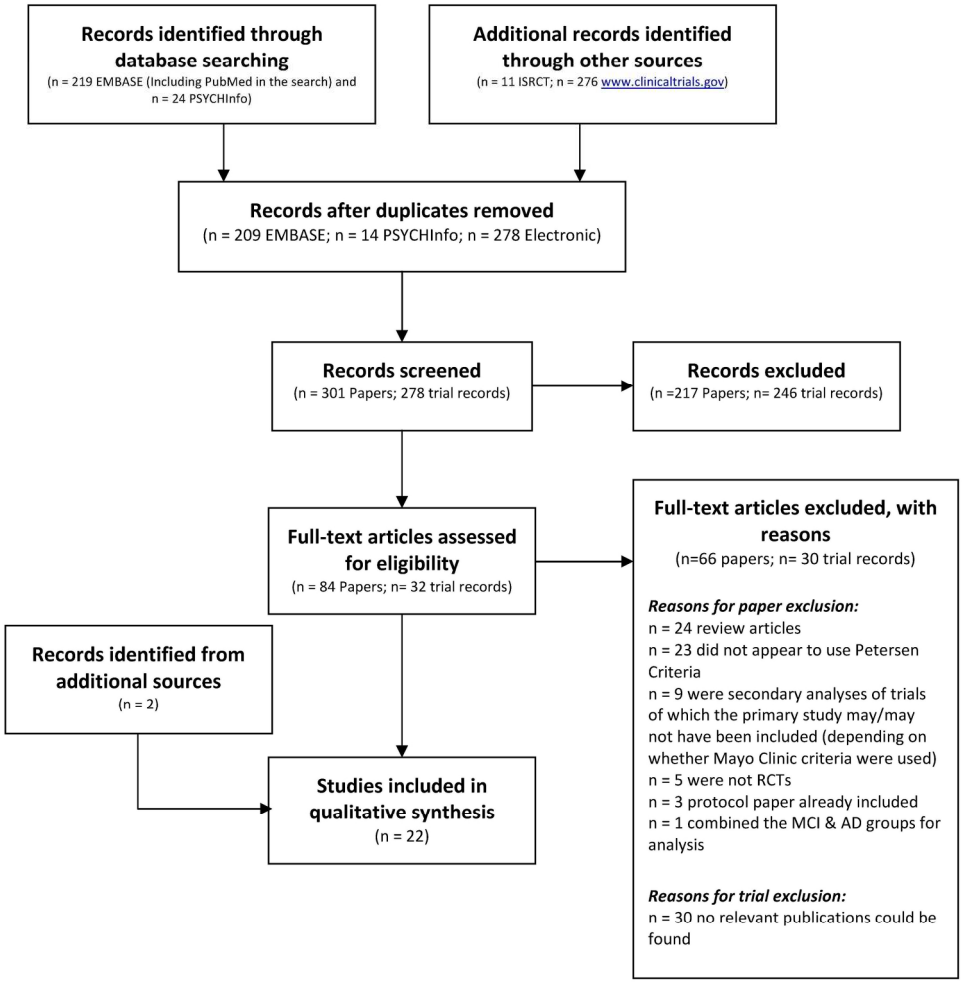

Figure 2. PRISMA (2009) flow diagram of article selection
191x205mm (300 x 300 DPI)

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)

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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]

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