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Abstract

Automated tests for diagnosing and monitoring cognitive impairment: a diagnostic accuracy review

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Background: Cognitive impairment is a growing public health concern, and is one of the most distinctive characteristics of all dementias. The timely recognition of dementia syndromes can be beneficial, as some causes of dementia are treatable and are fully or partially reversible. Several automated cognitive assessment tools for assessing mild cognitive impairment (MCI) and early dementia are now available. Proponents of these tests cite as benefits the tests' repeatability and robustness and the saving of clinicians' time. However, the use of these tools to diagnose and/or monitor progressive cognitive impairment or response to treatment has not yet been evaluated.

Objectives: The aim of this review was to determine whether or not automated computerised tests could accurately identify patients with progressive cognitive impairment in MCI and dementia and, if so, to investigate their role in monitoring disease progression and/or response to treatment.

Data sources: Five electronic databases (MEDLINE, EMBASE, The Cochrane Library, ISI Web of Science and PsycINFO), plus ProQuest, were searched from 2005 to August 2015. The bibliographies of retrieved citations were also examined. Trial and research registers were searched for ongoing studies and reviews. A second search was run to identify individual test costs and acquisition costs for the various tools identified in the review.

Review methods: Two reviewers independently screened all titles and abstracts to identify potentially relevant studies for inclusion in the review. Full-text copies were assessed independently by two reviewers. Data were extracted and assessed for risk of bias by one reviewer and independently checked for accuracy by a second. The results of the data extraction and quality assessment for each study are presented in structured tables and as a narrative summary.

Results: The electronic searching of databases, including ProQuest, resulted in 13,542 unique citations. The titles and abstracts of these were screened and 399 articles were shortlisted for full-text assessment. Sixteen studies were included in the diagnostic accuracy review. No studies were eligible for inclusion in the review of tools for monitoring progressive disease. Eleven automated computerised tests were assessed in the 16 included studies. The overall quality of the studies was good; however, the wide range of tests

assessed and the non-standardised reporting of diagnostic accuracy outcomes meant that meaningful synthesis or statistical analysis was not possible.

Limitations: The main limitation of this review is the substantial heterogeneity of the tests assessed in the included studies. As a result, no meta-analyses could be undertaken.

Conclusion: The quantity of information available is insufficient to be able to make recommendations on the clinical use of the computerised tests for diagnosing and monitoring MCI and early dementia progression. The value of these tests also depends on the costs of acquisition, training, administration and scoring.

Future work: Research is required to establish stable cut-off points for automated computerised tests that are used to diagnose patients with MCI or early dementia. Additionally, the costs associated with acquiring and using these tests in clinical practice should be estimated.

Study registration: The study is registered as PROSPERO CRD42015025410.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Accuracy A measure of the closeness of the experimental value to the actual amount of the substance in the matrix.

Area under the curve A measure of the diagnostic accuracy of a technology, which is based on the geometric inspection of a receiver operating characteristic curve. A receiver operating characteristic curve is a plot of the true-positive rate against the false-positive rate at different threshold settings. A technology with perfect diagnostic accuracy will have an area under the curve of 1; a technology that is no better than chance will have an area under the curve of 0.5; and a technology that miscategorises on every occasion will have an area under the curve of 0.

Cut-off point See *Threshold*.

Diagnostic accuracy The effectiveness of a diagnostic test to correctly categorise patients as either 'positive' or 'negative'. There are several ways that this can be expressed, for example as the area under the curve or as sensitivity and specificity.

False negative When a patient has been diagnosed with, for example, mild cognitive impairment using a standard test but the index test fails to detect this.

False positive When a patient has been diagnosed with, for example, mild cognitive impairment using the index test but they do not have this condition.

Index test The diagnostic test that is being evaluated.

Likelihood ratio A description of how many times more likely it is that a person with the disease will have a particular test result than a person without the disease.

National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria The prevalent criteria for the diagnosis of Alzheimer's disease, proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. These criteria require the presence of cognitive impairment and a suspected dementia syndrome to be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable Alzheimer's disease, while histopathologic confirmation is needed for the definitive diagnosis. These criteria specify eight cognitive domains that may be impaired in Alzheimer's disease: memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities.

Negative predictive value The proportion of people with negative test results who do not have the disease, for example the probability that a patient who is test negative on an index test does not have mild cognitive impairment or dementia on clinical diagnosis.

Petersen's criteria The criteria for mild cognitive impairment, as defined by Petersen, which include the following: memory problems, objective memory disorder, absence of other cognitive disorders or repercussions on daily life, normal general cognitive function and absence of dementia.

Positive predictive value The proportion of people with positive test results who actually have the disease, for example the probability that a patient who tests positive on an index test has mild cognitive impairment or dementia on clinical diagnosis.

Precision Measures how close individual measurements of a sample are to each other.

Receiver operating characteristic curve A plot of the true-positive rate against the false-positive rate of a test at different threshold settings.

Reference standard A diagnostic test used to estimate the sensitivity and specificity of another diagnostic test, known as an index test. The reference standard is assumed to have perfect sensitivity and specificity, and so in cases when both tests categorise something differently, the reference standard test categorisation is assumed to be correct (either true negative or true positive).

Sensitivity Also called the true-positive rate, measures the proportion of those who actually have the disease correctly identified with positive test results, for example the proportion of patients with mild cognitive impairment or dementia at clinical diagnosis identified by the index test.

Specificity The proportion of people who do not have the disease, correctly identified as having a negative test result, for example the proportion of patients without mild cognitive impairment or dementia on clinical diagnosis who are test negative on the index test.

Threshold (clinical) A value, within a range of values, used to categorise observations into one of two mutually exclusive groups. For example, guidelines suggest that the decision of whether or not to investigate for possible mild cognitive impairment or dementia is influenced by cognitive test scores (e.g. in the Mini-Mental State Examination, the threshold for mild Alzheimer's disease is a score of 21–26, whereas the threshold for moderate Alzheimer's disease is a score of 10–20).

True negative In the case of mild cognitive impairment, a patient who has been correctly identified by the index test as not having mild cognitive impairment.

True positive In the case of mild cognitive impairment, a patient who has been correctly identified by the index test as having mild cognitive impairment.

List of abbreviations

AD	Alzheimer's disease
AUC	area under the receiver operating characteristic curve
CAMCI	Computer Assessment of Mild Cognitive Impairment
CANTAB	Cambridge Neuropsychological Test Automated Battery
CANTAB-PAL	Cambridge Neuropsychological Test Automated Battery Paired Association Learning
FN	false negative
FP	false positive
GP	general practitioner
HAND	HIV-associated neurocognitive disorder
HIV	human immunodeficiency virus
LR	likelihood ratio
LRiG	Liverpool Review and Implementation Group
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
PPV	positive predictive value
QUADAS-2	Quality Assessment Tool for Diagnostic Accuracy Studies
TN	true negative
TP	true positive

Plain English summary

The number of people who have problems with their memory and thinking is rising. The testing of memory and thinking is difficult and, in the early stages, the person with problems may show only small changes.

Pen-and-paper tests are often used to test memory loss and thinking problems, alongside discussions with health-care specialists and the individual, often in the company of their families or caregivers. Depending on the level of memory loss and thinking problems, some people are offered treatment, whereas others are followed up to see if their symptoms become worse. New tests to assess these problems have been developed that are computer based and sometimes do not need a specialist to be involved.

We carried out a systematic review (a review of studies conducted by others) to look at how well these computer-based tests diagnosed people with memory loss and thinking problems. We found limited evidence to support the use of these computer-based tests in clinical practice without the involvement of a health-care specialist. For this reason, at this time, we would recommend against approaches that use computerised tests by themselves.

We also asked a person living with memory problems for their views on the results of this research.

Scientific summary

Background

Cognitive impairment is a growing public health concern, and is one of the most distinctive characteristics of all dementias. The timely recognition of dementia syndromes can be beneficial, as some causes of dementia are treatable and are fully or partially reversible. Health-care professionals in the NHS currently use a number of pen-and-paper-based tools to diagnose and monitor patients with cognitive impairment; the Mini-Mental State Examination and the General Practitioner Assessment of Cognition are two examples of such tests. Several automated computerised cognitive assessment tools for assessing mild cognitive impairment (MCI) and early dementia are also now available; however, their use in diagnosis and/or in monitoring the progression of cognitive impairment or response to treatment has not been evaluated.

Objectives

The aim of this review is to determine whether or not automated computerised tests accurately identify patients with progressive cognitive impairment in MCI and early in dementia and, if so, to investigate their role in monitoring disease progression and/or response to treatment.

Methods

Search strategy

Five electronic databases (MEDLINE, EMBASE, The Cochrane Library, ISI Web of Science and PsycINFO) were searched from 2005 to August 2015. Theses or PhD abstracts were accessed from ProQuest. Backwards and forwards citation tracking for all relevant studies and reviews for further possible titles was undertaken. Trial and research registers were searched for ongoing studies and reviews. After individual tests were identified, a second search was run to identify the individual test costs and acquisition costs for the various tools.

Study selection

The references identified were assessed for inclusion through two stages. In stage 1, two reviewers independently screened all relevant titles and abstracts identified via electronic searching and selected potentially relevant studies for inclusion in the review. In stage 2, full-text copies of the potentially relevant studies were obtained and assessed independently by two reviewers. Any disagreements between reviewers were resolved by discussion with a third reviewer at each stage. Studies that did not meet the inclusion criteria were excluded.

Data extraction and quality assessment strategy

Data extraction forms were developed and piloted in a Microsoft Excel® spreadsheet (Microsoft Corporation, Redmond, WA, USA) using a sample of included studies. One reviewer extracted data on study and population characteristics and outcomes, and a second reviewer independently checked the data for accuracy, with disagreements resolved through discussion with a third reviewer when necessary.

Evidence synthesis

The results of the data extraction and quality assessment for each study are presented in structured tables and as a narrative summary.

Results

The electronic searching of databases resulted in 13,352 references. An additional 5444 records were identified through ProQuest, hand-searching and citation tracking. After deduplication, 13,542 titles and abstracts were screened and 399 articles were shortlisted for full-text assessment. Sixteen studies were included in the diagnostic accuracy review. No studies were identified that described automated computerised tools used to monitor disease progression.

Owing to the heterogeneity of the included studies and the limited data available, it was not possible or appropriate to perform any statistical analyses.

At this time, owing to the limited and poor quality of the evidence base, the use of automated computerised tests in routine clinical practice cannot be recommended.

Conclusions

The overall quality and quantity of information currently available is insufficient to be able to make recommendations on the clinical use of computerised tests for diagnosing and monitoring MCI and early dementia progression.

These test scores do not always correlate with clinical history and, more importantly, with functioning. Hence the diagnosis of patients with MCI and early dementia is based on clinical judgement and medical history as well as the results of cognitive tests. For this reason, we would recommend against approaches that use computerised tests in isolation at this time.

Further research is required to establish stable cut-off points for each automated computerised test used to diagnose patients with MCI or early dementia. These cut-off points also need to be tested in specific patient populations, for example in patients of different age groups or education levels and from different geographical regions.

The prevalence of dementia and alternative diagnoses in the study populations should be clearly reported, making reference to standardised checklists for diagnostic reviews such as the Standards for Reporting Diagnostic Accuracy or the Standards for Reporting Diagnostic Accuracy – dementia.

Future research in this area should also focus on providing more information on the costs of computerised tests, including time for training, administration and scoring of the different tests, as these are important factors for their use in routine clinical practice. This type of information is currently lacking in the published studies describing computerised tests used to diagnose or monitor people with MCI or early dementia.

Study registration

This study is registered as PROSPERO CRD42015025410.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Decision problem

The aim of this review was to determine whether or not automated computerised tests accurately identify patients with progressive cognitive impairment and, if so, to investigate their role in monitoring disease progression and/or response to treatment.

Specifically, the research objectives were to:

1. determine the performance of automated computerised tests in detecting mild cognitive impairment (MCI) and early dementia
2. determine the performance of automated computerised tests in the monitoring of the disease post diagnosis, specifically in detecting disease progression
3. identify future research needs.

Chapter 2 Background and rationale for review

Cognitive impairment in dementia is progressive, and is a growing public health concern.[1] It is one of the most distinctive characteristics of all dementias. Consequently, the assessment of cognitive impairment is an essential element in the diagnosis of dementia.[2]

The timely recognition of dementia syndromes can be beneficial because some causes of dementia are treatable and are fully or partially reversible, for example dementias caused by vitamin B12 deficiency,[3] side effects of medications,[4] metabolic abnormality and certain brain tumours.[5] There is also some evidence from the USA that early recognition and treatment may delay the subsequent need for nursing home care and may reduce the risk of misdiagnosis and inappropriate management.[6] In the UK, the results of a recent trial showed that patients with moderate to severe Alzheimer's disease (AD) who continued donepezil treatment were at reduced risk of nursing home placement.[7] Early diagnosis can also assist in addressing anxiety about changes in memory, thinking, mood or behaviour for people with suspected dementia and their carers.[8]

A number of pen-and-paper-based tools for cognitive assessment are currently used in the UK, for example the Mini-Mental State Examination (MMSE) and the General Practitioner Assessment of Cognition.[9] A few automated cognitive assessment tools for assessing MCI and early dementia are now also available; however, their use in the diagnosis and/or in monitoring the progression of cognitive impairment or response to treatment has not been evaluated.[10]

The rationale for this review is to determine whether or not these automated computerised tests for cognitive impairment have the potential to contribute to early diagnosis and simplify the current monitoring and assessment process compared with standard NHS clinical practice.

Population

This review addresses patients in two specific diagnostic categories: those with MCI and those suffering from early dementia.

Mild cognitive impairment

Evidence from neuropathological and neuroimaging studies suggests that biological changes associated with dementia occur long before the onset of symptoms.[11] Extensive research has been devoted to identifying the characteristics of incipient dementia, which presents before the onset of the full dementia syndrome.[12,13]

This research has given rise to the concept of MCI, which is the state between the cognitive changes of normal ageing and very early dementia.[14,15] The transitional period has been described using a variety of terms such as MCI, dementia prodrome, incipient dementia, isolated memory impairment[16] and, more recently, mild neurocognitive disorder.[12] For the purposes of this report, the term 'mild cognitive impairment' or MCI has been used.

Mild cognitive impairment refers to the clinical condition used to describe people whose cognitive function is below that of the normal population for their educational level and age but who do not have any loss of functional abilities or skills.[17–20] The diagnosis of MCI is complicated by the fact that complaints of memory loss in people over the age of 65 years are common.[21] Some of the indicators of dementia, such as a reduction in activities of daily living, decreased attention or ability to plan, are absent in people with MCI.[20]

Mild cognitive impairment is a heterogeneous state, with possible trajectories including AD, other dementias, and even reversion to normal cognitive functioning.[12] It is also worth noting that the authors of a meta-analysis[22] of 41 inception cohort studies reported that the annual conversion rate from defined MCI to dementia was approximately 5–10%. The overall conversion rate from MCI to AD has been estimated to

be between 6% and 25% of cases per year.[23] However, these rates vary by subtype of disease. The variation in the conversion rates could be explained by the differing disease processes[13,24] and the heterogeneity which comes from different populations being studied.[25] In epidemiological samples, MCI has often been classified by applying a psychometric cut-off point to a proportion of cases without in-depth clinical examination, and a large proportion of these cases subsequently revert to normality.[25] In contrast, cases of MCI diagnosed in secondary care services, following detailed and comprehensive examination and investigations by a specialist, reveal fewer cases reverting to normality and much higher rates of progression. Therefore, the concept of MCI depends on how thoroughly the pre-diagnostic assessment is performed.

Mild cognitive impairment is subtyped in terms of the type and number of cognitive domains affected.[16] The classification of MCI is described in *Table 1*.

Different types of MCI have now been proposed, including 'amnestic form of MCI', when memory is affected, and non-amnestic form of MCI, when impairment is in a non-memory domain.[16] MCI is also classified as single-domain or multiple-domain according to the number of cognitive domains with objectively verified impairment.[26]

Early dementia

Early dementia is differentiated from MCI by the level of cognitive decline and changes in mood and behaviour. The common changes experienced by people with dementia can be understood in three stages: early, middle and late dementia (*Table 2*). Individuals diagnosed with early dementia present with multiple cognitive deficits and their memory loss is sufficient to impact on everyday social and occupational functioning. In the later stages, there is a noticeable deterioration in perception, comprehension and language. This is also often accompanied by an impaired ability to recognise objects (agnosia) and an inability to think abstractly and plan, initiate, sequence, monitor and stop complex behaviour.[28,29]

There are a number of conditions that result in dementia. The three most common reasons are AD vascular conditions (e.g. multiple cortical/subcortical infarcts), frontotemporal atrophy and Lewy body disease. Some rare causes of dementia include inherited metabolic disorders (e.g. porphyria), infectious causes, autoimmune causes and neoplasms (e.g. meningioma).[30,31] Irrespective of the primary cause, the outlook for people with most types of dementia is usually poor. Irreversible or untreated dementia usually continues to worsen over time until the person's death.[32,33]

There are subtle neuropsychological differences in patterns of cognitive deficit in different types of dementia but, as far as we are aware, there are no dedicated automated tests to specifically diagnose different types of dementia, such as vascular dementia, alcohol-related dementia or Lewy body dementia. Furthermore, this is complicated by the fact that authors of studies often use terms inconsistently and erroneously when describing dementia.

TABLE 1 Mild cognitive impairment subtypes by aetiology, presentation and long-term outcomes

Variable	Amnestic	Non-amnestic
Aetiology	Neurodegenerative disease	Vascular damage
	Apolipoprotein E	Cerebrovascular disease
Presentation	Memory impairment present	Impairment in non-memory domains
Long-term outcomes	Alzheimer's dementia (AD)	Non-Alzheimer dementias: vascular dementia, Lewy body dementia, frontotemporal dementia

Source: adapted from Roberts and Knopman.[16]

TABLE 2 Stages of dementia in AD

Stages of dementia	Common changes experienced by people with dementia
Early stage	• Become forgetful, especially regarding things that just happened • May have some difficulty with communication • Become lost in familiar places • Lose track of the time, including time of day, month, year, season • Have difficulty making decisions and handling personal finances • Have difficulty carrying out complex household tasks • Mood and behaviour
Middle stage	• Become very forgetful, especially of recent events and people's names • Have difficulty comprehending time, date, place and events • May become lost at home as well as in the community • Have increasing difficulty with communication (speech and comprehension) • Need help with personal care (i.e. toileting, washing, dressing) • Unable to successfully prepare food, cook, clean or shop • Unable to live alone safely without considerable support • Behaviour changes may include wandering, repeated questioning, hallucinations • May display inappropriate behaviour in the home or in the community
Late stage	• Usually unaware of time and place • Have difficulty understanding what is happening around them • Unable to recognise relatives, friends and familiar objects • Unable to eat without assistance, may have difficulty in swallowing • Increasing need for assisted self-care (bathing and toileting) • May have bladder and bowel incontinence • Change in mobility, may be unable to walk or be confined to a wheelchair or bed • Behaviour changes, including aggression towards carer, non-verbal • Unable to find his or her way around in the home

Reprinted from World Health Organization, *Dementia: A Public Health Priority*, © 2012, URL: www.who.int/iris/handle/10665/75263#sthash.yy7M37Ka.dpuf (accessed 21 July 2015).[27]

Epidemiology

Obtaining accurate incidence and prevalence figures for MCI is difficult, as people with memory decline may go undiagnosed. Prevalence and incidence estimates can also vary significantly depending on the definitions that are used. The variance in these estimates then poses a challenge to the understanding of the social burden of this disease. For example, the authors of a study utilising data from the Medical Research Council Cognitive Function and Ageing Study of people aged ≥ 65 years[29] estimated the prevalence of MCI to range from 2.5% to 41.0% in the UK. In addition, the rates of progression from MCI to dementia varied from 3.7% to 30.0%.[29]

The most common form of dementia in the UK is AD.[34] There are an estimated 163,000 new cases of dementia identified each year in England and Wales. The risk of being diagnosed with dementia rises with increasing age; however, a significant portion of people who are diagnosed with dementia are younger than 65 years.[35] The incidence of dementia ranges from 6.7 per 1000 person-years at age 65–69 years to 68.5 per 1000 person-years at age ≥ 85 years. Prevalence increases with age; it is estimated to be 3% by 70 years and then to double every 5.1 years thereafter.[36] A report published by the Alzheimer's Society predicts that there will be 1 million people living with dementia in the UK by 2025.[35]

Current diagnostic practice

The 2006 guidelines from the National Institute for Health and Care Excellence (NICE)[8] place emphasis on the early diagnosis of people with dementia to allow for effective management and planning with patients and carers. The projected increase[35] in the prevalence of dementia by the Alzheimer's Society highlights the importance of equitable and easy access to diagnosis in the UK patient population.

A schema of the pathway for assessing cognitive impairment in the UK is presented in *Figure 1*. The first point of contact with health-care services for a person with suspected cognitive impairment is with a health-care professional in primary care or in an acute hospital setting. In primary care, the general practitioner (GP) usually takes a brief history, conducts a physical examination and conducts a short test of cognitive function to establish a differential diagnosis for cognitive impairment. The NICE guidelines[8] recommend the use of the MMSE when aiming to diagnose people with dementia. It is possible to offer a diagnosis of dementia at this point if it is in an established state.[37] However, MMSE is insensitive to early-stage dementia[38] and does not effectively map the transition from MCI to early dementia.[39] The NICE guidelines[8] also recommend a number of pen-and-paper-based tools as suitable tests for screening people for cognitive impairment. Some of these tests, along others with others used in clinical practice, are further outlined in *Table 3*.

After this initial screening, the GP refers patients with suspected MCI or early dementia to a memory assessment service, which is usually based in secondary care and can involve the examination of older adults by community mental health teams. Memory assessment service teams play an important role in clarifying the diagnosis (MCI or dementia, subtype and severity of dementia), identifying which patients with MCI are at greatest risk of developing dementia and determining who are most in need of follow-up. Diagnoses are clarified by taking a detailed clinical history from the patient and a family member or carer, interpreting scan results (if needed) and interpreting the findings from cognitive function pen-and-paper diagnostic tests.[44]

In an acute hospital setting, patients can be 'incidentally' discovered to be living with cognitive impairment through routine testing for another medical condition, and/or patients may present with acute confusion secondary to a medical problem.[44] There are many different pen-and-paper tests used to aid diagnosis for MCI and early dementia available for use in a secondary setting; three of the tests most commonly used in the NHS are described in *Table 4*.

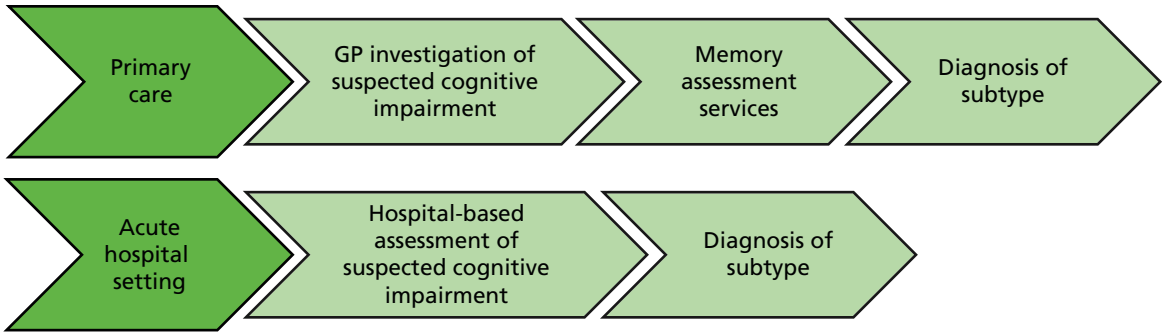

FIGURE 1 Adapted pathway for assessing cognitive impairment.

TABLE 3 Screening tests for cognitive impairment

Test	Administration time (minutes)	Sensitivity (%)	Specificity (%)
GPCOG[8]	5	82–85[40]	82–85[40]
6CIT[8]	3–4	78.5–83[41]	77–100[41]
Mini-Cog assessment instrument[42]	2–4	76–99[40]	89–96[40]
AMT[8]	2–4	Not validated in a primary care setting	Not validated in a primary care setting
Memory Impairment Screen[43]	4	74–86[40]	96–97[40]

6CIT, Six-Item Cognitive Impairment Test; AMT, Abbreviated Mental Test; GPCOG, General Practitioner Assessment of Cognition.
Source: NICE guidelines[8] and clinical advice.

TABLE 4 Tests used to aid diagnosis of MCI and early dementia

Test	Administration time (minutes)	Sensitivity (%)	Specificity (%)
DemTect[45,46]	8–10	92[45]	86[45]
The Montreal Cognitive Assessment: A Brief Screening Tool For Mild Cognitive Impairment[46]	10	90[47]	87[47]
Saint Louis University Mental Status[48]	7	98–100[49]	98–100[49]

Reference standard

A reference standard can be described as being the best available method for identifying patients who have the target condition.[50] The reference standard for this research is the clinical diagnosis of MCI and early dementia. It is recognised that clinical diagnosis itself has a degree of variability, but this is not unique to dementia studies and does not invalidate the basic diagnostic test accuracy approach. Any recognised diagnostic criteria (e.g. *International Classification of Diseases*, Tenth Edition;[2] *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition[51] or -Fifth Edition[52]) can be used.[53] Dementia diagnosis may specify a pathological subtype. Clinicians may use imaging, biomarkers or other data to aid diagnosis, for example the Clinical Dementia Rating[54] which is a gold-standard research criterion against which most rating scales have been compared.[55] However, in this report, diagnoses based only on these tests, without corresponding clinical assessment, were not included. It is recognised that different iterations of diagnostic criteria may not be directly comparable and that diagnosis may vary with the degree or manner in which the criteria have been operationalised (e.g. individual clinician vs. algorithm vs. consensus determination).

Index test

For the purpose of this report, the index test is any automated computerised assessment of cognitive impairment, which can either be self-administered or interviewer administered. In self-administered tests, patients may require help with accessing the necessary computer programs, login identification and simple start-up explanation. It is important to ensure that the patient can see and/or hear the instructions and test stimuli.

There are several automated tests available to help identify patients with MCI and early dementia. An accurate automated cognitive assessment tool would be clinically valuable if it were shown to work as well as clinician-delivered tests. However, there is limited clinical evidence to demonstrate their equivalence or superiority over standard practice.

The authors of a UK-based review[56] investigated the use of several available computerised automated tests and assessed their sensitivity and specificity for detection of MCI compared with two well-validated pen-and-paper tests: the Hopkins Verbal Learning Test and the MMSE.[56] The authors of the review concluded that the Hopkins Verbal Learning Test had better sensitivity for the detection of MCI in older adults than the computerised tests. They also identified that one automated test, CogState, enabled the identification of cognitive deficits beyond mild impairments in memory; for example, CogState detected more functional deficits than the Hopkins Verbal Learning Test or MMSE.[56] The authors, however, did not address if these tests had the potential to facilitate timely diagnosis or if they were effective in monitoring disease progression. *Appendix 1* explains measures for assessing an index test against a reference standard.

Table 5 provides a list of automated computerised tests that were identified during the initial scoping search that was conducted to inform the development of the protocol for this review.

TABLE 5 Sample of current automated computerised cognitive tests

Tool	Condition	Administration	Duration (minutes)	Domains
ANAM[56,57]	Cognitively impaired elderly; AD	Mouse/keyboard Self-administered	NR	Memory, attention, psychomotor speed, language, reaction time
CAMCI[56]	MCI	Touchscreen computer Self-administered	20	Attention, memory, executive function, working memory
CANS-MCI[56,57]	MCI	Touchscreen Self-administered	30	Memory, executive function, symbol fluency
CANTAB[56,57]	Early-stage AD; Parkinson's disease	Touchscreen Self-administered	30	Executive function, memory, attention, visuospatial function
CNSVS[56,57]	MCI; mild dementia	Keyboard Self-administered	30	Memory, psychomotor speed, reaction time, complex attention, cognitive flexibility
CNTB[56]	AD	Keyboard Technician administered	NR	Language, information processing, motor speed, attention, spatial, memory
COGDRAS-D[56,57]	Dementia; AD; Huntington's disease	Yes/no button Technician administered	20–25	Attention, memory, reaction time
CogState™[56,57]	MCI	Keyboard Self-administered	15–20	Working memory, attention, visuospatial memory
CSI[56,57]	Dementia	Keyboard Self-administered	25–35	Memory, attention, response speed, processing speed
CST[57]	NR	Technician assisted	15	Learning, memory, executive function
MCIS[56,57]	MCI	Technician records responses via telephone	10	Memory, executive function, language
MicroCog™[56,57]	MCI	Keyboard/pad Self-administered	> 60[a]	Reaction time, memory, attention, mental control, reasoning, spatial processing
Mindstreams™[56,57]	MCI; dementia	Mouse/pad Technician administered	45–60	Memory, executive function, visual and special ability

ANAM, Automated Neuropsychological Assessment Metrics; CAMCI, Computer Assessment of Mild Cognitive Impairment; CANS-MCI, Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment; CANTAB, Cambridge Neuropsychological Test Automated Battery; CNSVS, Central Nervous System Vital Signs; CNTB, Computerized Neuropsychological Test Battery; COGDRAS-D, Cognitive Drug Research Computerized Assessment System for Dementia Patients; CSI, Cognitive Stability Index; CST, Computerised Self-Test; MCIS, Mild Cognitive Impairment Screen; NR, not reported.
a Duration of short form is 30 minutes.

Chapter 3 Methods

The methods used in the review followed the systematic review principles outlined in the Centre for Reviews and Dissemination's[58] guidance for undertaking reviews in health care, the NICE *Diagnostic Assessment Programme Manual*[59] and publications from the Cochrane Collaboration Diagnostic Test Accuracy[60] Working Group.

Search strategy

The following electronic databases were searched for the period from 2005 to the latest available version (August 2015).

- MEDLINE (via OvidSP)
  - MEDLINE In Process & Other Non-Indexed Citations (via OvidSP)
- EMBASE (via OvidSP)
- The Cochrane Library
  - Central Register of Controlled Trials
  - Cochrane Database of Systematic Reviews
  - Database of Abstracts of Reviews of Effects
  - Health Technology Assessment database
  - NHS Economic Evaluation Database
- ISI Web of Science
  - Proceedings (via Index to Scientific and Technical Proceedings)
  - ISI Web of Science – Science Citation Index Expanded
- PsycINFO.

The search terms for electronic databases comprised a combination of medical subject heading terms and free-text words. The search had no language restrictions and there were no limits on specific study design. Animal studies were excluded, as were case reports, comments, editorials and letters. The details of the search strategies and the number of references retrieved are provided in *Appendix 2*.

Grey literature

Theses or PhD abstracts were accessed from ProQuest.

Reference lists

Backwards and forwards citation tracking for all relevant studies and reviews for further possible titles was undertaken.

Hand-searching

Trial and research registers were hand-searched for ongoing studies and reviews, including:

1. ClinicalTrials.gov
2. Register of Controlled Trials and International Standard Randomized Controlled Trial Number Register

3. World Health Organization International Clinical Trials Registry Platform
4. PROSPERO systematic review register
5. Epistemonikos.

The resulting database of potentially relevant studies was managed in EndNote X7 (Thomson Reuters, CA, USA). After individual tests were identified, a second search was run to identify individual test costs.

Study selection

The citations identified were assessed for inclusion through two stages using Covidence systematic review software (Veritas Health Innovation Ltd, Melbourne, VIC, Australia).[61] Two reviewers independently scanned all of the titles and abstracts and identified the potentially relevant articles to be retrieved. Full-text copies of the selected studies were subsequently obtained and assessed independently by two reviewers. Disagreements were resolved by consensus or in discussions with a third reviewer.

The eligibility criteria are listed in *Table 6* for the diagnostic accuracy studies and in *Table 7* for the studies monitoring disease progression.

TABLE 6 Eligibility criteria: diagnostic accuracy

Criteria	Included	Excluded
Study design	Index test and reference tests are evaluated in the same study population which are fully paired (all study participants receive the index test and the reference standard)	Any case studies, qualitative studies or studies with sample size of < 10 participants
Patient population	Adults (aged > 18 years) with suspected MCI or early dementia	Patients diagnosed with neurological damage caused by stroke or head injury, learning disabilities or brain tumours Studies that report on both late and early stages of dementia were included only if both the populations were reported separately
Setting	Primary care, secondary care, memory clinics, acute care settings, care homes, tertiary or community-based setting	
Index test	Any commercial or non-commercial computer-based cognitive diagnostic tool with automated interpretation, addressing one or more domains of cognitive impairment	Automated cognitive diagnostic tool in a language other than English
Outcomes	Diagnostic accuracy (e.g. specificity, sensitivity, likelihood ratios, diagnostic odds ratio, intrapatient variability) Acceptability (any studies recording a measure of acceptability)	Studies not reporting on at least one diagnostic accuracy outcome

TABLE 7 Eligibility criteria: monitoring

Criteria	Included	Excluded
Study design	Index test and reference tests are evaluated in the same study population which are fully paired (all study participants receive the index test and the reference standard)	Any case studies, qualitative studies or studies with sample size of < 10 participants
Patient population	Adults (aged > 18 years) with diagnosed MCI and early dementia	Patients diagnosed with neurological damage caused by stroke or head injury, learning disabilities or brain tumours Studies that report on both late and early stages of dementia were included only if both the populations were reported separately
Setting	Primary care, secondary care, memory clinics, acute care settings, care homes, tertiary or community-based setting	
Index test	Any commercial or non-commercial computer-based cognitive monitoring tool with automated interpretation, addressing one or more domains of cognitive impairment used for monitoring disease progression and treatment	Automated cognitive diagnostic tool in a language other than English
Outcomes	Monitoring accuracy (e.g. specificity, sensitivity, likelihood ratios, diagnostic odds ratio, intrapatient variability) Acceptability (any studies recording a measure of acceptability)	Studies not reporting on at least one monitoring outcome

Data extraction

Two reviewers developed, piloted and standardised two sets of data extraction forms. One form was designed to collect data on diagnostic accuracy and the other was designed to collect data related to monitoring disease progression. One reviewer extracted details of study design, participants, index and reference standard tests, outcome data and other relevant data, and a second reviewer checked the data extraction. Any discrepancies were resolved by consensus or in discussions with a third reviewer.

Assessment of methodological quality

The quality assessment of studies meeting the inclusion criteria was carried out by one reviewer and independently checked for accuracy by a second reviewer. The methodological quality of the included studies was assessed using the QUADAS-2 (Quality Assessment Tool for Diagnostic Accuracy Studies) tool.[62] This tool is designed to evaluate the risk of bias and applicability of primary diagnostic accuracy studies. The results of the quality assessment are presented in summary tables and as a narrative synthesis.

Outcomes

We recorded the following diagnostic accuracy outcome measures of automated computerised tests for MCI and early dementia:

1. sensitivity and specificity
2. area under the receiver operating characteristic curve (AUC).

Method of analysis/synthesis

Statistical analysis and data synthesis

Individual study results

The results of the individual diagnostic studies were tabulated and sensitivity, specificity, predictive values, likelihood ratios (LRs) and diagnostic odds ratios were calculated for the index test for each study where true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) data were available (see *Appendix 1*). These data were required to establish the actual sensitivity and specificity of a test for a given cut-off value. From this point onwards, TP, TN, FP and FN data will be referred to as 2 × 2 data. These terms are explained in detail in *Appendix 1*.

The authors of all of the studies included in this review were individually approached with a request for specific 2 × 2 data whether or not they were available in the published report. Out of 15 authors, only two responded and were able to provide these data.

Meta-analysis

It was not possible to perform a meta-analysis owing to non-comparable data; for example, study designs varied, the primary outcome measure cut-off points were heterogeneous, the likelihood of bias differed across the studies and the summary statistics were often inconsistently reported. The results of the included studies have been synthesised narratively and in tables. The possible effects of study quality (based on the assessment of risk of bias) on the 2 × 2 data and review findings have been considered.

Patient and public involvement

The review team was guided during the review by an Advisory Group comprising clinicians and service users. Building trusted contacts with service users led us to believe that the most effective way to obtain engagement with service users was through frontline agencies, for example the Alzheimer's Society and Dementia UK. We sent out a call for participation through these frontline groups to identify people interested in giving feedback on the results of the review and on the final report. We took guidance from these agencies when we planned and facilitated our meetings and consulted the guidance available from INVOLVE on the principles of involving the public in research from the National Institute for Health Research.[63]

Chapter 4 Results

Initial searches and application of inclusion criteria

The results of the searches and study selection are presented in *Figure 2*. The initial electronic search was conducted in August 2015 and 13,352 records were retrieved. An additional 5444 records were identified through ProQuest, hand-searching and citation tracking. After deduplication, 13,542 titles and abstracts were screened and 399 articles were shortlisted for full-text assessment. Four trials were identified during hand-searching:[64–67] two are still recruiting participants,[64,67] one has been completed but the results have not been published[66] and the status of one trial[65] is unknown. The authors of these studies were approached by e-mail and telephone for results, but no responses were received. These studies are tabulated in *Table 21* in *Appendix 2*.

The reasons for excluding studies are tabulated in *Appendix 3*.

All of the tests (computerised and pen-and-paper) identified during screening are listed in *Appendix 4*.

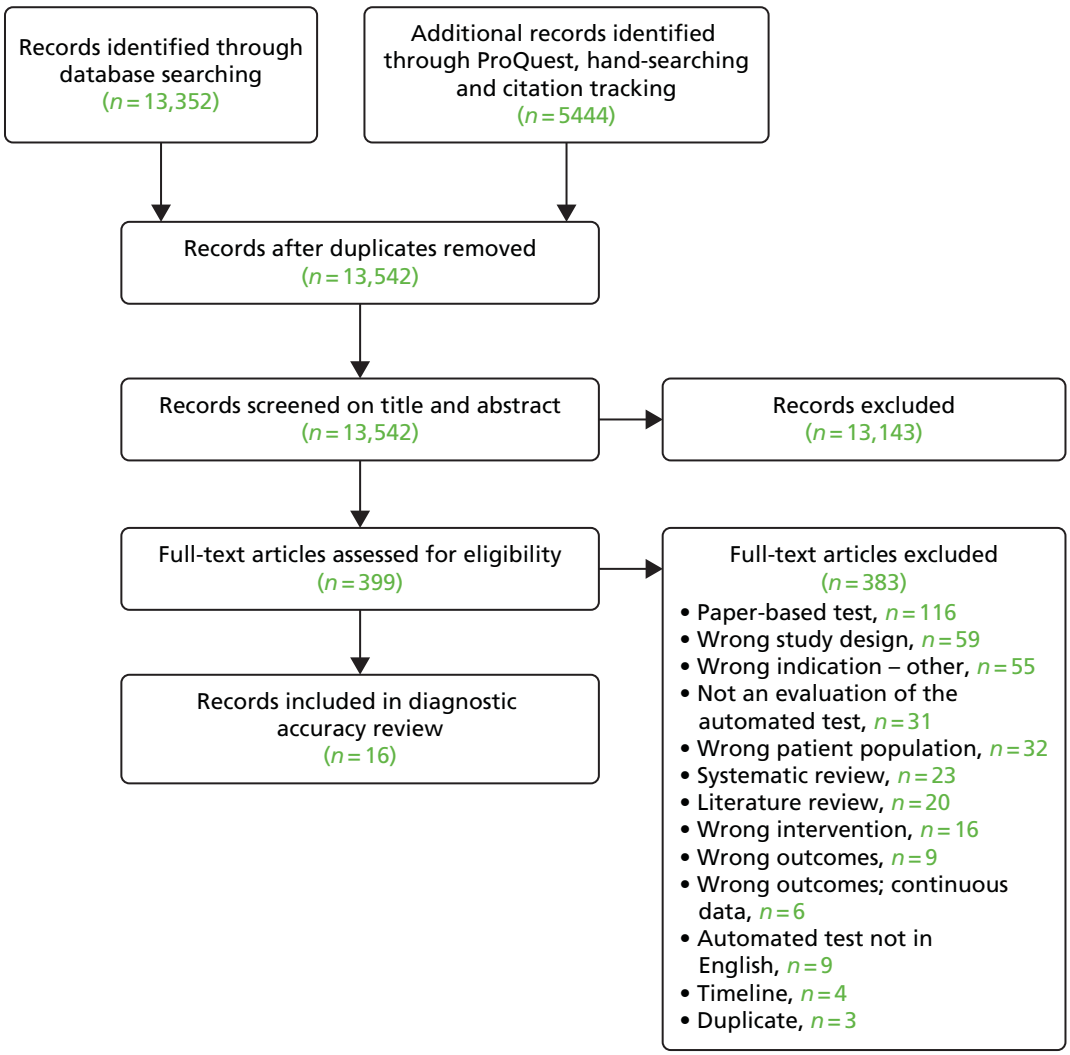

FIGURE 2 The PRISMA flow diagram.

Included studies

In total, 16 studies[68–72,74–81,83,85,86] were included in the diagnostic accuracy review.

No studies met the review inclusion criteria for monitoring progression in MCI or early dementia and, therefore, there is no further mention of monitoring disease progression in the results section.

The details of the 16 included studies[68–72,74–81,83,85,86] are summarised in *Tables 8–10*. Five studies reported results for more than two groups of participants: three included healthy controls, MCI and early dementia,[71,76,86] and two included healthy controls, early dementia and early dementia/MCI combined.[70,74]

In total, 10 studies[68,69,71,72,75,76,78,79,85,86] evaluated the use of automated computerised tests to detect MCI alone, seven studies[70,71,74,76,80,81,86] reported results for early dementia, three studies[70,74,77] reported results for combined MCI/early dementia and one study[83] reported results for human immunodeficiency virus (HIV)-associated neurocognitive disorder (HAND).

The information in *Table 8* shows that the index tests assessed in the included studies varied. However, the references tests used in the studies were generally consistent across studies for patients with MCI and for patients with early dementia.

TABLE 8 Included studies: summary

Study and year	Condition	Irrelevant study groups	Index test	Reference test	Company funding/ financial interest
Ahmed *et al.*[68] 2012	MCI	NA	CANS-MCI	Clinical diagnosis using Petersen's criteria	No
de Jager *et al.*[69] 2009	MCI	NA	CogState	Clinical diagnosis using battery of neurocognitive tests	No
Doniger *et al.*[70] 2005	MCI MCI/mild dementia	NA	Mindstreams	Clinical diagnosis using Petersen's criteria[20] for MCI and DSM-IV[51] for dementia	Yes Not-for-profit
Dwolatzky *et al.*[71] 2003	MCI Mild AD	No relevant results reported for mild AD group	Mindstreams	Clinical diagnosis using Petersen's criteria[20] for MCI and DSM-IV[51] for mild AD	Yes
Juncos-Rabadán *et al.*[72] 2014	aMCI	NA	CANTAB	Clinical diagnosis using neurocognitive tests and Albert criteria[73] and Peterson criteria[20] for aMCI	No
Junkkila *et al.*[74] 2012	aMCI/mild/ probable dementia Mild/probable dementia	NA	CANTAB-PAL	Clinical diagnosis using Petersen's criteria[20] and neurocognitive tests	No
Kingsbury *et al.*[75] 2010	MCI	Depressed	CogniScreen	Clinical diagnosis using Petersen's criteria[20]	NR

TABLE 8 Included studies: summary (*continued*)

Study and year	Condition	Irrelevant study groups	Index test	Reference test	Company funding/ financial interest
Kluger *et al.*[76] 2009	MCI Early dementia	Other dementias	No name	Diagnosed by a consensus of at least two clinicians	No
Lichtenberg *et al.*[77] 2006	MCI/early dementia		CST	Clinical diagnosis using Petersen's criteria;[20] clinical diagnosis of dementia using DSM-V[52]	NR
Maruff *et al.*[79] 2013	MCI	Mild to moderate AD	CBB	Clinical diagnosis using Peterson criteria[20]	Yes
Mundt *et al.*[80] 2001	Dementia	Moderate stage of dementia	Computer-automated telephone screening	Clinical diagnosis using CDR score	No
O'Connell *et al.*[81] 2004	Probable AD	NA	CANTAB-PAL	Clinical diagnosis using NINCDS-ADRDA[82] criteria	NR
Rosenthal *et al.*[83] 2013	HAND	HIV-negative people; HIV-positive people with asymptomatic neurocognitive impairment and minor neurocognitive disorder	CAMCI modified for use in HIV-positive population	HAND category using the Frascati criteria[84]	Yes
Saxton *et al.*[85] 2009	MCI	NA	CAMCI	Clinical diagnosis by consensus using battery of neurocognitive tests and functional and medical information	Yes
Tierney *et al.*[78] 2014	MCI	NA	CAMCI	Clinical diagnosis using battery of neurocognitive tests	No
Vacante *et al.*[86] 2013	MCI Early dementia	NA	TPT	Clinical diagnosis using Petersen's criteria[20]	No

aMCI, amnestic mild cognitive impairment; CAMCI, Computer Assessment of Mild Cognitive Impairment; CANS-MCI, Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment; CANTAB, Cambridge Neuropsychological Test Automated Battery; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associated Learning; CBB, CogState Brief Battery; CDR, Clinical Dementia Rating Scale; CST, Computerised Self-Test; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition; DSM-V, *Diagnostic and Statistical Manual of Mental Disorders*-Fifth Edition; HAND, HIV-associated neurocognitive disorder; HIV, human immunodeficiency virus; NA, not applicable; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NR, not reported; TPT, The Placing Test.

TABLE 9 Index test details

Study and year	Test name	Cognitive domains tested	Details of test platform used	Time (minutes)	Method of administration
Ahmed *et al.*[68] 2012	CANS-MCI	Memory Language Visuospatial Executive function	Desktop computer, a touchscreen system with both oral (loud speakers) and on-screen instructions	30	Self-administered Researcher in room
de Jager *et al.*[69] 2009	CogState	Memory Executive function Attention Processing speed	Internet	≈20	Self-administered Practice session with a psychologist
Doniger *et al.*[70] 2005	Mindstreams (abridged)	Memory Executive function Visuospatial Motor skills	Computer and mouse	30	Self-administered Practice session
Dwolatzky *et al.*[71] 2003	Mindstreams	Memory Executive function Visuospatial Verbal Attention Information processing Motor skills	Designed for use with the elderly. Mouse with the number pad on the keyboard (similar to the telephone keypad)	45	Self-administered Practice session with feedback prior to testing Research assistant
Juncos-Rabadán *et al.*[72] 2014	CANTAB-R (DMS, PAL and PRM)	Memory	Touchscreen computer	NR	Self-administered Researcher present
Junkkila *et al.*[74] 2012	CANTAB-PAL	Memory	Touchscreen computer	NR	Self-administered
Kingsbury *et al.*[75] 2010	CogniScreen	Memory	Laptop, headset with microphone	20–40	Self-administered Experimenter in room
Kluger *et al.*[76] 2009	Computerised test (no name)	Memory Praxis Naming Executive function	Laptop	12–15	Self-administered Screening test for computer competency

TABLE 9 Index test details (*continued*)

Study and year	Test name	Cognitive domains tested	Details of test platform used	Time (minutes)	Method of administration
Lichtenberg *et al.*[77] 2006	CST	Learning Memory Executive function	Internet based, interface with both written and oral instructions	15	Self-administered Keyboard proficiency test Administered by graduate psychology student
Maruff *et al.*[79] 2013	CBB	Memory	Desktop computer, yes/no button attached through USB port	10	Self-administered Verbal instructions by supervisor Practice session
Mundt *et al.*[80] 2001	Computer-automated telephone screening	Memory Spatial (auditory) Executive function Orientation Language	Standard touch-tone telephones	11–15	Self-administered Researcher provided assistance in dialling the number
O'Connell *et al.*[81] 2004	CANTAB-PAL	Memory	Touchscreen computer	10	NR
Rosenthal *et al.*[83] 2013	CAMCI Modified	Memory Attention Executive function Processing speed	Tablet with stylus	25	Self-administered
Saxton *et al.*[85] 2009	CAMCI	Memory Attention Executive function Processing speed	Desktop computer	≈20	Self-administered
Tierney *et al.*[78] 2014	CAMCI	Memory Attention Executive function Processing speed	Tablet computer	30	Self-administered some required researcher assistance
Vacante *et al.*[86] 2013	TPT	Memory	Computer	20	Self-administered Including practice pages

CAMCI, Computer Assessment of Mild Cognitive Impairment; CANS-MCI, Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment; CANTAB, Cambridge Neuropsychological Test Automated Battery; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associated Learning; CBB, CogState Brief Battery; CST, Computerised Self-Test; DMS, Delayed Matching to Sample; NR, not reported; PAL, Paired Associated Learning; PRM, Pattern Recognition Memory; TPT, The Placing Test.

TABLE 10 Study and participant characteristics

Study and year	Country, setting	*n*	Exclusion criteria	Mean age, years (SD, range)	Gender (male, %)	Mean education, years (SD, range)	Race/ethnicity (%)
Ahmed *et al.*[68] 2012	UK, primary care (Oxford OPTIMA Study)[a]	35 (control: 20; MCI: 15)	A history of any disease which in the investigator's opinion might confound the results of the study or pose an additional risk to the patient (e.g. diagnosis of psychiatric or endocrine disease, central neurological disorder, problems with eyesight, dementia treatment medication)	Control: 77.4 (4); MCI: 80.9 (7.2)	Control: 55.0; MCI: 33.3	Control: 14.7 (2.9); MCI: 13.1 (3)	NR
de Jager *et al.*[69] 2009	UK, community	119 (control: 98; MCI: 21)	NR	Control: 77.18 (5.9); MCI: 81.95 (5.4)	NR	Unclear	NR
Doniger *et al.*[70] 2005	USA, Israel and Canada, tertiary care, memory clinic	161 (control: 71; MCI: 58; mild AD: 32)	Diagnosis of neurological or psychiatric disease or colour-blindness Missing information on age and education levels	Entire group: 76.0 (8.2)	Entire group: 37.5	Entire group: 13.3 (3.6)	Entire group White American: 1.2 African American: 4.3 Afro-Caribbean American: 7.5 White Canadian: 36 White Hispanic: 0.6 Israeli: 50.3
Dwolatzky *et al.*[71] 2003	Canada/Israel, two tertiary care memory clinics	98 (control: 39; MCI: 30; mild AD: 29)	Prior history of major psychiatric disorder, major depression or any neurological disorder	Control: 73.41 (8.00); MCI: 77.15 (6.43); mild AD: 80.55 (4.91)	Control: 33.3; MCI: 56.7; mild AD: 44.8	Control: 14.95 (3.5); MCI: 13.07 (2.86); mild AD: 11.31 (2.85)	NR
Juncos-Rabadán *et al.*[72] 2014	Spain, primary care	162 (control: 85; mda-MCI: 29; sda-MCI: 48)	History of clinical stroke, traumatic brain injury, motor–sensory defects, alcohol or drug abuse/dependence, diagnosed with any significant medical or psychiatric illnesses	Control: 62.25 (8.26, 50–82); mda-MCI: 71.68 (7.74, 54–87); sda-MCI: 68.02 (9.04, 50–84)	All participants: 36.4	Control: 10.83 (5, 2–21); mda-MCI: 10.06 (3.99, 3–20); sda-MCI: 9.83 (3.96, 2–20)	NR

Study and year	Country, setting	*n*	Exclusion criteria	Mean age, years (SD, range)	Gender (male, %)	Mean education, years (SD, range)	Race/ethnicity (%)
Junkkila *et al.*[74] 2012	Finland, hospital	58 (control: 22; aMCI: 17; AD: 19)	Depression, known or suspected cerebral ischaemic event, alcohol abuse, head injury and other significant neurological or psychiatric illness	Control: 70 (4.48, 65–80); aMCI: 73 (6.3, 61–83); AD: 73 (6.76, 61–83)	Control: 36.36; aMCI: 64.7; AD: 26.35	Control: 10 (3.25); aMCI: 8 (3); AD: 8 (2.88)	NR
Kingsbury *et al.*[75] 2010	Australia, community, memory clinic	140 (control: 95; MCI: 30)[b]	Comorbidity of MCI and/or late-life depression, poor literacy, inability to give informed written consent	Controls: 68.85 (7.96, 53–89); MCI: 77.62 (7.45, 51–87)	Control: 37; MCI: 43	Controls: 4.93 (1.71); MCI: 3.07 (1.71) Unclear what is measured	NR
Kluger *et al.*[76] 2009	USA, memory clinic	101 (control: 39; MCI: 19; probable AD: 17; no diagnosis: 25)	Control participants were excluded if they had any history of significant neurological or psychiatric disease or if they scored < 27/30 on the MMSE	Control: 64 (11); MCI: 72 (10); probable AD: 78 (9)	NR	NR	NR
Lichtenberg *et al.*[77] 2006	USA, specialised geriatric clinic	102 (control: 55; MCI: 11; mild dementia: 36)	Significant motor, visual or cognitive impairments that prevented participants from using a computer or understanding directions, and individuals who were not fluent in English	All participants: 79.3 (6.6)	All participants: 46.1	All participants: 13.5 (2.9)	African American: 5.9; European American: 94.1 European American: 94.1
Maruff *et al.*[79] 2013	Australia, primary care Some participants were part of Australian Imaging, Biomarkers and Lifestyle Study of Ageing	766 (control: 659; aMCI: 107)	Schizophrenia, depression (15-item Geriatric Depression Score of ≥ 6), Parkinson's disease, cancer (except basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, or current regular alcohol use exceeding two standard drinks per day for women or four per day for men	Control: 69.5 (6.6); MCI: 75.7 (7.5)	Control: 42.2; MCI: 49.5	Control: 12[c] (9–15); MCI: 12[c] (9–15)	NR
Mundt *et al.*[80] 2001	USA, specialised geriatric clinic	116 (control: 74; mild dementia: 42	NR	All participants: 76.7 (7.0, 56–93)	All participants: 36.7	All participants: 13.3 (3, 6–22)	NR

continued

TABLE 10 Study and participant characteristics (*continued*)

Study and year	Country, setting	*n*	Exclusion criteria	Mean age, years (SD, range)	Gender (male, %)	Mean education, years (SD, range)	Race/ethnicity (%)
O'Connell *et al.*[81] 2004	Ireland, memory clinic	50 (control: 16; probable AD: 34)	NR	Control: 72.6 (7.7); probable AD: 73 (5.9)	Control: 12.5; probable AD: 32.4	NR	NR
Rosenthal *et al.*[83] 2013	USA, General Clinical Research Clinic	55 (HIV positive: 16; HAD: 39)	History or current opportunistic central nervous system infection, history or current schizophrenia, current severe affective disorder believed to explain a subject's cognitive impairment, history of a chronic neurological disorder including multiple sclerosis and epilepsy, and current intoxication on illegal drugs or alcohol	HIV-positive controls: 45.4 (6); HAD: 48.3 (6.3)	HIV-positive controls: 75.0; HAD: 71.8	HIV-positive controls: 12.3 (1.8); HAD: 12.6 (2.1)	Black people/ African American/ Caribbean: HIV-positive control; 81.3, HAD: 94.9
Saxton *et al.*[85] 2009	USA, primary care and community	524 (control: 296; MCI: 228)	Diagnosis of alcohol abuse, stroke, mental health disorder, presence of neurological disease and significant sensory deficit or physical limitation precluding performance on cognitive tests	Control: 71.84 (5.95); MCI: 75.18 (6.76)	MCI: 37.7; control: 32.8	Control 13.74 (2.69); MCI: 13.10 (2.61)	Control: white people (95.9); MCI: white people (92.1)
Tierney *et al.*[78] 2014	Canada, tertiary care	263 NR	Under 65 years old, documented diagnosis of dementia or who had been referred to, and worked up by, a specialist for a cognitive concern. Current diagnoses of major depressive disorder, schizophrenia, or bipolar disorder, those not fluent in English, unable to read normal print with or without glasses, unable to hear normal conversation with or without hearing aids, acutely ill, delirious or had a life expectancy of < 1 year	Completed without assistance: 78.7 (6.9); completed with assistance: 81.8 (6.5)	All participants: 41.4	Completed without assistance: 15.2 (3.2); completed with assistance: 13.9 (4.0)	White people 87

Study and year	Country, setting	*n*	Exclusion criteria	Mean age, years (SD, range)	Gender (male, %)	Mean education, years (SD, range)	Race/ethnicity (%)
Vacante *et al.*[86] 2013	UK, primary care (Oxford OPTIMA Study)[a]	78 (controls: 40; MCI: 20; early AD: 18)	NR	*Traditional version* Control: 74.7 (7.78); MCI: 78.3 (8.4); early AD: 73.67 (6.28) *Novel version* Control: 73.67 (7.14); MCI: 79.7 (6.07); early AD: 77.22 (4.94)	*Traditional version* Control: 50; MCI: 60; early AD: 66.7 *Novel version* Control: 45; MCI: 60; early AD: 77.8	*Traditional version* Control: 15.85 (3.36); MCI: 15.9 (3.32); early AD: 15 (3.04) *Novel version* Control:16.35 (3.18); MCI: 15 (2.66); early AD: 16.11 (2.97)	NR

aMCI, amnestic mild cognitive impairment; HAD, HIV-associated dementia; HIV, human immunodeficiency virus; mda-MCI, multiple-domain amnestic mild cognitive impairment; NR, not reported; OPTIMA, Oxford Project to Investigate Memory and Ageing; SD, standard deviation; sda-MCI, single-domain amnestic mild cognitive impairment.
a It is unclear if these cohorts were independent of each other.
b Fifteen participants were self-rated as depressed.
c Median.

Study quality assessment

A summary of the quality assessment conducted is presented in *Figures 3* and *4*.

We used the modified form of QUADAS-2,[62] which is recommended by the Cochrane Diagnostic Test Accuracy Reviews Guidelines,[87] to assess the quality of the included studies. Concerns regarding the risk of bias and applicability have been presented as a summary and as percentages in *Figures 3* and *4*, respectively.

The risk-of-bias criterion for patient selection was high for seven studies,[71,72,74–76,81,83] unclear for one study[86] and low for eight studies.[68–70,77–80,85] The studies were judged to be at high risk for this criterion because a case–control study design was used.

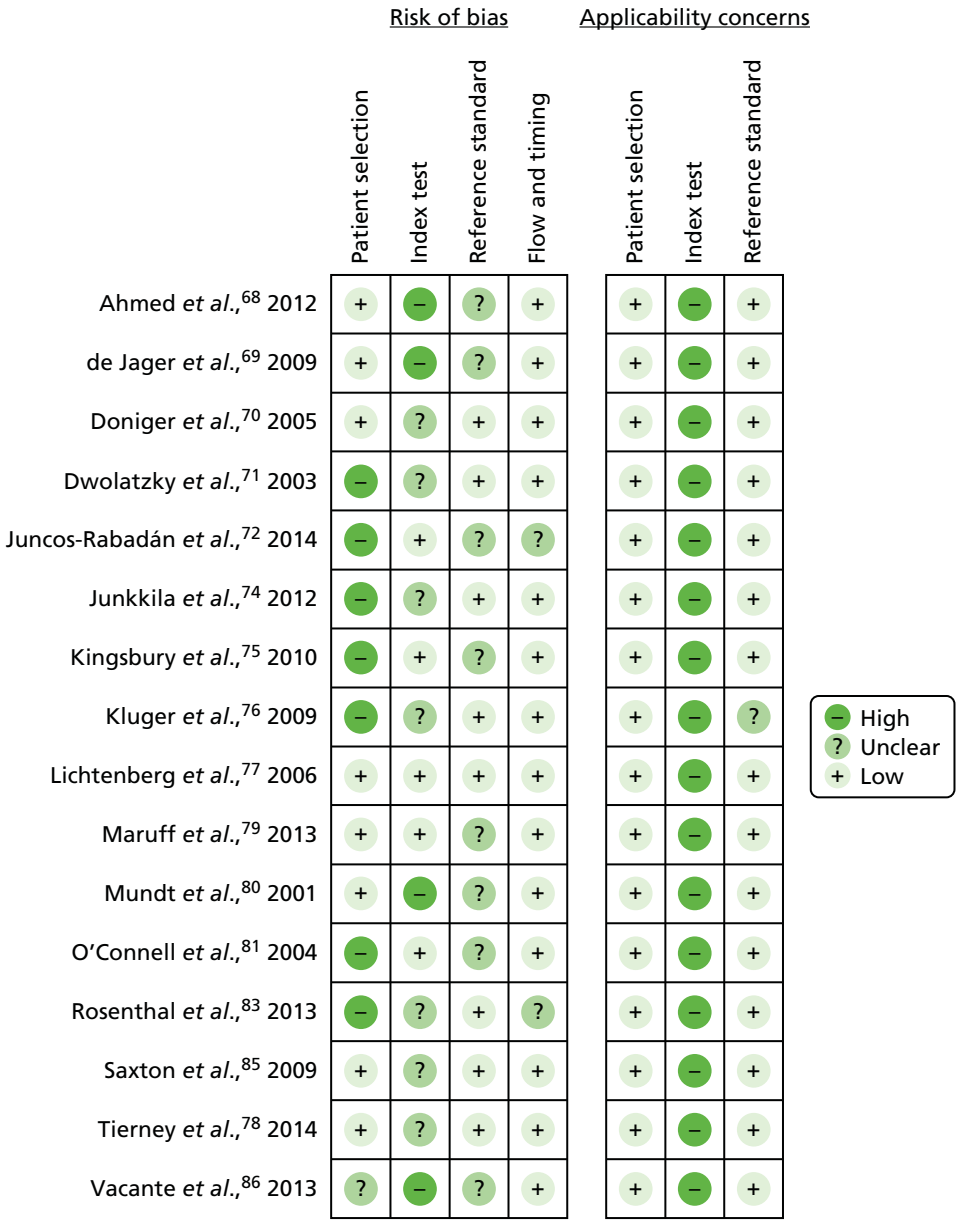

FIGURE 3 Risk of bias and applicability concerns: summary.

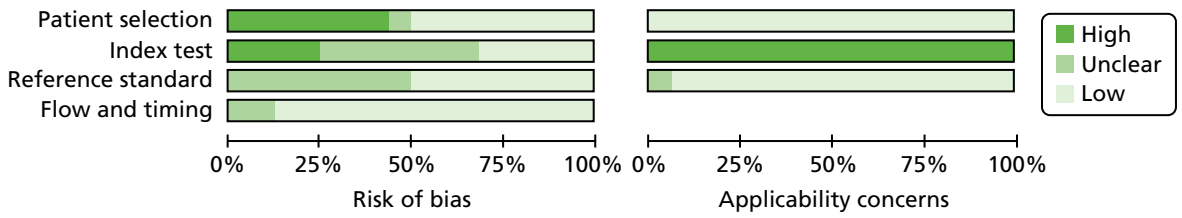

FIGURE 4 Risk of bias and applicability concerns graph: presented as percentages.

Regarding the index test criteria for risk of bias, seven studies[70,71,74,76,78,83,85] were judged to be at unclear risk. In these studies, the threshold values for the index tests were not pre-specified. However, for all of these studies, except Dwolatzky *et al.*,[71] it was clear that the index test results had been interpreted without knowledge of the results of the reference standard.

We gave a judgement of high concern regarding applicability of the index test for all of the studies[68–72,74–81,83,85,86] because the interpretation of the index test was different from the review question, as it is not possible to diagnose MCI and early dementia using automated computerised tests in isolation; specialist expertise is necessary to establish a diagnosis.

The reference standard domain for the risk of bias was unclear in eight studies,[68,69,72,75,79–81,86] as it was not possible to ascertain whether or not reference standard results were interpreted without knowledge of the results of the index tests. However, the reference standard used in each of the studies was likely to correctly classify the target condition. All studies but one[76] were judged to have low concern for applicability regarding the reference standard. The one study[76] used a consensus of two clinicians' opinions as the reference standard.

In the flow and timing domain for the risk of bias, a judgement of unclear risk of bias was given to two studies[72,83] as a result of there being no details of timing or attrition described in the published papers. Not all of the studies ($n = 11$)[68–71,74,76,77,79,80,85,86] reported whether or not there had been an appropriate interval between the index test and the reference standard. However, 14 studies[68–71,74–81,85,86] were assessed as being at low risk owing to all patients having received the same reference standard and all patients being included in the analysis.

Although only one study[77] was judged to be at low risk of bias across the four domains, the studies were considered to be of good quality. Patient selection issues were the most likely to introduce bias.

The only concern for applicability was the one previously mentioned, that is the interpretation of the index test was different from the review question as it is not possible to diagnose MCI and early dementia using automated computerised tests in isolation.

Index test details

The time required to self-administer the different index tests ranged from 10 minutes[79,81] to 45 minutes.[71] A range of cognitive domains was tested across the different tests, memory and executive function being the most common. Even though all of the tests were self-administered, a practice session was offered to participants in five studies[69–71,79,86] to make sure that patients were familiar with the software and platform for the index test. Nine studies[68,69,71,72,75,77–80] reported that support staff were present in the room to address any questions from participants about the software or platform.

Study and participant characteristics

The characteristics of the included studies are presented in *Table 10*. A total of 2832 people were included in the studies, with the number of people in each study ranging from 50[85] to 766.[81]

Two studies were multicentred[71,85] and one study[71] was carried out internationally, in Canada and Israel. The earliest study was published in 2001[80] and two were recently conducted in 2014.[72,78] The study participants were generally similar across the studies (owing to relatively similar study inclusion and exclusion criteria), although four studies[69,80,81,86] did not report their exclusion criteria.

The participants were mainly recruited through primary care[68,72,79,85,86] or from a memory clinic.[71,75,76,81] Six studies were based in the USA,[70,76,77,80,83,85] three were based in the UK,[68,69,86] two were based in Australia,[75,79] one was based in Ireland,[81] one was based in Canada and Israel,[71] one was based in Canada,[78] one was based in Spain[72] and one was based in Finland.[74] Participants in 13 studies[68,70–72,74,75,77–80,83,85,86] had 8[74] to 22[80] years of education; for the other three studies, data describing the education of the participants were not reported.[69,76,81] Only five studies[70,72,77,83,85] reported data on ethnicity. There is a lack of demographic data in two studies[69,76] for participants who were tested for MCI. Fifteen studies reported on cognitive impairment without comorbidities.[68–72,74–81,85,86] One of the included studies reported on cognitive impairment with a comorbidity (i.e. HIV).[83]

Results from studies on cognitive impairment without comorbidities

The diagnostic accuracy of 11 automated computerised tests for the detection of MCI and/or early dementia without comorbidities was evaluated in 15 studies.[68–72,74–81,85,86] One study[76] evaluated a test which did not have a name. Three studies[72,74,81] reported on multiple or singular domains of the Cambridge Neuropsychological Test Automated Battery *(*CANTAB). The pooling of data from these 15 included studies was considered inappropriate as there were few studies evaluating the same index test in the same population, and it was possible to extract 2 × 2 data from only five[72,74,80,81,85] of the 15 studies.

Studies reporting on diagnostic accuracy outcomes with 2 × 2 table

There were five studies[72,74,80,81,85] that reported diagnostic accuracy outcomes in a 2 × 2 table. Two studies[72,85] reported the diagnostic accuracy outcomes for MCI, three studies[74,80,81] reported outcomes for early dementia and one study[74] reported combined outcomes for both MCI/early dementia. When possible, the positive predictive value (PPV), negative predictive value (NPV), positive LR (LR+) and negative LR (LR–) were calculated using 2 × 2 data.

Mild cognitive impairment

The diagnostic accuracy outcomes for the two studies[72,85] reporting 2 × 2 data for MCI are presented in *Table 11*. The study by Juncos-Rabadán *et al.*[72] evaluated three different visual episodic memory tests included in the CANTAB; these memory tests were Pattern Recognition Memory, Delayed Matching to Sample and Paired Associated Learning. The overall sensitivity and specificity for the three visual episodic memory tests was moderate, at 79.7% and 76.3%, respectively. The AUC ranged from 0.623 to 0.747, which shows poor ability to discriminate between the MCI group and the non-MCI group. This test had a high overall PPV of 71.4%; this means that 71.4% of the people who tested positive for MCI with the reference standard actually had MCI. Similarly, the overall NPV for this test was 83.3%, meaning that 83.3% of people who tested negative for MCI on the reference standard did not have MCI. This test had a low overall LR+ of 3.4, which shows a low likelihood of the test to establish the presence of disease. It also had a low overall LR– of 0.3, which shows a low likelihood of the test to establish the absence of disease.

The study by Saxton *et al.*[85] evaluated the Computer Assessment of Mild Cognitive Impairment (CAMCI) and reported good sensitivity (86%) and exceptional specificity (94%), with an exceptional AUC of 0.91.

TABLE 11 Diagnostic accuracy outcomes with 2 × 2 table: MCI

Study and year	Index test	Cut-off point	Sensitivity (%)	Specificity (%)	AUC	TP	FN	TN	FP	PPV (%)	NPV (%)	LR+	LR–
Juncos-Rabadán *et al.*[72] 2014	CANTAB												
	Overall[a]		79.7	76.3	NR	55	14	71	22	71.4	83.3	3.4	0.3
	PRM	1.5 SD below controls	45.5[b]	92.9[b]	0.704[b]	35	42	79	6	85.4[b]	65.3[b]	6.44[b]	0.59[b]
	DMS	1.5 SD below controls	23.4[b]	97.6[b]	0.623[b]	18	59	83	2	90.0[b]	58.5[b]	9.94[b]	0.78[b]
	PAL	1.5 SD below controls	58.4[b]	89.4[b]	0.747[b]	45	32	76	9	83.3[b]	70.4[b]	5.52[b]	0.46[b]
Saxton *et al.*[85] 2009	CAMCI	Final tree model	86	94	91.22[b]	201	27	277	19	91.4[b]	91.1[b]	13.7[b]	0.127[b]

CAMCI, Computer Assessment of Mild Cognitive Impairment; DMS, Delayed Matching to Sample; NR, not reported; PAL, Paired Associated Learning; PRM, Pattern Recognition Memory; SD, standard deviation.
a The study details were provided by the primary author.
b Calculated by the research team.

Early dementia

The diagnostic accuracy outcomes for the three studies[74,80,81] reporting 2 × 2 data for patients with early dementia are presented in *Table 12*. The Cambridge Neuropsychological Test Automated Battery Paired Associated Learning (CANTAB-PAL) was evaluated in two of the studies.[74,81] The authors of one study[74] reported high sensitivity (81.8%) and specificity (97.2%) and an AUC of exceptional discrimination (0.914) for early dementia. It also had a PPV of 94.7% and a NPV of 89.7%.

The study by O'Connell *et al.*[81] reported poor sensitivity (67.6%) and high specificity (100%) and an AUC of moderate discrimination between the early dementia group and non-early dementia group (0.78). The authors also reported a PPV of 100.0% and a NPV of 59.3%. This test also had a low LR– of 0.324 for early dementia.

Mundt *et al.*[80] assessed the Computer Automated Telephone System and reported moderate sensitivity (79.17%) and high specificity (83.8%) for this test. The authors reported an AUC of 0.819, which shows good discrimination. The test also had a PPV of 76.0%, a NPV of 86.1%, a low LR+ of 4.88 and a low LR– of 0.249 for dementia.

Mild cognitive impairment/early dementia

The diagnostic accuracy outcomes for the one study[74] reporting 2 × 2 data for MCI/early dementia are presented in *Table 13*. This study evaluated CANTAB-PAL. The authors reported high sensitivity (96.9%) and high specificity (80.8%), with an AUC of good discrimination (0.897) between the MCI/early dementia group and non-MCI/early dementia group. The test had a PPV of 86.1% and a NPV of 95.5%; it also had a low LR+ of 5.04 and low LR– of 0.04 for MCI/early dementia.

Studies reporting on diagnostic accuracy outcomes without 2 × 2 table

The authors of 10 studies[68–71,75–79,86] reported diagnostic accuracy outcomes for nine different index tests without using 2 × 2 data. Instead, the authors of the studies calculated optimal sensitivity and specificity values using receiver operating characteristic curve analysis. The authors of seven studies reported the optimal sensitivity and specificity.[68,69,75,77–79,86] There were seven studies that reported AUC values.[68–71,75,76,79] Two studies reported PPV and NPV,[68,77] and no study reported LR+ and LR– results. The outcome measures presented in these studies are tabulated in *Tables 14–16*.

Mild cognitive impairment

The diagnostic accuracy outcomes reported in eight studies[68,69,71,75,76,78,79,86] for MCI are presented in *Table 14*. Ahmed *et al.*[68] evaluated Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment and reported high sensitivity (89.0%) and moderate specificity (73.0%) with an AUC of 0.867, which shows a good ability to discriminate between the MCI group and the non-MCI group.

Tierney *et al.*[78] evaluated the CAMCI test and reported a high sensitivity (80.0%) and a moderate specificity (74.0%); the authors did not report AUC PPV, NPV, LR+ or LR– values.

Maruff *et al.*[79] evaluated the CogState Brief Battery. The CogState Brief Battery has two composite scores for four tasks: psychomotor function, attention function, learning memory and working memory. The psychomotor/attention function had poor discrimination, as its AUC was 0.67. It also had poor sensitivity (41.1%) but high specificity (85.7%). The AUC for the learning/working memory was 0.91, which shows exceptional ability to discriminate between the MCI group and the non-MCI group. It also had high sensitivity (80.4%) and high specificity (84.7%). The overall sensitivity, specificity and AUC were not reported.

Early dementia

The diagnostic accuracy outcomes for early dementia were assessed in four studies[70,71,76,86] and are presented in *Table 15*.

TABLE 12 Diagnostic accuracy outcomes with 2 × 2 table: early dementia

Study and year	Index test	Cut-off point	Sensitivity (%)	Specificity (%)	AUC	TP	FN	TN	FP	PPV (%)	NPV (%)	LR+	LR–
Junkkila *et al.*[74] 2012	CANTAB-PAL	NR	81.8[a]	97.2[a]	0.914[a]	18	4	35	1	94.7[a]	89.7[a]	5.35[a]	0.0.3[a]
Mundt *et al.*[80] 2001	Computer Automated Telephone System	A derived scoring algorithm	79.17[a]	83.8[a]	0.819[a]	38	10	62	12	76.0[a]	86.1[a]	4.88[a]	0.249[a]
O'Connell *et al.*[81] 2004	CANTAB-PAL	32 errors	67.6	100	0.780	23	11	16	0	100	59.3		0.324

NR, not reported.
a Calculated by the research team.

TABLE 13 Diagnostic accuracy outcomes with 2 × 2 table: MCI/early dementia

Study	Index test	Cut-off point	Sensitivity (%)	Specificity (%)	AUC	TP	FN	TN	FP	PPV (%)	NPV (%)	LR+	LR–
Junkkila *et al.*[74] 2012	CANTAB-PAL	NR	96.9[a]	80.8[a]	0.897[a]	31	1	21	5	86.1[a]	95.5[a]	5.04[a]	0.04[a]

NR, not reported.
a Calculated by the research team.

TABLE 14 Diagnostic accuracy outcomes without 2 × 2 table: MCI

Study and year	Index test	Cut-off point	Sensitivity (%)	Specificity (%)	AUC (95% CI)	PPV (%)	NPV (%)	LR+	LR–
Ahmed *et al.*[68] 2012	CANS-MCI	0.5	89.0	73.0	0.867 (0.743 to 0.990)	60	84	NR	NR
de Jager *et al.*[69] 2009	CogState								
	Accuracy	82.6	78.0	90.0	0.86 (NR)	NR	NR	NR	NR
	Accuracy–speed ratio	3.54	76.0	79.0	0.84 (NR)	NR	NR	NR	NR
Dwolatzky *et al.*[71] 2003	Memory								
	Verbal memory (accuracy, first rep. trial)	NA for AUC	NR	NR	0.779 (0.668 to 0.890)	NR	NR	NR	NR
	Verbal memory (accuracy, second rep. trial)		NR	NR	0.838 (0.741 to 0.936)	NR	NR	NR	NR
	Verbal memory (accuracy, third rep. trial)		NR	NR	0.752 (0.629 to 0.876)	NR	NR	NR	NR
	Verbal memory (accuracy, final rep. trial)		NR	NR	0.783 (0.662 to 0.904)	NR	NR	NR	NR
	Verbal memory (accuracy, all rep. trials)		NR	NR	0.859 (0.765 to 0.953)	NR	NR	NR	NR
	Verbal memory (accuracy, delayed recognition)		NR	NR	0.771 (0.651 to 0.890)	NR	NR	NR	NR
	Non-verbal memory (accuracy, first rep. trial)		NR	NR	0.654 (0.522 to 0.786)	NR	NR	NR	NR
	Non-verbal memory (accuracy, second rep. trial)		NR	NR	0.698 (0.563 to 0.833)	NR	NR	NR	NR
	Non-verbal memory (accuracy, third rep. trial)		NR	NR	0.712 (0.585 to 0.839)	NR	NR	NR	NR
	Non-verbal memory (accuracy, final rep. trial)		NR	NR	0.773 (0.654 to 0.892)	NR	NR	NR	NR
	Non-verbal memory (accuracy, all rep. trials)		NR	NR	0.756 (0.633 to 0.879)	NR	NR	NR	NR
	Non-verbal memory (accuracy, delayed recognition)		NR	NR	0.728 (0.601 to 0.854)	NR	NR	NR	NR
	Executive function								
	Go/no go (accuracy)	NA for AUC	NR	NR	0.736 (0.608 to 0.863)	NR	NR	NR	NR
	Go/no go (performance index)		NR	NR	0.810 (0.701 to 0.920)	NR	NR	NR	NR
	Problem-solving (accuracy)		NR	NR	0.768 (0.653 to 0.884)	NR	NR	NR	NR
	Stroop interference (performance index)		NR	NR	0.703 (0.551 to 0.854)	NR	NR	NR	NR
	Catch game (accuracy)		NR	NR	0.696 (0.548 to 0.843)	NR	NR	NR	NR

Study and year	Index test	Cut-off point	Sensitivity (%)	Specificity (%)	AUC (95% CI)	PPV (%)	NPV (%)	LR+	LR–
	Visual spatial								
	Visual spatial imagery (accuracy)	NA for AUC	NR	NR	0.765 (0.648 to 0.881)	NR	NR	NR	NR
	Verbal								
	Verbal function (accuracy, naming)	NA for AUC	NR	NR	0.716 (0.584 to 0.848)	NR	NR	NR	NR
	Verbal function (accuracy, rhyming)		NR	NR	0.824 (0.724 to 0.923)	NR	NR	NR	NR
	Attention								
	Go/no go (RT)	NA for AUC	NR	NR	0.771 (0.648 to 0.893)	NR	NR	NR	NR
	Go/no go (SD of RT)		NR	NR	0.706 (0.576 to 0.835)	NR	NR	NR	NR
	Choice RT (performance index)		NR	NR	0.490 (0.326 to 0.653)	NR	NR	NR	NR
	Information processing								
	Staged information processing, low load (performance index)	NA for AUC	NR	NR	0.579 (0.416 to 0.743)	NR	NR	NR	NR
	Staged information processing, medium load (performance index)		NR	NR	0.783 (0.646 to 0.920)	NR	NR	NR	NR
	Staged information processing, high load (performance index)		NR	NR	0.688 (0.515 to 0.860)	NR	NR	NR	NR
	Motor skills								
	Finger tapping (inter-tap interval)	NA for AUC	NR	NR	0.595 (0.446 to 0.744)	NR	NR	NR	NR
	Finger tapping (SD of inter-tap interval)		NR	NR	0.625 (0.469 to 0.782)	NR	NR	NR	NR
	Catch game (time to first move)		NR	NR	0.521 (0.360 to 0.682)	NR	NR	NR	NR

continued

TABLE 14 Diagnostic accuracy outcomes without 2 × 2 table: MCI (*continued*)

Study and year	Index test	Cut-off point	Sensitivity (%)	Specificity (%)	AUC (95% CI)	PPV (%)	NPV (%)	LR+	LR–
Kingsbury *et al.*[75] 2010	CogniScreen								
	Pair recognition	0.47	76.0	60.0	0.72 (0.62 to 0.83)	NR	NR	NR	NR
	Cued recall	0.305	82.1	76.7	0.87 (0.80 to 0.95)	NR	NR	NR	NR
	Immediate and delayed serial recall	0.385	92.6	80.0	0.89 (0.81 to 0.97)	NR	NR	NR	NR
Kluger *et al.*[76] 2009	Computerised test (no name)	NR	NR	NR	0.89	NR	NR	NR	NR
Tierney *et al.*[78] 2014	CAMCI	2	80.0	74.0	NR	NR	NR	NR	NR
Maruff *et al.*[79] 2013	CBB								
	Psychomotor/attention	90	41.1	85.7	0.67 (0.6 to 0.73)	NR	NR	NR	NR
	Learning/working memory	90	80.4	84.7	0.91 (0.87 to 0.94)	NR	NR	NR	NR
Vacante *et al.*[86] 2013	Computerised total (novel and traditional)	19.5	70.0	76.2	NR	NR	NR	NR	NR
	Computerised objects and faces (novel and traditional)	12.5	50	64.3	NR	NR	NR	NR	NR
	Computerised objects and faces (novel and traditional)		75	52.4	NR	NR	NR	NR	NR

CANS-MCI, Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment; CBB, CogState Brief Battery; CI, confidence interval; NA, not applicable; NR, not reported; rep., repetition; RT, reaction time; SD, standard deviation.

TABLE 15 Diagnostic accuracy outcomes without 2 × 2 table: early dementia

Study and year	Index test	Cut-off point	Sensitivity (%)	Specificity (%)	AUC (95% CI)	PPV (%)	NPV (%)	LR+	LR–
Doniger *et al.*[70] 2005	Mindstreams (abridged)								
	Overall	NA for AUC	NR	NR	0.886	NR	NR	NR	NR
	Memory								
	Verbal memory	NA for AUC	NR	NR	0.830 (0.762 to 0.898)	NR	NR	NR	NR
	Non-verbal memory	NA for AUC	NR	NR	0.825 (0.756 to 0.893)	NR	NR	NR	NR
	Executive function								
	Go/no go	NA for AUC	NR	NR	0.733 (0.640 to 0.826)	NR	NR	NR	NR
	Stroop interference	NA for AUC	NR	NR	0.790 (0.690 to 0.890)	NR	NR	NR	NR
	Catch game	NA for AUC	NR	NR	0.748 (0.670 to 0.827)	NR	NR	NR	NR
	Visual spatial								
	Visual spatial imagery	NA for AUC	NR	NR	0.678 (0.567 to 0.789)	NR	NR	NR	NR
Dwolatzky *et al.*[71] 2003	Mindstreams Computerised Cognitive Testing	NR	NR	NR	NR	NR	NR	NR	NR
Kluger *et al.*[76] 2009	Computerised test (no name)	NR	NR	NR	0.97	NR	NR	NR	NR
Vacante *et al.*[86] 2013	TPT								
	Computerised total (novel and traditional)	15.5	88.9	92.9	NR	NR	NR	NR	NR
	Computerised objects and faces (novel and traditional)		94.4	78.6	NR	NR	NR	NR	NR
	Computerised objects and faces (novel and traditional)	13.5	94.4	52.4	NR	NR	NR	NR	NR

CI, confidence interval; NA, not applicable; NR, not reported; TPT, The Placing Test.

TABLE 16 Diagnostic accuracy outcomes without 2 × 2 table: MCI/early dementia

Study and year	Index test	Cut-off point	Sensitivity (%)	Specificity (%)	AUC (95% CI)	PPV (%)	NPV (%)	LR+	LR–
Doniger *et al.*[70] 2005	Mindstreams (abridged)								
	Overall	NA for AUC	NR	NR	0.823 (0.757 to 0.888)	NR	NR	NR	NR
	Memory								
	Verbal memory	NA for AUC	NR	NR	0.773 (0.697 to 0.849)	NR	NR	NR	NR
	Non-verbal memory	NA for AUC	NR	NR	0.767 (0.690 to 0.844)	NR	NR	NR	NR
	Executive function								
	Go/no go	NA for AUC	NR	NR	0.719 (0.639 to 0.800)	NR	NR	NR	NR
	Stroop interference	NA for AUC	NR	NR	0.671 (0.575 to 0.766)	NR	NR	NR	NR
	Catch game	NA for AUC	NR	NR	0.685 (0.595 to 0.776)	NR	NR	NR	NR
	Visual spatial								
	Visual spatial imagery	NA for AUC	NR	NR	0.721 (0.638 to 0.803)	NR	NR	NR	NR
Lichtenberg *et al.*[77] 2006	CST	1.5	80.0	87.0	NR	88.0	79.0	NR	NR

CI, confidence interval; CST, card sorting task; NA, not applicable; NR, not reported.

Dwolatzky *et al.*[71] did not report any results for early dementia patients, despite relevant data for this group having been collected during the study. Doniger *et al.*[70] evaluated an abridged version of Mindstreams and reported an overall AUC of 0.886, which showed a good ability to discriminate between the early dementia group and the non-early dementia group.

Kluger *et al.*[76] evaluated an automated computerised test, which did not have a specific name. This automated test examined the domains of memory, praxis, temporal, orientation, naming and crossed response inhibition. The authors reported an AUC of 0.97, which shows exceptional ability to discriminate between patients with early dementia and healthy control subjects.

Mild cognitive impairment/and early dementia

The diagnostic accuracy outcomes in two studies[70,77] for MCI/early dementia are presented in *Table 16*.

Doniger *et al.*[70] reported an overall AUC of 0.823, which showed a good ability to discriminate between the cognitively healthy group and the cognitive unhealthy group. AUC values for individual test results ranged from 0.671 to 0.773.

Lichtenberg *et al.*[77] reported values for sensitivity and specificity (80.0% and 87.0%, respectively), PPV (88.0%) and NPV (79.0%).

Results from studies on cognitive impairment with comorbidities

The diagnostic accuracy of one automated computerised test was evaluated in one study[83] that included people with cognitive impairment with comorbidities. This study examined HAND and used the automated test CAMCI. CAMCI assessed multiple domains with different tasks, which included simple reaction time, recurring picture, go/no go rule 1, go/no go rule 2, word recall, digit span forward, digit span reverse, shopping trip directions task, shopping list task, errand – bank, errand – post office, completion of the shopping list task and incidental recall task. The study set out to examine a range of diagnostic accuracy outcomes, but did not report the values for all of them.

The study authors state that the AUC analyses indicate that the digit span, forward digit span size and functional driving task differentiated between HIV-positive individuals with and without HAND.[83] However, the results presented show a low to moderate sensitivity but poor specificity. The authors of the study presented values for several, but not all, tests. It was reported that, in the forward digit span, a raw score cut-off point of ≥ 6 gives a sensitivity of 63.0% and a specificity of 19.0% and a forward span size raw score cut-off point of ≥ 5 gave a sensitivity of 80.0% and a specificity of 9.0%. The study also reported that the raw score on the shopping trip directions task of ≥ 13 gave a sensitivity of 75.0% and a specificity of 18.0%.[83]

Patient and public involvement

Data from the included studies describing the index test details, characteristics of study participants and diagnostic accuracy outcomes were presented and discussed with a service user. The structure of this meeting is described in *Appendix 5*. As some of the index tests showed high sensitivity and specificity when used to examine one or two cognitive domains, the service user thought that all of the index text domains ought to have been explored by the authors of the studies to enable a comprehensive overview of any cognitive impairment identified. In addition, the service user considered that more information on key domains would help clinicians and patients to address the challenges faced by patients with MCI or early dementia as they carry out their everyday activities. The service user thought that the studies covered

different populations very well, but raised concerns about the age of the study participants, as none of the tests evaluated cognitive impairment in people older than 90 years of age. A further concern was that the level of education of the person being tested might affect his or her performance on the test.

The discussion with the service user was mostly centred around the importance of the index tests being user-friendly and acceptable to patients. In a conversation about the different kinds of platforms used for the tests, the service user noted that if a patient had tremors then a desktop computer would be preferred to a touchscreen test, especially if the touchscreen test was very sensitive to touch.

When discussing the different types of tests available, the service user also highlighted the importance of ensuring that the test had a clear contrast between colours because it is likely that older people will have cataracts, colour blindness or other problems with their eyesight.

The service user also stated that some people might become frustrated with tests that lasted longer than 40 minutes, especially people who are not familiar with modern technology and people who are considered to be very elderly. The service user suggested that a patient's GP might be the best person to make a decision about whether or not the patient would be able to complete an automated test and generate meaningful results, as some people are more comfortable than others when using technology.

Individual test costs

After identifying the individual index tests via searching, a second search was run to identify the total costs of using these computerised tests and, where possible, to determine the acquisition costs of the tests. A number of grey literature sources generated some cost data, but it was not clear if these costs were yearly subscription costs for an organisation that had planned to use the test or if they were one-off costs for the use of one test by one person.[88–91] The authors of the publications did not state whether or not the costs also included the costs associated with training or administering the test, and the need for a health-care specialist to score/interpret the test was not discussed.

Chapter 5 Discussion

Summary of main results

We identified 16 studies[68–72,74–81,83,85,86] for inclusion in the diagnostic accuracy review of automated computerised tests to detect MCI or early dementia; only one study[83] included patients with comorbidities. No studies met the review inclusion criteria for monitoring disease progression.

Ten studies[68,69,71,72,75,76,78,79,85,86] evaluated the use of automated computerised tests to detect MCI alone, seven studies[70,71,74,76,80,81,86] reported results for early/mild dementia, three studies[70,74,77] reported results for combined MCI/early dementia and one study[83] reported results for HAND.

Eleven different index tests were evaluated. The only study which evaluated the diagnostic accuracy of automated computerised tests for people with cognitive impairment with comorbidities was conducted by Rosenthal *et al*.[83]

Most of the included studies had small sample sizes; 10 studies[68,69,71,72,74–77,81,86] had fewer than 150 participants and only two studies[79,85] had more than 500 participants. Differences in study design, primary outcome measure cut-off points, the likelihood of bias, the reporting of summary statistics (e.g. 2 × 2 data) and disparity in the index tests precluded a meta-analysis of the data reported in the included studies. Meaningful synthesis of the diagnostic outcomes from the included studies was not possible.

Of the 16 studies,[68–72,74–81,83,85,86] only one[77] was judged to be at low of risk of bias across the four domains examined; despite this, the overall quality of the included studies was considered to be good. Patient selection issues were the most likely to introduce bias. The only concern for applicability was the one previously mentioned, that is, the interpretation of the index test was different from the review question as it is not possible to diagnose MCI and early dementia using automated computerised tests in isolation.

Applicability of findings to the review question

Ideally, for diagnostic purposes, an index test with high specificity is preferable, and high sensitivity is preferred for screening.[92] When diagnosing patients with MCI and/or early dementia, an index test with both high sensitivity and specificity is needed to be able to appreciate a distinctive pattern of cognitive impairment in MCI and early dementia. This distinctive pattern of cognitive impairment is different from the cognitive impairment caused by other disease processes (e.g. cognitive impairment as presented in depression or HIV). The distinctive pattern of cognitive impairment caused by other conditions such as depression requires the use of elaborate scales such as the Cambridge Cognitive Examination,[93–95] the Alzheimer's Disease Assessment Scale[96,97] or the Repeatable Battery for the Assessment of Neuropsychological Status.[98,99] Current pen-and-paper tests screening instruments for MCI cannot do this.

In the case of HIV, however, it is difficult to draw a clearer distinction in the pattern of cognitive impairment, as no attempt has been made to adapt the diagnostic criteria for HAND to the pattern of cognitive domains that are affected in HIV.[84,100,101] Although it is difficult to find robust data, the dominant theory is that HAND causes deficits primarily in executive function, psychomotor speed and attention. Language is not thought to be affected, and neither are learning nor recall, although deficits in the other domains can present themselves to the patient as communication and memory difficulties in the 'real-life' scenario (as opposed to the testing environment).[102] This makes it difficult to separate it from or equate it to MCI or early dementia.

Most studies were not conducted in samples representative of the usual clinical population in which these tests might be used (e.g. patients coming to memory clinics with a mix of MCI and dementia of various aetiologies, some were the 'worried well' and others were depressed) but were conducted in convenience samples of patients with limited diagnoses (mostly MCI and AD). Furthermore, only three studies[68,69,86] out of 16 were conducted in the UK.

It is difficult to draw a clear picture of the diagnostic accuracy of the index tests that were assessed in this review, as there is not enough evidence to support the use of one test over another.

It is not clear from reviewing the included studies if these computerised tests ought to be used in primary and/or secondary care. In the UK, some GP practices take part in 'case finding' for dementia, for example specifically targeting 'high-risk' groups (e.g. older adults, or patients with high vascular risk, learning disability or Parkinson's disease), and hospital staff undertake brief cognitive assessments during all acute admissions for older adults.

The pen-and-paper tests currently used in clinical practice not only help clinicians differentiate between normal cognition, MCI and dementia,[45,46,48] but also assist in staging severity of illness. In contrast, CANTAB was the only automated test in this review that could stage severity.[72,74,81] The time taken to complete these computerised tests varied between 10 and 45 minutes but was not reported in two studies.[72,74] In contrast, pen-and-paper-based tests typically range from 7 to 10 minutes to complete.[45,46,48] Concern for the time it takes to complete the tests was raised by the service user, who pointed out the possibility of people becoming frustrated with tests that lasted for more than 40 minutes, especially if they were not familiar with using technology.

The data in the included papers did not describe the time required for training, administration, scoring and interpreting the test results.

Comparisons with previous research

None of the previously conducted relevant reviews[56,57,103] in this area carried out a diagnostic accuracy review. They were narrative reviews[56,57,103] that provided a summary of the battery of tests used and then rated this evidence on validity and reliability, comprehensiveness, and usability. Our review focused on automated computerised tests that were self-administered and had a minimum level of involvement from health-care professionals. In line with our review findings, the authors of the other reviews[56,57,103] concluded that there are significant differences in automated computerised tests and hence they must be judged on a case-by-case basis.[57]

Strengths and weaknesses of the review

The search strategy for this review was extensive and included multiple databases and grey literature sources. The majority of studies were identified by terms related to the index test, the terminology for which is reasonably standardised. To capture the difficult-to-locate studies where the index test is not referred to in the parts of the electronic record available for search retrieval, we searched the Cochrane Dementia and Cognitive Improvement Group's register of diagnostic test accuracy studies. The methodological rigour of the review process was enhanced by the use of two assessors to perform citation screening, quality assessment and data extraction/checking. We also contacted all of the primary study authors and asked them to fill in the actual values of a 2 × 2 table. Out of 15 authors, only two were able to send in the requested details. We also conducted a patient and public involvement exercise, but were able to receive feedback on our review findings from only one service user representative.

We excluded studies in which the automated tests or the studies evaluating the automated test were not described in English. The utility of this review is limited in part by the heterogeneity of the automated computerised tests assessed in the included studies. Owing to substantial diversity in the index tests and the characteristics of the participants, it was not appropriate to pool the data. The poor reporting of the diagnostic accuracy outcomes by the authors also hampered data extraction, quality assessment and meaningful synthesis.

We were also unable to identify any studies that reported on any measure of test acceptability. We did not identify any studies that reported outcomes related to monitoring disease progression.

Chapter 6 Conclusions

Implications for practice

The overall quality and quantity of information is insufficient to be able to make recommendations on the clinical use of the computerised tests for diagnosing and monitoring MCI and early dementia progression. The suitability of these tests also depends on the costs of the test, training, administration and scoring. Increased effectiveness of a test could offset the costs of the test, equipment and staff training.

The diagnosis of patients with MCI and early dementia is currently based on clinical judgement and medical history as well as on the results of cognitive tests. However, a 'definitive' diagnosis of dementia can be made only after a post-mortem analysis of the brain. We also note that autopsy studies in dementia have shown that there is little correlation of these results with the clinical diagnosis made when patients were alive. Therefore, the reference standard remains a clinical diagnosis based on history and physical and cognitive examination. For this reason, we would recommend against approaches that use computerised tests in isolation. Even with pre-specified cut-off values for a particular population, any cognitive testing measure alone is insufficient to render a diagnostic classification: other relevant clinical information must be taken into account.

Older people are more likely to have motor limitations (e.g. as a result of strokes, pain or tremor) or vision and hearing impairments that may render computerised testing impractical. This raises the issue of whether or not these tests can be truly self-administered and valid. For these patients, automated computerised tests may not offer benefits over current practice.

Implications for research

Further research is required in order to establish stable cut-off points for each automated computerised test used to diagnose patients with MCI or early dementia. These cut-off points need to be tested in specific patient populations, for example in patients of different age groups or education levels and from different geographical regions.

The prevalence of dementia and alternative diagnoses in the study populations should be clearly reported and make reference to standardised checklists for diagnostic reviews such as Standards for Reporting Diagnostic Accuracy[104] or Standards for Reporting Diagnostic Accuracy – dementia.[105] Investigators might consider evaluating automated computerised test performance at different cut-off points, across populations with varying prevalence of MCI and early dementia. Once sufficient studies in the defined populations are conducted, further reviews and meta-analyses can be carried out.

Future research in this area should also focus on providing more information on the costs of computerised tests and include time for training, administration and scoring of the different tests, as these are important factors for their use in routine clinical practice. This type of information is currently lacking in the published studies describing computerised tests used to diagnose or monitor people with MCI or early dementia.

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Contributions of authors

Dr Rabeea'h W Aslam drafted the review protocol, managed the process of study selection, data extraction and data checking, facilitated the service user feedback and drafted the final report.

Dr Vickie Bates commented on the protocol, contributed to study selection and data extraction and provided input into the final report.

Dr Yenal Dundar contributed to the initial search strategy, commented on the protocol, contributed to data checking and provided input into the final report.

Ms Juliet Hounsome commented on the protocol, contributed to data extraction and provided input into the final report.

Miss Marty Richardson commented on the protocol, contributed to the discussion on possible statistical analysis and provided input into the final report.

Mrs Ashma Krishan commented on the protocol, contributed to the discussion on possible statistical analysis and provided input into the final report.

Professor Rumona Dickson commented on the protocol and provided input into final report.

Dr Angela Boland provided input into the draft and final reports.

Ms Eleanor Kotas conducted the literature searches for studies and costs.

Miss Joanne Fisher contributed to data extraction.

Dr Sudip Sikda was clinical consultant, reviewed the protocol and provided input into the final report.

Professor Louise Robinson was clinical consultant, reviewed the protocol and provided input into the final report.

Data sharing statement

All available data can be obtained by contacting the corresponding author.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;**9**:63–75.e2. http://dx.doi.org/10.1016/j.jalz.2012.11.007
2. World Health Organization (WHO). *International Classification of Diseases – Classification of Diseases, Functioning, and Disability*. WHO; 2010. URL: www.who.int/classifications/icd/en/ (accessed 16 July 2015).
3. O'Neill D, Barber RD. Reversible dementia caused by vitamin B12 deficiency. *J Am Geriatr Soc* 1993;**41**:192–3. http://dx.doi.org/10.1111/j.1532-5415.1993.tb02058.x
4. Meador KJ. Cognitive side effects of medications. *Neurol Clin* 1998;**16**:141–55. http://dx.doi.org/10.1016/S0733-8619(05)70371-6
5. Muangpaisan W, Petcharat C, Srinonprasert V. Prevalence of potentially reversible conditions in dementia and mild cognitive impairment in a geriatric clinic. *Geriatr Gerontol Int* 2012;**12**:59–64. http://dx.doi.org/10.1111/j.1447-0594.2011.00728.x
6. Chang CY, Silverman DH. Accuracy of early diagnosis and its impact on the management and course of Alzheimer's disease. *Expert Rev Mol Diagn* 2004;**4**:63–9. http://dx.doi.org/10.1586/14737159.4.1.63
7. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, *et al.* Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses. *Lancet Neurol* 2015;**14**:1171–81. http://dx.doi.org/10.1016/S1474-4422(15)00258-6
8. National Institute for Health and Care Excellence. *Dementia. Supporting People with Dementia and Their Carers in Health and Social Care*. NICE; 2006. URL: www.nice.org.uk/guidance/cg42 (accessed 21 July 2015).
9. National Institute for Health and Care Excellence. *Dementia Diagnosis and Assessment*. NICE; 2015. URL: http://pathways.nice.org.uk/pathways/dementia (accessed 21 July 2015).
10. Brooks LG, Loewenstein DA. Assessing the progression of mild cognitive impairment to Alzheimer's disease: current trends and future directions. *Alzheimers Res Ther* 2010;**2**:28.
11. Braak H, Braak E. Evolution of neuronal changes in the course of Alzheimer's disease. In Jellinger K, Fazekas F, Windisch M, editors. *Ageing and Dementia*. Vienna: Springer; 1998. pp. 127–40. http://dx.doi.org/10.1007/978-3-7091-6467-9_11
12. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med* 2014;**275**:214–28. http://dx.doi.org/10.1111/joim.12190
13. Watkin A, Sikdar S, Majumdar B, Richman AV. New diagnostic concepts in Alzheimer's disease. *Adv Psychiatr Treat* 2013;**19**:242–9. http://dx.doi.org/10.1192/apt.bp.112.010462
14. Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. *Int Psychogeriatr* 2004;**16**:129–40. http://dx.doi.org/10.1017/S1041610204000092
15. Busse A, Angermeyer MC, Riedel-Heller SG. Progression of mild cognitive impairment to dementia: a challenge to current thinking. *Br J Psychiatry* 2006;**189**:399–404. http://dx.doi.org/10.1192/bjp.bp.105.014779
16. Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med* 2013;**29**:753–72. http://dx.doi.org/10.1016/j.cger.2013.07.003

17. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, *et al.* Mild cognitive impairment. *Lancet* 2006;**367**:1262–70. http://dx.doi.org/10.1016/S0140-6736(06)68542-5

18. Feldman HH, Jacova C. Mild cognitive impairment. *Am J Geriatr Psychiatry* 2005;**13**:645–55. http://dx.doi.org/10.1097/00019442-200508000-00003

19. Forlenza OV, Diniz BS, Stella F, Teixeira AL, Gattaz WF. Mild cognitive impairment. Part 1: clinical characteristics and predictors of dementia. *Rev Bras Psiquiatr* 2013;**35**:178–85. http://dx.doi.org/10.1590/1516-4446-2012-3503

20. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;**56**:303–8. http://dx.doi.org/10.1001/archneur.56.3.303

21. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. *Int J Geriatr Psychiatry* 2000;**15**:983–91. http://dx.doi.org/10.1002/1099-1166(200011)15:11<983::AID-GPS238>3.0.CO;2-5

22. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* 2009;**119**:252–65. http://dx.doi.org/10.1111/j.1600-0447.2008.01326.x

23. Petersen RC. Clinical practice. Mild cognitive impairment. *N Engl J Med* 2011;**364**:2227–34. http://dx.doi.org/10.1056/NEJMcp0910237

24. Bischkopf J, Busse A, Angermeyer MC. Mild cognitive impairment – a review of prevalence, incidence and outcome according to current approaches. *Acta Psychiatr Scand* 2002;**106**:403–14. http://dx.doi.org/10.1034/j.1600-0447.2002.01417.x

25. Launer LJ. Counting dementia: there is no one 'best' way. *Alzheimers Dement* 2011;**7**:10–4. http://dx.doi.org/10.1016/j.jalz.2010.11.003

26. Sachdev PS, Lipnicki DM, Crawford J, Reppermund S, Kochan NA, Trollor JN, *et al.* Risk profiles of subtypes of mild cognitive impairment: the Sydney memory and ageing study. *J Am Geriatr Soc* 2012;**60**:24–33. http://dx.doi.org/10.1111/j.1532-5415.2011.03774.x

27. World Health Organization (WHO). *Dementia: A Public Health Priority*. WHO; 2012. URL: www.who.int/iris/handle/10665/75263#sthash.yy7M37Ka.dpuf (accessed 21 July 2015).

28. Finkel SI. Behavioral and psychologic symptoms of dementia. *Clin Geriatr Med* 2003;**19**:799–824. http://dx.doi.org/10.1016/S0749-0690(03)00046-6

29. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ* 2015;**350**:h369. http://dx.doi.org/10.1136/bmj.h369

30. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *J Neurol Neurosurg Psychiatr* 2003;**74**:1206–9. http://dx.doi.org/10.1136/jnnp.74.9.1206

31. Marosi C, Hassler M, Roessler K, Reni M, Sant M, Mazza E, Vecht C. Meningioma. *Crit Rev Oncol Hematol* 2008;**67**:153–71. http://dx.doi.org/10.1016/j.critrevonc.2008.01.010

32. Patient. *Dementia*. Patient; 2015. URL: http://patient.info/doctor/dementia-pro (accessed 27 July 2015).

33. National Institute for Health and Care Excellence. *Dementia – Clinical Knowledge Summary*. NICE; 2015. URL: http://cks.nice.org.uk/dementia (accessed 21 July 2015).

34. National Audit Office. *Improving Services and Support for People with Dementia*. National Audit Office; 2007. URL: www.nao.org.uk/report/improving-services-and-support-for-people-with-dementia/ (accessed 24 November 2015).

35. Alzheimer's Society. *Dementia UK: The Full Report*. Alzheimer's Society; 2007. URL: www.alzheimers.org.uk/site/scripts/download_info.php?fileID=2 (accessed 21 July 2015).

36. Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera A, *et al. Dementia UK: Update*. Alzheimer's Society; 2014. URL: www.cfas.ac.uk/files/2015/07/P326_AS_Dementia_Report_WEB2.pdf (accessed 22 November 2015).

37. Alzheimer's Society. *Dementia – Assessment and Diagnosis*. Alzheimer's Society; 2014. URL: www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=260 (accessed 24 July 2015).

38. Herlitz A, Small BJ, Fratiglioni L, Almkvist O, Viitanen M, Bäckman L. Detection of mild dementia in community surveys. Is it possible to increase the accuracy of our diagnostic instruments? *Arch Neurol* 1997;**54**:319–24. http://dx.doi.org/10.1001/archneur.1997.00550150075019

39. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L. Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol* 2001;**58**:397–405. http://dx.doi.org/10.1001/archneur.58.3.397

40. Yokomizo JE, Simon SS, Bottino CM. Cognitive screening for dementia in primary care: a systematic review. *Int Psychogeriatr* 2014;**26**:1783–804. http://dx.doi.org/10.1017/S1041610214001082

41. Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. *Int J Geriatr Psychiatry* 1999;**14**:936–40. http://dx.doi.org/10.1002/(SICI)1099-1166(199911)14:11%3C936::AID-GPS39%3E3.0.CO;2-1

42. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry* 2000;**15**:1021–7. http://dx.doi.org/10.1002/1099-1166(200011)15:11%3C1021::AID-GPS234%3E3.0.CO;2-6

43. Buschke H, Kuslansky G, Katz M, Stewart WF, Sliwinski MJ, Eckholdt HM, Lipton RB. Screening for dementia with the memory impairment screen. *Neurology* 1999;**52**:231–8. http://dx.doi.org/10.1212/WNL.52.2.231

44. Longmore M, Wilkinson I, Baldwin A, Wallin E. Neurology. In Longmore M, Wilkinson I, Baldwin A, Wallin E, editors. *Oxford Handbook of Clinical Medicine*. Oxford: Oxford University Press; 2014. pp. 491–4. http://dx.doi.org/10.1093/med/9780199609628.003.0010

45. Kalbe E, Kessler J, Calabrese P, Smith R, Passmore AP, Brand M, Bullock R. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. *Int J Geriatr Psychiatry* 2004;**19**:136–43. http://dx.doi.org/10.1002/gps.1042

46. Velayudhan L, Ryu SH, Raczek M, Philpot M, Lindesay J, Critchfield M, Livingston G. Review of brief cognitive tests for patients with suspected dementia. *Int Psychogeriatr* 2014;**26**:1247–62. http://dx.doi.org/10.1017/S1041610214000416

47. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;**53**:695–9. http://dx.doi.org/10.1111/j.1532-5415.2005.53221.x

48. Tariq SH, Tumosa N, Chibnall JT, Perry MH, Morley JE. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder – a pilot study. *Am J Geriatr Psychiatry* 2006;**14**:900–10. http://dx.doi.org/10.1097/01.JGP.0000221510.33817.86

49. Kansagara D, Freeman M. *A Systematic Evidence Review of the Signs and Symptoms of Dementia and Brief Cognitive Tests Available in VA Department of Veterans Affairs (US)*. 2010. URL: www.ncbi.nlm.nih.gov/books/NBK49021/ (accessed 22 November 2015).

50. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM, Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008;**149**:889–97. http://dx.doi.org/10.7326/0003-4819-149-12-200812160-00008

51. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th edn, Text Revision. Washington, DC: American Psychiatric Association; 2000.

52. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th edn. Washington, DC: American Psychiatric Association; 2013.

53. Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. *Am J Psychiatry* 2003;**160**:4–12. http://dx.doi.org/10.1176/appi.ajp.160.1.4

54. Chang YL, Bondi MW, McEvoy LK, Fennema-Notestine C, Salmon DP, Galasko D, *et al.* Global clinical dementia rating of 0.5 in MCI masks variability related to level of function. *Neurology* 2011;**76**:652–9. http://dx.doi.org/10.1212/WNL.0b013e31820ce6a5

55. Sheehan B. Assessment scales in dementia. *Ther Adv Neurol Disord* 2012;**5**:349–58. http://dx.doi.org/10.1177/1756285612455733

56. Tierney MC, Lermer MA. Computerized cognitive assessment in primary care to identify patients with suspected cognitive impairment. *J Alzheimers Dis* 2010;**20**:823–32.

57. Wild K, Howieson D, Webbe F, Seelye A, Kaye J. Status of computerized cognitive testing in aging: a systematic review. *Alzheimers Dement* 2008;**4**:428–37. http://dx.doi.org/10.1016/j.jalz.2008.07.003

58. Centre for Reviews and Dissemination (CRD). *Systematic Reviews: CRD's Guidance on Undertaking Reviews in Health Care*. York: CRD, University of York; 2009. URL: www.york.ac.uk/media/crd/Systematic_Reviews.pdf (accessed 22 November 2015).

59. National Institute for Health and Care Excellence. *Diagnostics Assessment Programme Manual*. NICE; 2011. URL: www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf (accessed 27 July 2015).

60. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Analysing and Presenting Results. In Deeks JJ, Bossuyt PM, Gatsonis C, editors. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*. The Cochrane Collaboration; 2010. Version 1.0. URL: http://methods.cochrane.org/sdt/sites/methods.cochrane.org.sdt/files/uploads/Chapter%2010%20-%20Version%201.0.pdf (accessed 22 November 2015).

61. Babineau J. Product review: Covidence (systematic review software). *J Can Health Libr Assoc* 2014;**35**.

62. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529–36. http://dx.doi.org/10.7326/0003-4819-155-8-201110180-00009

63. Caress AL, Ford A, Roberts L, Turner K, Ward D, Williamson T. *INVOLVE: Briefing Notes for Researchers*. Southampton: National Institute for Health Research; 2012. URL: www.invo.org.uk/resource-centre/resource-for-researchers/ (accessed 22 November 2015).

64. Janssen Research & Development, LLC. *A Study of a Self-Administered Memory Screening Test With Automated Reporting (SAMSTAR) in Subjects With Mild Cognitive Impairment*. 2015. URL: www.clinicaltrials.gov/ct2/show/NCT02419183 (accessed 24 November 2015).

65. Singer A. *Pilot Testing a New Computer-Based Screening Tool to Detect Cognitive Impairment*. 2011. URL: https://clinicaltrials.gov/ct2/show/NCT01220674 (accessed 24 November 2015).

66. Martin CK. *Feasibility and Validity of A Novel Computer Based Battery of Assessments in the Elderly (HHT)*. 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02109419 (accessed 24 November 2015).

67. Soininen H. *Computational Tools for Early Diagnosis of Memory Disorders (ProsKuopio)*. 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02050464 (accessed 24 November 2015).

68. Ahmed S, de Jager C, Wilcock G. A comparison of screening tools for the assessment of mild cognitive impairment: preliminary findings. *Neurocase* 2012;**18**:336–51. http://dx.doi.org/10.1080/13554794.2011.608365

69. de Jager CA, Schrijnemaekers AC, Honey TE, Budge MM. Detection of MCI in the clinic: evaluation of the sensitivity and specificity of a computerised test battery, the Hopkins Verbal Learning Test and the MMSE. *Age Ageing* 2009;**38**:455–60. http://dx.doi.org/10.1093/ageing/afp068

70. Doniger GM, Zucker DM, Schweiger A, Dwolatzky T, Chertkow H, Crystal H, Simon ES. Towards practical cognitive assessment for detection of early dementia: a 30-minute computerized battery discriminates as well as longer testing. *Curr Alzheimer Res* 2005;**2**:117–24. http://dx.doi.org/10.2174/1567205053585792

71. Dwolatzky T, Whitehead V, Doniger GM, Simon ES, Schweiger A, Jaffe D, *et al.* Validity of a novel computerized cognitive battery for mild cognitive impairment. *BMC Geriatr* 2003;**3**:4. http://dx.doi.org/10.1186/1471-2318-3-4

72. Juncos-Rabadán O, Pereiro AX, Facal D, Reboredo A, Lojo-Seoane C. Do the Cambridge Neuropsychological Test Automated Battery episodic memory measures discriminate amnestic mild cognitive impairment? *Int J Geriatr Psychiatry* 2014;**29**:602–9. http://dx.doi.org/10.1002/gps.4042

73. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;**7**:270–9. http://dx.doi.org/10.1016/j.jalz.2011.03.008

74. Junkkila J, Oja S, Laine M, Karrasch M. Applicability of the CANTAB-PAL computerized memory test in identifying amnestic mild cognitive impairment and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2012;**34**:83–9. http://dx.doi.org/10.1159/000342116

75. Kingsbury R, Pachana NA, Humphreys M, Tehan G, Byrne GJA. Utility of a computerised cognitive screen in MCI and depression in an older population. *Aust J Rehabil Counsell* 2010;**16**:14–26.

76. Kluger BM, Saunders LV, Hou W, Garvan CW, Kirli S, Efros DB, *et al.* A brief computerized self-screen for dementia. *J Clin Exp Neuropsychol* 2009;**31**:234–44. http://dx.doi.org/10.1080/13803390802317559

77. Lichtenberg PA, Johnson AS, Erlanger DM, Kaushik T, Maddens ME, Imam K, *et al.* Enhancing cognitive screening in geriatric care: Use of an internet-based system. *Int J Healthcare Inf Sysinformatics* 2006;**1**:47–57. http://dx.doi.org/10.4018/jhisi.2006070103

78. Tierney MC, Naglie G, Upshur R, Moineddin R, Charles J, Jaakkimainen RL. Feasibility and validity of the self-administered computerized assessment of mild cognitive impairment with older primary care patients. *Alzheimer Dis Assoc Disord* 2014;**28**:311–19. http://dx.doi.org/10.1097/WAD.0000000000000036

79. Maruff P, Lim YY, Darby D, Ellis KA, Pietrzak RH, Snyder PJ, *et al.* Clinical utility of the Cogstate Brief Battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC Psychol* 2013;**1**:30. http://dx.doi.org/10.1186/2050-7283-1-30

80. Mundt JC, Ferber KL, Rizzo M, Greist JH. Computer-automated dementia screening using a touch-tone telephone. *Arch Intern Med* 2001;**161**:2481–7. http://dx.doi.org/10.1001/archinte.161.20.2481

81. O'Connell H, Coen R, Kidd N, Warsi M, Chin AV, Lawlor BA. Early detection of Alzheimer's disease (AD) using the CANTAB paired Associates Learning Test. *Int J Geriatr Psychiatry* 2004;**19**:1207–8. http://dx.doi.org/10.1002/gps.1180

82. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;**7**:263–9. http://dx.doi.org/10.1016/j.jalz.2011.03.005

83. Rosenthal LS, Skolasky RL, Moxley RT, Roosa HV, Selnes OA, Eschman A, *et al.* A novel computerized functional assessment for human immunodeficiency virus-associated neurocognitive disorder. *J Neurovirol* 2013;**19**:432–41. http://dx.doi.org/10.1007/s13365-013-0195-5

84. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, *et al.* Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007;**69**:1789–99. http://dx.doi.org/10.1212/01.WNL.0000287431.88658.8b

85. Saxton J, Morrow L, Eschman A, Archer G, Luther J, Zuccolotto A. Computer assessment of mild cognitive impairment. *Postgrad Med* 2009;**121**:177–85. http://dx.doi.org/10.3810/pgm.2009.03.1990

86. Vacante M, Wilcock GK, de Jager CA. Computerized adaptation of The Placing Test for early detection of both mild cognitive impairment and Alzheimer's disease. *J Clin Exp Neuropsychol* 2013;**35**:846–56. http://dx.doi.org/10.1080/13803395.2013.825235

87. Reitsma JB, Rutjes AWS, Whiting P, Vlassov VV, Leeflang MMG, Deeks JJ. Assessing Methodological Quality. In Deeks JJ, Bossuyt PM, Gatsonis C, editors. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*. Version 1.0. The Cochrane Collaboration; 2009. URL: http://srdta.cochrane.org/ (accessed 24 July 2015).

88. Gualtieri C. *Computerized Neurocognitive Test Batteries for Dementia Screening*. 2004. URL: www.ncneuropsych.com/research/ALZscreen_AAIC_pres.pdf (accessed 22 November 2015).

89. Neurocare. *Cambridge Neuropsychological Test Automated Battery*. 2012. URL: www.neurocare.org.uk/2012/09/cambridge-neuropsychological-test-automated-battery/ (accessed 13 December 2015).

90. Psychology Software Tools I. *CAMCI® Overview*. 2015. URL: www.pstnet.com/software.cfm?ID=98 (accessed 22 November 2015).

91. NeuroTrax Corporation. *Advanced Computerized Test Detects Early Signs of Dementia*. 2004. URL: www.prnewswire.com/news-releases/advanced-computerized-test-detects-early-signs-of-dementia-74997062.html (accessed 22 November 2015).

92. Gilbert R, Logan S, Moyer VA, Elliott EJ. Assessing diagnostic and screening tests: part 1. Concepts. *West J Med* 2001;**174**:405–9. http://dx.doi.org/10.1136/ewjm.174.6.405

93. Burns A, Jacoby R, Levy R. Progression of cognitive impairment in Alzheimer's disease. *J Am Geriatr Soc* 1991;**39**:39–45. http://dx.doi.org/10.1111/j.1532-5415.1991.tb05904.x

94. Roth M, Huppert FA, Mountjoy CQ, Tym E. *CAMDEX: The Cambridge Examination for Mental Disorders of the Elderly*. Cambridge: Cambridge University Press; 1988.

95. Lozano-Gallego M, Vilalta-Franch J, Llinàs-Reglà J, López-Pousa S. The Cambridge Cognitive Examination as a tool for detection of dementia. *Rev Neurol* 1999;**28**:348–52.

96. Rozzini L, Chilovi BV, Peli M, Conti M, Rozzini R, Trabucchi M, Padovani A. Anxiety symptoms in mild cognitive impairment. *Int J Geriatr Psychiatry* 2009;**24**:300–5. http://dx.doi.org/10.1002/gps.2106

97. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatr* 1984;**141**:1356–64.

98. Johnson LA, Mauer C, Jahn D, Song M, Wyshywaniuk L, Hall JR, *et al.* Cognitive differences among depressed and non-depressed MCI participants: a project FRONTIER study. *Int J Geriatr Psychiatry* 2013;**28**:377–82. http://dx.doi.org/10.1002/gps.3835

99. Randolph C, Tierney MC, Erich Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exper Neuropsychol* 1998;**20**:310–19. http://dx.doi.org/10.1076/jcen.20.3.310.823

100. Blackstone K, Moore DJ, Franklin DR, Clifford DB, Collier AC, Marra CM, *et al.* Defining neurocognitive impairment in HIV: deficit scores versus clinical ratings. *Clin Neuropsychol* 2012;**26**:894–908. http://dx.doi.org/10.1080/13854046.2012.694479

101. Gisslén M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? *BMC Infect Dis* 2011;**11**:356. http://dx.doi.org/10.1186/1471-2334-11-356

102. Cysique LA, Maruff P, Brew BJ. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. *J Neurovirol* 2004;**10**:350–7. http://dx.doi.org/10.1080/13550280490521078

103. Zygouris S, Tsolaki M. Computerized cognitive testing for older adults: a review. *Am J Alzheimers Dis Other Demen* 2015;**30**:13–28. http://dx.doi.org/10.1177/1533317514522852

104. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, *et al.* STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015;**351**:h5527. http://dx.doi.org/10.1136/bmj.h5527

105. Noel-Storr AH, McCleery JM, Richard E, Ritchie CW, Flicker L, Cullum SJ, *et al.* Reporting standards for studies of diagnostic test accuracy in dementia. The STARDdem Initiative. *Neurology* 2014;**83**:364–73. http://dx.doi.org/10.1212/WNL.0000000000000621

106. Nicholson A, Mahon J, Boland A, Beale S, Dwan K, Fleeman N, *et al. The Clinical and Cost-Effectiveness of the PROGENSA PCA3 Assay and the Prostate Health Index (phi) in the Diagnosis of Prostate Cancer: A Systematic Review and Economic Evaluation*. 2014. URL: www.nice.org.uk/guidance/DG17/documents/diagnosing-prostate-cancer-progensa-pca3-assay-and-prostate-health-index-diagnostics-assessment-report2 (accessed 22 November 2015).

107. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Analysing and Presenting Results. In Deeks JJ, Bossuyt PM, Gatsonis C, editors. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*. Version 1.0. The Cochrane Collaboration; 2010. URL: http://srdta.cochrane.org/ (accessed 22 November 2015).

Appendix 1 Measures for assessing an index test against a reference standard

The following section outlines the different methods of assessing diagnostic outcomes. It is adapted from a previous piece of work conducted by the Liverpool Review and Implementation Group (LRiG) and is reproduced here with permission.[106]

The classic presentation of the results of a clinical validity study is the so-called 2 × 2 table, as shown in *Table 17*.

The number entered into cell 'a' is the number of patients for whom the new test correctly diagnoses MCI (as determined by the reference standard, in this case a clinical diagnosis of MCI). For these people, the new test is positive as is the reference standard; these are TPs.

The number entered into cell 'b' is the number of patients for whom the new test is positive (i.e. indicates the presence of MCI) but who do not, according to the reference standard (clinical diagnosis), have MCI. The new test has incorrectly diagnosed MCI; these are FPs.

The number entered into cell 'c' is the number of patients who are identified through the reference standard (clinical diagnosis) as having MCI but for whom the new test gave negative results. The new test has incorrectly labelled the patient as having MCI; these are FNs.

The number in cell 'd' is the number of patients who do not, according to the reference standard (clinical diagnosis), have MCI and who are also shown by the new test to be free from disease; these are TNs.

The numbers displayed in a 2 × 2 table are used to generate other summary measures. These are set out in *Table 18*.

In an ideal world, a test would be 100% sensitive and 100% specific. However, in reality there is often a trade-off between the two, with tests that have high sensitivity having low specificity and vice versa.

TABLE 17 Example of a 2 × 2 table

	Clinical diagnosis (reference standard)	
Test result	MCI	No MCI
New test positive	a	b
New test negative	c	d

TABLE 18 Summary measures derived from numbers in a 2 × 2 table

Term	Formula	Notes
Sensitivity	a/(a + c)	Proportion of those who actually have disease and are correctly identified with positive test results. TP rate
		High sensitivity = few FNs
Specificity	d/(b + d)	Proportion of those who do not actually have the disease who are correctly identified with negative test results. 1–FP rate
		High specificity = few FPs
PPV	a/(a + b)	The proportion of those with positive test results who actually have the disease
NPV	d/(c + d)	The proportion of those with negative test results who do not have the disease

The use of a 2 × 2 tables requires that the test results are dichotomous, that is, they can be divided into two groups: test positive and test negative.

Receiver operating characteristic curve

When an intervention test has a range of possible thresholds that could be used to divide results into test positive and test negative, the relationship between the threshold used and the performance of the test can be examined in a receiver operating characteristic curve. This is a graphical plot of the sensitivity (TP rate) against 1 – specificity or the FP rate for each threshold; examples of a receiver operating characteristic curve are shown in *Figure 5*, with the associated distribution of the index tests in diseased and non-diseased populations. An ideal test would have a point in the top-left corner with 100% specificity and 100% sensitivity.

Area under a receiver operating characteristic curve

The receiver operating characteristic curve can be used to assess the degree to which sensitivity changes at different levels of specificity or vice versa. Some studies report AUC as a proportion of the total area of the graph. This is a measure of the predictive accuracy or discrimination of the diagnostic test, that is, the ability of the test to discriminate between those who have (or will develop) MCI from those who do not have (or will not develop) MCI.

The AUC can also be expressed as the probability that someone with the disease will have a higher test result than someone without the disease. It is also referred to as the *c*-statistic. An AUC of 1.0 indicates a perfect test, and an AUC of 0.5 (the diagonal line) indicates that the test is no better than chance (i.e. 50% probability) in predicting whether or not the disease is present. An AUC of 0.5 to 0.7 is considered as poor discrimination, 0.7 to 0.8 acceptable discrimination, 0.8 to 0.9 excellent discrimination and > 0.9 exceptional discrimination.

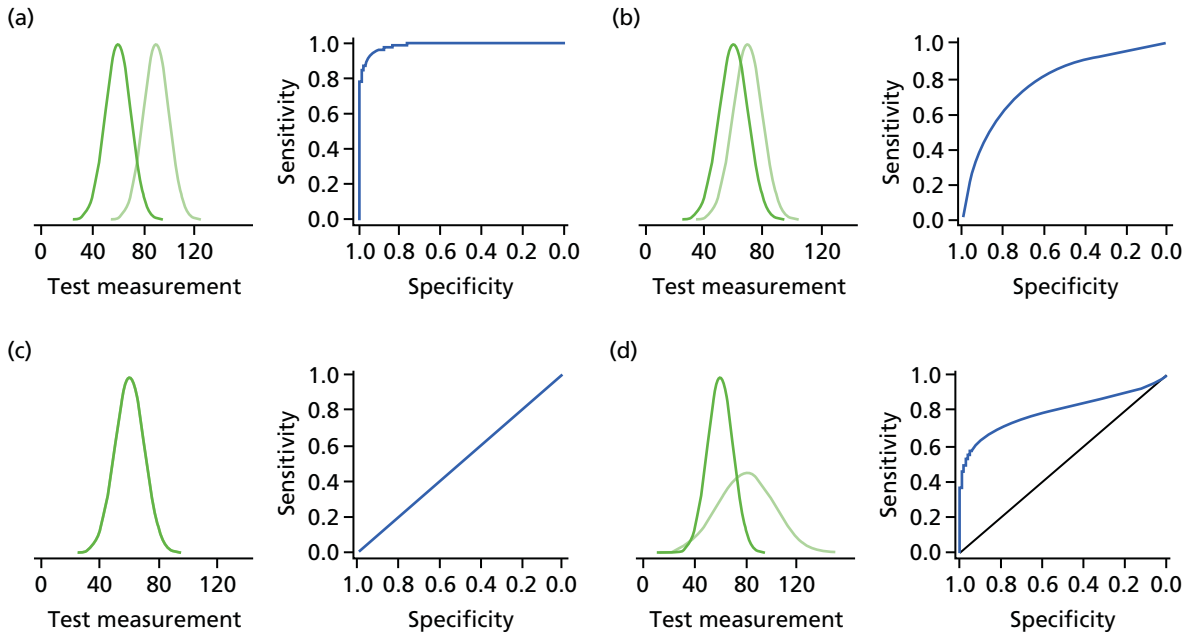

FIGURE 5 Examples of a receiver operating characteristic curve. (Image reproduced from *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* with permission.[107])

Positive predictive value and negative predictive value

The PPV is the probability that subjects with a positive screening test truly have the disease.

$$\text{PPV} = \text{number of TPs} / \text{number of TPs} + \text{number of FPs}. \quad (1)$$

The NPV is the probability that subjects with a negative screening test truly do not have the disease.

$$\text{NPV} = \text{number of TNs} / \text{number of TNs} + \text{number of FNs}. \quad (2)$$

The PPV and NPV are clinically significant, as they give probabilities that an individual is truly MCI/early dementia positive given that they tested positive or truly MCI/early dementia negative given that they tested negative.

Likelihood ratio

The LR gives another measure of performance for the disease, and is described in chapter 10 of the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*,[107] as follows:

The LR+ describes how many times more likely positive index test results were in the diseased group than in the non-diseased group. The LR+, which should be > 1 if the test informative, is defined as:

$$\text{LR}+ = \text{P}(\text{T}+|\text{D}+) / \text{P}(\text{T}+|\text{D}-) = \text{sens} / (1 - \text{spec}), \quad (3)$$

(where T+ is index test positive, T– is index text negative, D+ is diseased, D– is non-diseased, P means probability and | means 'given that' or 'on condition that') and is estimated as:

$$[a / (a + c)] / [b / (b + d)]. \quad (4)$$

The LR– describes how many times less likely negative index test results were in the diseased group than in the non-diseased group. The LR–, which should be < 1 if the test is informative, is defined as:

$$\text{LR}- = \text{P}(\text{T}-|\text{D}+) / \text{P}(\text{T}-|\text{D}-) = (1 - \text{sens}) / \text{spec}, \quad (5)$$

and is estimated as:

$$[c / (a + c)] / [d / (b + d)]. \quad (6)$$

Appendix 2 Search strategies

A draft search strategy for MEDLINE was prepared and run on 15 July 2015 as part of the scoping searches. The search was updated on 6 August 2015 alongside a search of additional databases. The search strategies for each database are reported in *Tables 19–22* and *Boxes 1–4*.

TABLE 19 Search strategy conducted in MEDLINE

	Search terms	Results
1	exp mild cognitive impairment/	3249
2	((early* or onset* or initial* or young* or incipient*) adj2 (dementia* or Alzheimer* or AD)).tw.	9646
3	((Mild* or early* or onset* or initial* or progress* or minor or young* or moderat* or suspect*) adj2 Cognit* adj1 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*)).tw.	11,933
4	MCI.tw.	11,603
5	NCD.tw.	1233
6	((memory* or neurocognitiv*) adj2 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*)).tw.	29,085
7	("preclinical alzheimer*" or "pre-clinical alzheimer*").tw.	293
8	(prodrom* adj2 dement*).tw.	84
9	*dementia/ or *alzheimer disease/ or *dementia, vascular/ or *dementia, multi-infarct/ or *frontotemporal dementia/	88,482
10	or/1-9	129,676
11	((computer* or automate*) adj2 (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*)).tw.	19,607
12	(automat* adj2 (interpretat* or test*)).tw.	2445
13	*Neuropsychological Tests/	13,160
14	((neuropsychological or neuro-psychological or psychometric*) adj5 (computer* or automate*) adj5 (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*)).tw.	831
15	psychometrics/	58,160
16	or/11-15	87,870
17	10 and 16	5551
18	Diagnosis, Computer-Assisted/	19,850
19	((computer* or automate*) adj4 (diagnos* or detect*)).tw.	13,645
20	or/18-19	30,836
21	10 and 20	366
22	disease progression/	114,210
23	((test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*) adj3 diseas* adj3 (progress* or exacerbat*)).tw.	4249
24	or/22-23	117,390
25	17 and 24	342

continued

TABLE 19 Search strategy conducted in MEDLINE (*continued*)

	Search terms	Results
26	"cambridge Neuropsychology Test*".tw.	0
27	Computerised Neuropsychological Test Battery.tw.	38
28	Six Item Cognitive Impairment Test.tw.	11
29	"Computer Assessment of Mild Cognitive Impairment".tw.	3
30	MindStream*.tw.	27
31	"Mild Cognitive Impairment Screen*".tw.	11
32	Computer Administered Neuropsychological Screen for Mild Cognitive Impairment.tw.	2
33	Automated Neuropsychological Assessment Metrics.tw.	90
34	CANS-MCI.tw.	2
35	"CNS Vital Signs".tw.	33
36	Cognitive Drug Research Computerised Assessment System for Dementia.tw.	1
37	CogState.tw.	93
38	"Cognitive Stability Index*".tw.	6
39	"Cognitive Screening Test*".tw.	183
40	Microcog.tw.	28
41	(COGDRAS-D or COGDRASD or COGDRAS).tw.	0
42	MCIS.tw.	167
43	(CAMCI or CNTB).tw.	20
44	6CIT.tw.	11
45	(CANTAB-A or CANTABA or CANTAB).tw.	343
46	ANAM.tw.	128
47	CADi2.tw.	1
48	or/26-46	1103
49	17 or 21 or 25 or 48	6733
50	animals/ not humans/	3,996,470
51	49 not 50	6691
52	comment/ or editorial/ or letter/	1,496,207
53	case reports/	1,764,849
54	(comment or editorial or letter or journal correspondence or opinion).pt.	1,496,207
55	or/52-54	3,069,853
56	51 not 55	6360
57	limit 56 to yr="2005 -Current"	3779

TABLE 20 Search strategy conducted in EMBASE

	Searches	Results
1	exp mild cognitive impairment/	12,572
2	((early* or onset* or initial* or young* or incipient*) adj2 (dementia* or Alzheimer* or AD)).tw.	12,911
3	((Mild* or early* or onset* or initial* or progress* or minor or young* or moderat* or suspect*) adj2 Cognit* adj1 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*)).tw.	18,245
4	MCI.tw.	18,975
5	NCD.tw.	1481
6	((memory* or neurocognitiv*) adj2 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*)).tw.	38,383
7	("preclinical alzheimer*" or "pre-clinical alzheimer*").tw.	374
8	(prodrom* adj2 dement*).tw.	124
9	*dementia/ or *alzheimer disease/ or *dementia, vascular/ or multiinfarct dementia/ or *frontotemporal dementia/	125,217
10	or/1-9	181,482
11	((computer* or automate*) adj2 (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*)).tw.	24,195
12	(automat* adj2 (interpretat* or test*)).tw.	3310
13	*Neuropsychological Test/	6554
14	((neuropsychological or neuro-psychological or psychometric*) adj5 (computer* or automate*) adj5 (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*)).tw.	1174
15	psychometry/	46,698
16	or/11-15	76,781
17	10 and 16	3845
18	computer assisted diagnosis/	36,170
19	((computer* or automate*) adj4 (diagnos* or detect*)).tw.	16,191
20	or/18-19	48,801
21	10 and 20	503
22	disease course/	323,960
23	((test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*) adj3 diseas* adj3 (progress* or exacerbat*)).tw.	6175
24	or/22-23	326,786
25	17 and 24	215
26	"cambridge Neuropsychology Test*".tw.	0
27	Computerised Neuropsychological Test Battery.tw.	50
28	Six Item Cognitive Impairment Test.tw.	14
29	"Computer Assessment of Mild Cognitive Impairment".tw.	4
30	MindStream*.tw.	76
31	"Mild Cognitive Impairment Screen*".tw.	17

continued

TABLE 20 Search strategy conducted in EMBASE (*continued*)

	Searches	Results
32	Computer Administered Neuropsychological Screen for Mild Cognitive Impairment.tw.	3
33	Automated Neuropsychological Assessment Metrics.tw.	120
34	CANS-MCI.tw.	4
35	"CNS Vital Signs".tw.	63
36	Cognitive Drug Research Computerised Assessment System for Dementia.tw.	1
37	CogState.tw.	232
38	"Cognitive Stability Index*".tw.	10
39	"Cognitive Screening Test*".tw.	288
40	Microcog.tw.	33
41	(COGDRAS-D or COGDRASD or COGDRAS).tw.	1
42	MCIS.tw.	257
43	(CAMCI or CNTB).tw.	33
44	6CIT.tw.	22
45	(CANTAB-A or CANTABA or CANTAB).tw.	626
46	ANAM.tw.	199
47	CADi2.tw.	1
48	or/26-46	1917
49	17 or 21 or 25 or 48	5930
50	nonhuman/ not human/	3,604,816
51	49 not 50	5870
52	comment/ or editorial/ or letter/	1,363,574
53	case reports/	2
54	(comment or editorial or letter or journal correspondence or opinion).pt.	1,375,197
55	or/52-54	1,407,178
56	51 not 55	5756
57	limit 56 to yr="2005 -Current"	4134
58	limit 57 to embase	3228
59	remove duplicates from 58	3191

TABLE 21 Number of studies retrieved from different databases

Databases	Date searched	Version/files	Number retrieved
Cochrane Database of Systematic Reviews (via Cochrane)	6 August 2015	Issue 7 of 12, July 2015	684
Database of Abstracts of Reviews of Effects (via Cochrane)	6 August 2015	Issue 7 of 12, July 2015	32
HTA database (via Cochrane)	6 August 2015	Issue 7 of 12, July 2015	4
Cochrane Central Database of Controlled Trials (via Cochrane)	6 August 2015	Issue 7 of 12, July 2015	1136
NHS Economic Evaluation Database	6 August 2015	Issue 7 of 12, July 2015	7
MEDLINE (via Ovid) and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid)	6 August 2015	Ovid MEDLINE(R) 1946 to week 5 July 2015, Database Field Guide Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 5 August 2015	3779
EMBASE (via Ovid)	6 August 2015	1980 to 2015 Week 31	3191
Web of Science	6 August 2015	N/A	3586
PsycINFO	6 August 2015	N/A	541
PubMed	3 September 2015	N/A	392
ProQuest theses and dissertations	3 September 2015	N/A	197 (main search); 1919 (search for test names)
Hand-searching	26 August 2015	N/A	4
Citation tracking	19 September 2015	N/A	3324

TABLE 22 Hand-searching for trials

Databases	Date searched	Links to results
ClinicalTrials.gov	26 August 2015	A Study of a Self-Administered Memory Screening Test With Automated Reporting (SAMSTAR) in Participants With Mild Cognitive Impairment[64] Pilot Testing a New Computer-based Screening Tool to Detect Cognitive Impairment[65] Feasibility and Validity of A Novel Computer Based Battery of Assessments in the Elderly (HHT)[66] Computational Tools for Early Diagnosis of Memory Disorders (ProsKuopio)[67]
*meta*Register of Controlled Trials and ISRCTN Register	26 August 2015	None found
World Health Organization International Clinical Trials Registry Platform	26 August 2015	None found
PROSPERO systematic review register	26 August 2015	None found
Epistemonikos	26 August 2015	No new references found

BOX 1 Search strategy conducted in PsycINFO

Strategy used

TI "Cognitive Stability Index*" OR TI "Cognitive Screening Test*" OR TI Microcog OR TI ((COGDRAS-D or COGDRASD or COGDRAS)) OR TI MCIS OR TI ((CAMCI or CNTB)) OR TI 6CIT OR TI ((CANTAB-A or CANTABA or CANTAB)) OR TI ANAM OR TI CADi2

TI "cambridge Neuropsychology Test*" OR TI Computerised Neuropsychological Test Battery OR TI Six Item Cognitive Impairment Test OR TI "Computer Assessment of Mild Cognitive Impairment" OR TI MindStream* OR TI "Mild Cognitive Impairment Screen*" OR TI Computer Administered Neuropsychological Screen for Mild Cognitive Impairment OR TI Automated Neuropsychological Assessment Metrics OR TI CANS-MCI OR TI "CNS Vital Signs" OR TI Cognitive Drug Research Computerised Assessment System for Dementia OR TI CogState

TI (((early* or onset* or initial* or young* or incipient*) near2 (dementia* or Alzheimer* or AD))) OR TI (((Mild* or early* or onset* or initial* or progress* or minor or young* or moderat* or suspect*) near2 Cognit* near1 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*))) OR TI (MCI or NCD) OR TI (((memory* or neurocognitiv*) near2 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*))) OR TI (("preclinical alzheimer*" or "pre-clinical alzheimer*")) OR TI (prodrom* near2 dement*) AND TI (((computer* or automate*) near4 (diagnos* or detect*)))

TI (((early* or onset* or initial* or young* or incipient*) near2 (dementia* or Alzheimer* or AD))) OR TI (((Mild* or early* or onset* or initial* or progress* or minor or young* or moderat* or suspect*) near2 Cognit* near1 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*))) OR TI (MCI or NCD) OR TI (((memory* or neurocognitiv*) near2 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*))) OR TI (("preclinical alzheimer*" or "pre-clinical alzheimer*")) OR TI (prodrom* near2 dement*) AND TI (((computer* or automate*) near2 (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*))) OR TI ((automat* near2 (interpretat* or test*))) OR TI (((neuropsychological or neuro-psychological or psychometric*) near5 (computer* or automate*) near5 (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*)))

BOX 2 Search strategy conducted in Web of Science

Strategy used

TITLE: (((early* or onset* or initial* or young* or incipient*) near2 (dementia* or Alzheimer* or AD))) *OR* **TITLE**:(((Mild* or early* or onset* or initial* or progress* or minor or young* or moderat* or suspect*) near2 Cognit* near1 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*))) *OR* **TITLE**: (MCI or NCD)*OR* **TITLE**: (((memory* or neurocognitiv*) near2 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*)))*OR* **TITLE**: (("preclinical alzheimer*" or "pre-clinical alzheimer*")) *OR***TITLE**: ((prodrom* near2 dement*))*OR* **TITLE**: (*dementia/ or *alzheimer disease/ or *dementia, vascular/ or *dementia, multi-infarct/ or *frontotemporal dementia/) *AND***TITLE**: (Diagnosis, Computer-Assisted/) *OR* **TITLE**: (((computer* or automate*) near4 (diagnos* or detect*)))

Refined by: PUBLICATION YEARS: (2013 OR 2011 OR 2014 OR 2010 OR 2009 OR 2012 OR 2005 OR 2008 OR 2007 OR 2006 OR 2015)

TITLE: (((early* or onset* or initial* or young* or incipient*) near2 (dementia* or Alzheimer* or AD))) *OR* **TITLE**:(((Mild* or early* or onset* or initial* or progress* or minor or young* or moderat* or suspect*) near2 Cognit* near1 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*))) *OR* **TITLE**: (MCI or NCD)*OR* **TITLE**: (((memory* or neurocognitiv*) near2 (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*)))*OR* **TITLE**: (("preclinical alzheimer*" or "pre-clinical alzheimer*")) *OR***TITLE**: ((prodrom* near2 dement*))*OR* **TITLE**: (*dementia/ or *alzheimer disease/ or *dementia, vascular/ or *dementia, multi-infarct/ or *frontotemporal dementia/) *AND***TITLE**: (((computer* or automate*) near2 (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*))) *OR* **TITLE**: ((automat* near2 (interpretat* or test*))) *OR***TITLE**: (((neuropsychological or neuro-psychological or psychometric*) near5 (computer* or automate*) near5 (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*)))

Refined by: PUBLICATION YEARS: (2013 OR 2011 OR 2014 OR 2010 OR 2009 OR 2012 OR 2005 OR 2008 OR 2007 OR 2006 OR 2015)

TITLE:("cambridge Neuropsychology Test*") *OR* **TITLE**: (Computerised Neuropsychological Test Battery) *OR***TITLE**: (Six Item Cognitive Impairment Test) *OR* **TITLE**:("Computer Assessment of Mild Cognitive Impairment") *OR* **TITLE**:(MindStream*) *OR* **TITLE**: ("Mild Cognitive Impairment Screen*") *OR***TITLE**: (Computer Administered Neuropsychological Screen for Mild Cognitive Impairment) *OR* **TITLE**:(Automated Neuropsychological Assessment Metrics) *OR* **TITLE**:(CANS-MCI) *OR* **TITLE**: ("CNS Vital Signs") *OR* **TOPIC**: (Cognitive Drug Research Computerised Assessment System for Dementia) *OR* **TITLE**:(CogState) *OR* **TITLE**: ("Cognitive Stability Index*") *OR* **TITLE**:("Cognitive Screening Test*") *OR***TITLE**: (Microcog) *OR* **TITLE**: ((COGDRAS-D or COGDRASD or COGDRAS)) *OR* **TITLE**: (MCIS) *OR***TITLE**: ((CAMCI or CNTB)) *OR***TITLE**: (6CIT) *OR* **TITLE**: ((CANTAB-A or CANTABA or CANTAB)) *OR***TITLE**: (ANAM) *OR* **TITLE**: (CADi2)

Refined by: PUBLICATION YEARS: (2014 OR 2012 OR 2005 OR 2013 OR 2007 OR 2006 OR 2010 OR 2009 OR 2011 OR 2015 OR 2008)

BOX 3 Search strategy conducted in PubMed

Strategy used

SearchAdd to builderQueryItems foundTime#10AddSearch (#8 and #9)39206:19:55#9AddSearch ("2015/03/03"[Date - Entrez] : "3000"[Date - Entrez])55757506:09:00#8AddSearch (#3 or #5 or #6) 780906:08:27#7AddSearch (#3 and #5 and #6)38906:07:46#6AddSearch ((((((((((((((((((((((((("cambridge Neuropsychology Test*") OR Computerised Neuropsychological Test Battery) OR Six Item Cognitive Impairment Test) OR "Computer Assessment of Mild Cognitive Impairment") OR MindStream*) OR "Mild Cognitive Impairment Screen*") OR Computer Administered Neuropsychological Screen for Mild Cognitive Impairment) OR Automated Neuropsychological Assessment Metrics) OR CANS-MCI) OR "CNS Vital Signs".) OR Cognitive Drug Research Computerised Assessment System for Dementia) OR CogState) OR "Cognitive Stability Index*") OR "Cognitive Screening Test*") OR Microcog) OR (COGDRAS-D or COGDRASD or COGDRAS)) OR MCIS) OR ((CAMCI or CNTB))) OR 6CIT) OR ((CANTAB-A or CANTABA or CANTAB))) OR ANAM) OR CADi2395306:06:42#5AddSearch (#1 and #4)266706:03:29#4AddSearch ((computer* or automate*)) AND (diagnos* or detect*)20789406:03:01#3AddSearch (#1 and #2)352806:02:34#2AddSearch (((((((computer* or automate*)) AND (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*)) OR automat*) AND (interpretat* or test*)) OR (neuropsychological or neuro-psychological or psychometric*)) AND (computer* or automate*)) AND (test* or assess* or evaluat* or screen* or battery or monitor* or identif* or assess* or evaluat* or interpret*)15364006:01:47#1AddSearch ((((((((early* or onset* or initial* or young* or incipient*)) AND (dementia* or Alzheimer* or AD)) OR (Mild* or early* or onset* or initial* or progress* or minor or young* or moderat* or suspect*)) AND Cognit*) AND (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*)) AND (MCI OR NCD)) OR (memory* or neurocognitiv*)) AND (impair* or disord* or diseas* or declin* or deteriorat* or fail* or complain* or dysfunct* or degenerat* or deficit*)11603206:00:22

BOX 4 Search strategy conducted in ProQuest

Strategy used

"cambridge Neuropsychology Test*" OR ("Computerised Neuropsychological Test Battery" OR "Six Item Cognitive Impairment Test") OR ("Computer Assessment of Mild Cognitive Impairment" OR (CANTAB-A or CANTABA or CANTAB)) OR ("Mild Cognitive Impairment Screen*" OR "Computer Administered Neuropsychological Screen for Mild Cognitive Impairment") OR ("Automated Neuropsychological Assessment Metrics" OR CANS-MCI) OR ("CNS Vital Signs" OR "Cognitive Drug Research Computerised Assessment System for Dementia") OR (CogState or microcog OR "Cognitive Stability Index*") OR ("Cognitive Screening Test*" OR (CAMCI or CNTB)) OR ((COGDRAS-D or COGDRASD or COGDRA) OR MCIS or 6CIT or ANAM or CADi2 or MindStream*) AND (dementia or alzheimers or MCI OR "Mild cognitive impairment")

((early* OR onset* OR initial* OR young* OR incipient*) NEAR/2 (dementia* OR Alzheimer* OR AD)) AND (((computer* or automate*) near/2 (test* or assess* or evaluate* or screen* or battery or monitor* or identif* or ssess* or evaluate* or interpret*)) OR (automat* near/2 (interpret* or test*)))

Appendix 3 Studies excluded, with reasons

The full list of excluded studies is available from the authors.

Reason for exclusion	Number of studies
Exclusion reason: paper-based test	116
Exclusion reason: wrong study design	59
Exclusion reason: not an evaluation of the automated test	31
Exclusion reason: wrong patient population	32
Exclusion reason: systematic review	23
Exclusion reason: literature review	20
Exclusion reason: wrong intervention	16
Exclusion reason: wrong indication – other	55
Exclusion reason: wrong outcome	9
Exclusion reason: wrong outcomes; continuous data	6
Exclusion reason: automated test not in English	9
Exclusion reason: timeline	4
Exclusion reason: duplicate	3

Appendix 4 Names of all of the tests identified

Test	Paper or computer or other
ANAM	Computer
Automated Cognitive Test	Computer
Automated Neuropsychological Assessment Metrics	Computer
CADi2	Computer
CAMCI	Computer
CANTAB	Computer
Central Nervous System Vital Signs Brief Clinical Evaluation Battery	Computer
CNS vital signs	Computer
CNTB	Computer
COAD	Computer
COGDRAS-D	Computer
Cognitive Drug Research Computerised Assessment System for Dementia	Computer
CogState MCI/AD battery	Computer
Community Screening Instrument for Dementia	Computer
Computer Assessment of MCI	Computer
Computer Self Test	Computer
Computer-Administered Neuropsychological Screen for MCI	Computer
CSI	Computer
CST	Computer
Dr Oz	Computer
Florida Brief Memory Scale	Computer
GrayMatters Assessment System	Computer
Groton Maze Learning Test	Computer
IntegNeuro and WebNeuro	Computer
MCIS	Computer
MCI Screen	Computer
MicroCog	Computer
Mindstreams	Computer
NeuroTrax	Computer
Nonverbal Medical Symptom Validity Test	Computer
Poon-Baro-Wens	Computer
TDAS	Computer
TPSP	Computer
Scenery Picture Memory Test	Other
Sweet 16	Other

APPENDIX 4

Test	Paper or computer or other
3MS	Paper
3TD	Paper
6CIT	Paper
AD8	Paper
ADAS-COG	Paper
Albert Einstein Health Self-Assessment Form	Paper
Animal Naming Test	Paper
BDRS	Paper
BEHAVE-AD	Paper
Benton Fluency Test	Paper
CAMCOG	Paper
CAMDEX	Paper
CERAD	Paper
CERAD-BRSD	Paper
Clock Drawing Test	Paper
Cued-Recall Retrieval Speed Task	Paper
GPCOG	Paper
Hopkins Verbal Learning Test-Revised	Paper
KICA-Cog	Paper
MIS	Paper
MMSE	Paper
MoCA	Paper
National Institutes of Health Toolbox	Paper
Neuropsychological Test Battery	Paper
Nishimura Mental State	Paper
NPI-NH	Paper
PAS	Paper
PBAC	Paper
RBANS	Paper
RUDAS	Paper
SIS	Paper
SLUMS	Paper
Social Cognition and Emotional Assessment	Paper
The Mini-Kingston Standardized Cognitive Assessment	Paper
Trail Making Test	Paper
Verbal Category Cued Memory Test	Paper
Verbal Fluency Test	Paper
Wechsler Adult Intelligence Scale	Paper

Test	Paper or computer or other
Cognistat	Paper/computer
MOST	Paper/computer
Rey-Osterrieth Figure Copy	Paper/computer
CUSPAD	Paper/other

3MS, Modified Mini-Mental State; 3TD, Treatment Target Test Dementia; 6CIT, Six-Item Cognitive Impairment Test; ADAS-COG, Alzheimer's Disease Assessment Scale; ANAM, Automated Neuropsychological Assessment Matrix; BDRS, Blessed Dementia Rated Scale; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; CADi2,Cognitive Assessment for Dementia, iPad Version; CAMCOG, Cambridge Cognitive Examination; CAMDEX, Cambridge Mental Disorders of the Elderly Examination; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CNTB, Computerized Neuropsychological Test Battery; COAD, Computerised Object and Abstract Designs; COGDRAS-D, Cognitive Drug Research Computerized Assessment System for Dementia Patients; CSI, Cognitive Stability Index; GPCOG, General Practitioner Assessment of Cognition; KICA-Cog, Kimberley Indigenous Cognitive Assessment; MCIS, Mild Cognitive Impairment Screen; MIS, Memory Impairment Screen; MoCA, Montreal Cognitive Assessment; MOST, Memory Orientation Screening Test; NPI-NH, Neuropsychiatric Inventory Nursing Home Version; PAS, Psychogeriatric Assessment Scale; PBAC, Philadelphia Brief Assessment of Cognition; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RUDAS, Rowland Universal Dementia Assessment Scale; SIS, Six-Item Screener; SLUMS, Saint Louis University Mental Status; TDAS, Touch Panel-type Dementia Assessment Scale.

Appendix 5 Patient and public involvement: structure of meeting

Brief chat, any difficulties with train trip, any questions he may have. Check for comfort with recording device, assure recording will be deleted. If not, use tablet for quick typing. He mentioned his caring responsibilities. Talk slowly, pay attention to ability to retain and analyse information. Simple language.

What is LRiG. Overview of the project. Brief discussion background MCI and dementia. Explain the review process very briefly.

Intro questions from protocol.

- Was the purpose of the review clear?
- Was the purpose of the review appropriate/valid/important?

Questions relating to technology.

Explain what computerised tests are briefly. Compare to tests used in his and/or carer's diagnosis.

(a) About the tests (show table on test, discuss table, clarify, make sure it is understood)

- Different types of tests (show table), some tests look at 1–2 aspects of memory and thinking, others look at all aspects of memory and thinking (cognitive domains).
- 2 tests look at the visual aspect (PAL), and make an assessment with a clinician present about existence of challenges with memory and thinking.
- Our findings say it works well. Does he have any thoughts about this?

(b) Platform used

- Internet-based test, iPad versus computer touchscreen versus desktop. Rating 1–4.
- Comfort in using platform (create flow from previous questions so would talk about use of technology in the elderly).

(c) Professionals involved

- Different papers used professionals differently.
- For test administration it was (1) self-administered with minimum assistance with nurse or technician; (2) self-administered with minimum assistance with nurse or technician, which also included them typing or using the mouse to manipulate the mouse or arrows for the patient or facilitate the typing and entering of patient responses; (3) verbal directions from administration; (4) interactive system provided oral instruction through speakers and written instructions on screen; (5) self-administration, but carer can assist needed them typing or using the mouse to manipulate the mouse or arrows for the patient or facilitate the typing and entering of patient responses.
- Rate tests from 1–5 with 1 being most preferable. Enter sixth option manually if a combination.
- Feedback on professionals conducting the test (who).
- What did he think of the level of involvement of the assessor in these scenarios in conducting the tests?
- What about monitoring?

(d) Patient characteristics

- Disease progression, do they go to the doctor
- Follow-up
- Study sample
- Where people were recruited from
- Only included patients (summary and variance of inclusion criteria)
- Summary of age, gender, education, ethnicity (race).

(e) Follow-up questions in the end

- Do we report on all of the important aspects of the research (show tables) (e.g. age of participants, practicality of computer tests for this age group)?
- Was the purpose of the review clear?
- Was the purpose of the review appropriate/valid/important?
- What do they see as the implications for clinical practice?
- What value do you see in the use of diagnostic tests for MCI?
- Do you feel that the inclusion of computerised tests is a good one?
- Should they be used instead of pen-and-paper tests?
- When do you think they should be used?
- What areas need further research?

Appendix 6 Organisations approached for service user involvement

- Liverpool Service User Reference Forum for Dementia.
- North West People in Research Forum.
- Salford Citizen Scientist – Francine Jury at People In Research Involve.
- Join Dementia Research – National Institute for Health Research.
- Dementias and Neurodegeneration National Institute for Health Research Clinical Research Network.
- National Institute for Health Research Clinical Research Network for Ageing.
- The Alzheimer's Society.

Using Twitter (Twitter Inc., San Francisco, CA, USA; www.twitter.com), we also sent out mass tweets to 72 other relevant organisations.

Appendix 7 Sample letter sent to organisations to invite service users

Advisory group members: computer based tests for mild cognitive impairment and dementia

By Aslam, 19 August 2015.

Do you want to get involved in research to find out whether computer-based tests for assessing a person's memory and thinking work?

The Liverpool Reviews and Implementation Group specialises in using a research method called a systematic review of the literature. This method provides an overview of the relevant research in the subject area.

The Liverpool Reviews and Implementation Group is currently working on a research project funded by the National Institute for Health Research. They are currently looking for people living with mild cognitive impairment (MCI) or early dementia as well as their carers who have an interest in assessment tools for thinking and memory.

As part of the research process, they would like to form an advisory group. The advisory group will have 2–3 service users or carers who have an interest in assessment tools for thinking and memory. The advisory group would be expected to attend two meetings between August 2015 and December 2015, and will need to be available for consultation via e-mail or face to face between meetings. They will pay a fee for consultation and travel expenses for all meetings. To apply, please complete the application form and return to the Liverpool Reviews and Implementation Group.

For more information contact:

Dr Rabeea'h Waseem Aslam, Liverpool Reviews and Implementation Group, University of Liverpool.

Telephone: XXX

E-mail: XXX

Deadline: 20 September 2015.

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