

Plasma and Cerebrospinal fluid (CSF) Abeta42 for the differential diagnosis of Alzheimer's disease dementia in participants diagnosed with any dementia subtype in a specialist care setting

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History

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Abstract

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Plain language summary

[Summary title]

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Background

Dementia is a syndrome of chronic and progressive cognitive impairment occurring in a setting of clear consciousness. It is due to underlying brain disease and impacts upon daily functioning to a significant degree. The ageing population will lead to an increased prevalence of neurodegenerative diseases presenting a huge socioeconomic burden with an annual estimated cost of currently over £17 billion in the UK.

Alzheimer's dementia is the most common dementia subtype, affecting 6% of individuals over the age of 65 and 20% over the age of 80 ([Knapp 2007](#)). In terms of prevalence, it is followed by vascular dementia, mixed Alzheimer's dementia/vascular dementia, dementia with Lewy bodies, alcohol-related dementia, frontotemporal dementia and then Huntington's disease ([Lopes 2010](#)). ↪ ↪

In this review, the target condition is the differential diagnosis of Alzheimer's disease dementia from other dementia subtypes.

Alzheimer's disease is thought to underlie Alzheimer's disease dementia which is a clinical syndrome manifest as progressive memory decline with impairment in at least one other domain of cognitive function which impacts on the person's function and behaviour. Other non-neurodegenerative causes for the clinical syndrome e.g. tumour or stroke need to be excluded before the diagnosis can be made. Alzheimer's pathology affects the limbic system (primarily the hippocampus) and other mesiotemporal structures. The pathology also extends to other regions of the neocortex including the frontal and parietal lobes generating executive dysfunction and problems with praxis respectively. Over a period of 5 to 20 years the patient will develop worsening functional impairment as a consequence of their cognitive symptoms. Other dementias have other clinical features, for instance dementia with Lewy bodies principally leads to impairment in attention with prominent, early neuropsychiatric symptoms, frontotemporal dementias tend to affect planning, judgement, personality and language early and vascular dementia tends to follow a step-wise deterioration that is unpredictable in both speed of progression and clinical features. Current diagnostic criteria for these conditions rely predominantly on the clinical phenotype as opposed to biomarker abnormalities.

Vascular dementia is caused by underlying cerebrovascular disease ([Burns 2005](#)), and the diagnosis for probable vascular dementia is based on the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria ([Roman 1993](#)), with 58% sensitivity and 80% specificity focusing on cerebrovascular disease consequences. These criteria are currently used for the differential diagnosis from Alzheimer's dementia in research settings.

Frontotemporal dementia, which is the second most common form of dementia in people below the age of 65 years, is a clinical syndrome associated with progressive change in personality, behaviour and language. Memory impairment is not a prominent feature but by late stage, multiple cognitive domains may be affected. ↪

In Parkinson's disease dementia and dementia with Lewy bodies, the characteristic pathology responsible for neurodegeneration in vulnerable neuronal populations is the presence of α -synuclein and ubiquitin aggregates within intraneuronal inclusion bodies known as Lewy bodies. These consist of a dense granular core surrounded by a halo of radiating filaments. According to Braak's and McKeith's staging/categorisation systems the pathology correlates with clinical symptoms such that brainstem pathology is responsible for the extrapyramidal side effects whereas dementia results from neocortical pathology, thus Parkinson's disease and dementia with Lewy bodies are likely to form a continuum ([Parkkinen 2008](#)).

Dementia originating primarily from chronic alcohol abuse or secondarily by alcohol-related syndromes such as Wernicke's encephalopathy is also a common form of dementia in older individuals ([Thomas 2001](#)). The similarities between Alzheimer's dementia and ethanol-related neurodegeneration in addition to the higher prevalence of Alzheimer's disease dementia in older patients and enhanced reluctance to admitting alcohol abuse increases the requirement for differential diagnosis between these dementia subtypes ([Kril 1999](#)). ↪ The clinical diagnosis of 'alcohol induced persisting dementia', [Kapaki 2005](#), is based on the criteria set out in the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

Sporadic Creutzfeldt Jacob disease and Alzheimer's disease share some clinical features as the former is characterised by promptly progressive dementia, implying the search for diagnostic tests for discrimination between the two disorders ([Otto 2000](#)). The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) clinical criteria such as clinical symptoms and characteristic electroencephalography (EEG) are used for diagnosis of Creutzfeldt Jacob disease including the presence of 14-3-3 protein in cerebrospinal fluid (CSF) ([Van Everbroeck 1999](#)).

In addition the discrimination of patients with dementia caused by normal pressure hydrocephalus from patients with Alzheimer's disease dementia or vascular dementia is important as dementia in normal pressure hydrocephalus is at the early stages considered surgically reversible ([Kapaki 2007](#)).

It can be seen therefore that dementia is a clinical syndrome that may have multiple aetiologies. Differentiating subtypes in clinical practice would, therefore, guide the clinician to optimal treatments as well as giving them the ability to convey prognosis and the risks to the off-spring of affected individuals. It is also the case that new treatments in development will be effective more specifically for dementia subtypes than is the case currently.

This review is concerned with the ability of the plasma and CSF amyloid beta protein 1-42 (Abeta42) tests in discriminating

between Alzheimer's disease dementia and other dementia subtypes in patients already diagnosed with a dementia syndrome. These tests are the index tests, and they are relevant as they may reflect the underlying pathology of Alzheimer's disease. In this disease, a critical part of the pathological cascade is the aggregation of soluble Abeta42 into insoluble oligomers and then plaques. As plaques sequester soluble Abeta42 into plaque, there is an observable decrease in levels of Abeta42 in both plasma and CSF. These reductions have been clearly associated with Alzheimer's disease dementia but it is not clear if these changes are specific to Alzheimer's disease dementia or are a marker of other dementias too.

We will be comparing the index test results with the results of the reference standard, which is the clinical diagnostic criterion for Alzheimer's disease dementia. The use of biomarkers to differentiate between Alzheimer's disease dementia and other sub-types may be advantageous if it can replace lengthy clinical examinations or other more expensive tests, e.g. neuroimaging.

Target condition being diagnosed

Target condition in this review is Alzheimer's disease dementia.

Index test(s)

Plasma and CSF Abeta42 levels

CSF serves as a good indicator of brain metabolism as it is in direct contact with the brain parenchyma ([Le Bastard 2009](#)). In Alzheimer's disease, Abeta aggregates to form plaques. These aggregates form from two species of Abeta being either 40 or 42 amino acids long. It is generally considered that Abeta42 is the more toxic species. This aggregation eventually culminating in the formation of plaque has the hypothesised effect of lowering CSF Abeta42 levels as there is the generation of a gradient between brain and ventriculo-subarachnoid space where Abeta passes to and from, respectively ([Shoji 2002](#)). This decrement in CSF Abeta relative to the increase in plaque formation is referred to as the amyloid sink hypothesis ([Fagan 2006](#)). There is less clarity with regards to the source of Abeta in plasma. Conflicting evidence suggests a decrease in plasma Abeta42 levels with an increase in Abeta40 levels, or a decrease in Abeta40 levels rather than Abeta42 levels for predicting Alzheimer's dementia ([Sundelöf 2008](#), [Van Oijen 2007](#)). It is thought that the majority of Abeta measurable in plasma is derived from platelets. However, the interaction between CSF/Plasma/Brain compartments for Abeta has not been clearly articulated.

Previous work suggested that the CSF Abeta42/40 ratio, as opposed to Abeta42 levels in isolation, can differentiate between Alzheimer's dementia and other types of dementia including vascular dementia and dementia with Lewy bodies ([Spies 2009](#)). Moreover, CSF Abeta42 levels in frontotemporal dementia patients have been shown to be significantly higher than levels in Alzheimer's dementia patients ([Riemenschneider 2002](#)). Moreover, Abeta42 deposition in the striatum of dementia with Lewy bodies and Parkinson's disease dementia patients has been recently demonstrated, possibly leading to alterations in CSF Abeta42 levels in these conditions too ([Mollenhauer 2006](#)). Decreases in CSF Abeta42 levels have also been shown in Creutzfeldt Jacob disease despite an absence of Abeta plaques; accordingly this alteration has been attributed to an alternative pathophysiological mechanism ([Otto 2000](#)). CSF Abeta42 levels have also been observed to be lowered in normal pressure hydrocephalus and alcohol related cognitive disorder patients ([Kapaki 2005](#)).

Clinical Pathway

Dementia develops over a trajectory of several years. There is a presumed period when people are asymptomatic, and when pathology is accumulating. Individuals or their relatives may then notice subtle impairments of recent memory. Gradually, more cognitive domains become observably affected, and difficulty planning complex tasks becomes increasingly apparent. In the UK, people usually present to their general practitioner, who may refer to a specialist memory clinic. Our clinical question relates to later stages in clinical pathway, when people are already diagnosed with dementia. Prior to biomarker testing, patients included in primary research would have undergone clinical assessment in order to be classified as Alzheimer's disease dementia positive or Alzheimer's disease dementia negative participants; the Alzheimer's disease dementia negative participants would have undergone further clinical assessment and would have been diagnosed with the other dementia subtype (see 'Appendix 4'). The importance of the plasma and CSF Abeta42 biomarkers would be to differentiate between the Alzheimer's disease dementia and other forms of dementia, with the aim to treat each dementia subtype differently if/when possible. If CSF samples were to be used, due to their invasive nature, this would be the reserve of the specialist clinic.

Alternative test(s)

We are not including alternative tests in this review because there are currently no standard practice tests available for the diagnosis of dementia. Although we are conducting reviews on individual tests compared to a reference standard, we plan to compare our results in an overview of reviews. The Cochrane Dementia and Cognitive Improvement Group is in a process of conducting a series of diagnostic test accuracy reviews of biomarkers and scales.

- Positron emission tomography F-2-fluoro-2-deoxy-D-glucose (¹⁸F-FDG-PET);
- Positron emission tomography Pittsburg Compound-C (¹¹C-PIB-PE);
- Structural magnetic resonance imaging (sMRI);
- Neuropsychological tests (e.g. Mini-mental state examination (MMSE); Mini-cognitive assessment (MiniCOG); Montreal Cognitive Assessment (MoCA))
- Informant interviews (e.g. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE); The Washington University Dementia Screening Test, "Eight-item Interview to Differentiate Aging and Dementia" (AD8))
- APOE e4 (Apolipoprotein E e4 variant)

- Fluoropropyl-Carbomethoxy-Iodophenil-Tropane Single-photon emission tomography (FP-CIT SPECT).

Rationale

The new diagnostic criteria for prodromal Alzheimer's dementia and Alzheimer's dementia incorporate and promote add-on biomarkers based on structural and functional imaging or CSF measures to improve diagnostic sensitivity and specificity ([Albert 2011](#); [Dubois 2010](#); [McKhann 2011](#)). These tests, added to core clinical criteria, might increase the sensitivity or specificity of a testing strategy. However, it is crucial that each of these biomarkers is assessed for their diagnostic accuracy before they are adopted as routine add-on tests in clinical practice.

The need for simple and accurate tests such as a blood test to accurately differentiate Alzheimer's disease dementia from other dementia subtypes may be effective and relatively easy in clinical practice. Moreover, it may enable the accurate identification of participants in clinical trials for testing the effectiveness of potential treatments specific for each dementia subtype.

However, the idea of this differentiation based on Abeta42 levels may not be relevant if it is shown that:

- CSF Abeta42 levels are affected in all subtypes since this would support the use of treatments, which alter Abeta42 levels in all subtypes; or
- patients are differentially diagnosed at a late disease stage reducing the possible therapeutic effectiveness of disease modifying drugs.

In view of this, the benefit of discriminating subtypes may be inversely proportional to the stage of illness. In early disease, discrimination may have major clinical benefit whereas in late stage disease, benefits of subtyping may be less relevant to the patients' management.

Objectives

To determine the diagnostic accuracy of the plasma and CSF Abeta42 index tests for distinguishing Alzheimer's disease dementia from each of the other forms of dementia in people who meet the general criteria for a dementia syndrome.

Secondary objectives

To investigate the heterogeneity of test accuracy in the included studies.

We expect that heterogeneity will be likely and that it will be an important component of the review. The potential sources of heterogeneity, which will be used as a framework for the investigation of heterogeneity, include target population, index test, target disorder and study quality and are detailed in the analysis section.

Methods

Criteria for considering studies for this review

Types of studies

We will consider cross-sectional studies in which the clinical diagnostic criteria and the plasma and CSF Abeta42 results were obtained within a narrow time-frame. Since the differentiation of Alzheimer's dementia patients from cognitively healthy controls is clinically irrelevant, studies that report Abeta42 levels between only these two groups as a diagnostic test will not be included as this would not be of particular clinical significance. Our study aims will only consider studies with a case control design in which Alzheimer's disease dementia patients were differentiated from patients with other dementia subtypes.

We will not consider longitudinal studies for inclusion. However, caution will be taken with the evaluation of inclusion of longitudinal studies since they may have taken data in a cross-sectional way enabling extraction, for instance in studies with a nested case-control design with delayed verification.

Participants

We will include all participants who have been recruited and clinically diagnosed with any form of dementia using the standard clinical diagnostic criteria ([Appendix 1](#)).

Diagnostic criteria used to establish the other dementia subtypes in those participants with non-Alzheimer's disease dementia are:

- for vascular dementia the NINDS ARIEN criteria ([Roman 1993](#)) or Alzheimer's Disease Diagnostic and Treatment Centers (ADDC) ([Chui 1992](#)) or DSM-III-R/-IV or ICD criteria;
- for frontotemporal dementia the Lund criteria ([The Lund Manchester Groups 1994](#)) or [Neary 1998](#) or [Boxer 2005](#) criteria;
- for dementia with Lewy bodies the reference standard is the McKeith criteria ([McKeith 1996](#) or [McKeith 2002](#) or [McKeith 2005](#));
- for dementia originating from chronic alcohol abuse the diagnostic criteria should follow DSM-III-R or -IV;
- for dementia in Creutzfeldt-Jakob disease, the ICD-10 clinical criteria and characteristic EEG should be used.

We will include all participants managed by specialist dementia teams whether outpatients, inpatients or in-residential care. Participants with mild cognitive impairment will not be eligible for this review.

Index tests

There are currently no generally accepted standard for plasma and CSF Abeta 42 tests positivity threshold, and therefore it is

not possible to pre-specify the positivity threshold for those biomarkers.

For criteria for plasma and CSF Abeta 42 tests positivity, we will classify participants assessed by the plasma or CSF ABeta42 biomarkers as either test positive (below study specific threshold on receiver operating characteristic (ROC) curve) or test negative (above study specific threshold on ROC curve) at baseline. We will use the criteria which were applied in each included primary study to make this distinction as it is likely that each study will have generated their own specific threshold for test positive/negative by examining their own data/ROC curves.

For measures of plasma and CSF Abeta42 level. we will consider double sandwich ELISA A β (1-42) Innogenetics kit or Athena Diagnostics, Worcester, Mass for CSF A β measurement or other assays to be found in the literature.

We will not include a comparator test because there are currently no standard practice tests available for the diagnosis of dementia. We will compare the diagnostic accuracy of the index tests with a reference standard in distinguishing Alzheimer's disease dementia from each of the other forms of dementia separately.

Target conditions

Target condition in this review is Alzheimer's disease dementia.

Reference standards

For the purpose of this review, several definitions of Alzheimer's disease dementia are acceptable, including DSM-III-R/IV and ICD-10 ([American Psychiatric Association 1987](#); [American Psychiatric Association 1994](#); [WHO 1993](#)) ([Appendix 1](#)). Included studies may apply probable or possible NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) criteria ([McKhann 1984](#)) as the most accepted ante-mortem clinical consensus gold standard.

Search methods for identification of studies

We will use a variety of information sources to ensure all relevant studies are included. The Cochrane Dementia and Cognitive Improvement Group will devise search strategies for electronic database searching.

Electronic searches

We will search MEDLINE (OvidSP), EMBASE (OvidSP), Science Citation Index (ISI Web of Knowledge), PsycINFO (Ovid), and LILACS (Bireme). We will adapt the search strategy for MEDLINE as illustrated in [Appendix 2](#) for use in other databases using search terms and syntax appropriate for each database. Initial searches will be performed by a single researcher with extensive experience of systematic review. We will request a search of the Cochrane Register of Diagnostic Test Accuracy Studies, which is maintained by the Cochrane Renal Group.

We will apply no language restrictions on the study reports and will request translation services for non-English articles where necessary.

Searching other resources

For grey literature we will assess conference proceedings in chosen electronic databases.

We will not perform handsearching as there is little published evidence of the benefits of hand searching for reports of diagnostic test accuracy studies ([Glanville 2012](#)).

We will also scan reference lists of all eligible studies and reviews in the field for further possible titles and repeat the process until no new titles are found ([Greenhalgh 2005](#)).

In addition, we will contact research groups who have published or are conducting work on Abeta42 tests for dementia diagnosis and inform them of the initial results of our literature search.

Data collection and analysis

Selection of studies

One review author (ANS) will screen all titles and abstracts generated by electronic database searches for relevance. The first assessment of the search results will be performed by the Cochrane Dementia and Cognitive Improvement Group. Four review authors (MK, RW, AH and MD) will then perform the second assessment of the titles and abstracts independently to identify potentially eligible studies. Two review authors (MK and NS) will further assess full manuscripts against the inclusion criteria. Where necessary, a third arbitrator (CR) will resolve disagreements that the two reviewers cannot resolve through discussion.

Where a study may include useable data but these are not presented in the published manuscript, we will contact the authors directly to request further information. If the same data set is presented in more than one paper we will include the primary paper, which is the paper with the largest number of patients or with the most informative data.

We will detail the numbers of studies selected at each point in a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram ([Moher 2009](#)).

Data extraction and management

We will extract the following data into a pre-standardised data extraction form.

- Bibliographic details of the primary paper:
 - Author, title, year of publication and journal.

- Basic clinical and demographic details:
 - number of subjects;
 - clinical diagnosis;
 - age;
 - gender;
 - ApoE status;
 - MMSE score;
 - setting;
 - participant recruitment;
 - sampling procedures.
- Details of index test:
 - thresholds used to define positive and negative tests;
 - assay type.
- Reference standard ([Table 1](#)):
 - definition of Alzheimer's disease dementia;
 - time between reference standards and index tests applied.
- Drop-outs:
 - missing data due to a number of participants who may be missing an index test or reference standard result, after their recruitment to the study.

Assessment of methodological quality

We will assess methodological quality of each study using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool as recommended by the Cochrane Collaboration ([Whiting 2011](#)). The tool is made up of four domains ([Appendix 3](#)):

1. patient selection;
2. index test;
3. reference standard;
4. patient flow.

Each domain is assessed in terms of risk of bias, with the first three domains also considered in terms of applicability. The components of each of these domains and a rubric which details how judgements concerning risk of bias are made are detailed in [Appendix 3](#). Certain key areas important to quality assessment are participant selection, blinding and missing data.

We will pilot a QUADAS-2 assessment on two papers. If agreement is poor, we will refine the signalling questions. QUADAS-2 data will not be used to form a summary quality score. We will produce a narrative summary describing numbers of studies that found high/low/unclear risk of bias as well as concerns regarding applicability.

Statistical analysis and data synthesis

We will apply the diagnostic test accuracy framework for the analysis of a single test and extract the data from each study into a 2x2 table, showing the binary test results cross-classified with the binary reference standard. We will enter data from the included studies (True positive, false negative, false positive, and true negative) into the Cochrane Collaboration's statistical software, [Review Manager 2013](#), to calculate sensitivity, specificity and their 95% confidence intervals. We will also present individual study results graphically by plotting estimates of sensitivity and specificity in both a forest plot and ROC space. If more than one threshold is published in primary studies we will explore accuracy estimates for all thresholds.

If there are sufficient data we will meta-analyse the pairs of sensitivity and specificity values. We will use the version of the bivariate model that models the within-study variability as binomial ([Macaskill 2010](#)). If studies report multiple thresholds the most frequently used cut-off, across all included studies, will be included in meta-analysis. We recognise the limitation of this data-driven approach ([Leeflang 2006](#)), but there are no standard thresholds used in practice. We will acknowledge and consider this further in the 'Discussion' section of our review. We might investigate how sensitive the findings are to the choice of threshold. Meta-analyses will be carried out using the Stata software command *metandi* under the frequentist framework ([Stata 2013](#)), and using the WinBUGS software to fit models under the Bayesian framework ([Lunn 2000](#)). The Stata software currently does not have commands for the hierarchical summary receiver-operator curves (HSROC) model so WinBUGS will be used for this purpose. We will provide details of the prior, likelihood and posterior distribution for analyses conducted using WinBUGS. We will report results from the HSROC framework. If pooled studies use a common threshold, we will also report pooled estimates of sensitivity and specificity from the bivariate model. If pooled studies do not share a common threshold, then to examine threshold effects we will investigate the summary receiver operating characteristic (sROC) curve for all studies across all thresholds and examine the results of the HSROC model, when fitted to studies across different thresholds.

We will examine model fit using the likelihood ratio test when using the frequentist framework and the deviance information criterion when using the Bayesian framework.

We will explore the implications of any credible summary accuracy estimates emerging by considering the numbers of false positive and false negatives in populations with different prevalence of dementia subtypes. In addition we will present the

results as natural frequencies and use alternative metrics such as likelihood ratios and predictive values.

Alternatively given the pre-test probabilities and likelihood ratios, the likelihood ratio nomogram can be employed to generate the post-test probabilities of disease ([Fagan 1975](#)).

Investigations of heterogeneity

We will include a number of factors in the framework for the investigation of possible sources of heterogeneity .

1. Index test

- Thresholds, if stated: if there is explicit variation in the index test cut-off used, the effect of this will be investigated as a priority
- Method used to measure Abeta42 levels may differ between or even within laboratories: double sandwich ELISA A β (1-42) Innogenetics kit vs. Athena Diagnostics, Worcester vs other assays found in the literature

2. Target disorder

- Reference standards used: e.g. NINCDS-ADRDA vs. DSM vs. ICD10 for Alzheimer's disease dementia.
- Operationalisation of criteria used for the definition of a dementia syndrome: e.g. individual clinician / algorithm / consensus group.

3. Target population

- Spectrum of patients: age, gender, education, sampling strategy, MMSE score and APOE status of study participants. Concerning age, any studies that include 30% patients below the age of 65 will be examined separate
- Clinical settings within secondary care: outpatients vs inpatients vs residential care

4. Study quality (QUADAS-2)

- Blinding: prior clinical information will increase accuracy of the index test
- Time between administering index test(s) and reference standard(s)
- Amount of loss to drop-outs (a number of participants who may be missing an index test or reference standard result, after their recruitment to the study): we will consider separately those studies that have more than 20% drop-outs

All of the above factors are important as they relate to the interpretation of the test result. In clinical practice the most relevant sources of heterogeneity are considered to be:

- patient factors such as age, genetic risk and different clinical criteria used to define clinical population; and
- differences in test threshold and differing assay methods for plasma and CSF Abeta analysis.

To investigate the effects of the sources of heterogeneity, we will perform a descriptive analysis by visual examination of the forest plot of sensitivity and specificity and the ROC plot in [Review Manager 2013](#).

If there are sufficient studies we will use meta-regression ((bivariate or HSROC models ([Macaskill 2010](#))) as appropriate)) to investigate heterogeneity. We will carry out these analyses using Stata or WinBUGS software. We will then enter the parameter estimates into RevMan which will be used to draw the summary ROC plot including: summary ROC curves, summary points and confidence regions and prediction regions, as appropriate.

If appropriate, we might consider investigating differences in diagnostic accuracy across subgroups. We acknowledge that the sub-group analyses are purely exploratory and will be reported with the level of caution that is appropriate for such investigations.

Sensitivity analyses

If not already explored as part of the investigation of heterogeneity above, we will perform a sensitivity analysis on other aspects of study quality.

In addition, we will evaluate the effects of data-driven threshold selection studies on overall diagnostic accuracy of the plasma and CSF Abeta42 tests by excluding them.

Assessment of reporting bias

We will not investigate reporting bias because of current uncertainty about how it operates in test accuracy studies and the interpretation of existing analytical tools such as funnel plots.

Results

Results of the search

Methodological quality of included studies

Findings

Discussion

Summary of main results

Strengths and weaknesses of the review

Applicability of findings to the review question

Authors' conclusions

Implications for practice

Implications for research

Acknowledgements

Contributions of authors

All authors contributed to the drafting of the protocol.

Declarations of interest

None known.

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of results tables

Additional tables

1 A series of two by two tables constructed by the first column and each of the subsequent columns, cross-relating index test results (rows) with the reference standards (columns)

	Reference standard (diagnostic criteria for Alzheimer's disease dementia) information							
	ADD present	FTD (ADD absent)	VD (ADD absent)	DLB (ADD absent)	PDD (ADD absent)	CJD (ADD absent)	DARCD (ADD absent)	NPH (ADD absent)
Index test positive	TP	FP	FP	FP	FP	FP	FP	FP
Index test negative	FN	TN	TN	TN	TN	TN	TN	TN

Footnotes

ADD = Alzheimer's disease dementia; FTD = Frontotemporal dementia; DLB=Dementia with Lewy bodies; PDD= Parkinson's disease dementia; CJD = Creutzfeldt Jacob disease; DARCD = Dementia alcohol related cognitive decline; NPH=Normal pressure hydrocephalus; TP= true positive; FP=false positive; TN= true negative; FN=false negative

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Included studies

Excluded studies

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Classification pending references

Data and analyses

Data tables by test

Test Studies Participants

Figures

Sources of support

Internal sources

- None, Not specified

External sources

- None, Not specified

Feedback

Appendices

1 Diagnostic criteria

Table 1: Reference standards for Alzheimer's disease dementia

NINCDS-ADRDA[\(McKhann 1984\)](#)**I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:**

- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests:
 - deficits in two or more areas of cognition:
 - progressive worsening of memory and other cognitive functions;
 - no disturbance of consciousness;
 - onset between ages 40 and 90, most often after age 65;
 - absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically;
- laboratory results of:
 - normal lumbar puncture as evaluated by standard techniques;
 - normal pattern or nonspecific changes in EEG. such as increased slow-wave activity;
 - evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease;
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness;
- seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia;
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

- the clinical criteria for probable Alzheimer's disease;
- histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- familial occurrence;
- onset before age of 65;
- presence of trisomy-21;
- coexistence of other relevant conditions such as Parkinson's disease.

<p>DSM-IV (American Psychiatric Association 1994);</p> <p>DSM-IV-TR (American Psychiatric Association 2000)</p>	<p>Diagnostic and Statistical Manual of Mental Disorders (DSM)IV-TR,</p> <p>A. The Development of multiple cognitive deficits manifested by both:</p> <ul style="list-style-type: none"> • memory impairment (impaired ability to learn new information or to recall previously learned information); and • one (or more) of the following cognitive disturbances: <ul style="list-style-type: none"> ◦ (aphasia (language disturbance); ◦ apraxia (impaired ability to carry out motor activities despite intact motor function); ◦ agnosia (failure to recognize or identify objects despite intact sensory function); ◦ disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting). <p>B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.</p> <p>C. The course is characterized by gradual onset and continuing cognitive decline.</p> <p>D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:</p> <ul style="list-style-type: none"> • other central nervous system conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumour); • systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin B₁₂ or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection); • substance-induced conditions. <p>E. The deficits do not occur exclusively during the course of a delirium.</p> <p>F. The disturbance is not better accounted for by another Axis I disorder (e.g. major depressive disorder, schizophrenia).</p> <p>Diagnostic Criteria for 294.1x Dementia of the Alzheimer's Type</p> <p>294.11 Without Behavioral Disturbance: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g. wandering, agitation).</p> <p><i>Specify</i> subtype:</p> <p>With Early Onset: if onset is at age 65 years or below</p> <p>With Late Onset: if onset is after 65 years</p>
<p>ICD-10 (WHO 1993)</p>	<p>Diagnostic guidelines</p> <p>The primary requirement for diagnosis is evidence of a decline in both memory and thinking which is sufficient to impair personal activities of daily living, as described above. The impairment of memory typically affects the registration, storage, and retrieval of new information, but previously learned and familiar material may also be lost, particularly in the later stages. Dementia is more than dysmnnesia: there is also impairment of thinking and of reasoning capacity, and a reduction in the flow of ideas. The processing of incoming information is impaired, in that the individual finds it increasingly difficult to attend to more than one stimulus at a time, such as taking part in a conversation with several persons, and to shift the focus of attention from one topic to another. If dementia is the sole diagnosis, evidence of clear consciousness is required. However, a double diagnosis of delirium superimposed upon dementia is common (F05.1). The above symptoms and impairments should have been evident <i>for at least 6 months</i> for a confident clinical diagnosis of dementia to be made.</p> <p>Differential diagnosis</p> <p>Consider: a depressive disorder (F30-F39), which may exhibit many of the features of an early dementia, especially memory impairment, slowed thinking, and lack of spontaneity; delirium (F05); mild or moderate mental retardation (F70-F71); states of subnormal cognitive functioning attributable to a severely impoverished social environment and limited education; iatrogenic mental disorders due to medication (F06.-). Dementia may <i>follow</i> any other organic mental disorder classified in this block, or <i>coexist</i> with some of them, notably delirium (see F05.1).</p> <p>F00 Dementia in Alzheimer's disease</p> <p>Alzheimer's disease is a primary degenerative cerebral disease of unknown etiology, with characteristic neuropathological and neurochemical features. It is usually insidious in onset and develops slowly but steadily over a period of years. This period can be as short as 2 or 3 years, but can occasionally be considerably longer. The onset can be in middle adult life or even earlier (Alzheimer's disease with early onset), but the incidence is higher in later life (Alzheimer's disease with late onset). In cases with onset before the age of 65-70, there is the likelihood of a family history of a similar dementia, a more rapid course, and prominence of features of temporal and parietal lobe damage, including dysphasia or dyspraxia. In cases with a later onset,</p>

the course tends to be slower and to be characterized by more general impairment of higher cortical functions. Patients with Down's syndrome are at high risk of developing Alzheimer's disease.

There are characteristic changes in the brain: a marked reduction in the population of neurons, particularly in the hippocampus, substantia innominata, locus ceruleus, and temporoparietal and frontal cortex; appearance of neurofibrillary tangles made of paired helical filaments; neuritic (argentophil) plaques, which consist largely of amyloid and show a definite progression in their development (although plaques without amyloid are also known to exist); and granulovacuolar bodies. Neurochemical changes have also been found, including a marked reduction in the enzyme choline acetyltransferase, in acetylcholine itself, and in other neurotransmitters and neuromodulators.

As originally described, the clinical features are accompanied by the above brain changes. However, it now appears that the two do not always progress in parallel: one may be indisputably present with only minimal evidence of the other. Nevertheless, the clinical features of Alzheimer's disease are such that it is often possible to make a presumptive diagnosis on clinical grounds alone.

Dementia in Alzheimer's disease is at present irreversible.

Diagnostic guidelines

The following features are essential for a definite diagnosis:

(a) Presence of a dementia as described above.

(b) Insidious onset with slow deterioration. While the onset usually seems difficult to pinpoint in time, realization by others that the defects exist may come suddenly. An apparent plateau may occur in the progression.

(c) Absence of clinical evidence, or findings from special investigations, to suggest that the mental state may be due to other systemic or brain disease which can induce a dementia (e.g. hypothyroidism, hypercalcaemia, vitamin B12 deficiency, niacin deficiency, neurosyphilis, normal pressure hydrocephalus, or subdural haematoma).

(d) Absence of a sudden, apoplectic onset, or of neurological signs of focal damage such as hemiparesis, sensory loss, visual field defects, and incoordination occurring early in the illness (although these phenomena may be superimposed later).

In a certain proportion of cases, the features of Alzheimer's disease and vascular dementia may both be present. In such cases, double diagnosis (and coding) should be made. When the vascular dementia precedes the Alzheimer's disease, it may be impossible to diagnose the latter on clinical grounds.

Includes: primary degenerative dementia of the Alzheimer's type

Differential diagnosis.

Consider: a depressive disorder (F30-F39); delirium (F05.-); organic amnesic syndrome (F04); other primary dementias, such as in Pick's, Creutzfeldt-Jakob or Huntington's disease (F02.-); secondary dementias associated with a variety of physical diseases, toxic states, etc. (F02.8); mild, moderate or severe mental retardation (F70-F72).

Dementia in Alzheimer's disease may coexist with vascular dementia (to be coded F00.2), as when cerebrovascular episodes (multi-infarct phenomena) are

superimposed on a clinical picture and history suggesting Alzheimer's disease. Such episodes may result in sudden exacerbations of the manifestations of dementia. According to postmortem findings, both types may coexist in as many as 10-15% of all dementia cases.

F00.0 Dementia in Alzheimer's disease with early onset

Dementia in Alzheimer's disease beginning before the age of 65. There is relatively rapid deterioration, with marked multiple disorders of the higher cortical functions. Aphasia, agraphia, alexia, and apraxia occur relatively early in the course of the dementia in most cases.

Diagnostic guidelines

As for dementia, described above, with onset before the age of 65 years, and usually with rapid progression of symptoms. Family history of Alzheimer's disease is a contributory but not necessary factor for the diagnosis, as is a family history of Down's syndrome or of lymphoma.

Includes: Alzheimer's disease, type 2 presenile dementia, Alzheimer's type

F00.1 Dementia in Alzheimer's disease with late onset

Dementia in Alzheimer's disease where the clinically observable onset is after the age of 65 years and usually in the late 70s or thereafter, with a slow progression, and usually with memory impairment as the principal feature.

Diagnostic guidelines

As for dementia, described above, with attention to the presence or absence of features differentiating the

disorder from the early-onset subtype (F00.0).

Includes: Alzheimer's disease, type 1 senile dementia, Alzheimer's type

F00.2 Dementia in Alzheimer's disease, atypical or mixed type

Dementias that do not fit the descriptions and guidelines for either F00.0 or F00.1 should be classified here; mixed Alzheimer's and vascular dementias are also included here.

Table 2: Diagnostic criteria for vascular dementia

**NINDS –
AIREN**[\(Wetterling
1996\)](#)**I. The criteria for the clinical diagnosis of probable vascular dementia include all of the following:**

1. Dementia defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferable established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.

Exclusion criteria: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.

2. Cerebrovascular disease, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of nof relevant CVD by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof.

3. A relationship between the above two disorders, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features consistent with the diagnosis of probable vascular dementia include the following:

(a) Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait);

(b) history of unsteadiness and frequent, unprovoked falls;

(c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease;

(d) pseudobulbar palsy; and

(e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include

(a) early onset of of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging;

(b) absence of focal neurological signs, other than cognitive disturbance; and

(c) absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of possible vascular dementia may be made:

· in the presence of dementia (section I-1) with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or

· in the absence of clear temporal relationship between dementia and stroke;

· or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of definite vascular dementia are

(a) clinical criteria for probable vascular dementia;

(b) histopathologic evidence of CVD obtained from biopsy or autopsy;

(c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and

(d) absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, BD, and thalamic dementia.

The term "AD with CVD" should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD. Traditionally, these patients have been included with VaD in epidemiologic studies. The term "mixed dementia," used hitherto, should be avoided.

<p>NINDS – AIREN (Roman 1993)</p>	<p>Diagnosis of Probable VD</p> <ol style="list-style-type: none"> 1. Dementia Impairment of memory / Impairment of memory and ≥ 2 cognitive domains / Orientation / Attention / Language / Visuospatial functions / Executive functions, motor control, and praxis / Dementia according to NINDS-AIREN criteria 2. Cerebrovascular disease Focal signs on neurological examination (hemiparesis, lower facial weakness, Babinski's sign, sensory deficit, hemianopia, and dysarthria) / Evidence of relevant cerebrovascular disease by brain imaging (CT) / Large-vessel infarcts / Single strategically placed infarct / Multiple basal ganglia and white matter lacunes / Extensive periventricular white matter lesions / Combinations thereof 3. A relationship between the above disorders manifested or inferred by the presence of ≥ 1 of the following / Onset of dementia within 3 mo after a recognized stroke / Abrupt deterioration in cognitive functions / Fluctuating, stepwise progression of cognitive deficits 4. Clinical features consistent with the diagnosis of probable VD Early presence of a gait disturbance / History of unsteadiness or frequent, unprovoked falls / Early urinary incontinence / Pseudobulbar palsy / Personality and mood changes 5. Features that make the diagnosis of VD uncertain Early onset of memory deficit and progressive worsening of memory and other cognitive functions in the absence of focal neurological signs and cerebrovascular lesions on CT or MRI
<p>DSM-IV-TR (American Psychiatric Association 2000)</p>	<p>Diagnosis of vascular dementia</p> <p>A. The development of multiple cognitive deficits manifested by both:</p> <ol style="list-style-type: none"> 1. Memory impairment (impaired ability to learn new information or to recall previously learned information) 2. One or more of the following cognitive disturbances: <ol style="list-style-type: none"> (a) aphasia (language disturbance) (b) apraxia (impaired ability to carry out motor activities despite intact motor function) (c) agnosia (failure to recognize or identify objects despite intact sensory function) (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting) <p>B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.</p> <p>C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.</p> <p>D. The deficits do not occur exclusively during the course of a delirium.</p>

<p>ICD10 Criteria (WHO 1993)</p>	<p>F01 Vascular dementia</p> <p>Vascular (formerly arteriosclerotic) dementia, which includes multi-infarct dementia, is distinguished from dementia in Alzheimer's disease by its history of onset, clinical features, and subsequent course. Typically, there is a history of transient ischaemic attacks with brief impairment of consciousness, fleeting pareses, or visual loss. The dementia may also follow a succession of acute cerebrovascular accidents or, less commonly, a single major stroke. Some impairment of memory and thinking then becomes apparent. Onset, which is usually in later life, can be abrupt, following one particular ischaemic episode, or there may be more gradual emergence. The dementia is usually the result of infarction of the brain due to vascular diseases, including hypertensive cerebrovascular disease. The infarcts are usually small but cumulative in their effect.</p> <p><i>Diagnostic guidelines</i></p> <p>The diagnosis presupposes the presence of a dementia as described above.</p> <p>Impairment of cognitive function is commonly uneven, so that there may be memory loss, intellectual impairment, and focal neurological signs. Insight and judgement may be relatively well preserved. An abrupt onset or a stepwise deterioration, as well as the presence of focal neurological signs and symptoms, increases the probability of the diagnosis; in some cases, confirmation can be provided only by computerized axial tomography or, ultimately, neuropathological examination. Associated features are: hypertension, carotid bruit, emotional lability with transient depressive mood, weeping or explosive laughter, and transient episodes of clouded consciousness or delirium, often provoked by further infarction. Personality is believed to be relatively well preserved, but personality changes may be evident in a proportion of cases with apathy, disinhibition, or accentuation of previous traits such as egocentricity, paranoid attitudes, or irritability.</p> <p><i>Includes:</i> arteriosclerotic dementia</p> <p><i>Differential diagnosis.</i></p> <p>Consider: delirium (F05.-); other dementia, particularly in Alzheimer's disease (F00.-); mood [affective] disorders (F30-F39); mild or moderate mental retardation (F70-F71); subdural haemorrhage (traumatic (S06.5), nontraumatic (162.0)).</p> <p>Vascular dementia may coexist with dementia in Alzheimer's disease (to be coded F00.2), as when evidence of a vascular episode is superimposed on a clinical picture and history suggesting Alzheimer's disease.</p> <p>A. Evidence of each of the following</p> <ol style="list-style-type: none"> 1. Decline in memory (mainly short-term memory) 2. Decline in other cognitive abilities <p>Deficits in criterion A cause a significant impairment of social functioning</p> <p>B. Absence or clouding of consciousness</p> <p>C. Decline in emotional control or motivation or a change in social behaviour</p> <p>D. Symptoms in criterion A have been present ≥ 6 months</p> <p>Dementia according to DCR-10 criteria</p> <p>Unequal distribution of deficits in higher cognitive functions</p> <p>Evidence of focal brain damage</p> <p>Evidence of cerebrovascular disease</p>
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<p>ADDC Criteria (Chui 1992)</p>	<p>Diagnosis of Probable Ischemic VD</p> <ol style="list-style-type: none"> 1. Dementia (as defined in the text) 2. History, neurological signs, and/or Neuroimaging studies (CT or T₁-weighted MRI), or Occurrence of a single stroke with a clearly documented temporal relationship to the onset of dementia 3. Evidence of ≥1 infarct outside the cerebellum by CT or T₁-weighted MRI <p>B. Diagnosis of probable IVD is supported by</p> <ol style="list-style-type: none"> 1. Evidence of multiple infarcts in brain regions known to affect cognition (as defined by NINDS-AIREN criteria) 2. History of multiple transient ischemic attacks 3. History of vascular risk factors (eg, hypertension, heart disease, diabetes mellitus) 4. Elevated Hachinski Ischemia Scale score (≥7) <p>C. Clinical features that are thought to be associated with ischemic VD but await further research</p> <ol style="list-style-type: none"> 1. Relatively early appearance of gait disturbance and urinary incontinence 2. Periventricular and deep white matter changes on T₂-weighted MRI that are excessive for age² 3. Focal changes in electroencephalographic studies³ <p>D. Other clinical features that do not constitute strong evidence either for or against a diagnosis of probable ischemic VD</p> <ol style="list-style-type: none"> 1. Periods of slowly progressive symptoms 2. Illusions, psychoses, hallucinations, delusions 3. Seizures <p>E. Clinical features that cast doubt on a diagnosis of probable ischemic VD</p> <ol style="list-style-type: none"> 1. Transcortical sensory aphasia in the absence of corresponding focal lesions on neuroimaging studies 2. Absence of central neurological symptoms/signs other than cognitive disturbance
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Table 3: Diagnostic criteria for Frontotemporal Dementia

<p>Lund criteria (The Lund Manchester Groups 1994)</p>	<p>CORE DIAGNOSTIC FEATURES</p> <p>Behavioural disorder</p> <ul style="list-style-type: none"> * Insidious onset and slow progression * Early loss of personal awareness (neglect of personal hygiene and grooming) * Early loss of social awareness (lack of social tact, misdemeanours such as shoplifting) * Early signs of disinhibition (such as unrestrained sexuality, violent behaviour, inappropriate jocularity, restless pacing) * Mental rigidity and inflexibility * Hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and alcohol consumption, oral exploration of objects) * Stereotyped and perservative behaviour (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation)
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such as hoarding, toileting, and dressing)

* Utilisation behaviour (unrestrained exploration of objects in the environment)

* Distractibility, impulsivity, and impersistence

* Early loss of insight into the fact that the altered condition is due to a pathological change of own mental state.

Affective symptoms

* Depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion (early and evanescent)

* Hypochondriasis, bizarre somatic preoccupation (early and evanescent)

* Emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy)

* Amimia (inertia, aspontaneity).

Speech disorder

* Progressive reduction of speech (aspontaneity and economy of utterance)

- Stereotypy of speech (repetition of limited repertoire of words, phrases, or themes)

* Echolalia and perseveration

* Late mutism.

Spatial orientation and praxis preserved

(intact abilities to negotiate the environment).

Physical signs

* Early primitive reflexes

* Early incontinence

* Late akinesia, rigidity, tremor

* Low and labile blood pressure.

Investigations

* Normal EEG despite clinically evident dementia

* Brain imaging (structural or functional, or both): predominant frontal or anterior temporal abnormality, or both

* Neuropsychology (profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder).

SUPPORTIVE DIAGNOSTIC FEATURES

* Onset before 65

* Positive family history of similar disorder in a first degree relative

* Bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease).

DIAGNOSTIC EXCLUSION FEATURES

- * Abrupt onset with ictal events
- * Head trauma related to onset
- * Early severe amnesia
- * Early spatial disorientation, lost in surroundings, defective localisation of objects
- * Early severe apraxia
- * Logoclonic speech with rapid loss of train of thought
- * Myoclonus
- * Cortical bulbar and spinal deficits
- * Cerebellar ataxia
- * Chorea-athetosis
- * Early, severe, pathological EEG
- * Brain imaging (predominant post-central structural or functional deficit. Multifocal cerebral lesions on CT or MRI)
- 0 Laboratory tests indicating brain involvement or inflammatory disorder (such as multiple sclerosis, syphilis, AIDS and herpes simplex encephalitis).

RELATIVE DIAGNOSTIC EXCLUSION FEATURES

- * Typical history of chronic alcoholism
- * Sustained hypertension
- * History of vascular disease (such as angina, claudication).

<p>Neary criteria (Neary 1998)</p>	<p>Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved.</p> <ol style="list-style-type: none"> 1. Core diagnostic features 2. Insidious onset and gradual progression 3. Early decline in social interpersonal conduct 4. Early impairment in regulation of personal conduct 5. Early emotional blunting 6. Early loss of insight 7. Supportive diagnostic features 8. Behavioral disorder <ul style="list-style-type: none"> • Decline in personal hygiene and grooming • Mental rigidity and inflexibility • Distractibility and impersistence • Hyperorality and dietary changes • Perseverative and stereotyped behavior • Utilization behavior 9. Speech and language <ul style="list-style-type: none"> • Altered speech output <ul style="list-style-type: none"> ◦ Spontaneity and economy of speech ◦ Press of speech • 2. Stereotype of speech • 3. Echolalia • 4. Perseveration • 5. Mutism 10. Physical signs <ul style="list-style-type: none"> • Primitive reflexes • Incontinence • Akinesia, rigidity, and tremor • Low and labile blood pressure 11. Investigations <ul style="list-style-type: none"> • Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder • Electroencephalography: normal on conventional EEG despite clinically evident dementia • Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality
<p>Boxer criteria (Boxer 2005)</p>	<p>The three clinical subtypes of FTD underlined in the clinical diagnostic criteria (Neary 1998) are described.</p>

Table 4: Diagnostic criteria for Lewy Body Dementia

<p>McKeith criteria (McKeith 2002)</p>	<p>Consensus criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies</p> <p>a. The central feature required for a diagnosis of dementia with Lewy bodies (DLB) is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.</p> <p>b. Two of the following core features are essential for a diagnosis of probable DLB, one is essential for possible DLB.</p> <p>i. Fluctuating cognition with pronounced variations in attention and alertness.</p> <p>ii. Recurrent visual hallucinations which are typically well formed and detailed.</p> <p>iii. Spontaneous motor features of parkinsonism.</p> <p>c. Features supportive of the diagnosis are:</p> <p>i. Repeated falls</p> <p>ii. Syncope</p> <p>iii. Transient loss of consciousness</p> <p>iv. Neuroleptic sensitivity</p> <p>v. Systematised delusions</p> <p>vi. Hallucinations in other modalities.</p> <p>d. A diagnosis of DLB is less likely in the presence of:</p> <p>i. Stroke disease, evident as focal neurological signs or on brain imaging.</p> <p>ii. Evidence on physical examination and investigation of any physical illness, or other brain disorder, sufficient to account for the clinical picture.</p>
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Table 5: Diagnostic criteria for alcohol abuse and dependence

<p>DSM-IV-TR (American Psychiatric Association 2000)</p> <p>DSM-IV (American Psychiatric Association 1994)</p>	<p>Alcohol abuse</p> <p>(A) A maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by at least one of the following occurring within a 12-month period.</p> <ul style="list-style-type: none"> • Recurrent use of alcohol resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household). • Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by alcohol use). • Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct). • Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication). <p>(B) Never met criteria for alcohol dependence.</p> <p>Alcohol dependence</p> <p>(A) A maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by three or more of the following occurring at any time in the same 12-month period.</p> <ul style="list-style-type: none"> • Need for markedly increased amounts of alcohol to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of alcohol. • The characteristic withdrawal syndrome for alcohol; or drinking (or using a closely related substance) to relieve or avoid withdrawal symptoms • Drinking in larger amounts or over a longer period than intended. • Persistent desire or one or more unsuccessful efforts to cut down or control drinking. • Important social, occupational, or recreational activities given up or reduced because of drinking. • A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of drinking. • Continued drinking despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by drinking. <p>(B) No duration criterion separately specified, but several dependence criteria must occur repeatedly as specified by duration qualifiers associated with criteria (e.g. "persistent", "continued").</p>
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Table 6: Diagnostic criteria for Creutzfeldt-Jakob disease

<p>ICD-10 (WHO 1993)</p>	<p>F02.1 Dementia in Creutzfeldt-Jakob disease</p> <p>A progressive dementia with extensive neurological signs, due to specific neuropathological changes (subacute spongiform encephalopathy) that are presumed to be caused by a transmissible agent. Onset is usually in middle or later life, typically in the fifth decade, but may be at any adult age. The course is subacute, leading to death within 1-2 years.</p> <p>Diagnostic guidelines</p> <p>Creutzfeldt-Jakob disease should be suspected in all cases of a dementia that progresses fairly rapidly over months to 1 or 2 years and that is accompanied or followed by multiple neurological symptoms. In some cases, such as the so-called amyotrophic form, the neurological signs may precede the onset of the dementia.</p> <p>There is usually a progressive spastic paralysis of the limbs, accompanied by extrapyramidal signs with tremor, rigidity, and choreoathetoid movements. Other variants may include ataxia, visual failure, or muscle fibrillation and atrophy of the upper motor neuron type. The triad consisting of</p> <ul style="list-style-type: none"> - rapidly progressing, devastating dementia, - pyramidal and extrapyramidal disease with myoclonus, and - a characteristic (triphasic) electroencephalogram is thought to be highly suggestive of this disease. <p>Differential diagnosis</p> <p>Consider: Alzheimer's disease (F00.-) or Pick's disease (F02.0); Parkinson's disease (F02.3); postencephalitic parkinsonism (G21.3).</p> <p>The rapid course and early motor involvement should suggest Creutzfeldt-Jakob disease.</p>
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<p>Creutzfeldt-Jakob disease, 2010 (WHO 1998; Zerr 2009)</p>	<p>1. Sporadic Creutzfeldt-Jakob disease</p> <p>Definite: Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and /or presence of scrapie-associated fibrils.</p> <p>Probable: Rapidly progressive dementia; <u>and</u> at least two out of the following four clinical features:</p> <ul style="list-style-type: none"> i. Myoclonus ii. Visual or cerebellar signs iii. Pyramidal/extrapyramidal signs iv. Akinetic mutism <p><u>AND</u> a positive result on at least one of the following laboratory tests:</p> <ul style="list-style-type: none"> a. a typical EEG (periodic sharp wave complexes) during an illness of any duration; and/or b. a positive 14-3-3 cerebrospinal fluid (CSF) assay in patients with a disease duration of less than 2 years c. Magnetic resonance imaging (MRI) high signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) <p><u>AND</u> without routine investigations indicating an alternative diagnosis.</p> <p>Possible: Progressive dementia; <u>and</u> at least two out of the following four clinical features:</p> <ul style="list-style-type: none"> i. Myoclonus ii. Visual or cerebellar signs iii. Pyramidal/extrapyramidal signs iv. Akinetic mutism <p><u>AND</u> the absence of a positive result for any of the three laboratory tests that would classify a case as "probable" (see tests a-c above) <u>AND</u> duration of illness less than two years <u>AND</u> without routine investigations indicating an alternative diagnosis.</p> <p>2. Iatrogenic Creutzfeldt-Jakob disease</p> <p>Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; <u>or</u> sporadic Creutzfeldt-Jakob disease with a recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation.</p> <p>3. Familial Creutzfeldt-Jakob disease</p> <p>Definite or probable Creutzfeldt-Jakob disease <u>plus</u> definite or probable Creutzfeldt-Jakob disease in a first degree relative; and/or Neuropsychiatric disorder <u>plus</u> disease-specific PrP gene mutation.</p>
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2 MEDLINE search strategy

1. exp Dementia/
2. Cognition Disorders/
3. exp Neurofibrils/
4. Neurofilament Proteins/
5. Senile Plaques/
6. Neuropil Threads/
7. (alzheimer\$ or dement\$).ti,ab.
8. (neurofibril\$ adj3 tangle\$).ti,ab.
9. (neurofilament adj3 protein\$).ti,ab.
10. ((senile or amyloid or neuritic) adj3 plaque\$).ti,ab.
11. (neuropil adj3 thread\$).ti,ab.
12. or/1-11
13. exp Amyloid Beta-Protein/

14. Peptide Fragments/
15. ABPP.ti,ab.
16. APP.ti,ab.
17. beta?A4.ti,ab.
18. (beta adj3 A4).ti,ab.
19. Abeta\$.ti,ab.
20. amyloid.ti,ab.
21. (amyloidogenic adj3 (peptide\$ or protein\$)).ti,ab.
22. (Innotest or Inno-bia or Alzbio3).ti,ab.
23. or/13-22
24. 12 and 23
25. (cerebrospinal fluid\$ or csf or spinal fluid\$).ti,ab.
26. (blood or plasma).ti,ab.
27. Cerebrospinal Fluid/
28. Blood-Brain Barrier/
29. or/25-28
30. (cf or bl or di or du).fs.
31. 29 or 30
32. 24 and 31
- 33 Cerebrospinal Fluid Proteins/
- 34 Biological Markers/cf, bl [Cerebrospinal Fluid, Blood]
- 35 33 or 34
- 36 1 and 35
- 37 32 or 36
- 38 exp Animals/ not Humans.sh.
- 39 37 not 38

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3 The QUADAS-2 tool

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/ unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/ unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

4 Anchoring statement for quality assessment of plasma and CSF Abeta42 diagnostic study

Table 1: Review question and inclusion criteria

Category	Review Question	Inclusion Criteria
Patients	Participants diagnosed with any dementia subtypes	Participants fulfilling the criteria for the clinical diagnosis of any forms of dementia in secondary care setting
Index Test	Plasma and CSF Abeta42 tests	Plasma and CSF Abeta42 tests
Target Condition	Alzheimer's disease dementia ↯	Differential diagnosis of Alzheimer's disease dementia from other dementia subtypes ↯
Reference Standard	NINCDS-ADRDA (McKhann 1984);↯ Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC), International Classification of Diseases (ICD10) and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSMIV) definitions of Alzheimer's disease dementia ↯	NINCDS-ADRDA (McKhann 1984);↯ CERAD, ADDTC, ICD10 and DSMIV definitions of Alzheimer's disease dementia National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), ADDTC, DSMIV, ICD10, Cambridge Mental Disorders of the Elderly Examination (CAMDEX) criteria were acceptable for VD Lund criteria for FTD (The Lund Manchester Groups 1994) BRAAK stage and McKeith criteria for DLB ICD10 for CJD DSMIV for alcohol induced dementia
Outcome	N/A	Data to construct 2X2 table
Study Design	N/A	Cross-sectional studies in which: i) plasma and CSF Aβ 42 metrics and the clinical diagnostic criteria were obtained within a narrow time-frame, and ii) Alzheimer's disease patients were differentiated from patients with other dementia subtypes

Anchoring statements for quality assessment of plasma and CSF Abeta42 studies

We provide some core anchoring statements for quality assessment of diagnostic test accuracy review of plasma and CSF Abeta42 tests in dementia.↯ These statements are designed for use with the QUADAS-2 tool and are based on the guidance for quality assessment of diagnostic test accuracy reviews of IQCODE in dementia ([Quinn 2012](#)).↯

During the two day, multidisciplinary focus group and the piloting / validation of the↯ guidance, it was clear that certain issues were key to assessing quality, while other issues were important to record but less important for assessing overall quality.↯ To assist, we describe a "weighting" system.↯ Where an item is weighted "high risk" then that section of the QUADAS-2 results table is likely to be scored as high risk of bias.↯ For example in dementia diagnostic test accuracy studies, ensuring that clinicians performing dementia assessment are blinded to results of index test is fundamental.↯ If this blinding was not present then the item on reference standard should be scored "high risk of bias", regardless of the other contributory elements.

In assessing individual items, the score of unclear should only be given if there is genuine uncertainty.↯ In these situations review authors will contact the relevant study teams for additional information.

Table 2: Anchoring statements to assist with assessment for risk of bias

Question	Response and weighting	Explanation
Patient Selection		
Was the sampling method appropriate?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	Where sampling is used, the designs least likely to cause bias are consecutive sampling or random sampling. Sampling that is based on volunteers or selecting subjects from a clinic or research resource is prone to bias.

Question	Response and weighting	Explanation
Was a case-control or similar design avoided?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	Designs similar to case control that may introduce bias are those designs where the study team deliberately increase or decrease the proportion of subjects with the target condition, which may not be representative. Some case control methods may already be excluded if they mix subjects from various settings.
Are exclusion criteria described and appropriate?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	Study will be automatically graded unclear if exclusions are not detailed (pending contact with study authors). Where exclusions are detailed, the study will be graded as "low risk" if exclusions are felt to be appropriate by the review authors. Certain exclusions common to many studies of dementia are: medical instability; terminal disease; alcohol/substance misuse; concomitant psychiatric diagnosis; other neurodegenerative condition. Exclusions are not felt to be appropriate if 'difficult to diagnose' patients are excluded. Post hoc and inappropriate exclusions will be labelled "high risk" of bias.
Index Test		
Was Plasma and CSF Abeta42 biomarkers' assessment/interpretation performed without knowledge of clinical dementia diagnosis?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	Terms such as "blinded" or "independently and without knowledge of" are sufficient and full details of the blinding procedure are not required. Interpretation of the results of the index test may be influenced by knowledge of the results of reference standard. If the index test is always interpreted prior to the reference standard then the person interpreting the index test cannot be aware of the results of the reference standard and so this item could be rated as 'yes'. For certain index tests the result is objective and knowledge of reference standard should not influence result, for example level of protein in cerebrospinal fluid, in this instance the quality assessment may be "low risk" even if blinding was not achieved.
Were Plasma and CSF Abeta42 biomarkers' thresholds pre-specified?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	For scales and biomarkers there is often a reference point (in units or categories) above which subjects are classified as "test positive"; this may be referred to as threshold; clinical cut-off or dichotomisation point. A study is classified high risk of bias if the authors define the optimal cut-off post-hoc based on their own study data because selecting the threshold to maximise sensitivity and specificity may lead to overoptimistic measures of test performance. Certain papers may use an alternative methodology for analysis that does not use thresholds and these papers should be classified as not applicable.
Reference Standard		
Is the assessment used for clinical diagnosis of dementia acceptable?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	Commonly used international criteria to assist with clinical diagnosis of dementia include those detailed in DSM-IV and ICD-10. Criteria specific to dementia subtypes include but are not limited to NINCDS-ADRDA criteria for Alzheimer's dementia; McKeith criteria for Lewy Body dementia; Lund criteria for frontotemporal dementia; and the NINDS-AIREN criteria for vascular dementia. Where the criteria used for assessment is not familiar to the review authors or the Cochrane Dementia and Cognitive Improvement group ('unclear') this item should be classified as "high risk of bias".
Was clinical assessment for dementia performed without knowledge of the Plasma and CSF Abeta42 biomarkers?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	Terms such as "blinded" or "independently and without knowledge of" are sufficient and full details of the blinding procedure are not required. Interpretation of the results of the reference standard may be influenced by knowledge of the results of index test.

Question	Response and weighting	Explanation
Patient flow		
Was there an appropriate interval between Plasma and CSF Abeta42 biomarkers and clinical dementia assessment?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	As we test the accuracy of the Plasma and CSF Abeta42 biomarkers for MCI conversion to dementia, there will always be a delay between the index test and the reference standard assessments. The time between reference standard and index test will influence the accuracy, and therefore we will note time as a separate variable (both within and between studies) and will test its influence on the diagnostic accuracy. We have set a minimum mean time to follow-up assessment of 1 year. If more than 16% of subjects of subjects have assessment for MCI conversion before nine months this item will score 'no'.
Did all subjects get the same assessment for dementia regardless of Plasma and CSF Abeta42 biomarkers?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	There may be scenarios where subjects who score "test positive" on index test have a more detailed assessment. Where dementia assessment differs between subjects this should be classified as high risk of bias.
Were all patients who received Plasma and CSF Abeta42 biomarker's assessment included in the final analysis?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	If the number of patients enrolled differs from the number of patients included in the 2X2 table then there is the potential for bias. If patients lost to drop-outs differ systematically from those who remain, then estimates of test performance may differ. If drop outs these should be accounted for; a maximum proportion of drop outs to remain low risk of bias has been specified as 20%
Were missing Plasma and CSF Abeta42 biomarkers' results or uninterpretable Plasma and CSF Abeta42 biomarkers' biomarker results reported?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	Where missing or uninterpretable results are reported, and if there is substantial attrition (we have set an arbitrary value of 50% missing data), this should be scored as 'no'. If those results are not reported, this should be scored as 'unclear' and authors will be contacted.
Anchoring statements to assist with assessment for applicability		
Question	Explanation	
Were included patients representative of the general population of interest?	The included patients should match the intended population as described in the review question. The review authors should consider population in terms of symptoms; pre-testing; potential disease prevalence; setting. If there is a clear ground for suspecting an unrepresentative spectrum the item should be rated poor applicability.	
Index test		
Were sufficient data on Plasma and CSF Abeta42 biomarkers' application given for the test to be repeated in an independent study?	Variation in technology, test execution, and test interpretation may affect estimate of accuracy. In addition, the background, and training/expertise of the assessor should be reported and taken in consideration. If plasma and CSF Abeta42 biomarkers were not performed consistently this item should be rated poor applicability.	
Reference Standard		
Was clinical diagnosis of dementia made in a manner similar to current clinical practice?	For many reviews, inclusion criteria and assessment for risk of bias will already have assessed the dementia diagnosis. For certain reviews an applicability statement relating to reference standard may not be applicable. There is the possibility that a form of dementia assessment, although valid, may diagnose a far larger proportion of subjects with disease than usual clinical practice. In this instance the item should be rated poor applicability.	