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^{18}F PET ligands for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI) (Protocol)

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[Diagnostic Test Accuracy Protocol]

^{18}F PET ligands for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the diagnostic test accuracy (DTA) of the ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) as the index tests for detecting participants with mild cognitive impairment (MCI) at baseline who would clinically progress to Alzheimer's disease dementia (ADD), or other forms of non-ADD, or any form of dementia at follow-up.

To investigate the heterogeneity of the DTA in the included studies, we will evaluate the spectrum of people, referral centres, clinical criteria of MCI, ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) techniques, reference standards used, duration of follow-up, aspects of study quality, and conflicts of interest.

BACKGROUND

Dementia is a syndrome due to a brain disease - usually of a chronic or progressive nature - in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. However, consciousness remains unaffected. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by a deterioration in emotional control, social behaviour, motivation, and the impairment is sufficient to interfere with everyday activities. Dementia is a collective of different subtypes distinguished by the underlying pathology. Alzheimer's disease dementia (ADD) is the most common form of dementia

and other important pathologies associated with dementia are vascular disease, Lewy bodies, and frontotemporal pathology (WHO 2012).

Dementia is a serious worldwide public health problem, with a prevalence of 4.7% in adults older than 60 years (6.2% and 6.5% in Europe and the Americas, respectively). Due to its prevalence in older people, it is expected that the number of people with dementia will increase dramatically. Consequently, in the year 2050, an expected 115 million people will have dementia. This will result in a considerable economic burden, which currently stands at 1% of the world's Gross National Product (GNP) in direct and indirect costs (WHO 2012). These financial costs are in addition to the devastating personal and social consequences of the condition.

The definition of MCI applies to people without evidence of significant deterioration in activities of daily living, but with subjective memory complaints and cognitive impairment detected by standardised tests. MCI often precedes clinical dementia, but there is no consensus regarding how to operationalise the MCI diagnosis. There are several clinical criteria to define which people have MCI, including the Petersen criteria or Petersen Revisited Criteria (Petersen 1999; Petersen 2004; Winblad 2004), Clinical Dementia Rating Scale (CDR= 0.5) (Morris 1993), or 16 other different classifications of MCI (Matthews 2008).

A diagnosis of MCI reputedly allows testing of preventive interventions that would decelerate or slow the progression of MCI to dementia. If the progression of MCI to dementia could be deferred by five years, the prevalence of dementia would decrease by 43% in 2050 (Alzheimer's Association 2010). MCI has an annual progression rate to ADD from 5% to 15%. However, not every person with MCI develops dementia, and a significant number of people recover or stabilise. Therefore, future research should try to clarify which people with MCI develop dementia in order to be able to focus specifically on people who are at high risk of developing dementia. This may possibly explain the failure of therapy to alter the progression to dementia in people with MCI. Other aspects that may contribute to this failure are the disparity in diagnostic criteria and different settings of the studied participants: community, primary, secondary, and research centres (Bruscoli 2004; Mattsson 2009; Petersen 1999; Petersen 2009).

The definition of Alzheimer's disease pathology is over 100 years old. This pathology includes neuritic plaques that contain deposits of amyloid beta (Aβ) and neurofibrillary tangles (Goedert 2006). This pathology is present in approximately 84% of all dementia people (Schneider 2007). Furthermore, Alzheimer's disease pathology is found in 88% of people diagnosed with probable ADD (Schneider 2009). Despite this, Alzheimer's disease pathology may be found concomitantly at autopsy in people thought to have other forms of dementia, such as vascular dementia, Lewy body dementia, or frontotemporal dementia (FTD) (Jellinger 2006). Furthermore, at least five common pathologies have been found in the brains of people who died and were thought to have ADD prior to death (White 2009). Also, Alzheimer's disease pathology was found in 42% of community-dwelling older people without dementia (Schneider 2007). This has generated controversy about the importance of the presence of Alzheimer's disease pathology. The pathology can be associated with aging per se, and for older people the relationship between amyloid plaque burden and cognitive impairment diminishes as age progresses (Savva 2009). Thus this pathology could be an epiphenomenon associated with the presence of dementia, e.g. a by-product of repair mechanisms by vascular damage (de la Torre 2004; Garcia-Alloza 2011).

More recently, the development of Aβ pathology biomarkers in vivo has been suggested as an important advance as a diagnostic tool in the field of Alzheimer's disease, and has promoted the creation of new diagnostic criteria for people without symptoms (preclinical stages), people with MCI, and people with ADD, based on the presence of biomarkers of Alzheimer's disease. These have included Aβ tracers by positron emission tomography (PET) (Albert 2011; Dubois 2014; McKhann 2011; Sperling 2011). However, uncertainties regarding the usability of biomarkers in the diagnosis of dementia still exist, mainly due to variation between biomarker types, criteria for positivity, and differences in methodology (Noel-Storr 2013). This prompted formation of an important initiative called the Standards for Reporting of Diagnostic Accuracy Studies in dementia studies (STARDdem) statement (Noel-Storr 2014). Consequently, clinical properties of dementia biomarkers should not be assumed, and formal systematic evaluations of sensitivity, specificity, and other properties of biomarkers should be performed (Davis 2013).

PET is an imaging technique using compounds labelled with short-lived positron-emitting radionuclides. The use of Aβ ligands permits the in vivo detection of amyloid deposition in the brain. ^{18}F PET ligands, such as ^{18}F-Florbetapir and ^{18}F-Florbetaben, are stilbene derivatives and demonstrate a high binding affinity to A β aggregates. ^{18}F-Florbetapir has excellent uptake by brain tissue and washout kinetics in mice and monkeys (Choi 2009) and in vitro binding of Aβ plaques in postmortem ADD brain samples (Choi 2009; Lin 2010). In 2010 it was evaluated for the first time in people with ADD and healthy people without ADD". (Lin 2010; Wong 2010). Similarly, ^{18}F-Florbetaben, which was first described 10 years ago, is characterised by a high affinity for Aβ (Zhang 2005) and could more accurately diagnose people with ADD (Villemagne 2011).

Another ^{18}F PET ligand is Flutemetamol. It is a fluorinated tracer, derived from the Pittsburgh Compound B (the first tracer developed). It is characterised by a longer median life of 110 minutes, and has a high affinity for Aβ. Flutemetamol functioning was tested in vivo with healthy people, people with ADD (Nelissen 2009), and in people with MCI (Vandenberghe 2010). Flutemetamol could eventually be used to differentiate between different de-

mentia types, specifically between FTD and ADD, like the other fluorinated tracers ^{18}F-Florbetaben (Villemagne 2011) and ^{18}F-Florbetapir (Kobylecki 2015).

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved these three ^{18}F PET ligands for Aβ. These agencies have stated that a negative scan indicates sparse or no plaques, which is inconsistent with a diagnosis of ADD, thus effectively excluding this diagnosis. A positive ^{18}F PET ligands scan indicates moderate to frequent or pronounced amyloid neuritic plaques. However, this might also occur in people with other neurological conditions (e.g. Lewy body dementia, Parkinson's disease dementia) and in older adults with normal cognition. Therefore, a positive result of an ^{18}F PET ligand scan does not establish the diagnosis of ADD or any other cognitive disorder definitely, and it should be combined with other diagnostic evaluations or instruments. Additionally, the effectiveness and safety of the tests have not been established by predicting development of dementia or other neurological conditions, or by monitoring responses to therapies (EMA 2013; EMA 2014a; EMA 2014b; FDA 2013; FDA 2014a; FDA 2014b).

Despite not being approved for this purpose by the regulatory agencies, research has been conducted in people with MCI to determine whether biomarkers, such as ^{18}F PET ligands for Aβ, increase the risk of developing dementia over time. The evidence for this is uncertain. For this and other reasons, the National Institute on Aging-Alzheimer's Association (NIA-AA) in the USA established two different criteria for MCI. Firstly, they established the Core Clinical Criteria for use in all clinical settings, without use of biomarkers, and characterised by concerns regarding a change in cognition with impairment in one or more cognitive domains with preservation of independence in functional abilities, therefore no dementia. Secondly, they established the Clinical Research Criteria, which incorporate the use of biomarkers, such as PET amyloid scans, intended for use exclusively in research settings, including academic centres and clinical trials. This will help determine whether positive scans increase the likelihood of progression from MCI to clinical dementia (Albert 2011). Lastly, it is hoped that people with MCI and positive scans will "enrich" clinical trials, and more people who will progress to dementia in a shorter time will be included to allow more efficient studies of treatments and prevention strategies of ADD (CMS 2013).

It is an assumption for some researchers and, in fact, one assumption on which this Cochrane review is predicated, that if a person has both MCI and the pathology of Alzheimer's disease and develops clinical ADD subsequently, then the cause of the initial MCI and of the ADD was the Alzheimer's pathology. Our approach is an example of assessing diagnostic test accuracy (DTA) using delayed verification of diagnosis. Instead of the reference standard being based on pathology, it is based on a clinical standard and the progression from MCI to ADD or any other form of non-ADD or any dementia. Although, for the reasons stated above, a degree of unreliability has been introduced, defining progression has the advantage of being based on what matters most to people with MCI, their carers, and clinicians involved in their care.

This is a common Cochrane protocol that we will apply to the conduct three separate systematic reviews to assess the DTA of ^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol Aβ binding in the brain and progression of the following:

- From MCI to ADD.
- From MCI to any other form of non-ADD.
- From MCI to any form of dementia

Target condition being diagnosed

These three Cochrane reviews will assess the following three target conditions.

- ADD (progression from MCI to ADD).
- Any other form of dementia (progression from MCI to any other form of non-ADD).
- Any form of dementia (progression from MCI to any form of dementia).

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

Index test(s)

The ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) scans are the index tests for the detection of Aβ deposition in the brain region of interest (ROI). The ROI is a selected brain area that physicians create for further study in various anatomical areas of the brain. ^{18}F PET ligands are molecular biomarkers, and are described as follows.

- ^{18}F-Florbetapir: (E)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridine-3-yl)vinyl)-N-methylbenzamine and also referred to as ^{18}F-AV-45 (Choi 2009).
- ^{18}F-Florbetaben:^{18}F-Florbetaben Aβ is a molecular biomarker, ([^{18}F]BAY 94-9172, trans-4-(N-methyl-amino)-4'-2-[2-(2-[^{18}F]fluoro-ethoxy)-ethoxy]-ethoxy-stilbene), and is also referred to as BAY 94-9172 or ZK 6013443, which is a polyethylene glycol stilbene derivative (Zhang 2005).
- ^{18}F-Flutemetamol:^{18}F-Flutemetamol Aβ is a molecular biomarker, described as 6-benzothiazolol, 2-[3-[^{18}F]fluoro-4-(methylamino)phenyl], and is also referred to as ^{18}F-3'-F-6-OH-BTA1, ^{18}F-GE067, AH110690 (Koole 2009; Nelissen 2009).

Image Interpretation

Both the FDA and EMA have described the criteria for ^{18}F PET ligands (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol)

for Aβ positivity (EMA 2013; EMA 2014a; EMA 2014b; FDA 2013; FDA 2014a; FDA 2014b).

^{18} F-Florbetapir:

^{18}F-Florbetapir diagnosis is by PET image assessment and is designated as either positive or negative by comparison of the radioactivity in cortical grey matter with activity in the adjacent white matter. This determination is made only in the cerebral cortex; the signal uptake in the cerebellum does not contribute to the scan interpretation (e.g. a positive scan may show retained cerebellar grey-white contrast even when the cortical grey-white contrast is lost). Specifically, a positive scan will exhibit one of the following.

- Two or more brain areas (each larger than a single cortical gyrus) in which there is reduced or absent grey-white contrast. This is the most common appearance of a positive scan.
- One or more areas in which grey matter radioactivity is intense and clearly exceeds radioactivity in adjacent white matter.

^{18} F-Florbetaben:

^{18}F-Florbetaben diagnosis is by PET image assessment, and is defined as positive if the analysis shows the following.

- Moderate or smaller area(s) of tracer uptake equal to or higher than that are presented in the white matter: extending beyond the white matter rim to the outer cortical margin involving the majority of the slices within the respective region.
- Pronounced Aβ deposition (a large confluent area of tracer uptake equal to or higher than that presented in white matter extending beyond the white matter rim to the outer cortical margin and involving the entire region including the majority of slices within the respective region) in the grey matter of the following four brain regions: the temporal lobes, the frontal lobes, the posterior cingulate cortex/precuneus, and the parietal lobes.

^{18} F-Flutemetamol:

^{18}F-Flutemetamol diagnosis is by PET image assessment, and is defined as positive if analysis shows the following.

- At least one cortical region (Frontal lobes, posterior cingulate and precuneus, lateral temporal lobes, inferolateral parietal lobes, striatum) with reduction or loss of the normally distinct grey-white matter contrast. These scans have one or more regions with increased cortical grey matter signal (above 50% to 60% peak intensity) or reduced (or absent) grey-white matter contrast (white matter sulcal pattern is less distinct), or both.
- A positive scan may have one or more regions in which grey matter radioactivity is as intense or exceeds the intensity in adjacent white matter.

Readers trained in PET images with the ligands of ^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol, should interpret the Aβ PET images made with those ligands (EMA 2013; EMA 2014a; EMA 2014b; FDA 2013; FDA 2014a; FDA 2014b).

Before the FDA and EMA described the criteria for ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) positivity, the diagnosis of dementia was made using different thresholds. Therefore, it is plausible that we will find studies with differing ^{18}F PET ligands for Aβ thresholds. Therefore, we plan to use the FDA or EMA criteria applied in each included study to classify participants as either test-positive or test-negative, or alternatively if the ^{18}F PET ligands for Aβ uptake and retention exceed a certain threshold.

We will consider the measurement of the ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) retention (retention ratio): distribution volume ratio (DVR), standardised uptake value ratio (SUVR), or other ratios. DVR refers to the ratio of the ^{18}F PET ligands distribution volume in the selected area (ROI) to the distribution volume in the reference area. SUVR is the measured activity in the ROI, which is normalised for body weight, surface area, and injected dose.

The unit of analysis of our Cochrane reviews is the person. It is likely that we will encounter studies that analyse multiple ROIs per person. However, we will only include the pooled results of the ROI in our reviews.

Image analysis: not prespecified (e.g. Statistical Parametric Mapping (SPM) or other image analysis techniques).

Administration Instructions and Recommended Dosing

- Time between ^{18}F PET ligands for Aβ injection and PET acquisition:
  - ^{18}F-Florbetapir PET images should be acquired in 10 minutes starting from 30 to 50 minutes after intravenous administration (EMA 2013; FDA 2013);
  - ^{18}F-Florbetaben PET images should be acquired in 15 to 20 minutes starting from 45 to 130 minutes after intravenous administration (FDA 2014a) or acquired in 20 minutes starting from 90 minutes after intravenous administration (EMA 2014a);
  - ^{18}F-Flutemetamol PET images should be acquired in 20 minutes starting from 90 minutes after intravenous administration (EMA 2014b; FDA 2014b).
- ^{18}F PET ligands for Aβ injection dose:
  - the recommended dose for ^{18}F-Florbetapir Aβ PET is 370 MBq (10 mCi) as a single intravenous bolus in a total volume of 10 mL or less (EMA 2013; FDA 2013);
  - the recommended dose for ^{18}F-Florbetaben Aβ PET is 300 MBq (8.1 mCi), maximum 30 mcg mass dose (FDA 2014a) or 300 MBq (240 to 360 MBq) administered as a single slow intravenous bolus (6 sec/mL) in a total volume of up to 10 mL (EMA 2014a);
  - the recommended dose for ^{18}F-Flutemetamol Aβ PET is 185 MBq (5.0 mCi) administered as a single slow intravenous bolus (EMA 2014b; FDA 2014b).

Although it is inevitable that included studies will have used different imaging protocols, readers' expertise, and varied parameters, the amyloid PET data in these included studies should be technically adequate and acquired at a fully qualified and certified facility.

Clinical pathway

At this time, the clinical evaluation often has similarities between different countries (Cordella 2013; NICE 2006). It often starts with people experiencing memory complaints detected by themselves or their relatives. Frequently general practitioners or family physicians are consulted, and they often conduct a medical evaluation using a screening test for cognitive impairment. Whenever this screening test is positive, they complete an assessment with a clinical evaluation conducted with laboratory studies that can rule out a secondary cause of cognitive impairment (e.g. hypothyroidism, renal failure, liver failure, vitamin B12 or folate deficiency, and others). In addition, these people are then referred to medical specialists in cognitive disorders (preferably a geriatrician, psychiatrist, or neurologist) in a secondary centre or directly to memory clinics where further clinical assessment, laboratory studies, and cerebral image studies are conducted to confirm the dementia diagnosis.

People with dementia, or their relatives, often directly consult these specialists or specialised memory clinics in the study of cognitive disorders. Therefore, the performed diagnostic tests will probably vary according as to whether it is a primary consultation or already referred from primary to specialist care, or if the people have different clinical stages of the disease (MCI, mild, moderate, or severe dementia). Due to these differing pathways, the use of ^{18}F PET ligands for Aβ will be mainly used in specialist consultations and memory clinics as an addition to clinical evaluation or other tests, helping in a clinical setting to discard a diagnosis of Alzheimer's dementia with a negative scan in a person with clinical dementia and doubts about the ethology (e.g. FTD versus ADD). Otherwise, it might be used solely in the research field in people with an MCI for the enrichment of clinical trials with people with MCI with positive PET scan to study preventive interventions or if the results of PET Aβ imaging lead to improved health outcome.

Alternative test(s)

Currently there are no standard practice tests available for the diagnosis of dementia. Below, we have listed the alternative tests that we have excluded from this Cochrane review. The Cochrane Dementia and Cognitive Improvement Group is in the process of conducting a series of DTA reviews of biomarkers and scales (see list below).

- ^{18}F-FDG-PET (PET F-fluorodeoxyglucose) (Smailagic 2015).
- 11C-PIB-PET (PET-Pittsburgh compound B) (Zhang 2014).
- Cerebrospinal fluid (CSF) analysis of Aβ and tau (Kokkinou 2014; Ritchie 2013; Ritchie 2014).
- Structural magnetic resonance imaging (sMRI) (Filippini 2012).
- Neuropsychological tests (Mini-Mental State Examination (MMSE); MiniCOG; Montreal Cognitive Assessment (MoCA) (Arevalo-Rodriguez 2015; Chan 2014; Creavin 2016; Davis 2015; Fage 2015; Seitz 2014).
- Informant interviews (Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE); AD8) (Harrison 2014; Hendry 2014; Lees 2014; Harrison 2015; Quinn 2014).
- APOE-ϵ4 (Elias-Sonnenschein 2014a; Elias-Sonnenschein 2014b; Elias-Sonnenschein 2014c).
- Single-photon emission computed tomography (SPECT) brain imaging (Archer 2015; McCleery 2015).

Rationale

Accurate and early diagnosis of Alzheimer's disease is crucial for planning healthcare systems, because the costs of dementia are currently at least 1% of the world's GNP (WHO 2012).

^{18}F PET ligands for Aβ biomarkers are approved for use in the clinical field mainly in people who are diagnosed clinically with dementia of uncertain aetiology, in which case diagnosis of ADD can be discarded if the test is negative. Even though ^{18}F PET ligands for amyloid biomarkers are not approved for this purpose, these biomarker tests are currently being used in the research field to search for the accurate identification of people with MCI who would progress to Alzheimer's disease or other forms of dementia. Amyloid β tracers by PET have been included in newly diagnostic criteria in the study in people with MCI (Albert 2011; Dubois 2014). However, some uncertainties exist about DTA performance in clinical settings, especially in older people (Richard 2012).

It is currently believed that if the health system can identify which people are at high-risk of progressing from MCI to dementia, it can focus on improving opportunities for appropriate contingency planning for them. Proper recognition of the disease may also help prevent inappropriate and potentially harmful admissions to hospital or institutional care (NAO 2007), and enable the development of new treatments designed to delay or prevent progression to more debilitating stages of the disease. Additionally, this may demonstrate a real clinical benefit for people and caregivers, and will reduce health system costs.

These three separate Cochrane reviews will assess DTA with ^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol Aβ PET in people with MCI.

OBJECTIVES

To determine the diagnostic test accuracy (DTA) of the ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) as the index tests for detecting participants with mild cognitive impairment (MCI) at baseline who would clinically progress to Alzheimer's disease dementia (ADD), or other forms of non-ADD, or any form of dementia at follow-up.

Secondary objectives

To investigate the heterogeneity of the DTA in the included studies, we will evaluate the spectrum of people, referral centres, clinical criteria of MCI, ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) techniques, reference standards used, duration of follow-up, aspects of study quality, and conflicts of interest.

METHODS

Criteria for considering studies for this review

Types of studies

We will include longitudinal studies that have prospectively defined cohorts with any accepted definition of mild cognitive impairment (MCI) with baseline ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) scans and the reference standard (see Index tests and Reference standards below). We will obtain the results at the follow-up of the studies. These studies necessarily will employ delayed verification of progression to dementia and are sometimes labelled as 'delayed verification cross sectional studies' (Bossuyt 2008; Knottnerus 2002). We will include case control studies when they incorporate a delayed verification design. This will occur 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 will be eligible for inclusion. We will establish the diagnosis of MCI using the Petersen criteria or revised Petersen criteria (Petersen 1999; Petersen 2004; Winblad 2004), the Matthews criteria (Matthews 2008), CDR = 0.5 (CDR structured interviews collects information from both the collateral source and the subject regarding memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, where the range of possible scores varies from none=0 point to severe=3 points) (Morris 1993), the National Institute on Aging-Alzheimer's Association (NIA-AA) core clinical criteria (Albert 2011), or a combination.

We will exclude studies that included people with MCI possibly caused by any of the following.

- Current or a history of alcohol or drug abuse.
- Central nervous system (CNS) trauma (e.g. subdural hematoma), tumour, or infection.
- Other neurological conditions (e.g. Parkinson's or Huntington's diseases).

Index tests

The index test in these three Cochrane reviews will be ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarker tests. We will use the criteria and cut-off values for test positivity as reported in the included studies. We will consider positivity for^{18}F PET ligands for Aβ scans (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) uptake and retention exceeding a certain threshold.

Target conditions

There are three target conditions in these three Cochrane reviews.

- Alzheimer's disease dementia (ADD) (progression from MCI to ADD).
- Any other forms of dementia (progression from MCI to any other forms of non-ADD).
- Any form of dementia (progression from MCI to any form of dementia).

Reference standards

The reference standard will be the progression to the target conditions evaluated by a physician with expertise in the dementia field (preferably a geriatrician, psychiatrist, or neurologist). For the purpose of these three Cochrane reviews, we will accept several definitions of ADD. We will include studies that applied the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDSADRDA) criteria (McKhann 1984), the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (APA 1987; APA 1994), and the International Classification of Diseases (ICD) (ICD-10) criteria for ADD. Notably, different iterations of these standards may not be directly comparable over time (e.g. APA 1987 versus APA 1994). Moreover, the validity of the diagnoses may vary with the degree or manner in which the criteria have been operationalised (e.g. individual clinician versus algorithm versus consensus determination). We will consider all these issues when we interpret the results, and will use sensitivity analyses when appropriate.

Similarly, we will accept differing clinical definitions of other dementias. For Lewy Body Dementia the reference standard is the McKeith criteria (McKeith 1996; McKeith 2005); for Fronto-Temporal Dementia the Lund criteria (Boxer 2005; Brun 1994; Neary 1998), the DSM criteria (APA 1987; APA 1994), the ICD criteria (ICD-10), or the International Behavioural Variant FTD Criteria Consortium (Rascovsky 2011); and for vascular dementia the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (Román 1993), the DSM criteria (APA 1987; APA 1994), or the ICD criteria (ICD-10).

The time interval over which the progression from MCI to ADD (or other forms of dementia) occurs is very important. We will use

one year as the minimum period of delay in the verification of the diagnosis (the time between the assessment at which a diagnosis of MCI is made and the assessment at which the diagnosis of dementia is made).

Search methods for identification of studies

Electronic searches

We will search MEDLINE (Ovid SP) from 1946 to present; EMBASE (Ovid SP) from 1974 to present ; PsycINFO (Ovid SP) from 1806 to present ; BIOSIS Citation Index (Thomson Reuters Web of Knowledge) from 1922 to present; Web of Science Core Collection, including the Science Citation Index (ISI Web of Knowledge) and the Conference Proceedings Citation Index (Thomson Reuters Web of Knowledge) from 1946 to present; LILACS (Bireme); CINAHL (EbscoHOST) from 1980 to present; ClinicalTrials.gov (https://clinicaltrials.gov); and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (http://www.who.int/ictrp/search/en/). We will also search ALOIS (Cochrane Register of Studies Software).

See Appendix 1 for details of the sources and search strategies that we will use. We will not apply any language restrictions to the electronic searches. The searches are entirely index test focused for maximum sensitivity and we will not apply any methodological filters.

Searching other resources

We will examine the reference lists of all relevant studies for additional studies. We will also search the Database of Abstracts of Reviews of Effects (DARE) via the Cochrane Library: www.cochranelibrary.com), the HTA Database (via the Cochrane Library: www.cochranelibrary.com), the Aggressive Research Intelligence Facility (ARIF) database (www.arif.bham.ac.uk) for other related systematic diagnostic accuracy reviews, and the International Federation of Clinical Chemistry and Laboratory Medicine Committee for Evidence-based Laboratory Medicine database (C-EBLM) (http://www.ifcc.org/ifcc-education-division/emd-committees/c-eblm/evidence-based-laboratory-medicine-c-eblm-base).

We will check the reference lists of any relevant studies and systematic reviews, and perform citation tracking using Science Citation Index to identify any relevant studies.

Data collection and analysis

Selection of studies

Two review authors (GM, RV) will independently screen the retrieved titles and abstracts for potentially eligible studies. A third review author (PF) will resolve any disagreements between the two review authors. The two review authors (GM, RV) will then independently assess the full-text articles of the selected studies against the inclusion criteria. They will resolve any disagreements through discussion or, where necessary, will consult a third review author (PF) who will act as an arbitrator. When a study does not present all relevant data for creating 2×2 table, we will contact the study authors directly to request further information. When more than one article presents data on the same population, we will include the primary article, which will be the article with the largest number of people or with the most informative data (e.g. longest time of follow-up in the primary outcome).

Data extraction and management

We plan to extract the following data regarding the study characteristics.

- 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 ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) tests administration, including those 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; one year to less than years; two years to less than four years; and more than four years. If participants have been followed for varied amounts of time we will record a mean follow-up period for each included study. If possible, we will group those data into minimum, maximum, and median follow-up periods, which may then become the subject of subgroup analyses;
  - prevalence or proportion of population developing ADD and other dementias, with severity if described.

We will create 2×2 tables (cross-relating index test results of the

reference standards) as shown in Appendix 2. For each included study, we will record the number of people lost to follow-up. We will also extract data necessary for the assessment of quality as defined below. Two review authors (GM, RV) will independently perform data extraction. We will resolve any disagreements regarding data extraction by discussion, or consult a third review author (PF) if necessary.

Assessment of methodological quality

We will assess the methodological quality of each included study using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2) (Whiting 2011), as recommended by Cochrane. This tool is comprised of four domains: patient selection, index test, reference standard, and patient flow.

Two review authors (GM, RV), who will be blinded to each other's scores, will independently perform the QUADAS-2 assessment. They will resolve any disagreements by discussion or, if necessary, consult a third review author (PF) who will act as an arbitrator. We will assess each domain in terms of risk of bias, and will also consider the first three domains in terms of applicability concerns. In Appendix 3 we have detailed the components of each of these domains and provided a rubric that shows how we will make judgements concerning risk of bias. Key areas important to quality assessment are participant selection, blinding, and missing data.
We will include three additional signalling questions on our checklist.

- Was the PET scan interpretation done by a trained reader physician? (We will included this under the 'Index test' domain.)
- Was there a clear definition of a positive result? (We will included this under the 'Index test' domain.)
- Was the study free of commercial funding? (We will included this under the 'flow and timing' domain.)

We will include the item pertaining to the PET scan interpretation and the definition of positive results to take into account the subjective nature of ^{18}F- PET scan image interpretation, which may be based on a variety of different criteria, such as extensive clinical experience, different standard uptake values (SUV), different morphological features, or a combination of the aforementioned. We will include the third additional item in order to record any potential bias resulting from commercial interest in the results.
We will not use QUADAS-2 data to form a summary quality score. We will produce a narrative summary that describes the numbers of included studies that are at high, low, or unclear risk of bias as well as concerns regarding applicability, which we have described in Appendix 4.

Statistical analysis and data synthesis

We will apply the DTA framework for the analysis of a single test and will extract the data from each included study into a 2×2 table, we will show the binary test results cross-classified with the binary reference standard, and we will ignore any censoring that might have occurred. We acknowledge that such a reduction in the data may represent a significant oversimplification. We will therefore adopt an intention-to-diagnose (ITD) approach as well. If possible, we will present what the result would be if all dropouts (Individuals who leave the study prior to completion of follow up) would have developed dementia, and if all dropouts would not have developed dementia.
We will use data from the 2×2 tables abstracted from the included studies: true positive (TP), false negative (FN), false positive (FP), true negative (TN) and entered into Review Manager (RevMan) (Review Manager 2014) to calculate the sensitivities, specificities, and their 95% confidence intervals. We will also present individual study results graphically by plotting estimates of sensitivities and specificities in both a forest plot and a receiver operating characteristic (ROC) space. If an individual included study publishes more than one threshold, we will present the graphical findings for all reported thresholds. However we will avoid inclusion of study data in the calculation of a summary statistic on more than one occasion (in the same setting) by using only the threshold, which is considered to be 'standard practice' for the target population in question. We will not pool studies across settings. If we are unable to agree upon a standard practice for the index test and the target population in question, we will use the optimal threshold (i.e. the threshold nearest to the upper left corner of the ROC curve) in calculating the summary ROC curve in RevMan (Review Manager 2014) and for any subsequent meta-analyses; we recognise that this may lead to an overestimation of diagnostic accuracy (Leeflang 2008). If there are common thresholds across included studies we will also consider the bivariate random-effects approach (Reitsma 2005).
If there is sufficient data we will meta-analyse the pairs of sensitivity and specificity. The preferred approach would be the hierarchical summary ROC curve (HSROC) method proposed by Macaskill 2010 and Rutter 2001 because implicit thresholds are expected in primary studies. We will conduct these analyses using the Statistical Analysis Software (SAS) (SAS Institute 2011).
We plan 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 we plan to clearly note where the same included studies contributed to the analysis for more than one reference standard follow-up interval.
We will explore the implications of any summary accuracy estimates not affected by heterogeneity emerging by considering the numbers of FP and FNs in populations with different prevalence of MCI, and by presenting the results as natural frequencies and using alternative metrics such as likelihood ratios and predictive values.
We will prepare a summary of findings table irrespectively.

Investigations of heterogeneity

We plan to investigate the effects of the following factors.

- Spectrum of people (mean age, gender, Mini-Mental State Examination (MMSE) score, APOE $\epsilon 4$ status). For age, we will separately examine any studies that included 30% of people below the age of 65.
- Referral centres: primary care, memory clinics, and hospitals.
- Clinical criteria of MCI: Petersen criteria, revised Petersen criteria, CDR = 0.5 criteria, and different MCI classification (Matthews 2008).
- Index test: thresholds, if stated; differences in ^{18}F-PET ligands for Aβ retention ratio; differences in image analysis; differences in time between ^{18}F-PET ligands for Aβ and PET acquisition; differences in^{18}F-PET ligands for Aβ injection dose; differences in ^{18}F-PET ligands for Aβ retention detecting regions.
- Reference standard(s) used: NINCDS-ADRDA, DSM, or ICD-10 for ADD.
- Duration of follow-up: one year to less than two years; two to less than four years; and greater than four years.
- Aspects of study quality, particularly inadequate blinding, and loss to follow-up: we will consider separately those studies that have more than 20% drop-outs.
- Conflicts of interest.

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

Sensitivity analyses

We will investigate the influence of study quality on overall DTA of the^{18}F-PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) index, using QUADAS-2. In a sensitivity analysis we will exclude studies at high risk of bias in any domain or high concern applicability as assessed by QUADAS-2, and we will compare the results with those from the primary analysis.

We will ignore any losses to follow-up in the primary analyses. Such a reduction in the data might represent a significant over-simplification. Therefore, we will adopt an ITD approach in sensitivity analyses wherein we will impute missing data under these following assumptions.

- All dropouts developed dementia.
- All dropouts did not develop dementia.

Differing length of follow-up may affect outcomes. We have set a minimum mean time to follow-up assessment of 12 months. We will investigate the stability of results when we exclude studies with a follow-up period of between one year to less than two years from the analyses.

When the criteria used for the clinical diagnosis of dementia are not among the acceptable reference standards of this Cochrane review, we will likewise exclude these studies in a sensitivity analysis to test whether the results differ from the analysis including all studies.

Assessment of reporting bias

We will not investigate reporting bias because of current uncertainty about how it operates in DTA studies and the interpretation of existing analytical tools, such as funnel plots (Leeflang 2008).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy for ^{18}F PET ligands (^{18}F-Florbetapir, ^{18}F-Florbetaben, ^{18}F-Flutemetamol)

Source	Search strategy
MEDLINE In-process and other non-indexed citations and MEDLINE® 1946 to present (Ovid SP)	1. Florbetapir.ti,ab,nm. 2. (AMYViD or amyvid*).ti,ab,nm. 3. "florbetapir-fluorine-18".ti,ab,nm. 4. "18F-AV-45" or "(18)F-AV-45" or "[18F]AV-45" or "[(18)F]AV-45".ti,ab 5. "[18F]Florbetapir".ti,ab,nm.

(*Continued*)

	6. "florbetapir-PET".ti,ab,nm. 7. or/1-6 8. Fluorine Radioisotopes/du 9. Aniline Compounds/du 10. Ethylene Glycols/du 11. Stilbenes/du 12. Radioligand Assay/ 13. radioligand*.ti,ab. 14. or/8-13 15. Alzheimer Disease/ri [Radionuclide Imaging] 16. Plaque, Amyloid/ri [Radionuclide Imaging] 17. or/15-16 18. 14 and 17 19. 7 or 18 1. Florbetaben.ti,ab,nm. 2. (NEURACEQ or neuraceq*).ti,ab,nm. 3. "florbetaben-fluorine-18".ti,ab,nm. 4. "18F-BAY94-9172".ti,ab,nm. 5. "[18F]Florbetaben".ti,ab,nm. 6. "florbetaben-PET".ti,ab,nm. 7. or/1-6 8. Fluorine Radioisotopes/du 9. Aniline Compounds/du 10. Ethylene Glycols/du 11. Stilbenes/du 12. Radioligand Assay/ 13. radioligand*.ti,ab. 14. or/8-13 15. Alzheimer Disease/ri [Radionuclide Imaging] 16. Plaque, Amyloid/ri [Radionuclide Imaging] 17. or/15-16 18. 14 and 17 19. 7 or 18 1. Flutemetamol.ti,ab,nm. 2. (VIZAMYL or vizamyl*).ti,ab,nm. 3. "flutemetamol-fluorine-18".ti,ab,nm. 4. "18F-GE067".ti,ab,nm. 5. "[18F]Flutemetamol".ti,ab,nm. 6. "flutemetamol-PET".ti,ab,nm. 7. or/1-6 8. Fluorine Radioisotopes/du 9. Aniline Compounds/du 10. Ethylene Glycols/du 11. Stilbenes/du 12. Radioligand Assay/ 13. radioligand*.ti,ab. 14. or/8-13 15. Alzheimer Disease/ri [Radionuclide Imaging]

(*Continued*)

	16. Plaque, Amyloid/ri [Radionuclide Imaging] 17. or/15-16 18. 14 and 17 19. 7 or 18
EMBASE 1974 to present (Ovid SP)	1. Florbetapir.ti,ab. 2. (AMYViD or amyvid*).ti,ab. 3. "florbetapir-fluorine-18".ti,ab. 4. "18F-AV-45" or "(18)F-AV-45" or "[18F]AV-45" or "[(18)F]AV-45".ti,ab 5. "[18F]Florbetapir".ti,ab. 6. "florbetapir-PET".ti,ab. 7. exp florbetapir f 18/ 8. or/1-7 9. exp *radioligand/ 10. Alzheimer disease/ 11. Alzheimer*.ti,ab. 12. amyloid plaque/di [Diagnosis] 13. mild cognitive impairment/ 14. or/10-13 15. 9 and 14 16. 8 or 15 1. Florbetaben.ti,ab. 2. (NEURACEQ or neuraceq*).ti,ab. 3. "florbetaben-fluorine-18".ti,ab. 4. "18F-BAY94-9172".ti,ab. 5. "[18F]Florbetaben".ti,ab. 6. "florbetaben-PET".ti,ab. 7. exp florbetaben f 18/ 8. or/1-7 9. exp *radioligand/ 10. Alzheimer disease/ 11. Alzheimer*.ti,ab. 12. amyloid plaque/di [Diagnosis] 13. mild cognitive impairment/ 14. or/10-13 15. 9 and 14 16. 8 or 15 1. Flutemetamol.ti,ab. 2. (VIZAMYL or vizamyl*).ti,ab. 3. "flutemetamol-fluorine-18".ti,ab. 4. "18F-GE067".ti,ab. 5. "[18F]Flutemetamol".ti,ab. 6. "flutemetamol-PET".ti,ab. 7. exp flutemetamol f 18/ 8. or/1-7 9. exp *radioligand/ 10. Alzheimer disease/ 11. Alzheimer*.ti,ab.

(*Continued*)

	12. amyloid plaque/di [Diagnosis] 13. mild cognitive impairment/ 14. or/10-13 15. 9 and 14 16. 8 or 15
PsycINFO 1806 to present (Ovid SP)	1. Florbetapir.ti,ab. 2. (AMYViD or amyvid*).ti,ab. 3. "florbetapir-fluorine-18".ti,ab. 4. "18F-AV-45" or "(18)F-AV-45" or "[18F]AV-45" or "[(18)F]AV-45".ti,ab 5. "[18F]Florbetapir".ti,ab. 6. "florbetapir-PET".ti,ab. 7. or/1-6 1. Florbetaben.ti,ab. 2. (NEURACEQ or neuraceq*).ti,ab. 3. "florbetaben-fluorine-18".ti,ab. 4. "18F-BAY94-9172".ti,ab. 5. "[18F]Florbetaben".ti,ab. 6. "florbetaben-PET".ti,ab. 7. or/1-6 1. Flutemetamol.ti,ab. 2. (VIZAMYL or vizamyl*).ti,ab. 3. "flutemetamol-fluorine-18".ti,ab. 4. "18F-GE067".ti,ab. 5. "[18F]Flutemetamol".ti,ab. 6. "flutemetamol-PET".ti,ab. 7. or/1-6
BIOSIS Citation Index (Thomson Reuters Web of Knowledge) (1922 to present)	Topic=(Florbetapir OR AMYViD OR amyvid* OR "florbetapir-fluorine-18" OR "18F-AV-45" OR "[18F]Florbetapir" OR "florbetapir-PET") Timespan=All years. Databases=BCI Topic=(Florbetaben OR NEURACEQ OR neuraceq* OR "florbetaben-fluorine-18" OR "18F-BAY94-9172" OR "[18F]Florbetaben" OR "florbetaben-PET") Timespan=All years. Databases=BCI Topic=(Flutemetamol OR VIZAMYL OR vizamyl* OR "flutemetamol-fluorine-18" OR "18F-GE067" OR "[18F]Flutemetamol" OR "flutemetamol-PET") Timespan=All years. Databases=BCI
Web of Science Core Collection, including the Science Citation Index and the Conference Proceedings Citation Index (Thomson Reuters Web of Knowledge) (1946 to present)	Topic=(Florbetapir OR AMYViD OR amyvid* OR "florbetapir-fluorine-18" OR "18F-AV-45" OR "[18F]Florbetapir" OR "florbetapir-PET") Timespan=All years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Topic=(Florbetaben OR NERACEQ

(*Continued*)

	OR neuraceq* OR "florbetaben-fluorine-18" OR "18F-BAY94-9172" OR "[18F]Florbetaben" OR "florbetaben-PET") Timespan=All years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Topic=(Flutemetamol OR VIZAMYL OR vizamyl* OR "flutemetamol-fluorine-18" OR "18F-GE067" OR "[18F]Flutemetamol" OR "flutemetamol-PET") Timespan=All years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC
LILACS (BIREME)	Florbetapir OR AMYViD OR amyvid* OR "florbetapir-fluorine-18" OR "18F-AV-45" OR "[18F]Florbetapir" OR "florbetapir-PET" [Words] Florbetaben OR NEURACEQ OR neuraceq* OR "florbetaben-fluorine-18" OR "18F-BAY94-9172" OR "[18F]Florbetaben" OR "florbetaben-PET" [Words] Flutemetamol OR VIZAMYL OR vizamyl* OR "flutemetamol-fluorine-18" OR "18F-GE067" OR "[18F]Flutemetamol" OR "flutemetamol-PET" [Words]
CINAHL (EbscoHOST) (1980 to present)	S1 TX Florbetapir S2 TX AMYViD S3 TX amyvid* S4 TX "florbetapir-fluorine-18" S5 TX "18F-AV-45" S6 TX "[18F]Florbetapir" S7 TX "florbetapir-PET" S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 S1 TX Florbetaben S2 TX NEURACEQ S3 TX neuraceq* S4 TX "florbetaben-fluorine-18" S5 TX "18F-BAY94-9172" S6 TX "[18F]Florbetaben" S7 TX "florbetaben-PET" S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 S1 TX Flutemetamol S2 TX VIZAMYL S3 TX vizamyl* S4 TX "flutemetamol-fluorine-18" S5 TX "18F-GE067" S6 TX "[18F]Flutemetamol" S7 TX "flutemetamol-PET" S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
ClinicalTrials.gov (www.clinicaltrials.gov)	Florbetapir OR AMYViD OR amyvid* OR "florbetapir-fluorine-18" OR "18F-AV-45" OR "[18F]Florbetapir" OR "florbetapir-PET"

(*Continued*)

	Florbetaben OR NEURACEQ OR neuraceq* OR "florbetaben-fluorine-18" OR "18F-BAY94-9172" OR "[18F]Florbetaben" OR "florbetaben-PET" Flutemetamol OR VIZAMYL OR vizamyl* OR "flutemetamol-fluorine-18" OR "18F-GE067" OR "[18F]Flutemetamol" OR "flutemetamol-PET"
World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (http://apps.who.int/trialsearch)	Florbetapir OR AMYViD OR amyvid OR "florbetapir-fluorine-18" OR "18F-AV-45" OR "[18F]Florbetapir" OR "florbetapir-PET" Florbetaben OR NEURACEQ OR neuraceq OR "florbetaben-fluorine-18" OR "18F-BAY94-9172" OR "[18F]Florbetaben" OR "florbetaben-PET" Flutemetamol OR VIZAMYL OR vizamyl OR "flutemetamol-fluorine-18" OR "18F-GE067" OR "[18F]Flutemetamol" OR "flutemetamol-PET"
ALOIS (Cochrane Register of Studies Software)	Imaging AND PET

Appendix 2. Tables (2×2) cross-relating index test results of the reference standards

Table 1. Progression from mild cognitive impairment (MCI) to Alzheimer's disease dementia (ADD)

Index test information	**References standard information**	
	ADD present	**ADD absent**
Index test positive	^{18}F PET ligands for Aβ + who progress to ADD (TP)	^{18}F PET ligands for Aβ + who remain MCI (FP) and ^{18}F PET ligands for Aβ + who progress to non-ADD (FP)
Index test negative	^{18}F PET ligands for Aβ - who progress to ADD (FN)	^{18}F PET ligands for Aβ - who remain MCI (TN) and ^{18}F PET ligands for Aβ - who progress to non-ADD (TN)

ADD: Alzheimer's disease dementia TP: true positive FP: false positive FN: false negative TN: true negative

Table 2. Progression from mild cognitive impairment (MCI) to non-Alzheimer's disease dementia (ADD)

Index test information	**References standard information**	
	Non-ADD present	**Non-ADD absent**
Index test positive	^{18}F PET ligands for Aβ positive who progress to non-ADD (TP)	^{18}F PET ligands for Aβ positive who remain MCI (FP) and ^{18}F PET ligands Aβ positive

(*Continued*)

		who progress to ADD (FP)
Index test negative	^{18}F PET ligands for Aβ negative who progress to non-ADD (FN)	^{18}F PET ligands for Aβ negative who remain MCI (TN) and ^{18}F PET ligands for Aβ negative who progress to ADD (TN)

ADD: Alzheimer's disease dementia MCI: mild cognitive imapirment
TP: true positive FP: false positive FN: false negative TN: true negative
Table 3. Progression from mild cognitive impairment (MCI) to any form of dementia

Index test information	**References standard information**	
	Any forms of dementia present	**Dementia absent**
Index test positive	^{18}F PET ligands for Aβ + who progress to any form of dementia (TP)	^{18}F PET ligands for Aβ + who remain MCI (FP)
Index test negative	^{18}F PET ligands for Aβ - who progress to any form of dementia (FN)	^{18}F PET ligands for Aβ - who remain MCI (TN)

TP: true positive FP: false positive FN: false negative TN: true negative

Appendix 3. Assessment of methodological quality table: Quality Assessment of Diagnostic Accuracy Studies 2 (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) or reference standard, or both, or who were excluded from the 2×2 table (refer to flow diagram): describe the time interval and any interventions between index test(s) and reference standard

(*Continued*)

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 prespecified?	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?	

Appendix 4. Anchoring statements for quality assessment of ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) diagnostic studies

Table 4. Review question and inclusion criteria

Category	Review question	Inclusion criteria
Patients	Participants with mild cognitive impairment (MCI), no dementia	Participants that fulfil the criteria for the clinical diagnosis of MCI at baseline
Index test	^{18}F PET ligands for Aβ biomarkers	^{18}F PET ligands for Aβ biomarkers
Target condition	Alzheimer's disease dementia (ADD) (progression from MCI to ADD) Any other forms of dementia (progression from MCI to any other forms of dementia	ADD (progression from MCI to ADD) Any other forms of dementia (progression from MCI to any other forms of dementia)
Reference standard	NINCDS-ADRDA; DSM; ICD; McKeith criteria; Lund criteria; International Behavioural Variant FTD Criteria Consortium; NINDS-ARIEN criteria	NINCDS-ADRDA; DSM; ICD; McKeith criteria; Lund criteria; International Behavioural Variant FTD

(*Continued*)

		Criteria Consortium; NINDS-ARIEN criteria
Outcome	N/A	Data to construct a 2×2 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)

MCI: mild cognitive impairment ADD: Alzheimer's disease dementia NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association DSM: Diagnostic and Statistical Manual of Mental Disorders
ICD: International Classification of Diseases NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences FTD: Frontotemporal dementia

Anchoring statements for quality assessment of ^{18}F PET ligands for Aβ diagnostic studies

We have provided some core anchoring statements for quality assessment in the diagnostic test accuracy (DTA) review of the ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarkers in dementia. These statements are designed for use with the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool and are based on the guidance for quality assessment of DTA reviews of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) in dementia (Quinn 2014). In assessing individual items, the score of unclear should only be given if there is genuine uncertainty. In these situations we will contact the relevant study teams for additional information. Whenever we score one question as high risk of bias, we will consider the study having a high risk of bias.
Table 5. Anchoring statements to assist with the 'Risk of bias' assessment

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	We will automatically grade the study as unclear if the study authors do not detail exclusions (pending contact with study au-

(*Continued*)

		thors) Where a study details exclusions, we will grade the study as 'low risk' if we consider exclusions to be appropriate. Certain exclusions common to many studies of dementia are: medical instability; terminal disease; alcohol/substance misuse; concomitant psychiatric diagnosis; other neurodegenerative conditions Exclusions are not appropriate if they comprise 'difficult to diagnose' patients We will label post hoc and inappropriate exclusions as at 'high risk' of bias
Index test		
Were ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) 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, e.g. level of protein in cerebrospinal fluid, in this instance the quality assessment may be 'low risk' even if blinding was not achieved
Were ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarker's thresholds prespecified?	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 study authors define the optimal cut-off post-hoc based on their own study data because selecting the threshold to maximise sensitivity and/or 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

(*Continued*)

Was the ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamo PET scan interpretation done by a trained reader physician?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	If a trained reader physician performed the scan interpretation, we will score this item as 'yes' If no definition of trained reader was done, we will score this item as 'unclear' If a non-trained reader physician performed the scan interpretation, we will score this item as 'no'
Did the study provide a clear definition of what was considered to be a ^{18} F PET ligand for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarker's positive result?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	If the study clearly states the definition of a positive result (e.g. SUV), we will score this item as 'yes' If the study does not give a definition of what it considered a positive result or the definition of a positive result varied between the participants, we will score this item as 'no' If the study gives insufficient information to permit judgement, we will score the item as 'unclear'
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 and International Behavioural Variant FTD Criteria Consortium 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') we will classify this item as "high risk of bias"
Were clinical assessments for dementia performed without knowledge of the ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarkers?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	Terms such as "blinded" or "independently and without knowledge of " are sufficient and full details of the blinding procedure are not required. Interpretation of the results of the reference standard may be influenced by knowledge of the results of index test

(*Continued*)

Patient flow		
Was there an appropriate interval between ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarkers and clinical dementia assessment?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	As we test the accuracy of the ^{18}F PET ligands for Aβ biomarkers for MCI progression 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 2007; 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 have assessment for MCI progression before nine months this item will score 'no'
Did all subjects get the same assessment for dementia regardless ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarkers?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	There may be scenarios where participants who score "test positive" on index test have a more detailed assessment. Where dementia assessment differs between participants, this should be classified as high risk of bias
Were all patients who received ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) 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 2×2 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 ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarker's 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), we will score this as 'no'. If the study does not report these results, we will score this as 'unclear' and we will contact the study authors
Was the study with ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) biomarker free of commercial funding?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	If the funding source is clearly stated and is not commercial, this should be scored as 'no' If the funding source is clearly stated and is commercial, this should be scored as 'yes '

(*Continued*)

		If not enough information is given to assess whether the funding source is commercial, the scored is 'unclear'

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 ^{18}F PET ligands for Aβ (^{18}F-Florbetapir, ^{18}F-Florbetaben, and ^{18}F-Flutemetamol) 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 ^{18}F PET ligands for Aβ biomarkers were not performed consistently this item should be rated poor applicability
Reference standard	
Was clinical diagnosis of dementia made in a manner similar to current clinical practice?	For many reviews, inclusion criteria and 'Risk of bias' assessments 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 people with disease than usual clinical practice. In this instance the item should be rated poor applicability

DSM: Diagnostic and Statistical Manual of Mental Disorders ICD: International Classification of Diseases NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association FTD: Frontotemporal dementia NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences MCI: mild cognitive impairment

CONTRIBUTIONS OF AUTHORS

Gabriel Martínez and Leon Flicker conceived, designed and drafted the protocol.

Robin WM Vernooij, Paulina Fuentes Padilla, Javier Zamora, Marta Roqué i Figuls, Gerard Urrútia, and Xavier Bonfill Cosp designed and drafted the protocol.

DECLARATIONS OF INTEREST

Gabriel Martínez has no known conflicts of interest.

Leon Flicker has no known conflicts of interest.

Robin WM Vernooij has no known conflicts of interest.

Paulina Fuentes Padilla has no known conflicts of interest.

Javier Zamora has no known conflicts of interest.

Marta Roqué i Figuls has no known conflicts of interest.

Gerard Urrútia has no known conflicts of interest.

Xavier Bonfill Cosp has no known conflicts of interest.

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