^{11}C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

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Abstract

Background

According to the latest revised National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association) (NINCDS-ADRDA) diagnostic criteria for Alzheimer's disease dementia, the confidence in diagnosing mild cognitive impairment (MCI) due to Alzheimer's disease dementia is raised with the application of imaging biomarkers. These tests, added to core clinical criteria, might increase the sensitivity or specificity of a testing strategy. However, the accuracy of biomarkers in the diagnosis of Alzheimer's disease dementia and other dementias has not yet been systematically evaluated. A formal systematic evaluation of the sensitivity, specificity, and other properties of positron emission tomography (PET) imaging with the ^{11}C-labelled Pittsburgh Compound-B (^{11}C-PIB) ligand was performed.

Objectives

To determine the diagnostic accuracy of the ^{11}C-PIB-PET scan for detecting participants with MCI at baseline who will clinically convert to Alzheimer's disease dementia or other forms of dementia over a period of time.

Search methods

The most recent search for this review was performed on 12 January 2013. We searched MEDLINE (OvidSP), EMBASE (OvidSP), BIOSIS Previews (ISI Web of Knowledge), Web of Science and Conference Proceedings (ISI Web of Knowledge), PsycINFO (OvidSP), and LILACS (BIREME). We also requested a search of the Cochrane Register of Diagnostic Test Accuracy Studies (managed by the Cochrane Renal Group).

No language or date restrictions were applied to the electronic searches and methodological filters were not used so as to maximise sensitivity.

Selection criteria

We selected studies that had prospectively defined cohorts with any accepted definition of MCI with baseline ^{11}C-PIB-PET scan. In addition, we only selected studies that applied a reference standard for Alzheimer's dementia diagnosis for example NINCDS-ADRDA or Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria.

Data collection and analysis

We screened all titles generated by electronic database searches. Two review authors independently assessed the abstracts of all potentially relevant studies. The identified full papers were assessed for eligibility and data were extracted to create two by two tables. Two independent assessors performed quality assessment using the QUADAS 2 tool. We used the hierarchical summary receiver operating characteristic (ROC) model to produce a summary ROC curve.

Main results

Conversion from MCI to Alzheimer's disease dementia was evaluated in nine studies. The quality of the evidence was limited. Of the 274 participants included in the meta-analysis, 112 developed Alzheimer's dementia. Based on the nine included studies, the median proportion converting was 34%. The studies varied markedly in how the PIB scans were done and interpreted.

The sensitivities were between 83% and 100% while the specificities were between 46% and 88%. Because of the variation in thresholds and measures of ^{11}C-PIB amyloid retention, we did not calculate summary sensitivity and specificity. Although subject to considerable uncertainty, to illustrate the potential strengths and weaknesses of ^{11}C-PIB-PET scans we estimated from the fitted summary ROC curve that the sensitivity was 96% (95% confidence interval (CI) 87 to 99) at the included study median specificity of 58%. This equated to a positive likelihood ratio of 2.3 and a negative likelihood ratio of 0.07. Assuming a typical conversion rate of MCI to Alzheimer's dementia of 34%, for every 100 PIB scans one person with a negative scan would progress and 28 with a positive scan would not actually progress to Alzheimer's dementia.

There were limited data for formal investigation of heterogeneity. We performed two sensitivity analyses to assess the influence of type of reference standard and the use of a pre-specified threshold. There was no effect on our findings.

Authors' conclusions

Although the good sensitivity achieved in some included studies is promising for the value of ^{11}C-PIB-PET, given the heterogeneity in the conduct and interpretation of the test and the lack of defined thresholds for determination of test positivity, we cannot recommend its routine use in clinical practice.^{11}C-PIB-PET biomarker is a high cost investigation, therefore it is important to clearly demonstrate its accuracy and standardise the process of the ^{11}C-PIB diagnostic modality prior to it being widely used.

Plain language summary

^{11}C-PIB-PET scan for early prediction of developing Alzheimer's disease or other dementia in people with mild cognitive impairment (MCI)

The numbers of people with dementia and other cognitive problems are increasing globally. A diagnosis of the pre-dementia phase of disease is recommended but there is no agreement on the best approach. A range of tests have been developed which healthcare professionals can use to assess people with poor memory or cognitive impairment. Based on the published data, we have found that the ^{11}C-PIB-PET scan as a single test lacks the accuracy to identify those patients with MCI who would develop Alzheimer's disease dementia or other forms of dementia. The findings indicate that for every 100 PIB scans, one person with a negative scan will progress to Alzheimer's disease dementia and 28 with a positive scan will not. Therefore, a positive PIB scan in patients with MCI is of no clinical value in the early prediction of Alzheimer's disease dementia developing.

Background

The pathology of Alzheimer's disease is present in the majority of cases of dementia. As the dominant or sole pathology, it accounts for over 50% of dementia, afflicting 5% of men and 6% of women over the age of 60 years worldwide (World Health Organization 2002). However, the strength of the link between cognitive impairment and the pathological features of Alzheimer's disease varies with age and with each of the different pathological features. It has also been recognised that a significant number of individuals without clinical evidence of Alzheimer's disease have amyloid deposition at death (Dickson 1992). Indeed, epidemiological neuropathological studies have established that there is no significant relationship between amyloid plaque burden and cognitive impairment in those over the age of 90 years (Savva 2009).

The term 'Alzheimer's disease dementia' is used to describe those in whom the symptoms of cognitive impairment have

gradually progressed to the point where the ability of the patient to perform everyday functions has been affected. Before this, there is a stage, known as mild cognitive impairment (MCI), in which the patient has a degree of cognitive impairment which is greater than expected for age but he or she is not impaired in function. Before MCI, there is a stage in which the pathology is present and increasing but has not yet affected cognitive function, known as 'preclinical Alzheimer's disease'.

MCI is a heterogeneous condition. In this review MCI refers to the clinical criteria defined by Petersen or the revised Petersen criteria (Petersen 1999; Petersen 2004; Winblad 2004), the Cognitive Dementia Rating (CDR = 0.5) scale (Morris 1993), or to the 16 different classifications of MCI (Matthews 2008). There are four outcomes for those within an MCI population, progression to Alzheimer's disease dementia, progression to another dementia, maintaining stable MCI, or recovery. At present, there is no clinical method to determine who of these patients will experience Alzheimer's disease dementia (ADD) or other forms of dementia.

The main concern of patients who present with worries about their cognitive function is whether there is a treatment which will either improve or delay progression of their symptoms. The rate at which patients cross the boundary between preclinical Alzheimer's disease and MCI, and between MCI and Alzheimer's disease dementia, depends on several factors. Patients presenting to primary care are different from those in secondary care, who are different again from those in research settings. Those with the apolipoprotein E4 (ApoE4) genotype progress more rapidly. Within the 'MCI band', those with worse cognitive function also progress more rapidly. Studies indicate that an annual average of 5% to 15% of MCI patients progress to ADD (Petersen 1999; Bruscoli 2004; Mattsson 2009; Petersen 2009).

Alzheimer's disease pathology is associated with cerebral amyloidosis and the presence of amyloid-beta (Abeta) plaques and neurofibrillary tangles in brain tissues at autopsy has been considered a 'gold standard' for the definitive diagnosis of Alzheimer's disease (Mirra 1991; Newell 1999). However, Abeta plaques are present in conditions other than ADD (Villemagne 2008). Abeta amyloid deposits, measured with a Pittsburgh Compound-B (PIB) radioactive substance, are greater in congophilic angiopathy (Johnson 2007) and dementias other than ADD. PIB retention and Abeta imaging in vivo could indicate more accurate differential diagnosis of the dementias. For instance, PIB could differentiate Alzheimer's disease from frontotemporal dementia (FTD) (Rabinovici 2007; Rowe 2007; Drzezga 2008; Engler 2008). The role of the PIB positron emission tomography (PET) biomarker in dementia differential diagnostics is being evaluated in a number of separate Cochrane systematic reviews.

The U.S. Food and Drug Administration (FDA) position on recently licensed amyloid ligands is that such tests do not establish a positive diagnosis of Alzheimer's disease nor, if positive, predict progression from MCI to ADD (http://www.alzforum.org/news/research-news/fda-approves-second-amyloid-imaging-agent; http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm372261.htm).

It is a reasonable assumption, and one on which this review is predicated, that if a patient has both MCI and the pathology of Alzheimer's disease and then goes on to develop clinical ADD then the cause of the initial MCI and of the ADD was the Alzheimer's pathology.

Our approach is an example of assessing diagnostic accuracy using delayed verification of diagnosis. Instead of the reference standard being based on pathology, however, it is based on a clinical standard, the progression from MCI to ADD or other dementias. Although, for the reasons stated above, this introduces a degree of unreliability it has the advantage of being based on what matters to patients, which is progression.

The PIB-PET biomarker results represent Abeta amyloid deposition in the brain. We looked at at the relation between ^{11}C-PIB ligand binding in the brain and: i) conversion from MCI to ADD; or ii) conversion from MCI to other forms of dementia.

Target condition being diagnosed

In this review there are two target conditions: i) Alzheimer's disease dementia (ADD); and ii) other forms of dementia, which are assessed at follow-up.

We compared the index test results obtained at baseline with the results of the reference standards obtained at follow-up (delayed verification).

Index test(s)

The ^{11}C-PIB-PET scan is an index test for the detection of Abeta deposition in the brain region of interest (ROI). The ROI is a selected brain area that physicians create for futher study, in various anatomical areas of the brain.

^{11}C-PIB is a molecular biomarker, a N-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothyazole radiotracer derived from thioflavin T (Klunk 2004). Price 2005 fully evaluated quantitative ^{11}C-PIB-PET data in order to identify a valid, simple and reliable PET quantisation method for the routine measure of brain amyloid retention in vivo.

- Criteria for ^{11}C-PIB-PET positivity: there are currently no generally accepted standards for ^{11}C-PIB threshold, and therefore it was not possible to pre-specify it. We planned to use the criteria that were applied in each included primary study to classify participants as either test positive or test negative. Positivity is a ^{11}C-PIB-PET uptake and retention exceeding a certain threshold.
- Measure of ^{11}C-PIB amyloid retention (retention ratio): distribution volume ratio (DVR), standardized uptake value ratio (SUVR), or other ratios will be considered. DVR refers to the ratio of the ^{11}C-PIB ligand distribution volume in the selected area (ROI) to the distribution volume in the reference area (usually cerebellum). SUVR is the measured activity in the ROI, which is normalised for body weight, surface area, and injected dose.
- Image analysis: not pre-specified (e.g. Statistical Parametric Mapping (SPM), MilxView medical image, and analysis

software or other image analysis techniques).
- Time between ^{11}C-PIB injection and PET acquisition: not pre-specified (e.g. 40 minutes, 60 minutes, 50 to 70 minutes, 90 minutes).
- ^{11}C-PIB injection dose: not pre-specified (e.g. 300 MBq, 370 MBq).
- ^{11}C-PIB retention detecting regions: not pre-specified ROI (e.g. global cortex, thalamus, frontal, parietal, temporal cortices or posterior cingulum, or a combination of these) (e.g. global cortex, caudate nucleus, putamen, thalamus, pons, etc.).

Although it is inevitable for included studies to use different imaging protocols and varied parameters, the amyloid PET data in these included studies should be technically adequate and should be acquired at a fully qualified and certified facility. The protocol for the qualitative read that determines positivity or negativity should be be standardized and should conform to a specific guideline.

Clinical Pathway

Dementia develops over several years. There is a presumed period when people are asymptomatic but when pathology is accumulating. Individuals or their relatives may then notice subtle impairments of recent memory. Gradually more cognitive domains become involved and difficulty in planning complex tasks becomes increasingly apparent. In the UK, people usually present to their general practitioner, who may administer cognitive tests and refer the person to a hospital memory clinic. However, many people with dementia do not present until much later in the disorder and will follow a different pathway to diagnosis, for example being identified during an admission to a general hospital for a physical illness. Thus the pathway influences the accuracy of the diagnostic test. The accuracy of the test will vary with the experience of the administrator, and the accuracy of the subsequent diagnosis will vary with the history of referrals to the particular healthcare setting. Diagnostic assessment pathways may vary in other countries and diagnoses may be made by a variety of specialists including neurologists and geriatricians. We anticipated that the main way in which ^{11}C-PIB-PET scans will be used is as an additive test to clinical signs and other tests.

Alternative test(s)

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

- ^{18}F-FDG-PET (^{18}F-2-fluoro-2-deoxy-D-glucose).
- Cerebrospinal fluid (CSF) analysis of Abeta and tau.
- Structural magnetic resonance imaging (sMRI).
- Neuropsychological tests (Mini-Mental State Examination (MMSE); MiniCOG; Montreal Cognitive Assessment (MoCA)).
- Informant interviews (Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE); AD8).
- ApoE4.
- Fluoropropil-carbomethoxy-iodophenil-tropane single-photon emission tomography (FP-CIT SPECT).

Rationale

The new diagnostic criteria for Alzheimer's disease and MCI due to Alzheimer's disease (Dubois 2010; Albert 2011; McKhann 2011; Sperling 2011) incorporate add-on biomarkers based on imaging or CSF measures. These tests added on to core clinical criteria might increase the sensitivity or specificity of a testing strategy.

The ^{11}C-PIB-PET scan might facilitate accurate identification of those patients with MCI who would convert to Alzheimer's disease or other forms of dementia. At the present time there is no 'cure' for dementia, but there are some treatments which can slow cognitive and functional decline, or reduce the associated behavioural and psychiatric symptoms of dementia (Birks 2006; McShane 2006). In addition, the accurate early diagnosis of dementia may improve opportunities for the use of newly-evolving interventions designed to delay or prevent progression to more debilitating stages of dementia (Oddo 2004).

The disappointing clinical trial result for Alzheimer's disease-modifying therapies in people suggests that treatment should be targeted at earlier stages in the disease, such as MCI (Friedrich 2014). Abeta biomarkers such as PIB-PET imaging may be essential to allow for testing an Abeta immunotherapy drug on MCI patients with evidence of brain Abeta pathology, and seem to be useful in assessing the effects of pre-dementia phase preventive treatments of potential Alzheimer's disease on cortical fibrillar Abeta load in vivo (Rinne 2010; Blennow 2014; Salloway 2014).

It is crucial that the ^{11}C-PIB-PET scan is assessed for its diagnostic accuracy in patients with MCI before being adopted as a routine add-on test in clinical practice.

Objectives

To determine the diagnostic accuracy of the ^{11}C- PIB-PET scan as the index test for detecting participants with mild cognitive impairment (MCI) at baseline who would clinically convert to Alzheimer's disease dementia (ADD) or other forms of dementia at follow-up.

Secondary objectives

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

Methods

Criteria for considering studies for this review

Types of studies

We considered longitudinal studies that had prospectively defined cohorts with any accepted definition of MCI with baseline ^{11}C-PIB-PET scan and the reference standard results obtained at follow-up (see Index tests and Reference standards below). These studies necessarily employ delayed verification of conversion to dementia and are sometimes labelled as 'delayed verification cross-sectional studies' (Knotnerus 2002; Bossuyt 2008).

We included case control studies when they incorporated a delayed verification design. This occurred in the context of a cohort study, so these studies are invariably diagnostic nested case-control studies.

Participants

Participants recruited and clinically classified as those with MCI at baseline were eligible for this review. The diagnosis of MCI was established using the Petersen criteria or revised Petersen criteria (Petersen 1999; Petersen 2004; Winblad 2004), the Matthews 2008 criteria, or CDR = 0.5 (Morris 1993), or a combination. These criteria include: subjective complaints; a decline in memory objectively verified by neuropsychological testing in combination with a history from the patient; a decline in other cognitive domains; no or minimal impairment of activities of daily living; not meeting the criteria for dementia. Therefore, the eligible participants had a number of tests, for example neuropsychological tests for cognitive deficit and checklists for activities of daily living, prior to study entry. Participants in some studies were defined as amnestic single domain, amnestic multiple domain, non-amnestic single domain, non-amnestic multiple domain, or non-specified MCI participants. We considered these studies for inclusion. We also considered studies without reference to a particular source of recruitment (participant setting) for inclusion.

We excluded studies that involved patients with MCI possibly caused by: i) current or a history of alcohol or drug abuse; ii) central nervous system (CNS) trauma (for example subdural haematoma), tumour, or infection; iii) other neurological conditions (for example Parkinson's or Huntington's diseases).

Index tests

^{11}C-PIB-PET imaging test

We used the criteria that were applied in each included primary study to classify participants as either ^{11}C-PIB positive or ^{11}C-PIB negative. We considered positivity as ^{11}C-PIB ligand uptake and retention exceeding a certain threshold.

Target conditions

There were two target conditions in this review:

1. Alzheimer's disease dementia (ADD) (conversion from MCI to ADD);
2. Any other forms of dementia (conversion from MCI to any other forms of dementia).

Reference standards

The reference standard was progression to the target conditions. For the purpose of this review, several definitions of ADD were acceptable. Included studies applied probable or possible National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association) (NINCDS-ADRDA) criteria (McKhann 1984). The Diagnostic and Statistical Manual of Mental Disorders (DSM) (DSMIII 1987; DSMIV 1994) and International Classification of Diseases (ICD) (World Health Organization 2010) definitions for ADD were also acceptable.

Similarly, differing clinical definitions of other dementias were acceptable. For Lewy body dementia the reference standard is the McKeith criteria (McKeith 1996; McKeith 2005); for frontotemporal dementia (FTD) the Lund criteria (Neary 1988; Brun 1994; Boxer 2005), DSM (DSMIII 1987; DSMIV 1994), ICD (World Health Organization 2010); and for vascular dementia the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS ARIEN) criteria (Roman 1993), DSM (DSMIII 1987; DSMIV 1994), and ICD (World Health Organization 2010).

The time interval over which progression from MCI to ADD or other forms of dementia occurred is very important. We chose one year as the minimum period of delay in the verification of the diagnosis (that is the time between the assessment at which a diagnosis of MCI is made and the assessment at which the diagnosis of dementia is made). We planned to segment analyses into separate follow-up mean periods for the delay in verification: one year to less than two years; two to less than four years; and greater than four years. In this eventuality we planned to clearly note where the same included studies contributed to the analysis for more than one reference standard follow-up interval.

Search methods for identification of studies

Electronic searches

On 12 January 2013 we searched MEDLINE (OvidSP), EMBASE (OvidSP), BIOSIS Previews (ISI Web of Knowledge), Science Citation Index (ISI Web of Knowledge), PsycINFO (OvidSP), and LILACS (BIREME). See Appendix 1 for details of the sources searched, the search strategies used, and the number of hits retrieved. No language restriction was applied to the electronic searches.

Searching other resources

The reference lists of all relevant studies were checked for additional studies. Searches were also

conducted in the MEDION database (Meta-analyses van Diagnostisch Onderzoek) (www.mediondatabase.nl), DARE (Database of Abstracts of Reviews of Effects) (www.york.ac.uk/inst/crd/crddatabases.htm#DARE), HTA Database (Health Technology Assessments Database) (www.york.ac.uk/inst/crd/crddatabases.htm#HTA), and ARIF database (Aggressive Research Intelligence Facility) (www.arif.bham.ac.uk) for other related systematic diagnostic accuracy reviews; and a dataset of systematic reviews of diagnostic studies from the International Federation of Clinical Chemistry and Laboratory Medicine Committee for Evidence-based Laboratory Medicine database (C-EBLM) was sought. Reference lists of any relevant systematic reviews were checked for additional studies.

Data collection and analysis

Selection of studies

The Cochrane Dementia and Cognitive Impairment Group (CDCIG) Trial Search Co-ordinator, a researcher with experience of diagnostic test accuracy systematic reviews, performed the first assessment of the search results in order to remove the obvious non-relevant studies. Two authors independently reviewed the remaining titles and abstracts for potentially eligible studies for full paper review. Two authors independently assessed the full manuscripts against the inclusion criteria. Where necessary, a third review author acted as arbitrator to resolve disagreements that the two review authors were not able to resolve through discussion.

Where a study did not present all relevant data for creating a 2 x 2 table, we contacted the authors directly to request further information. When the same data set was presented in more than one paper, we included as the primary paper the paper with the largest number of patients or with the most informative data.

Data extraction and management

We planned to extract the following data on study characteristics if reported.

Bibliographic details of primary paper:

- author, title of study, year, and journal.

Basic clinical and demographic details:

- number of participants;
- clinical diagnosis;
- MCI clinical criteria;
- age;
- gender;
- sources of referral;
- participant recruitment;
- sampling procedures.

Details of the index test:

- method of the PIB test administration, including who administered the test;
- thresholds used to define positive and negative tests;
- other technical aspects as seemed relevant to the review, e.g. brain areas.

Details of the reference standard:

- definition of ADD and other dementias used in reference standard;
- duration of follow-up from time of index test performed to defining ADD and other dementias by reference standard;
- prevalence or proportion of population developing ADD and other dementias, with severity if described.

We created 2 x 2 tables (cross-relating index test results of the reference standards) as shown in Appendix 2.

The numbers lost to follow-up were recorded for each included study.

We also extracted data necessary for the assessment of quality as defined below.

Data extraction was performed independently by two blinded review authors (NS, ZS). Disagreement in data extraction was resolved by discussion, with the potential to involve a third author (CH) as arbitrator if necessary.

Assessment of methodological quality

We assessed the methodological quality of each study using the QUADAS-2 tool (Whiting 2011) as recommended by The Cochrane Collaboration. The tool is made up of four domains:

- patient selection;
- index test;
- reference standard;
- patient flow.

Two independent raters (NS, MW), blinded to each other's scores, performed the QUADAS-2 assessment. Disagreement was resolved by further review and discussion with the potential to involve a third author (CH) as arbitrator if necessary.

We assessed each domain in terms of risk of bias, with the first three domains also considered in terms of applicability concerns. The components of each of these domains and a rubric which details how judgements concerning risk of bias were made are detailed in Appendix 3. Key areas important to quality assessment are participant selection, blinding, and

missing data.

We did not use QUADAS-2 data to form a summary quality score. We produced a narrative summary describing the numbers of studies that were found to have high, low, or unclear risk of bias as well as concerns regarding applicability.

Statistical analysis and data synthesis

We evaluated test accuracy according to the target condition. There are no accepted thresholds to define PIB-PET positivity for ADD and other forms of dementia, and so the estimates of diagnostic accuracy reported in primary studies were likely to be based on data-driven threshold selection (Leeflang 2008) unless pre-specified. We conducted exploratory analyses by plotting estimates of sensitivity and specificity from each study on forest plots and in receiver operating characteristic (ROC) space. We meta-analysed pairs of sensitivity and specificity using the hierarchical summary ROC (HSROC) model (Rutter 2001) that allows for the possibility of variation in threshold between studies. Where adequate studies were available to estimate all parameters, we assumed a symmetrical shape to the summary ROC curve. Estimates of summary sensitivities and specificities are not clinically interpretable when studies with mixed thresholds are included in the HSROC model, and so we derived estimates of sensitivity and likelihood ratios at fixed values (lower quartile, median, and upper quartile) of specificity from the HSROC models. The analyses were performed using the NLMIXED procedure in the SAS software (version 9.2; SAS Institute 2011, Cary, NC).

Investigations of heterogeneity

We planned to investigate the effects of the following factors.

- Spectrum of patients (mean age, gender, MMSE score, APOE ε4 status). For age, we planned to separately examine any study that included 30% of patients below the age of 65 years.
- Referral centres: primary care, memory clinic, and hospital.
- Clinical criteria of MCI: Petersen criteria, revised Petersen criteria, CDR = 0.5 criteria, and different MCI classification (Matthews 2008).
- ^{11}C-PIB retention ratio.
- Image analysis techniques.
- Time between ^{11}C-PIB injection and PET acquisition.
- ^{11}C-PIB injection dose.
- ^{11}C-PIB retention detecting regions.
- Reference standard(s) used: NINCDS-ADRDA, DSM, and ICD 10 for ADD.
- Duration of follow-up: 1 year to < 2 years, 2 to < 4 years, and > 4 years.
- Aspects of study quality, particularly inadequate blinding and loss to follow-up: we considered separately those studies that had more than 20% dropouts.
- Conflict of interest.

In preliminary analyses, we visually examined forest plots of sensitivity and specificity, and summary ROC plots to explore the effect of each of these factors. If there were sufficient studies, we planned to perform meta-regression by including each potential source of heterogeneity as a covariate in the HSROC model.

Sensitivity analyses

We investigated the effect of pre-specification of threshold and PIB positivity on diagnostic accuracy by performing sensitivity analyses.

Assessment of reporting bias

We did 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

The total number of records identified by the searches for this review was 14,951. After de-duplication, a small team of assessors performed a first-assess on the remaining records. The PRISMA diagram (Figure 1) shows the flow of studies through the screening and selection processes. In total, 103 studies (94 full text papers and 11 conference publications) were assessed for eligibility. We included nine studies and one was identified as an ongoing study. We excluded 93 studies. Nineteen studies were multiple publications and 11 did not have extractable data for constructing 2 x 2 tables (see Characteristics of excluded studies). The remaining 63 studies were excluded as they did not meet the inclusion criteria: i) not MCI participants at baseline (n = 10); ii) not a delayed verification study (n = 40); iii) index test not PIB-PET scan (n = 1); iv) discussion papers (n = 3); and v) conference publications and no reply when authors were contacted (n = 9) (Okello 2007; Ellis 2011; Maruff 2011; Perrotin 2011; Rentz 2011; Villain 2011; Villemagne 2011a; Hatashita 2012; Mosconi 2012). No extra studies were found through reference checking. Usable data were obtained for three studies (Jack 2010; Ossenkoppele 2012; Ossenkoppele 2012a) by contacting the authors of the studies.

Included studies

The Characteristics of included studies table lists the characteristics of the nine included studies containing a total of 300 participants with MCI at baseline.

Of the 274 participants with analysable data, 112 developed Alzheimer's dementia and nine non-Alzheimer's

dementia. The remaining 26 participants were reported to be lost to follow-up. The majority (n = 18) of participants were missing from a single study (Ossenkoppele 2012a). All the studies were published in recent years (2009 to 2013). Most of them (6/9) were conducted in Europe (two in the Netherlands, one in the UK and Finland, one in Finland alone, one in Sweden, one in Germany); two in the USA; and one in Australia. All included studies used one version or another of the Petersen criteria for MCI. Eight studies applied NINCDS-ADRDA criteria as a reference standard for ADD; Koivunen 2011 also used DSM-IV criteria; Ossenkoppele 2012a did not explicitly state what reference standard was used at follow-up.

Demographic and patient characteristics are summarised in Table 1. Study sizes were small and ranged from 15 to 67. Four papers reported a mean age of over 70 years (Jack 2010; Koivunen 2011; Villemagne 2011; Wolk 2009) while five papers reported a mean age below 70 years (Okello 2009; Forsberg 2010; Ossenkoppele 2012; Ossenkoppele 2012a; Grimmer 2013). The youngest study population was aged 64 ± 9 years (Ossenkoppele 2012a) and the oldest study population was aged 73.4 ± 8.5 years (Villemagne 2011). Gender, APOE Ɛ4 carriers, years of education, and sampling procedure were poorly reported. Participants were mainly recruited from secondary care (five studies from outpatient clinics and one study from inpatient department), one study recruited the participants from a tertiary setting (Wolk 2009), one from a mixed setting (Jack 2010), and one did not report the sources of recruitment (Ossenkoppele 2012).

Table 2 and Table 3 summarise the data regarding the threshold used, the measure of PIB amyloid retention, image analysis, PIB dose and the time between PIB injection and performing a PET scan, and PIB retention detecting region of interest (ROI). The studies applied different analytic approaches to PET data, ranging from quantitative binding potentials (BPs) or distribution volume ratios (DVRs) using invasive arterial sampling to semi-quantitative standardized uptake value ratios (SUVR). Seven studies used seven different thresholds and two studies did not report the threshold used. Six different measures were used for PIB retention and six different ROIs were investigated for detecting PIB retention in nine included studies. The timing of the scans and data acquisition (dynamic versus static) also varied greatly across studies. Duration of follow-up was reported as the mean and SD, median, or maximum duration, or it was not reported at all. Duration of follow-up varied substantially but was mostly within the 18 to 36 months range. PIB positivity ranged from 42% (Ossenkoppele 2012) to 72% (Koivunen 2011). Conversion to ADD ranged from 22% (Wolk 2009) to 59% (Koivunen 2011). The included studies varied markedly in how the PIB scans were done and interpreted.

Excluded studies

Eleven studies were excluded as they failed on the inclusion criteria for participants, index test, or target condition (Characteristics of excluded studies).

Methodological quality of included studies

Methodological quality was assessed using the QUADAS 2 tool (Whiting 2011). Review authors' judgements about each methodological quality item for each included study are presented in the Characteristics of included studies table and Figure 2. The overall methodological quality of the studies is summarised in Figure 3.

In the patient selection domain, we considered seven studies (78%) to be at unclear risk of bias due to poor reporting on sampling procedures and exclusion criteria. We stated that all included studies avoided a case-control design because we only considered data on performance of the index test to discriminate between patients with MCI who converted to dementia and those who remained stable. We considered two remaining studies to be at high (Jack 2010) and low (Koivunen 2011) risk of bias because the participants were not systematically enrolled or were consecutively or randomly enrolled, respectively.

In the index test domain, we considered six studies (67%) at low risk of bias because the threshold used was pre-specified and the index test results were interpreted without knowledge of the results of the reference standard. We considered two studies (Forsberg 2010; Ossenkoppele 2012a) to be at high risk of bias because the threshold used was not pre-specified and the optimal cut-off level was determined from ROC analyses; therefore, the accuracy of the ^{11}C-PIB biomarker that was reported in these studies appeared to be overestimated. We considered the remaining one study (Ossenkoppele 2012) to be at unclear risk of bias due to poor reporting.

In the reference standard domain, we considered five studies (55%) to be at unclear risk of bias because it was not reported whether the clinicians conducting follow-up were aware of the initial ^{11}C-PIB biomarker analysis results. We were not able to obtain the information about how the reference standard was obtained and by whom due to poor reporting. We considered three studies to be at high risk of bias (Wolk 2009; Ossenkoppele 2012; Ossenkoppele 2012a) and one study (Grimmer 2013) to be at low risk of bias.

In the flow and timing domain, we judged eight studies (89%) to be of low concern for risk of bias because all patients were accounted for in the analysis or the reasons for missing data were given, and the time interval between the index test and reference standard was appropriate (duration of follow-up was longer than one year). Shorter durations of follow-up may yield low conversion rates and this might have an effect on the diagnostic accuracy of the index test; therefore, these scores might be overstated and should be interpreted with caution. We considered one remaining study (Ossenkoppele 2012a) to be at high risk of bias because a large number of patients were excluded from the analyses.

For assessment of applicability, there was no concern that the included patients and setting, the conduct and interpretation of the index test, and the target condition (as defined by the reference standard) in each of the included studies did not match the review question.

It should be noted that the lack of concern about the applicability of the three domains mentioned above was based on

the inclusion criteria that were set for the review. Considering the level of heterogeneity with respect to the nature of the index test (Table 2; Table 3), it appeared that the judgement about applicability may be overstated.

Findings

The key characteristics of each study are summarised in Table 1 and Table 2. The summary of main results for nine included studies is presented in the Summary of findings table 1.

^{11}C-PIB-PET for Alzheimer's disease dementia (ADD)

Individual study estimates of sensitivity and specificity, and the threshold used to define test positivity, are shown in Figure 4 for each of the nine studies (112 cases and 162 non-cases) that evaluated ADD. The sensitivities were between 83% and 100% while the specificities were between 46% and 88%. The criteria for ^{11}C-PIB positivity varied between studies: five studies used a quantitative threshold while the remaining four studies used visual inspection. The nine studies used different measures of ^{11}C-PIB amyloid retention (ROI to cerebellar ratio, average neocortical to cerebellar ratio, posterior cingulate to cerebellar ratio, or visual inspection of parametric nondisplaceable binding potential (BP_{ND}) images or SUVR images). The mode of image analysis also varied between studies.

The summary ROC curve summarising the accuracy of PIB-PET across the nine studies is shown in Figure 5. Because of the variation in thresholds and measures of ^{11}C-PIB amyloid retention, we did not estimate summary sensitivity and specificity. However, we derived estimates of sensitivity and likelihood ratios at fixed values of specificity (see Table 4) from the model we fitted to produce a summary ROC curve. At the median specificity of 58%, the estimated sensitivity was 96% (95% CI 87 to 99), the positive likelihood ratio was 2.29 (95% CI 2.17 to 2.41), and the negative likelihood ratio was 0.07 (95% CI 0.02 to 0.24).

^{11}C-PIB-PET for all types of dementia (combined Alzheimer's disease and non-ADD)

Four studies (59 cases and 58 non-cases) evaluated the accuracy of PIB-PET for all types of dementia (Figure 6) in addition to evaluating ADDa. The sensitivities were between 75% and 86% while the specificities were between 50% and 86%. Two studies used a quantitative threshold while the other two used visual inspection to determine test positivity. Meta-analysis was not performed because the studies were few and small, and there was considerable heterogeneity. Figure 7 shows study specific estimates of sensitivity and specificity in the ROC space together with their 95% CIs.

Investigation of heterogeneity

The planned investigations were not possible due to the limited number of studies available for each analysis. For type of reference standard, seven of the nine studies used NINCDS-ADRDA. Therefore, we conducted sensitivity analyses restricting the analysis to only studies that used NINCDS-ADRDA as the reference standard.

Sensitivity analyses

Due to the limited number of studies evaluating ^{11}C-PIB-PET for all dementia, we performed sensitivity analyses only for studies of ADD.

Type of reference standard

Of the nine studies that evaluated ^{11}C-PIB-PET for ADD, seven used NINCDS-ADRDA as the reference standard. To explore the impact of type of reference standard on the summary estimates, we excluded one study (Koivunen 2011) that used NINCDS-ADRDA and DSM IV as the reference standard and another study (Ossenkoppele 2012a) where the reference standard used was unclear. There was no impact on our findings (Table 4).

Threshold pre-specified

Seven studies pre-specified thresholds for test positivity. The two studies that did not pre-specify the threshold (Forsberg 2010) or did not report whether or not thresholds were pre-specified (Ossenkoppele 2012) were excluded in this analysis. There was no impact on our findings (Table 4).

Discussion

Summary of main results

The volume and quality of evidence on the diagnostic accuracy of ^{11}C-PIB-PET for early diagnosis of ADD and other dementias in patients with MCI was limited. The results are summarised in Summary of findings table 1. Due to variations in thresholds and the measurement of ^{11}C-PIB amyloid retention, we estimated a summary ROC curve for studies that evaluated conversion from MCI to AD dementia; we did not estimate a summary sensitivity and specificity on the curve because with mixed thresholds a summary point lacks a clnically meaningful interpretation. At the median specificity of 58% the estimated sensitivity of ^{11}C-PIB-PET for identifying patients with MCI that will convert to AD, derived from the summary ROC curve, was 96% (95% CI 87% to 99%).

Data were not pooled for the four studies that evaluated conversion from MCI to all types of dementia; the sensitivities were between 75% and 86%, and the specificities were between 50% and 86%.

^{11}C-PIB-PET for Alzheimer's disease dementia (ADD)

PIB had high sensitivity for predicting conversion to Alzheimer's disease but poor specificity. In other words, the high false positive rate suggested that amyloid imaging was not only an imaging biomarker for Alzheimer's disease but perhaps also for other neurodegenerative diseases and 'asymptomatic' neurological disease, even in healthy people (Chen

2014). It has been demonstrated that PIB binds to amyloid in vessel walls (Bacskai 2007; Johnson 2007), in particular to cerebral amyloid angiopathy. Therefore, vascular Abeta could be another major contributor to the in vivo PIB signal.

A recent study (Ducharme 2013) reported that a patient met clinical criteria for probable Alzheimer's DD but had a higher than expected burden of white matter disease on magnetic resonance imaging (MRI). A ^{11}C-PIB-PET scan was highly positive in typical Alzheimer's disease distribution. Six months after the assessment the patient died of an intracerebral haemorrhage and an autopsy revealed cerebral amyloid angiopathy (CAA) in the complete absence of amyloid plaques or neurofibrillary tangles (NFT). So it is suggested that an uncertain percentage of cognitively normal individuals or with clinical MCI who have positive amyloid PET imaging (Sperling 2011) in fact could have CAA rather than AD. On the other hand, we did not estimate a summary specificity and so far there is no large-scale ^{11}C-PIB-PET study with MCI pathology, therefore it is unknown whether there are 'false positives' that may in fact be vascular MCI due to CAA in some of the included studies. We would also speculate that the final pathological diagnosis of some patients with clinical probable AD may be vascular dementia secondary to CAA.

^{11}C-PIB-PET may not be able to detect more soluble species of Abeta-42 or other atypical amyloid deposits (Leinonen 2008) thus producing false negative results. This is rare, however, and it is more likely that these patients present with an AD-like phenotype that originates from non-amyloidogenic neuropathology. Indeed, multiple contradictory PIB binding results in humans have been reported and a study demonstrating that PIB brain accumulation may be at least in part mediated by PIB sulfation via estrogen sulfotransferase (Cole 2010) has cast doubts on the purported human amyloid specificity of PIB. This phenomenon emphasizes the potential that there might be types of Abeta deposits that PIB does not detect (Shin 2011). Another study (Shin 2010) demonstrated that NFTs, rather than amyloid plaques, were predominantly accumulated in the hippocampal formation in some patients with ADD. PIB can only be bound to senile plaques specifically, but not tangles, sp we can speculate that NFTs might be more pronounced or have happened earlier than amyloid plaques in some PIB negative MCI converters. The notion about NFT pathology has been further strengthened by some neuropathologic studies with autopsy data from ADD. The data from cohort research (Serrano-Pozo 2013) indicated that plaques and tangles independently contribute to cognitive impairment in AD pathology without any other primary neuropathologic diagnosis. Furthermore, NFT formation must be either unrelated to amyloid plaques formation or a temporally distinct process, or both. (Royall 2014).

Another hypothesis that can explain false negative results is that those with probable ADD may have multiple brain pathologies, most commonly AD with macroscopic infarcts, followed by AD with neocortical Lewy body disease. Similar to AD, the pathology underlying MCI is heterogeneous (Schneider 2007; Schneider 2009). Until now, it is unknown whether the complicated and mixed pathology can have an effect on imaging and diagnosis with ^{11}C-PIB-PET, but we speculate that mixed neuropathology of probable Alzheimer's disease and MCI may play a role in PIB negative MCI converters.

Duration of follow-up is also important in predicting conversion to ADD. Although the mean, median, or maximum follow-up period of the included studies was more than one year, the variability in the duration of follow-up was considerable. The reported conversion rate of MCI to AD is between 8% and 16% per year (Mitchell 2009), and the cumulative conversion rate ranged from 22% to 69%, but unfortunately we were not able to calculate conversion rate per year of each of the included studies because of insufficient data. Conversion rates of MCI could have influenced the test results in our review. We took it for granted that given a long follow-up period, a high percentage of patients with baseline MCI would progress to Alzheimer's disease thus affecting the predictive accuracy of ^{11}C-PIB-PET. However, there was not a positive correlation between follow-up time and percentage of conversions. For example, the cumulative conversion rate of MCI in Villemagne 2011 was 68.9%, which was the highest among these included studies, but the maximum follow-up period did not exceed two years in this study. The range of follow-up in Ossenkoppele 2012 was from two to four years, whereas the corresponding cumulative conversion rate did not exceed 34% (Table 2). The differences are significant among these studies. As a consequence, we were not able to investigate the effect of duration of follow-up on the conversion rate due to a high level of heterogeneity and the small number of included studies.

The length of follow-up duration also may have a direct effect on diagnostic accuracy for progression of MCI to dementia. So far the results of the longest follow-up study with two times for ^{11}C-PIB-PET scans (two and five years), conducted by Kemppainen (Kemppainen 2014) and only including 10 MCI participants, were consistent with a 100% specificity of a positive ^{11}C-PIB-PET scan for predicting five year MCI to Alzheimer's disease conversion. This differs from our review, which reports 46% to 88% specificity of PIB PET for predicting one to four 4 year conversion. Furthermore, the estimated 75% sensitivity of baseline ^{11}C-PIB PET scans for predicting MCI to Alzheimer's disease conversion in Kemppainen 2014 is in turn lower than the reported 83% to 100% sensitivity in our review. The inconsistent estimates might be explained by the longer duration of the follow-up period. Additionally, only one MCI participant was diagnosed with Alzheimer's disease at the time of the two year scan, while the others converted between the two year and five year scans. The interval between the two scans and inconsistent accuracy thus reflect the fact that a complete understanding of the role of ^{11}C-PIB-PET in the prediction of decline in MCI will not only require both short and long-term periods of observation but will also need to clarify inter-individual variation in the cerebral amyloid load in MCI, and in the course of amyloid accumulation in relation to the clinical diagnosis of disorders associated with cognitive impairment.

Some demographic and MCI characteristics may be other underlying factors that can increase the conversion rate. More and more attention has been paid to the relationship between MCI subtypes and conversion to dementia. The largest ever longitudinal study, with results from the follow-up of 550 MCI patients, indicated that the MCI subtype, presence of storage memory impairment, multiple domain condition, and presence of APOE ε4 allele increased the risk of conversion to dementia. Multivariate survival and Kaplan-Meier analyses showed that amnestic MCI with storage memory impairment had the most and closest risk of conversion to dementia (Espinosa 2013). In our review the

only longitudinal study with MCI subtypes (Wolk 2009) found that both amnestic MCI and non-amnestic MCI subtype were associated with a significant proportion of amyloid positive scans and, in particular, there were no obvious differences in the distribution of PIB retention between the two groups (Wolk 2009). None of the included studies had analysed the underlying correlation or relationship between ^{11}C-PIB-PET imaging with conversion rate and clinical classification of MCI. In addition, some 'high risk factors' such as positive family history of dementia, presence of Abeta and tau protein in cerebrospinal fluid, and the APOE ε4 allele may also contribute to a faster conversion rate to dementia. Although some studies had reported the status of 'risk factors' of MCI at baseline, these were not fully described to include in the meta-regression. In conclusion, further updated reviews that include high quality research and can provide more detailed data about the characteristics of MCI are required to not only explore the underlying mechanisms but also to elucidate the causal pathways that link PIB positivity of diverse MCI subtypes and disease progression.

^{11}C-PIB-PET for any other forms of dementia (non-Alzheimer's disease dementia (non-ADD))

We were not able to evaluate the accuracy of the index test for conversion from MCI to non-ADD. Only four included studies (Villemagne 2011; Ossenkoppele 2012; Ossenkoppele 2012a; Grimmer 2013) reported a small number (nine) of converters to non-ADD. As a result of the information available from these four studies, we evaluated the target condition ^{11}C-PIB-PET for all types of dementia (combined Alzheimer's disease and non-ADD) (Figure 6; Figure 7).

^{11}C-PIB-PET positive scans are regularly observed in patients with non-ADD and patients with MCI who progress to non-ADD, especially FTD and dementia with Lewy bodies (DLB) (Rabinovici 2011; Albin 2013).

Both DLB and Parkinson's disease dementia (PDD) are characterised at autopsy by the presence of subcortical or cortical Lewy bodies, or both. Patients with DLB frequently have levels of PIB uptake above that of controls and occasionally equivalent to Alzheimer's disease (Rowe 2007). Most studies have found higher amyloid plaques in DLB than in PDD or non-demented Parkinson's disease patients, and in some studies PIB positivity was associated with greater cognitive deficits and more rapid disease progression (Foster 2010). Shimada et al (Shimada 2013) reported that amyloid deposits are associated with AD-like atrophy in patients with DLB and PDD. Patients with DLB have higher levels of amyloid deposits than patients with PD and PDD. There was one autopsy-based study of a patient with DLB with a positive PIB scan due to CAA, but the concurrent pathological evidence of amyloid plaques and NFTs complicated this case (Bacskai 2007), while Lewy bodies themselves contributed little if at all to the overall PIB-PET signal, and α-synuclein and Aβ-42 increased each other's toxicity (Masliah 2001). Amyloid deposits have been linked to cognitive impairment in DLB (Gomperts 2012) and Parkinson's disease without dementia (Gomperts 2013), which may contribute to the timing of the onset of dementia relative to that of Parkinsonism in DLB.

Frontotemporal lobe degeneration (FTLD) is an umbrella term used for disorders associated with neurodegeneration of the frontal and anterior temporal lobes. Clinical syndromes that are in the FTLD spectrum include the behavioural variant of frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA). A study of PIB retention in patients with FTD reported that most patients with FTD displayed no PIB retention and that ^{11}C-PIB-PET could potentially aid in differentiating FTD and Alzheimer's disease (Engler 2008). However, FTD cases have occasionally demonstrated PIB positive scans and it remains unclear whether these cases represent mixed FTLD and Alzheimer's disease, Alzheimer's disease manifesting clinically as FTD, or false-positive cases of FTD (Rabinovici 2007), which may suggest the mimicking of Alzheimer's disease pathology; SD and PNFA are less likely to demonstrate PIB uptake, and it is known from postmortem studies that about 15% to 20% of clinical FTD patients actually have Alzheimer's disease (Forman 2006). Four out of nine included studies (Villemagne 2011; Ossenkoppele 2012; Ossenkoppele 2012a; Grimmer 2013) reported that five MCI participants converted to FTD during the course of the study. All five ^{11}C-PIB-PET scans of those with MCI were negative suggesting the test is insufficient to evaluate the early diagnostic value for progression from MCI to FTD.

Data for all types of dementia are limited in this systematic review. Although high PIB retention is common in MCI and is a powerful predictor of subsequent conversion to Alzheimer's disease, the current available data suggest that PIB may play a similar role in all dementia; at baseline, imaging Abeta may seem bland but deleterious effects emerge as patients with MCI decline cognitively over time to dementia.

Strengths and weaknesses of the review

Our review was planned and conducted following the criteria and methods set out in our published protocol. Our searches were comprehensive and sensitive. We used major electronic databases and wide search terms, and also checked the reference lists of systematic review databases for additional studies. Our searches were not limited by language. We contacted study authors and usable data were obtained for three studies (Jack 2010; Ossenkoppele 2012; Ossenkoppele 2012a). Our methodological quality assessment and data syntheses were based on recommended methods. To increase the reliability of our findings, we included only studies that fulfilled delayed verification of conversion to dementia.

Our review has some limitations. The clinical diagnosis of ADD or other forms of dementia is imperfect, therefore the findings from studies with postmortem confirmation of the diagnosis are more convincing than those from studies with clinical diagnosis in the evaluation of the accuracy of PET imaging in the early detection of the dementia process in MCI.

Considerable attention should be paid to risk stratification of MCI participants (Holland 2012). The stratification of biomarker and risk factors could enable potentially informative MCI subgroup analyses to emerge, which is helpful for ^{11}C-PIB-PET to detect the progression in MCI. Besides amyloid positive imaging, several predisposing factors have been recognized such as FDG-PET hypometabolism, cognitive task-associated changes in functional MRI, abnormality in structural MRI, presence of APOE ε4 allele, MCI subtypes, age and abnormal cerebrospinal fluid findings that conferred increased risk for progression to dementia in MCI participants. Most included studies provided some raw data on MCI at

baseline, nevertheless there are still not enough details reported by included studies for stratifying MCI individuals based on risk factors. For instance, only one study (Wolk 2009) performed the MCI subtypes analysis. A clear classification and stratification of MCI may reduce a potential bias in the procedure of patient sampling (Hampel 2012). As a result of poorly standardized MCI, we suggest that international collaboration should introduce a standardization grading scale or system, with or without ^{11}C-PIB-PET, to more accurately reflect the conversion risk for 'various types' of MCI.

Applicability of findings to the review question

There was no applicability concern that the included patients and setting, the conduct and interpretation of the index test, and the target condition (as defined by the reference standard) in each of the included studies did not match the review question: Could the ^{11}C-PIB biomarker identify those MCI participants with Alzheimer's disease pathology at baseline who would convert clinically to dementia at follow up? However, due to the limited number of included studies and levels of heterogeneity with respect to the three domains mentioned above, it was difficult to determine to what extent the findings from this meta-analysis could be applied to clinical practice.

The diagnostic utility of ^{11}C-PIB-PET scans for identifying Alzheimer's disease pathology and identifying those patients with MCI who would convert to ADD could be affected by a number of factors that have not been determined so far. First, PIB binds to both plaques and cerebral amyloid angiopathy, and the relative contribution of each to the in vivo signal is unknown. Second, it is not yet clear whether the ^{11}C-PIB-PET scan should be interpreted as a dichotomous test (that is positive versus negative) or whether the degree and spatial distribution of binding offer additional diagnostic information. Third, it has not yet been established whether the ^{11}C-PIB threshold should be adjusted based on demographic factors such as age, education, or genetic variables such as the ApoE ε4 genotype, although the relationship between amyloid and dementia is significantly weaker in older versus younger individuals.

The ^{11}C-PIB-PET biomarker is a high cost investigation, therefore it is important to clearly demonstrate its accuracy prior to recommending its adoption in clinical practice.

Authors' conclusions

Implications for practice

At present, a ^{11}C-PIB-PET scan is not indicated in patients with MCI except in clinical trials and research studies (Albert 2011). However, the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association have proposed the usage of amyloid PET in patients with persistent or progressive unexplained MCI (Johnson 2013). The diagnostic accuracy of a ^{11}C-PIB-PET scan as determined in this review suggests that the diagnostic modality has been expected to be a potentially valuable technique for prediction of progression in people with MCI and the detection method used in clinical practice in the near future.

However, given the heterogeneity in the conduct and interpretation of the test, the lack of defined thresholds for determination of test positivity and the inconsistency of length of follow-up, we cannot recommend the routine use of ^{11}C-PIB-PET in clinical practice. The^{11}C-PIB-PET biomarker is a high cost investigation, therefore it is important to clearly demonstrate its accuracy and to standardize the process for the ^{11}C-PIB diagnostic modality prior to it being widely used.

Implications for research

Although the National Institute on Aging and the Alzheimer's Association workgroup had recommended that the diagnostic criteria for MCI due to Alzheimer's disease in research settings and clinical trials should incorporate the use of biomarkers based on imaging, such as ^{11}C-PIB-PET (Albert 2011), there is a lack of a generally accepted standardization process and diagnostic criteria for ^{11}C-PIB-PET for detecting the amyloid image in participants with MCI. We recommend better standardization of image analysis, the threshold, and other ^{11}C-PIB-PET parameters in research studies. Moreover, the procedure for acquisition and analysis of the sample need to be established to implement ^{11}C-PIB-PET criteria on a broad scale. Although we consider biomarkers as 'negative' or 'positive' for the purposes of classification, it is recognized that varying severities of an abnormality may confer different likelihoods or prognoses, which is currently difficult to quantify accurately for broad application in research.

Since neurodegenerative diseases are complex disorders with occasionally multiple and overlapping pathophysiological processes, multitracer imaging may be helpful in combining metabolic, inflammation, or apoptosis markers with those labelling typical protein aggregations seen in the progression of MCI to Alzheimer's disease. In future, various PET imaging modalities are needed to evaluate the usefulness of the various PET tracers as predictors of conversion to Alzheimer's disease in MCI studies with clinical follow-up. There is a hypothesis that amyloid deposition is an early event in Alzheimer's disease that reaches a relative plateau even at the MCI stage, while downstream biomarkers measure neuronal loss and dysfunction, and cognitive measures are more dynamic at the symptomatic disease stage. Based on this hypothesis, the combination of structural imaging, functional imaging, and cognitive tests may be better predictors of when an individual will convert. Some studies (Ossenkoppele 2012a; Zhang 2012; Trzepacz 2014) of clinical relevance have shown that the combination of biomarker modalities, such as PIB-PET, FDG-PET, and structural MR, is likely to provide the best additional neuroimaging information over that of single imaging. Some comparative studies (Jack 2008; Trzepacz 2014) suggest that structural MRI combined with ^{11}C-PIB-PET produces the highest accuracy for the prediction of conversion from MCI to Alzheimer's disease and is superior to using either in isolation. Moreover, the combined use of ^{11}C-PIB and ^{18}F-FDG plus PET provided beneficial information for MCI due to non-ADD (Banzo 2014).

It is worth mentioning the greater consistency in sensitivity as an aspect of the results in our review, suggesting potential

value of the test as a rule-out test. This needs to be confirmed in larger studies with standardized PIB-PET techniques. We were not able to fully explore the causes of heterogeneity in specificity, so understanding the variability in specificity (if it persists when PIB-PET has been standardized) should also be an objective of further research. The above implications suggest that well designed studies and standardization through international collaboration are required.

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Contributions of authors

SZ: contributed to drafting protocol; data extraction; overall responsibility of study selection and data extraction; drafted Discussion and Authors' conclusion sections

CH: conception, funding, design, reviewing draft protocol and finalising manuscript

RMS: conception, funding, design, reviewing draft protocol and manuscript

ANS: developed search strategy and performed searches; contacted the authors

YT: performed statistical analyses, updated statistical methods section, wrote findings section and reviewed the draft manuscript

NS: designed and drafted protocol; study selection and data-extraction; characteristics of included and excluded studies tables; entered data and data entry check; QUADAS-2 assessment; set up data and analysis tables; created additional tables; drafted manuscript; managed the review process and produced progress reports, attended progress meetings and worked with all review authors to ensure that the review met publication deadlines

Declarations of interest

None known

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

Forsberg 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	Twenty-one patients with MCI and 37 patients with mild AD were recruited from Department of Geriatric Medicine at University Hostpital. No further details of recruitment were reported. Participants were referred from the primary care centres in the community (Forsberg 2008). We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable. No exclusion criteria were reported
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	21 MCI participants diagnosed by the modified Petersen criteria (Winblad 2004) at baseline (Forsberg 2008). All subjects lived independently in the community and a majority of the subjects below 65 years of age had still a professional job Gender: 8 male; 13 female AGE: mean: 63.3±7.8 years (range 50–78); MCI-AD: 63.4±7.9 years; MCI-MCI: 62.6±8.4 years APOE ε4 carrier: 14 (67%) (8 MCI-MCI; 6 MCI-AD) MMSE: mean 28.2±1.4 (range 25–30); MCI-AD 27.0±1.3; MCI-MCI 28.9±0.9 Sources of referral: primary care centres in community Setting: secondary care - outpatients (Department of Geriatric Medicine clinic)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	The PET examination with ^{11}C-PIB was performed at Uppsala PET centre/Uppsala Imanet AB in Uppsala, Sweden. Production of ^{11}C-PIB, tracer doses, and scanner protocol for transmissions, emissions and reconstructions have been described in detail previously (Klunke 2004) Time between PIB injection and PET acquisition: 60 minutes PIB administration dose: 300MBq Quantitative data on ^{11}C-PIB retention were generating giving late scan ratio data for ^{11}C-PIB retention (Forsberg 2008). ROIs (regions of interest) included the frontal, parietal and temporal cortices divided right and left, posterior cingulate, striatum, primary visual cortex and thalamus Threshold: ROI to-cerebellar ratio > 1.6 (PIB retention detecting regions: global cortex and thalamus). Threshold determined at follow-up. Index test was conducted at baseline

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: Alzheimer's disease dementia (conversion from MCI to AD) Reference standard: NINCDS-ADRDA criteria Details of follow-up procedures were not specified. Unclear whether clinicians conducting follow-up were aware of PIB-PET analysis results
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	All participants received the same reference standard Duration of follow-up: within 8.1±0.5 months (2-16 months) after their PET scans 7 MCI patients converted to AD; after 45.5±8.5 months of clinical follow-up 14 patients remained MCI stable; mean duration for all participants was not reported; average: 33.3±19.3 months (the data was calculated by ZS) Number included in analysis: 21 MCI: 11 MCI with positive PIB test: 7 converted to AD and 4 remained stable; 10 MCI with negative PIB test remained stable TP=7; FP=4; FN=0; TN=10 Loss to follow-up: data appeared to have been reported for all 21 participants
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Grimmer 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Participants had been referred for the diagnostic evaluation by general practitioners, specialists, or other institutions. No further details of recruitment were reported Exclusion criteria: psychotropic medication, substance misuse, major abnormalities in routine blood testing, or other neurological or psychiatric disorders
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	28 MCI participants diagnosed by the modified Petersen criteria (Winblad 2004) and CDR=0.5 (Morris 1993) criteria at baseline Gender: 14 male; 14 female AGE: mean: 67.9±7.4 years (range 50–79) APOE ε4 carrier: not reported MMSE: mean 26.0±3.19 (range 15–30) Education: 11.8±2.2 years (range 8-17) Sources of referral: mixed: primary and secondary care, and other institutions Setting: secondary care - outpatients (Psychiatry and Psychotherapy Department clinic)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Time between PIB injection and PET acquisition: 40-60 minutes PIB administration dose: 628 MBq (range 385 to 723 MBq Threshold: PIB-PET findings at baseline were dichotomised into amyloid positive or amyloid-negative using a cerebrum to cerebellar vermis ratio threshold of 1.4 as cut-off using proposed methods described above (Jack 2008). Threshold determined at baseline. Index test was conducted at baseline.

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: Alzheimer's disease dementia and other forms of dementia Reference standard: NINCDS-ADRDA criteria for Alzheimer's disease dementia and the Land criteria (Brun 1994) for FTD Clinicians conducting follow-up were blinded for the baseline PIB-PET findings
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	All participants received the same reference standard Duration of follow-up: mean was 31.2±7.8 months Number included in analysis: 28 MCI: 17 MCI with PIB positive test: 9 converted to AD and 8 remained stable; 11 MCI with PIB negative test: 3 converted to non-AD (2 FTD; 1 dementia not specified), 7 remained stable and 1 reverted to normal Conversion from MCI to AD dementia: TP=9; FP=8 FN=0; TN=11 Conversion from MCI to all dementia: TP=9; FP=8 FN=3; TN=8 Loss to follow-up: data appeared to have been reported for all 28 participants
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Jack 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	218 MCI participants were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (retrospective study). No discussion on when patients were recruited. 53 participants assessed by PIB-PET imaging and 165 by cerebrospinal fluid Aβ42 methods. No sampling criteria specified. We only included data on performance of the PIB-PET index test to discriminate between patients with MCI who convert to dementia and those who remained stable at follow-up. No exclusion criteria were reported
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	53 MCI participants diagnosed by the Petersen 2001 criteria. Demographic data reported on 218 participants Gender: 72 (33%) female AGE: 75 year APOE ε4 carrier not reported: MMSE: median (IQR) 27 (25, 29) Education: median duration (IQR) 16 (14, 18) Sources of referral: mixed: the local Alzheimer's Disease Research Center (ADRC), memory clinics, newspaper ads, radio and other public media campaigns Setting: mixed (ADNI participants at 13 different sites)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	A global cortical PIB PET retention summary was formed by combining the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate and posterior cingulate/precuneus values for each subject, using a weighted average of these regions of interest values Larger regions of interest were given greater weight. PIB PET ratio values calculated by dividing the median value in each target cortical region of by the median value in the cerebellar grey matter region of interest of the atlas Time between PIB injection and PET acquisition: 50-70 minutes PIB administration dose: not reported Threshold: mean neocortical distribution volume ratio (DVR) > 1.5 (PIB retention detecting regions: global cortex). Threshold determined at baseline. Index test was conducted at baseline

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: Alzheimer's disease (conversion from MCI to AD) Reference standard: NINCDS-ADRDA criteria Unclear whether clinicians conducting follow-up were aware of PIB-PET analysis results
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	No discussion on when patients were recruited All participants received the same reference standard Duration of follow-up: a median progression-free follow-up time of 1.7 years Number included in analysis: 53 MCI: 34 MCI with PIB positive test: 15 converted to AD and 19 remained stable; 19 MCI with PIB negative test: 3 converted to AD and 16 remained stable TP=15; FP=19; FN=3; TN=16 Loss to follow-up: data appeared to have been reported for all 53 participants
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	
Notes	The trial investigators contacted; they provided requested data tor the 2X2 table to be completed; email from Dr Weigand on 11/5/12

Koivunen 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	Twenty-nine consecutive MCI patients seen at the memory clinic and who volunteered for PET scanning, and thirteen healthy controls were included in the study. We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable. No inclusion or exclusion criteria described
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	29 participants diagnosed by Petersen 2004 criteria: all patients had subjective memory impairment that was confirmed in neuropsychological testing, and some patients had mild decline in other cognitive domains. Clinical Dementia Rating (CDR) was 0.5, global cognition was normal, activities of daily living were not impaired, and no subject had dementia at baseline Gender: 11 women, 18 men Age: total sample 71.3±6.4 years; MCI converters 73.6±7.2 years; non-MCI converters 70.8±4.9 years APOE ε4 carrier: total sample 17; MCI converters 14; non-MCI converters 3 MMSE: total sample 26.9±1.6; MCI converters 26.2±1.5; non-MCI converters 27.9±1.3 Sources of referral: not reported Setting: secondary care - outpatients (memory clinic)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	An Advance PET scanner was used in the 3D scanning mode.ROIs were drawn on the anterior and posterior cingulate, lateral frontal cortex, caudate nucleus, putamen, thalamus, lateral temporal cortex, parietal cortex, medial temporal lobe, and pons. Average regional ratio values of 11C-PIB uptake were calculated using these ROIs from spatially normalised parametric ratio images Time between PIB injection and PET acquisition: 90 minutes. PIB administration dose: not reported Threshold: region-to-cerebellum ratio≥1.5 (PIB retention detecting regions: global cortex, caudate nucleus, putamen, thalamus, pons). Threshold determined at baseline Index test was conducted at baseline

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: Alzheimer's disease dementia (conversion from MCI to AD) Reference standard: NINCDS-ADRDA criteria; DSM-IV criteria Unclear whether clinicians conducting follow-up were aware of PIB-PET analysis results
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	It was not clear whether all participants received the both reference standards Duration of follow-up: 2 years Number included in analysis: 29 MCI: 17 MCI converted to AD and 12 remained stable 1) Anterior cingulate: sensitivity=82%; specificity=58% TP=14; FP=5; FN=3; TN=7 2) Posterior cingulate: sensitivity=94%; specificity=58% TP=16; FP=5; FN=1; TN=7 3) Lateral frontal cortex: sensitivity=65%; specificity=67% TP=11; FP=4; FN=6; TN=8 4) Parietal cortex: sensitivity=41%; specificity=67% TP=7; FP=4; FN=11; TN=8 5) Temporal cortex: 53%; specificity=67% TP=9; FP=4; FN=8; TN=8 Loss to follow-up: data appear to have been included for all 29 participants
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

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Okello 2009

Patient Selection

A. Risk of Bias	
Patient Sampling	Thirty-one participants were recruited from UK and Finnish Hospitals. No further details of recruitment were reported Patients with significant white matter disease in the view of an experienced radiologist were excluded from the study. No further exclusion criteria were reported
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	31 MCI participants diagnosed by the Petersen 2001 criteria: subjective memory complaint by the patient, preferably corroborated by an informant; objective memory impairment as assessed by performance below age-matched normals on at least one neuropsychological measure of memory; relatively normal performance in other cognitive domains; intact activities of daily living; no dementia. A strict cut-off score was not applied for the definition of objective memory impairment Gender: 19 male, 12 female Age: total sample 69.4±7.9 years; MCI converters 71.6±6.3 years; non-MCI converters 67.9±9.0 years APOE ε4 carrier: not reported MMSE: total sample 27.5±1.5; MCI converters 27.1±1.5; non-MCI converters 27.9±1.3 Sources of referral: not reported Setting: secondary - inpatients (three UK hospitals and one Finland hospital)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	All UK participants were scanned using a Siemens ECAT EXACT HR+ camera in 3-dimensional acquisition mode. The Finland sample were scanned with a GE advance camera, using previously described protocol (Kemppainen 2006) Time between PIB injection and PET acquisition: 90 minutes for DVR; 40-60 minutes for SUVR PIB administration dose: 367±25 MBq in UK; 487±44 MBq in Finland Threshold: region to cerebellum ratio ≥ 2SD greater than the control mean in all 6 ROIs (regions of interest). PIB retention ratio values for each MCI participant were compared to that of the control mean of their scanning site (visual assessment) Threshold determined at baseline Index test was conducted at baseline

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: Alzheimer's dementia (conversion from MCI to Alzheimer's dementia) Reference standard: NINCDS-ADRDA criteria Unclear whether clinicians conducting follow-up were aware of PIB-PET analysis results
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	All participants received the same reference standard Duration of follow-up: total sample: mean 2.68±0.6 years (32.2±7.2 months), range 1-3 years; mean 2.9±0.5 years in converters; 2.5±0.7 years in non-converters At follow-up: 15 MCI-converters and 17 MCI-nonconverters Number included in analysis=31: 17 with positive PIB tests: 14 MCI-AD, 3 MCI-MCI; 14 with negative PIB tests: 1 MCI-AD, 13 MCI-MCI TP=14; FP=3; FN=1; TN=13 Loss to follow-up: data appeared to have been reported for all 31 participants
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Ossenkoppele 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	At baseline 15 participants were included in each group: MCI, AD and controls. No further details of patient sampling and recruitment were reported. We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable Exclusion criteria were a history of major psychiatric or neurological illness (other than AD) and the use of nonsteroidal antiinflammatory drugs Patients with severe vascular events during the follow-up period, such as stroke or haemorrhage, were also excluded
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	15 participants diagnosed by the Petersen 1999 criteria Gender: male 9; female 3 Age: 67±7 APOE ε4 carrier: 8 MMSE: 27±3 Education: median (range): 6 (3-7) Sources of referral: not reported Setting: not reported
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	A dynamic emission scan in three-dimensional acquisition mode was used Time between PIB injection and PET acquisition: 90 minutes PIB administration dose: 351± 82 MBq Threshold: Visual assessment. ^{11}CPIB scans were classified as either positive or negative, based on visual inspection of parametric BPND images by a trained nuclear medicine physician. Not reported when threshold was determined Index test was conducted at baseline

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: conversion from MCI to AD or other type of dementia Reference standards: NINCDS-ADRDA criteria for AD (McKhann 1984); Reference standard for the clinical criteria for FTD not reported
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Duration of follow-up: 2.5 years (range 2.0–4.0 years) Number included in analysis: 12 MCI: 5 PIB+: 4 MCI-AD, 1MCI-non-converter: 7 PIB-: 1 MCI-FTD; 6 MCI-non-converters Conversion from MCI to AD: 5 PIB+: 4 MCI-converters and 1 MCI-non-converter; 7 PIB-: 0 MCI-converters and 7 MCI-non-converters (6 MCI-MCI; 1 MCI-FTD) TP=4; FP=1; FN=0; TN=7 Conversion from MCI to all dementia: 5 PIB+: 4 MCI-converters and 1 MCI non-converter; 7 PIB-: 1 MCI-converter and 6 MCI- non-converters. Two out of seven MCI-non-converters converted to 'cognitively improved' and five remained stable TP=4; FP=1; FN=1; TN=6 Loss to follow-up: 3 MCI patients refused to participate in the follow-up study due to lack of motivation
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	
Notes	The trial investigators contacted; they provided requested data tor the 2X2 table to be completed and confirmed there are no overlapping patients with the Ossencoppele 2012a study; email from Dr Ossenkopele on 5/3/13

Ossenkoppele 2012a

Patient Selection

A. Risk of Bias	
Patient Sampling	154 participants included from the outpatient memory clinic of the VU University Medical centre for assessing the impact of molecular imaging on the diagnostic process. Among those participants there were 30 MCI participants. No further details of patient sampling and recruitment were reported. We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable. Exclusion criteria: major clinical and psychiatric disorders, recent vascular events and excessive substance abuse
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	30 MCI participants diagnosed by the Petersen 2001 criteria Gender: male 23; female 7 Age: 64±9 APOE ε4 carrier: not reported MMSE: 27±2 Sources of referral: not reported Setting: secondary care - outpatients (memory clinic)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	A dynamic emission scan in three-dimensional acquisition mode was used Time between PIB injection and PET acquisition: 90 minutes PIB administration dose: 367± 43 MBq at baseline Threshold: Visual assessment: [11C]PIB PET scans were rated as either PIB-positive (PIB1; binding in more than one cortical brain region; i.e., frontal, parietal, temporal, or occipital) or PIB-negative (PIB2, predominantly white matter binding), based on visual inspection of parametric BPND images by a trained nuclear medicine physician. Not reported when threshold was determined. Index test was conducted at baseline and at follow up. It was not reported whether the index test baseline results were interpreted without knowledge of the results of the reference standard. Outcome measures were changes in clinical diagnosis and confidence in that diagnosis before and after disclosing PET results. The main focus of this study was not 'conversion from MCI to dementia; however, the author provided us with the relevant information for creating 2X2 table and, therefore, this study has been included.

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: conversion from MCI to AD or other type of dementia Reference standards: not explicitly stated, although NINCDS-ADRDA criteria for AD (McKhann 1984), Neary 1998 criteria for FTD were baseline diagnostic criteria
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Duration of follow-up: 2 years Number included in analysis: 12 MCI: 7 PIB+: 6 MCI-AD and 1 MCI-MCI; 5 PIB-: 1 MCI-FTD and 2 MCI-MCI and 1 MCI-cognitively improved and 1MCI-psychiatric disorder Conversion from MCI to AD: 7 PIB+: 6 MCI-converters and 1 MCI-non-converter; 5 PIB-: 0 MCI-converters and 5 MCI-non-converters TP=6; FP=1; FN=0; TN=5 Conversion from MCI to all dementia: 7 PIB+: 6 MCI-converters and 1 MCI non-converter; 5 PIB-: 1 MCI-converter and 4 MCI- non-converters. TP=6; FP=1; FN=1; TN=4 Loss to follow-up: 18 MCI patients. No further information
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Notes

Notes	
Notes	The trial investigators contacted; they provided requested data tor the 2X2 table to be completed and confirmed there are no overlapping patients with the Ossencoppele 2012 study; email from Dr Ossenkopele on 5/3/13

Villemagne 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	MCI and DAT participants were recruited from the Austin Health Memory Disorders Clinic. Controls were recruited by advertisement and from the Melbourne Healthy Aging Study. We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable.. No further details on recruitment are presented. No inclusion or exclusion criteria are described
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	67 MCI participants diagnosed by the Petersen 1999 criteria. Demographic data were reported for 65 MCI participants who were further classified as a amnestic MCI (n=53) or nonamnestic MCI (4 nonamnestic single domain and 8 nonamnestic multiple domain) Gender: 36 male, 29 female Age:73.4±8.5 years APOE ε4 carrier: 41 (63%) MMSE: 26.5±2.9 Years of education: 12.2±4.3 Sources of referral: mixed: advertisements and the Melbourne Healthy Aging Study Setting: secondary care - outpatients (memory clinic)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Standardized uptake values (SUVs) for PiB were calculated for all brain regions examined and SUV ratios (SUVRs) were generated by dividing all regional SUVs by the cerebellar cortex SUV. ROI measurements were averaged across both hemispheres. Neocortical Ab burden was expressed as the average SUVR of the area-weighted mean of frontal, and posterior cingulate regions Time between PIB injection and PET acquisition: 40 minutes PIB administration dose: 370MBq Threshold: neocortical standardised uptake values ratio (SUVR) > 1.5 (PIB retention detecting regions: global cortex). To define a PiB SUVR cut-off, a hierarchical cluster analysis was performed on all healthy controls. Threshold determined at baseline and was consistent with cutoff values used in previous PIB-PET studies (Bourgeat 2010; Jack 2008) Index test was conducted at baseline

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: Alzheimer's disease dementia and other forms of dementia Reference standard: NINCDS-ADRDA criteria for Alzheimer's disease dementia. Neurologist and a neuropsychologist conducting follow-up blind to PIB status Reference standards for VD and FTD not reported
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Duration of follow-up: mean was 20±3 months. All participants received the same reference standard Number included in analysis: 65 MCI: 45 'amyloid positive': 30 MCI-AD, 15 MCI-MCI; 20 'amyloid negative': 5 converters (1 MCI-AD; 1 MCI-VD; 1 MCI-FTD; 2 LBD); 15 non-converters (13 MCI-MCI; 2 MCI-HC) Conversion from MCI to AD: 45 PIB+: 30 MCI-converters (MCI-AD) and 15 MCI-non-converter (MCI-MCI); 20 PIB-: 1 MCI-converter (MCI-AD) and 19 MCI-non-converters (1 MCI-VD; 1 MCI-FTD; 2 LBD; 13 MCI-MCI; 2 MCI-HC) TP=30; FP=15; FN=1; TN=19 Conversion from MCI to all dementia: 45 PIB+: 30 MCI-converters and 15 MCI non-converter; 20 PIB-: 5 MCI-converters (1 MCI-AD; 1 MCI-VD; 1 MCI-FTD; 2 LBD) and 15 MCI- non-converters. Two out of seven MCI-non-converters converted to 'cognitively improved' and five remained stable TP=30; FP=15; FN=5; TN=15 Loss to follow-up: 2 MCI participants: 1 participant was withdrawn by their caregivers and 1 participant was not contactable
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Wolk 2009

Patient Selection

A. Risk of Bias	
Patient Sampling	Twenty-six patients with MCI, 22 patients with mild Alzheimer's disease and 35 healthy elderly participants. The clinical diagnosis for those who entered the University of Pittsburgh Alzheimer’s Disease Research Center (ADRC) was made through consensus at a conference. The conference was attended by neurologists, psychiatrists, and neuropsychologists experienced in the diagnosis of dementia. Assessment included medical and neurological history and examination, a semi-structured psychiatric evaluation, and psychometric testing. We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable. MCI participants were recruited from ADRC. Nine participants already had PiB PET data. No further details of recruitment were reported. Inclusion criteria: age 40 years or older, proficient English speaker, and a reliable caregiver Exclusion criteria: lifetime history of schizophrenia, manic-depressive disorder, or schizoaffective disorder; prior electroconvulsive therapy; current substance abuse/dependence or within 2 years of symptom onset; and any medical condition that could affect neuropsychological testing
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	26 MCI participants diagnosed by the Petersen 2004 and modified Petersen (Winblad 2004) criteria. MCI-multiple cognitive domain cases were reviewed and subdivided according to the Gauthier et al. scheme (Gauthier 2008). No strict cutoffs on psycho-metric testing were used. Impairment was "generally" less than 1.5 SDs of University of Pittsburgh ADRC age-adjusted norms (13 single-domain amnestic-MCI; 6 multi-domain a-MCI; 7 non-amnestic MCI). The clinicians were aware of the previous year's diagnosis at follow-up consensus discussions Gender: total 7 female and 19 male; 3 of 19 amnestic-MCI is female, 4 of 7 nonamnestic-MCI is female Age: total 70.2±8.8 years; amnestic-MCI is 71.6±8.0, noamnestic-MCI is 69.6±9.2 APOE ε4 carrier: total 14 APOE4 carrier; 9 out of 11 a-MCI Amyloid-Positive; 4 out of 8 a-MCI Amyloid-Negative; 0 out of 3 na-MCIAmyloid-Positive; 1 out of 3 na-MCIAmyloid-Negative. One a-MCI patient did not have ApoE results available MMSE: total 27.3±1.9 (calculated by ZS); amnestic-MCI is 27.2±2.1; noamnestic-MCI is 27.7±1.1 Education: mean 16.6± 3.3 years for a-MCI; mean 18.7± 2.6 years for na-MCI Sources of referral: not reported Setting: tertiary setting - Pittsburg Alzheimer's Disease Research Center
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PET imaging was conducted on a Siemens/CTI ECAT HR+(Siemens, Erlangen, Germany). The scanner was equipped with Neuro-insert (CTI PET Systems, Knoxville, TN) to reduce the contribution of scattered photons Time between PIB injection and PET acquisition: 90 minutes for DVR; 40–60 minutes for SUR PIB administration dose: 14.3±2.2mCi Threshold:DVR or SUR of region of interest > upper-inner fence of the control subjects. To avoid a strict cutoff, authors defined an intermediate range 2.5% greater than and less than this cutoff (Aizenstein 2008). Subjects who had a PiB DVR value exceeding the intermediate range in any ROI was defined as amyloid-positive, and those under the intermediate range were defined as amyloid-negative. For the two MCI patients who did not have DVR values SUV ratios were used to determine cutoffs (these are not described). Threshold determined at baseline. ROIs were defined on a co-registered magnetic resonance image, as described previously (Price 2005); these included frontal, anterior cingulate, precuneus, lateral temporal, parietal, medial temporal, occipital, and sensorimotor cortices, anterior ventral striatum, subcortical white matter, and pons. A cerebellar ROI served as reference region, and the pons and subcortical white matter ROIs were measures of nonspecific ligand retention. Scanning was performed within approximately 6 months of ADRC evaluation (mean SD, 14.9 ± 7.3 weeks) Index test was conducted at baseline and the results were available for all participants

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Target condition: conversion from MCI to Alzheimer's disease dementia Reference standard: the clinical diagnosis was made through consensus at a conference, attended by neurologists, psychiatrists and neuropsychologists experienced in the diagnosis of dementia It was not reported whether the reference standard results were interpreted without knowledge of the results of the index test
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Duration of follow-up: mean 21.2 ± 16.0 months subsequent to their PiB scan All participants received the same reference standard Number included in analysis: 23 MCI: 13 'amyloid positive': 5 MCI-AD, 8 MCI-MCI; 10 'amyloid negative': 0 MCI-AD; 10 non-converters (7 MCI-MCI; 3 MCI-normal) TP=5; FP=8; FN=0; TN=10 Loss to follow-up: 3 MCI participants; they did not have follow-up assessment; two of those patients did not complete the entire protocol
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Footnotes

Characteristics of excluded studies

Choo 2011

Reason for exclusion	Target condition: not looking at conversion from MCI to dementia. The focus of the study is the annual change in PIB retention

Driscoll 2011

Reason for exclusion	Target condition: not looking at conversion from MCI to dementia

Ellis 2010

Reason for exclusion	Target condition: not looking at conversion from MCI to dementia

Fagan 2007

Reason for exclusion	Index test: PIB-PET test performed at follow-up Target condition: not looking at conversion from MCI to dementia

Kadir 2012

Reason for exclusion	Target condition: not looking at conversion from MCI to dementia

Kadir 2012a

Reason for exclusion	Target condition: not looking at conversion from MCI to dementia

Resnick 2010

Reason for exclusion	Target condition: not looking at conversion from MCI to dementia. The focus of the study is the association abeta deposition and cognitive decline

Rowe 2010

Reason for exclusion	Target condition: not looking at conversion from MCI to dementia

Shinotoh 2011

Reason for exclusion	Index test: threshold not used Target condition: not looking at conversion from MCI to dementia. The focus of the study is the change in PIB retention over time

Sojkova 2008

Reason for exclusion	Participants: 28 non-demented subjects; only 6 participants with mild cognitive impairment (CDR=0.5) at baseline Target condition: not looking at conversion to dementia. The focus of the study is the annual change in PIB retention in high and low PIB retention groups

Sojkova 2011

Reason for exclusion	Target condition: not looking at conversion from MCI to dementia. The focus of the study is the annual change in PIB retention over time

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

DeKosky 2006

Study name	Human amyloid-imaging studies with Pittsburgh Compound-B in Mild Cognitive Impairment (MCI): Is MCI the critical period of amyloid plaque deposition?
Target condition and reference standard(s)	Target condition: conversion from MCI to Alzheimer's disease dementia Reference standard: not reported
Index and comparator tests	11C-PIB-PET
Starting date	not reported
Contact information	sd3zc@hscmail.mcc.virginia.edu
Notes	

Footnotes

Summary of results tables

1 Performance of ^{11}C-PIB-PET amyloid biomarker for detecting Alzheimer's disease dementia and predicting progression to dementia in patients with MCI

What is the diagnostic accuracy of ^{11}C-PIB-PET amyloid biomarker for detecting Alzheimer's disease and predicting progression to dementia in patients with MCI?	
Descriptive	
Patient population	Participants diagnosed with MCI at baseline using any of the Petersen criteria or CDR=0.5 or any 16 definitions included by Matthews (Matthews 2008)
Sources of referral	· primary care centres in community (n=1) · mixed (community/primary care/secondary care/other) (n=3) · not reported (n=5)
MCI criteria	· Petersen criteria (n=6) · Petersen and modified Petersen criteria (n=1) · modified Petersen criteria (n=1) · CDR=0.5 criteria and modified Petersen criteria (n=1)
Sampling procedure	· consecutive or random (n=1) · not consecutive or random (n=1) · unclear (n=7)
Prior testing	The only testing prior performing the ^{11}C-PIB-PET biomarker was the application of diagnostic criteria for identifying participants with MCI
Settings	· secondary care – outpatients (n=5) · secondary care – inpatients (n=1) · mixed setting (n=1) · tertiary setting (n=1) · not reported (n=1)
Index tests	^{11}C-PIB-PET
Threshold pre-specified at baseline	· Yes (n=6) · No (n=1) · Not reported (n=2)
Threshold interpretation	· quantitative (n=5) · visual (n=4)

Threshold	· DVR (Distribution Volume Ratio) of ROI: >1.5 (n=1) · SUVR (Standardised Uptake Volume ratio) of ROI: > 1.5 (n=1) · not specified analytical approach of ROI: 1.4; >1.5; >1.6 (n=3) · RATIO > 2SD than control mean in 6 ROI (n=1) · DVR or SVR of ROI > upper-inner fence of the control (n=1) · not reported (n=2)						
PIB retention region	· Global cortex (n=5) · Global cortex and other brain region (n=4)						
Reference standard	For Alzheimer's disease dementia: · NINCDS-ADRDA (n=7) · DSM-IV and/ or NINCDS-ADRDA (n=1) · unclear (n=1) For FTD: Land criteria or Neary 1998 criteria						
Target condition	Conversion from MCI to Alzheimer's disease dementia and any other forms of dementia						
Included studies	Prospectively well-defined cohorts with any accepted definition of MCI (as above). Nine studies (N=300 participants) were included. Number included in analysis: 274						
Quality concerns	Patient characteristics and conduct of the index and reference standard were poorly reported. Applicability concerns were generally low.						
Limitations	Limited investigation of heterogeneity due to insufficient number of studies. Lack of common thresholds.						
Test	**Studies**	**Cases/ Participants**	**Median / lower quartile / upper quartile specificity from included studies**	**Sensitivity (95% CI)[1] at / lower quartile / upper quartile median specificity**	**Consequences in a cohort of 100**		
					Median proportion converting (range)[2]	Missed cases[3]	Over diagnosed[3]
Alzheimer's disease							
^{11}C-PIB-PET	9	112/274	58 (median)	96 (87, 99)	34 (33 to 48)	1	28
^{11}C-PIB-PET	9	112/274	56 (lower quartile)	96 (88, 99)			
^{11}C-PIB-PET	9	112/274	81 (upper quartile)	89 (68, 97)			
Investigation of heterogeneity: The planned investigations were not possible due to the limited number of studies available for each analysis. For type of reference standard, most studies belonged to the same subgroup and so we conducted sensitivity.							
Conclusions: ^{11}C PIB-PET scan is not an accurate test for detecting conversion from MCI to Alzheimer's disease or other forms of dementia. The strength of the evidence is weak because of considerable variation in study methods and unclear methodological quality due to poor reporting. There is a need for conducting studies using standardised PIB-PET methodology in larger populations.							

Footnotes

[1] Meta-analytic estimate of sensitivity derived from the HSROC model at a fixed value of specificity. Summary estimates of sensitivity and specificity were not computed because the studies that contributed to the estimation of the summary ROC curve used various thresholds.

[2] The median proportion converting (reported in percentage) and range were computed using all the studies included in the analysis for each target condition.

[3] Missed and over-diagnosed numbers were computed using the median proportion converting to each target condition.

Additional tables

1 Demographic and patient characteristics

Study	N/n	Age	Gender M (%)	MMSE score	APOE Ɛ4 carrier (%)	Years of education/ Verhage's classification*	MCI diagnostic criteria	Sampling	Sources of referral	Setting
Forsberg 2010 (Sweden)	21/21	63.3 ± 7.8	8 (38.1)	28.2±1.4	14 (66.7)	12.7 ±3.1	Winblad 2004	Not reported	Primary care centers in community	Secondary care: outpatients
Grimmer 2013 (Germany)	28/28	67.9±7.4	14 (50)	26.0±3.2	Not reported	11.8 ±2.2 (range 8-17)	CDR=0.5 and Winbald 2004	Not reported	GP surgeries or specialists or other institutions	Secondary care: outpatients
Jack 2010 (USA)	53/53	75	Not reported	27	Not reported	16	Petersen 2010	ADNI participants	Mixed	Mixed: 13 different sites
Koivunen 2011 (Finland)	29/29	71.3 ± 6.4	18 (62.1)	26.9±1.6	17 (58.6)	Not reported	Petersen 2004	Consecutive sample	Not reported	Secondary care: outpatients: memory clinic:
Okello 2009 (UK/Finland)	31/31	69.4 ± 7.9	19 (61.3)	27.5±1.5	Not reported	Not reported	Petersen 2010	Not reported	Not reported	Secondary care: inpatients
*Ossenkoppele 2012 (Netherland)	15/12	67±7	Not reported	27±3	Not reported	median 6 (range 3-7)*	Petersen 2001	Not reported	Not reported	Not reported
Ossenkoppele 2012a (Netherland)	30/12	64±9	Not reported	27±2	Not reported	Not reported	Petersen 1999	Not reported	Not reported	Secondary care: outpatients: memory clinic:
Villemagne 2011 (Australia)	67/65	73.4±8.5	36 (55.4)	26.5±2.9	41 (63)	12.2 ±4.3	Petersen 1999	Not reported	Mixed (advertisements and the Melbourne Healthy Aging Study	Secondary care: outpatients: memory clinic:
Wolk 2009 (USA)	26/23	70.2±8.8	Not reported	27.3±1.9	Not reported	17.2 ±3.2	Petersen 2004; Winbald 2004	Not reported	Not reported	Tertiary setting: Pittsburg ADRC

Footnotes

N=number of MCI participants at baseline; n=number of participants included in analysis at follow-up; M=number of males

*Study used Verhage's classification on a scale of 1-7 (means 6; range 3-7), not years, for the unit of education

2 Index test and number of converters to Alzheimer's disease dementia

Study	Threshold (pre-specified Yes/No)	Measure of PIB amyloid retention	Image analysis	Time between PIB injection and PET acquisition (min)	PIB dose	PIB retention detecting regions	Number of PIB positive (%)	Number of converters (%)	Duration of follow-up Mean (months) / Maximum (years)
Forsberg 2010 (Sweden)	Not specified analytical approach of ROI to-cerebellar ratio >1.6 (No)	ROI to-cerebellar ratio	SPM2 and MATLAB 7.1	60	300 MBq	Global cortex and thalamus	11 (52.4)	7 (33.3)	33.3 ±19.3 / Not reported

Grimmer 2013 (Germany)	Not specified analytical approach of ROI to-cerebellar vermis ratio of 1.4 (Yes)	ROI to-cerebellar ratio	Not reported	40-60	628 MBq (range 385 to 723 MBq)	Global cortex	17 (60.7)	9 (32.2)	31.2 ±7.8 / Not reported
Jack 2010 (USA)	DVR of ROI to-cerebellar ratio >1.5 (Yes)	Average neocortical to-cerebellar ratio	Automated image processing pipeline	Range 50-70	Not reported	Global cortex	34 (64.2)	18 (34.0)	Not reported / 1.7 (median)
Koivunen 2011 (Finland)	Not specified analytical approach of ROI to-cerebellar ratio > 1.5 (Yes)	Posterior cingulate to-cerebellar ratio	SPM2	90	Not reported	Global cortex, caudate nucleus, putamen, thalamus, pons	21 (72.4)	17 (58.6)	Not reported / 2
Okello 2009 (UK/Finland)	RATIO > 2 SD greater than the control mean in all 6 ROI (visual interpretation) (Yes)	RATIO	SPM	Range 60–90	367 ± 25 MBq	Global cortex	17 (54.8)	15 (48.4)	27.5±1.5 / 3 (range 1-3)
Ossenkoppele 2012 (Netherland)	Not reported (visual interpretation)	Visual inspection of parametric BP_{ND} images by a trained nuclear medicine physician	BP_{ND}	90	351 ± 82 MBq	Global cortex, frontal, parietal and lateral temporal and medial temporal lobe and posterior cingulate	5 (41)	4 (33.3)	30.0±6.0 / 4 (range 2-4)
Ossenkoppele 2012a (Netherland)	Not reported (visual interpretation)	Visual inspection of parametric BP_{ND} and SUVr images by a trained nuclear medicine physician	BP_{ND}	Range 60-90	367 ± 43 MBq	Frontal, parietal, temporal and occipital lobe	7 (58.3)	6 (50.0)	Not reported / 2
Villemagne 2011 (Australia)	SUV of ROI >1.5 (Yes)	Average neocortical to-cerebellar ratio	MilxView	40	370 MBq	Global cortex	45 (69.2)	31 (68.9)	20.0±3.0 / Not reported

Wolk 2009 (USA)	DVR or SUV of ROI > upper-inner fence of the controls; an intermediate range 2.5% greater than and less than this cut-off subjects (visual interpretation) (Yes)	ROI to-cerebellar ratio	SPM5	90 for DVR; range 40–60 for SUVR	14.3 ± 2.2 mCi	Global cortex, anterior ventral striatum, subcortical white matter, pons	13 (56.5)	5 (21.7)	21.2±16.0 / Not reported

Footnotes

3 Index test: Criteria for quantitative or visual interpretation and PIB retention in brain ROI areas

Threshold for a positive PIB-PET test	
Quantitative interpretation:	
1. DVR (Distribution Volume Ratio) of ROI: >1.5 (n=1)	
2. SUVR (Standardised Uptake Volume ratio) of ROI: > 1.5 (n=1)	
3. Not specified analytical approach of ROI: 1.4; >1.5; >1.6 (n=3)	
Visual interpretation:	
1. RATIO > 2SD than control mean in 6 ROI (n=1)	
2. DVR or SVR of ROI > upper-inner fence of the control (n=1)	
3. Threshold not reported in 2 studies	
Measure of PIB amyloid retention	**PIB retention in brain areas (ROI)**
1. ROI to cerebellar ratio (n=3)	Global cortex
	Global cortex and thalamus
	Global cortex, anterior ventral striatum, subcortical white matter, pons
2. Average neocortical to cerebellar ratio (n=2)	Global cortex
3. Posterior cingulate to cerebellar ratio (n=1)	Global cortex, caudate nucleus, putamen, thalamus, pons
4. RATIO (n=1)	Global cortex
5. Visual inspection of parametric BP_{ND} images (n=1)	Global cortex, frontal, parietal and lateral temporal and medial temporal lobe and posterior cingulate
6. Visual inspection of parametric BP_{ND} and SUVR images (n=1)	Frontal, parietal, temporal and occipital

Footnotes

4 Sensitivity and likelihood ratios for ^{11}C-PIB-PET at fixed values of specificity for Alzhemer's dementia

Statistic	Fixed value of specificity %	Estimated sensitivity % (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)
All studies (n = 9; cases = 112 ; non-cases = 162)				
Lower quartile	56	96 (88, 99)	2.19 (2.09, 2.29)	0.07 (0.02, 0.23)
Median	58	96 (87, 99)	2.29 (2.17, 2.41)	0.07 (0.02, 0.24)
Upper quartile	81	89 (68, 97)	4.66 (4.03, 5.39)	0.14 (0.05, 0.44)
Sensitivity analyses				
Reference standard NINCDS-ADRDA only (n = 7; cases = 89; non-cases = 144)				
Lower quartile	56	96 (84, 99)	2.18 (2.06, 2.32)	0.07 (0.02, 0.30)
Median	58	96 (83, 99)	2.28 (2.14, 2.43)	0.07 (0.02, 0.31)
Upper quartile	81	88 (62, 97)	4.62 (3.86, 5.55)	0.15 (0.04, 0.56)
Threshold pre-specified (n = 7; cases = 101; non-cases = 140)				
Lower quartile	56	95 (84, 99)	2.16 (2.02, 2.30)	0.09 (0.03, 0.30)
Median	58	94 (83, 98)	2.25 (2.10, 2.41)	0.10 (0.03, 0.32)
Upper quartile	81	85 (61, 95)	4.46 (3.67, 5.42)	0.19 (0.06, 0.55)

Footnotes

The middle 50% of specificities from the studies are between the lower and upper quartile, i.e. the interquartile range

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Other published versions of this review

Classification pending references

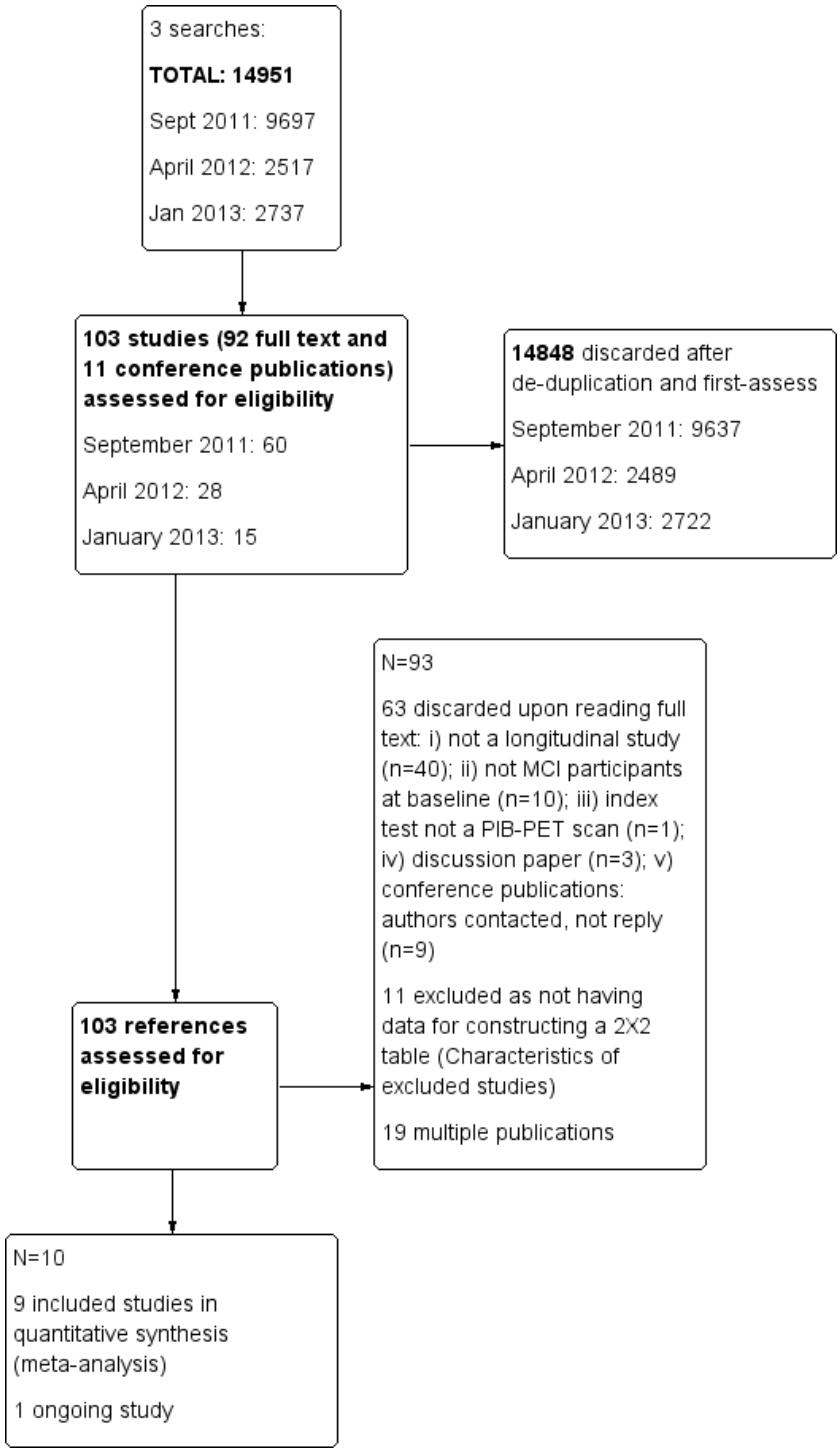
Data and analyses

Data tables by test

Test	Studies	Participants
1 ^{11}C-PIB-PET AD dementia	9	274
2 ^{11}C-PIB-PET All dementia	4	117

Figures

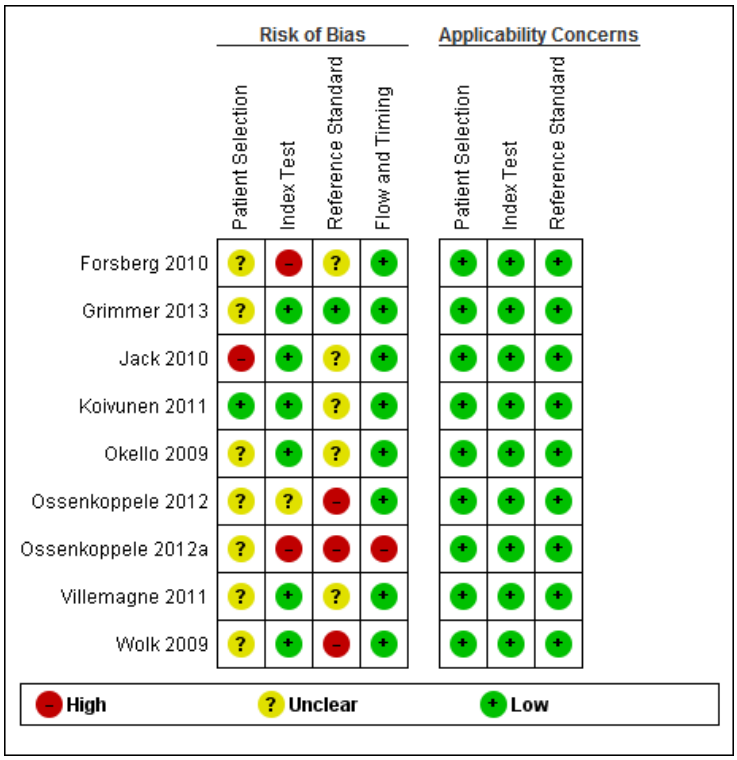
Figure 1



Caption

Study flow diagram.

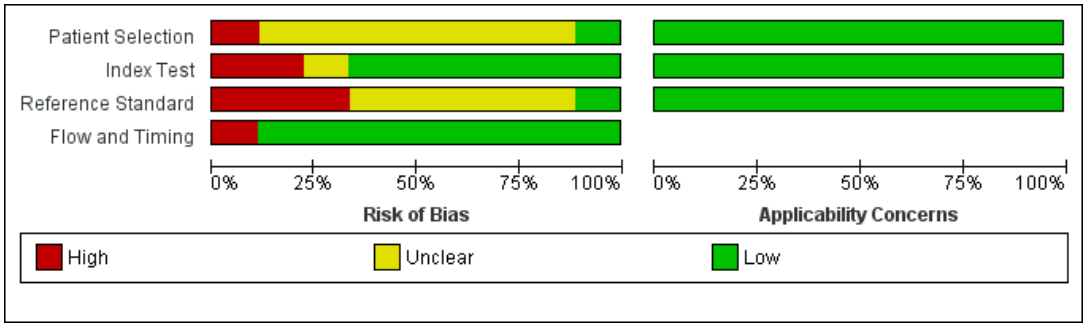
Figure 2



Caption

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

Figure 3

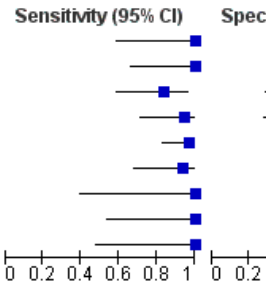


Caption

Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

Figure 4 (Analysis 1)

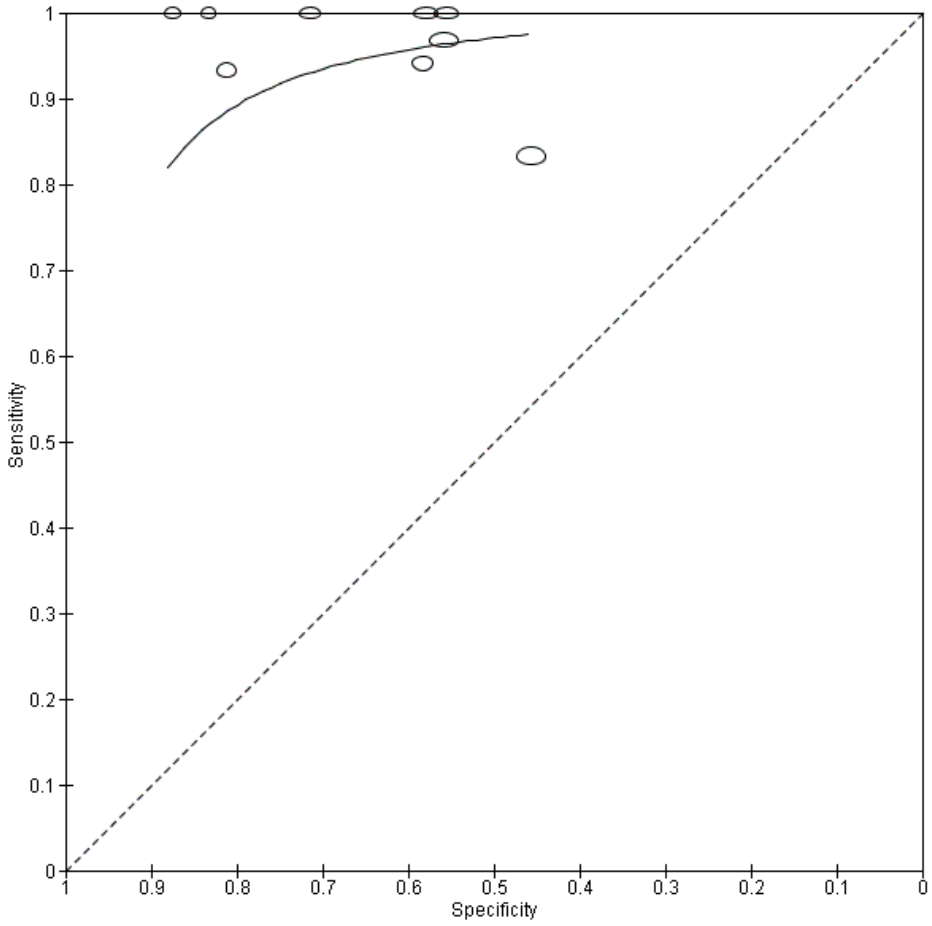
Study	TP	FP	FN	TN	Threshold type	Threshold pre-specified	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Spec
Forsberg 2010	7	4	0	10	quantitative	No	1.00 [0.59, 1.00]	0.71 [0.42, 0.92]		
Grimmer 2013	9	8	0	11	quantitative	Yes	1.00 [0.66, 1.00]	0.58 [0.33, 0.80]		
Jack 2010	15	19	3	16	quantitative	Yes	0.83 [0.59, 0.96]	0.46 [0.29, 0.63]		
Koivunen 2011	16	5	1	7	quantitative	Yes	0.94 [0.71, 1.00]	0.58 [0.28, 0.85]		
Villemagne 2011	30	15	1	19	quantitative	Yes	0.97 [0.83, 1.00]	0.56 [0.38, 0.73]		
Okello 2009	14	3	1	13	visual inspection	Yes	0.93 [0.68, 1.00]	0.81 [0.54, 0.96]		
Ossenkoppele 2012	4	1	0	7	visual inspection	Not reported	1.00 [0.40, 1.00]	0.88 [0.47, 1.00]		
Ossenkoppele 2012a	6	1	0	5	visual inspection	Yes	1.00 [0.54, 1.00]	0.83 [0.36, 1.00]		
Wolk 2009	5	8	0	10	visual inspection	Yes	1.00 [0.48, 1.00]	0.56 [0.31, 0.78]		



Caption

Forest plot of ^{11}C-PIB-PET AD dementia.

Figure 5 (Analysis 1)

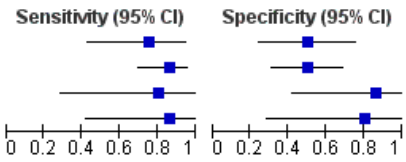


Caption

Summary ROC plot of ^{11}C-PIB-PET AD dementia.

Figure 6 (Analysis 2)

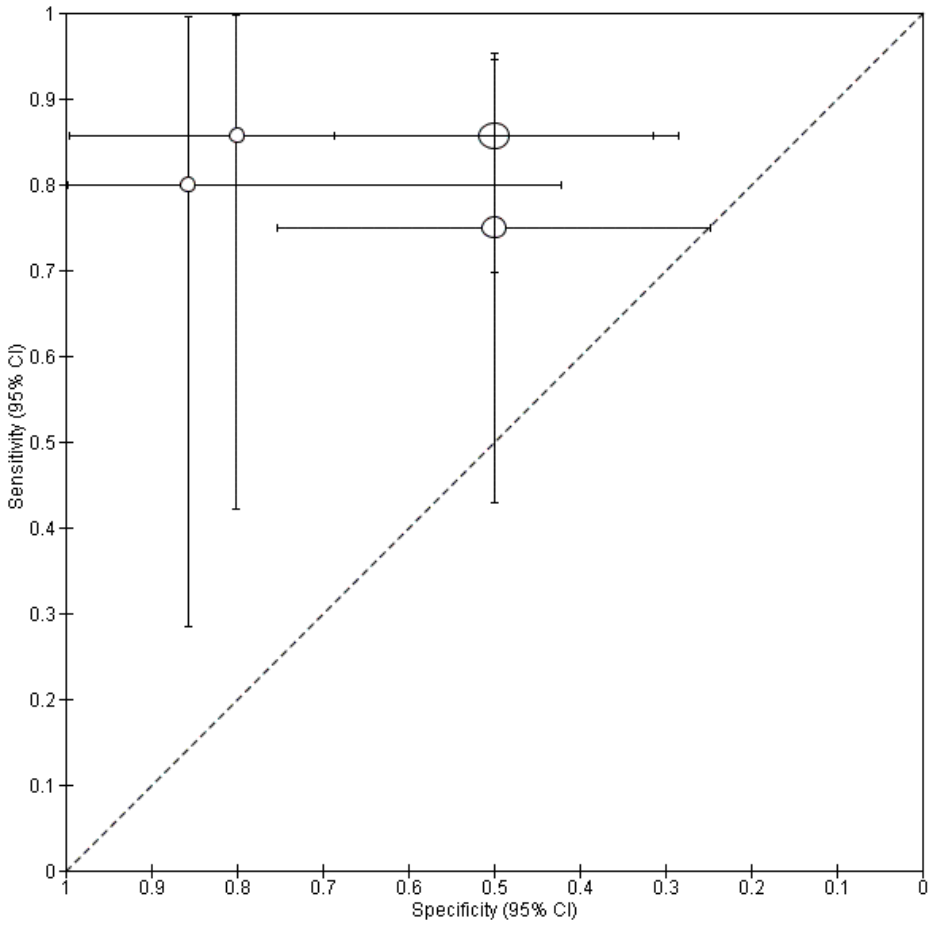
Study	TP	FP	FN	TN	Threshold type	Sensitivity (95% CI)	Specificity (95% CI)
Grimmer 2013	9	8	3	8	quantitative	0.75 [0.43, 0.95]	0.50 [0.25, 0.75]
Villemagne 2011	30	15	5	15	quantitative	0.86 [0.70, 0.95]	0.50 [0.31, 0.69]
Ossenkoppele 2012	4	1	1	6	visual inspection	0.80 [0.28, 0.99]	0.86 [0.42, 1.00]
Ossenkoppele 2012a	6	1	1	4	visual inspection	0.86 [0.42, 1.00]	0.80 [0.28, 0.99]



Caption

Forest plot of ^{11}C-PIB-PET All dementia.

Figure 7 (Analysis 2)



Caption

Summary ROC Plot of ^{11}C-PIB-PET All dementia. Each point represents a pair of sensitivity and specificity for each study, and the cross hairs correspond to their 95% CIs.

Sources of support

Internal sources

- No sources of support provided

External sources

- A programme of Diagnostic Test Accuracy(DTA) reviews and of updates of interventionreviews in dementia: 10/4001/05, UK
  This project was funded by the National Institute for Health Research. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health

Feedback

Appendices

1 Searches performed: January 2013, April 2012, September 2011

Source	Search strategy	Hits retrieved
1. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. 10 and 31 33. (animals not (humans and animals)).sh. 34. 32 not 33 35. (2012* or 2013*).ed. 36. 34 and 35	500

Source	Search strategy	Hits retrieved
2. EMBASE 1980-2012 April 10 (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. or pittsburgh compound B/ 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. 10 and 31 33. (2012* or 2013*).em. 34. 32 and 33	1516

Source	Search strategy	Hits retrieved
3. PsycINFO 1806-April week 2 2012 (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. or pittsburgh compound B/ 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. 10 and 31 33. (2012* or 2013*).up. 34. 32 and 33	276
4. Biosis previews (ISI Web of Knowledge)	Topic=(PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR "PiB-PET" OR "PET-PiB" OR "amyloid ligand*" OR "[11C]PiB" OR "amyloid deposition") AND Topic=(alzheimer* OR AD OR dement* OR lewy OR VAD OR VCI OR cognit* OR MCI OR memory) AND Year Published=(2012-2013) Timespan=All Years. Databases=BIOSIS Previews. Lemmatization=On	162

Source	Search strategy	Hits retrieved
5. Web of Science and conference proceedings (1945-present)	Topic=(PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR "PiB-PET" OR "PET-PiB" OR "amyloid ligand*" OR "[11C]PiB" OR "amyloid deposition") AND Topic=(alzheimer* OR AD OR dement* OR lewy OR VAD OR VCI OR cognit* OR MCI OR memory) AND Year Published=(2012-2013) Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH. Lemmatization=On	276
6. LILACS (BIREME)	PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR PiB-PET OR PET-PiB OR "amyloid ligand*" OR "amyloid deposition" [Words]	7
TOTAL before de-duplication		2737
TOTAL after de-duplication and first-assessment		74

April 2012

Source	Search strategy	Hits retrieved
1. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. 10 and 31 33. (animals not (humans and animals)).sh. 34. 32 not 33 35. (2011* or 2012*).ed. 36. 34 and 35	502

Source	Search strategy	Hits retrieved
2. EMBASE 1980-2012 April 10 (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. or pittsburgh compound B/ 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. 10 and 31 33. (2011* or 2012*).em. 34. 32 and 33	1154

Source	Search strategy	Hits retrieved
3. PsycINFO 1806-April week 2 2012 (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. or pittsburgh compound B/ 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. 10 and 31 33. (2011* or 2012*).up. 34. 32 and 33	298
4. Biosis previews (ISI Web of Knowledge)	Topic=(PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR "PiB-PET" OR "PET-PiB" OR "amyloid ligand*" OR "[11C]PiB" OR "amyloid deposition") AND Topic=(alzheimer* OR AD OR dement* OR lewy OR VAD OR VCI OR cognit* OR MCI OR memory) AND Year Published=(2011-2012) Timespan=All Years. Databases=BIOSIS Previews. Lemmatization=On	236

Source	Search strategy	Hits retrieved
5. Web of Science and conference proceedings (1945-present)	Topic=(PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR "PiB-PET" OR "PET-PiB" OR "amyloid ligand*" OR "[11C]PiB" OR "amyloid deposition") AND Topic=(alzheimer* OR AD OR dement* OR lewy OR VAD OR VCI OR cognit* OR MCI OR memory) AND Year Published=(2011-2012) Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH. Lemmatization=On	321
6. LILACS (BIREME)	PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR PiB-PET OR PET-PiB OR "amyloid ligand*" OR "amyloid deposition" [Words]	193-187=6
TOTAL before de-duplication		2517
TOTAL after de-duplication and first-assessment		28

September 2011

Source	Search strategy	Hits retrieved
1. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. (2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011*).ed. 33. 10 and 31 and 32 34. (animals not (humans and animals)).sh. 35. 33 not 34	2510

Source	Search strategy	Hits retrieved
2. EMBASE 1980-2011 week 34 (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. or pittsburgh compound B/ 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. 10 and 31 33. (2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011*).em. 34. 32 and 33 35. limit 34 to human	3597

Source	Search strategy	Hits retrieved
3. PsycINFO 1806-February week 2 2011 (OvidSP)	1. Positron-Emission Tomography/ 2. (PiB or PIB).ti,ab. or pittsburgh compound B/ 3. "Pittsburgh compound B".ti,ab. 4. "C Pittsburgh".ti,ab. 5. (PIB-PET or PET-PIB).ti,ab. 6. "amyloid deposition".ti,ab. 7. "[11C]PIB".ti,ab. 8. "amyloid ligand*".ti,ab. 9. ((PET and (scan* or imag*)) or "positron emission tomography").ti,ab. 10. or/1-9 11. (alzheimer* or dement* or AD or lewy* or DLB or LBD).ti,ab. 12. exp dementia/ 13. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 14. MCI.ti,ab. 15. ACMI.ti,ab. 16. ARCD.ti,ab. 17. SMC.ti,ab. 18. CIND.ti,ab. 19. BSF.ti,ab. 20. AAMI.ti,ab. 21. LCD.ti,ab. 22. QD.ti,ab. 23. AACD.ti,ab. 24. MNCD.ti,ab. 25. MCD.ti,ab. 26. (nMCI or aMCI or mMCI).ti,ab. 27. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 28. ("CDR 0.5" or "clinical dementia rating scale 0.5" or "0.5 CDR").ti,ab. 29. ("GDS 3" or "3 GDS").ti,ab. 30. ("global deterioration scale" and "stage 3").ti,ab. 31. or/11-30 32. 10 and 31 33. (2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011*).up. 34. 32 and 33	1226

Source	Search strategy	Hits retrieved
4. ISI Web of Knowledge: BIOSIS Previews (1926-present)	Topic=(PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR "PiB-PET" OR "PET-PiB" OR "amyloid ligand*" OR "[11C]PiB" OR "amyloid deposition") AND Topic=(alzheimer* OR AD OR dement* OR lewy OR VAD OR VCI OR cognit* OR MCI OR memory) AND Year Published=(2003-2011) Timespan=2003-2011. Databases=BIOSIS Previews. Lemmatization=On	826
5. ISI Web of Knowledge: Citation Databases : Science Citation Index Expanded (SCI-EXPANDED); Social Sciences Citation Index (SSCI); Arts & Humanities Citation Index (A&HCI); Conference Proceedings Citation Index- Science (CPCI-S); Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)	Topic=(PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR "PiB-PET" OR "PET-PiB" OR "amyloid ligand*" OR "[11C]PiB" OR "amyloid deposition") AND Topic=(alzheimer* OR AD OR dement* OR lewy OR VAD OR VCI OR cognit* OR MCI OR memory) AND Year Published=(2003-2011) Timespan=2003-2011. Databases=BIOSIS Previews. Lemmatization=On	1227
6. LILACs (BIREME)	PiB OR PIB OR "Pittsburgh compound B" OR "C Pittsburgh" OR PiB-PET OR PET-PiB OR "amyloid ligand*" OR "amyloid deposition" [Words]	187
7. Clinicaltrials.gov (www.clinicaltrials.gov)	#1 11-C Pib = 3 #2 amyloid ligand OR amyloid ligands = 5 #3 radioligand = 38 #4 Pittsburgh compound = 27	3+5+38+27=73
TOTAL before de-duplication		9697
TOTAL after de-duplication and first-assessment		60

2 Two times two tables

Table 1: Conversion from MCI to Alzheimer's disease dementia

Index test information	References standard information	
	ADD present	ADD absent
Index test positive	PIB+ who convert to ADD (TP)	PIB+ who remain MCI (FP) & PIB+ who convert to non-ADD (FP)
Index test negative	PIB- who convert to ADD (FN)	PIB- who remain MCI (TN) & PIB- who convert to non-ADD (TN)

Table 2: Conversion from MCI to non-Alzheimer's disease dementia

Index test information	References standard information	
	Non-ADD present	Non-ADD absent
Index test positive	PIB+ who convert to non-ADD (TP)	PIB+ who remain MCI (FP) & PIB+ who convert to ADD (FP)
Index test negative	PIB- who convert to non-ADD (FN)	PIB- who remain MCI (TN) & PIB- who convert to ADD (TN)

Table 3: Conversion from MCI to any forms of dementia

Index test information	References standard information	
	Any forms of dementia present	Dementia absent
Index test positive	PIB+ who convert to any form of dementia (TP)	PIB+ who remain MCI (FP)
Index test negative	PIB- who convert to any form of dementia (FN)	PIB- who remain MCI (TN)

3 Assessment of methodological quality table 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 statements for quality assessment of PIB-PET diagnostic studies

Table 4: Review question and inclusion criteria

Category	Review Question	Inclusion Criteria
Patients	Participants with mild cognitive impairment, no dementia	Participants fulfilling the criteria for the clinical diagnosis of MCI at baseline
Index Test	^{11}C-PIB-PET biomarker	^{11}C-PIB-PET biomarker
Target Condition	Alzheimer's disease dementia (conversion from MCI to Alzheimer's disease dementia) Any other forms of dementia (conversion from MCI to any other forms of dementia	Alzheimer's disease dementia (conversion from MCI to Alzheimer's disease dementia) Any other forms of dementia (conversion from MCI to any other forms of dementia)
Reference Standard	NINCDS-ADRDA; DSM; ICD; McKeith criteria; Lund criteria; NINDS-ARIEN criteria	NINCDS-ADRDA; DSM; ICD; McKeith criteria; Lund criteria; NINDS-ARIEN criteria
Outcome	N/A	Data to construct 2x2 table
Study Design	N/A	• Longitudinal cohort studies and • Nested case-control studies if they incorporate a delayed verification design (case-control nested in cohort studies)

Anchoring statements for quality assessment of PIB-PET diagnostic studies

We provide some core anchoring statements for quality assessment of diagnostic test accuracy review of the PIB-PET biomarker 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 2014)

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 the index test is fundamental. If this blinding was not present then the item on the 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 5: 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.*
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 PIB-PET biomarker's 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 PIB-PET biomarker's 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		

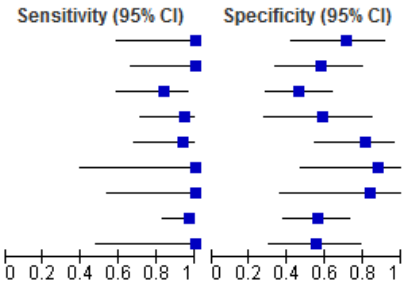
Is the assessment used for clinical diagnosis of dementia acceptable?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	*Commonly used international criteria to assist with clinical diagnosis of dementia include those detailed in DSM-IV and ICD-10. Criteria specific to dementia 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 PIB-PET biomarker?	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.*
Patient flow		
Was there an appropriate interval between PIB-PET biomarker 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* PIB-PET biomarker *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 (* Geslani 2005 *;* Okello 2009 *;* Visser 2006 *), 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 PIB-PET biomarker?	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 PIB-PET 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 PIB-PET 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 PIB-PET biomarker's 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* PIB-PET biomarker was *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.*

Graphs

^{11}C-PIB-PET AD dementia

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Forsberg 2010	7	4	0	10	1.00 [0.59, 1.00]	0.71 [0.42, 0.92]
Grimmer 2013	9	8	0	11	1.00 [0.66, 1.00]	0.58 [0.33, 0.80]
Jack 2010	15	19	3	16	0.83 [0.59, 0.96]	0.46 [0.29, 0.63]
Koivunen 2011	16	5	1	7	0.94 [0.71, 1.00]	0.58 [0.28, 0.85]
Okello 2009	14	3	1	13	0.93 [0.68, 1.00]	0.81 [0.54, 0.96]
Ossenkoppele 2012	4	1	0	7	1.00 [0.40, 1.00]	0.88 [0.47, 1.00]
Ossenkoppele 2012a	6	1	0	5	1.00 [0.54, 1.00]	0.83 [0.36, 1.00]
Villemagne 2011	30	15	1	19	0.97 [0.83, 1.00]	0.56 [0.38, 0.73]
Wolk 2009	5	8	0	10	1.00 [0.48, 1.00]	0.56 [0.31, 0.78]



^{11}C-PIB-PET All dementia

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grimmer 2013	9	8	3	8	0.75 [0.43, 0.95]	0.50 [0.25, 0.75]
Ossenkoppele 2012	4	1	1	6	0.80 [0.28, 0.99]	0.86 [0.42, 1.00]
Ossenkoppele 2012a	6	1	1	4	0.86 [0.42, 1.00]	0.80 [0.28, 0.99]
Villemagne 2011	30	15	5	15	0.86 [0.70, 0.95]	0.50 [0.31, 0.69]