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Departamento de Pediatría, de Obstetricia y Ginecología,
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Evidencias en exactitud de pruebas diagnósticas en la enfermedad de Alzheimer y otras demencias

TESIS DOCTORAL

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Cita

Ojalá encuentre camino para seguir caminando.

Víctor Jara

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1. Resumen

1. Resumen

1.1. Resumen

Antecedentes

La captación de 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol por el tejido cerebral a través de una tomografía por emisión de positrones (TEP) está aceptada por agencias reguladoras como la Administración de Medicamentos y Alimentos (FDA) y la Agencia Europea de Medicamentos (EMA) para evaluar la carga de amiloide en personas con demencia, siendo esta carga amiloidea uno de los hallazgos histopatológicos en la enfermedad de Alzheimer. Su valor añadido se demuestra principalmente cuando la captación de amiloide es negativa, lo que permite excluir la patología Alzheimer en un diagnóstico de demencia establecido. Sin embargo, el Instituto Nacional sobre el Envejecimiento y la Asociación de Alzheimer (NIA-AA) revisaron los criterios diagnósticos para la enfermedad de Alzheimer y establecieron que la presencia de patología amiloidea, detectada por alguno de estos marcadores en una persona con un cuadro de deterioro cognitivo leve (DCL) estaría determinada por una enfermedad de Alzheimer. A pesar de lo anterior, la exactitud diagnóstica del 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol para predecir la progresión desde un DCL a una demencia por enfermedad de Alzheimer (DEA) u otras demencias aún no ha sido evaluada sistemáticamente.

Objetivos

Determinar la exactitud de la prueba diagnóstica (EPD) TEP con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol para detectar personas con un DCL y que progresarán clínicamente a una DEA, otras formas de demencia no Alzheimer (no-DEA) o cualquier forma de demencia durante el seguimiento.

Métodos

Se elaboraron tres revisiones sistemáticas siguiendo los estándares metodológicos Cochrane, una para cada uno de los marcadores mencionados.

Búsquedas

Se realizaron búsquedas en MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), BIOSIS Citation Index (Thomson Reuters Web of Science), Web of Science Core Collection, incluido el Science Citation Index (Thomson Reuters Web of Science) y el Conference Proceedings Citation Index (Thomson Reuters Web of Science), LILACS (BIREME), CINAHL (EBSCOhost), ClinicalTrials.gov (https://clinicaltrials.gov) y el Registro de la Plataforma Internacional de Registro de Ensayos Clínicos de la Organización Mundial de la Salud (ICTRP de la OMS) (http://www.who.int/ictrp/search/en/). También se realizaron búsquedas en ALOIS, el registro especializado de estudios sobre demencia del Grupo Cochrane de Demencia y Mejora Cognitiva (http://www.medicine.ox.ac.uk/alois/). Verificamos las listas de referencias de cualquier estudio relevante o revisión sistemática y realizamos un seguimiento de citas mediante el Science Citation Index para identificar estudios relevantes adicionales. No se aplicaron restricciones de idioma o fecha a las búsquedas electrónicas. Las búsquedas bibliográficas realizadas están actualizadas hasta mayo de 2017.

Criterio de Selección

Se incluyeron estudios que habían definido prospectivamente cohortes con cualquier definición aceptada de DCL en el momento de realizar la prueba y el uso de la exploración con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol para evaluar la EPD en la progresión desde un DCL a una DEA u otras formas de demencia. Además, solo se seleccionaron estudios que aplicaron un estándar de referencia para el diagnóstico de la DEA, por ejemplo, el Instituto Nacional de Trastornos Neurológicos y Comunicativos y Accidentes Cerebrovasculares y la

Asociación de Enfermedad de Alzheimer y Trastornos Relacionados (NINCDS-ADRDA) o los criterios del Manual Diagnóstico y Estadístico de Trastornos Mentales IV (DSM-IV).

Recolección de datos y análisis

Se examinaron todos los títulos y resúmenes identificados en las búsquedas en las bases de datos electrónicas. Dos revisores seleccionaron de forma independiente los estudios para su inclusión y extrajeron los datos para crear tablas de 2x2 para las pruebas evaluadas en forma visual y en forma cuantitativa, mostrando los resultados de las pruebas binarias clasificados de forma cruzada con el estándar de referencia binario. Usamos estos datos para calcular la sensibilidad, la especificidad y los intervalos de confianza al 95%. Dos evaluadores independientes realizaron la evaluación de la calidad mediante la herramienta QUADAS-2 más algunos elementos adicionales para evaluar la calidad metodológica de los estudios incluidos.

Resultados

18F-Florbetapir: Se incluyeron tres estudios en la respectiva revisión sistemática, dos de los cuales evaluaron la progresión desde un DCL a una DEA, y uno evaluó la progresión desde un DCL a cualquier forma de demencia.

Al evaluar el riesgo de sesgo, se consideró que la selección de pacientes y el estándar de referencia en los tres estudios fue poco claro. Con respecto al dominio del flujo de pacientes, se consideró que dos estudios tenían un alto riesgo de sesgo.

La progresión desde un DCL a una DEA en aquellos con un seguimiento de entre dos y menos de cuatro años tuvo una sensibilidad de 67% (IC 95%: 30 a 93) y una especificidad de 71% (IC 95%: 54 a 85) según la evaluación visual (n = 47, 1 estudio).

La progresión desde un DCL a una DEA en aquellos con un seguimiento entre uno y menos de dos años tuvo una sensibilidad de 89% (IC 95%: 78 a 95) y una especificidad de 58% (IC 95%:

53 a 64) por evaluación visual y una sensibilidad de 87% (IC 95%: 76 a 94) y una especificidad de 51% (IC 95%: 45 a 56) mediante la evaluación cuantitativa (n = 401, 1 estudio).

La progresión desde un DCL a cualquier forma de demencia en aquellos con un seguimiento entre uno y menos de dos años tuvo una sensibilidad de 67% (IC 95%: 9 a 99) y una especificidad de 50% (IC 95%: 1 a 99) por evaluación visual (n = 5, 1 estudio).

18F-Florbetaben: Se incluyó un estudio que evaluó la progresión desde un DCL a una DEA, a cualquier forma de demencia no-DEA y a cualquier forma de demencia.

Al evaluar el riesgo de sesgo se consideró que el estudio tenía un alto riesgo de sesgo en los dominios del estándar de referencia, el flujo y el tiempo.

La progresión desde un DCL a una DEA por evaluación visual tuvo una sensibilidad de 100% (IC 95%: 84 a 100) y una especificidad de 83% (IC 95%: 63 a 98). Analizada cuantitativamente, la sensibilidad fue de 100% (IC 95%: 84 a 100) y la especificidad de 88% (IC 95%: 68 a 97) en el seguimiento a cuatro años (n = 45, 1 estudio).

La progresión desde un DCL a cualquier forma de demencia no-DEA por evaluación visual tuvo una sensibilidad de 0% (IC 95%: 0 a 52) y una especificidad de 38% (IC 95%: 23 a 54). Analizada cuantitativamente, la sensibilidad fue de 0% (IC 95%: 0 a 52) y la especificidad fue de 40% (IC 95%: 25 a 57) para el diagnóstico de cualquier forma de demencia no-DEA en el seguimiento (n = 45, 1 estudio).

La progresión desde un DCL a cualquier forma de demencia por evaluación visual tuvo una sensibilidad de 81% (IC 95%: 61 a 93) y una especificidad de 79% (IC 95%: 54 a 94). Analizado cuantitativamente, la sensibilidad fue 81% (IC 95: 61 a 93%) y la especificidad fue 84% (IC 95%: 60 al 97) para el diagnóstico de cualquier forma de demencia en el seguimiento (n = 45 , 1 estudio).

18F-Flutemetamol: Se incluyeron dos estudios que evaluaron la progresión desde un DCL a una DEA. Ambos estudios se consideraron con un alto riesgo de sesgo en los dominios de flujo y tiempo.

La progresión desde un DCL a una DEA a los dos años de seguimiento tuvo una sensibilidad de 89% (IC 95%: 52 a 100) y una especificidad de 80% (IC 95%: 44 a 97) según la evaluación cuantitativa (n = 19, 1 estudio).

La progresión desde un DCL a una DEA a los tres años de seguimiento tuvo una sensibilidad de 64% (IC 95%: 53 a 75) y una especificidad de 69% (IC 95%: 60 a 76) según la evaluación visual (n = 224, 1 estudio).

Conclusiones

Debido a las sensibilidades y especificidades variables para predecir la progresión desde un DCL a una DEA y a los pocos datos disponibles, no se puede recomendar el uso rutinario de 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol en la práctica clínica.

Los biomarcadores 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol son de alto costo económico; por lo tanto, es importante demostrar con suficiente certidumbre su exactitud diagnóstica y estandarizar sus modalidades de proceso antes de ser usados en forma amplia.

1.2. Resum

Antecedents

La captació de 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol pel teixit cerebral a través d'una tomografia per emissió de positrons (TEP) està acceptada per agències reguladores com l'Administració de Medicaments i Aliments (FDA) i l'Agència Europea de Medicaments

(EMA) per avaluar la càrrega d'amiloide en persones amb demència, essent aquesta càrrega amiloide una de les troballes histopatològiques en la malaltia d'Alzheimer. El seu valor afegit es demostra principalment quan la captació d'amiloide és negativa, fet que permet excloure la patologia d'Alzheimer en un diagnòstic de demència establert. No obstant això, l'Institut Nacional sobre l'Envelliment i l'Associació d'Alzheimer (NIA-AA) van revisar els criteris diagnòstics per a la malaltia d'Alzheimer i van establir que la presència de patologia amiloide, detectada per algun d'aquests marcadors en una persona amb un quadre de deteriorament cognitiu lleu (DCL) estaria determinada per una malaltia d'Alzheimer. Malgrat això, la exactitud diagnòstica del 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol per predir la progressió de DCL a una demència clínica per malaltia d'Alzheimer o altres demències encara no ha estat avaluada sistemàticament.

Objectius

Determinar la exactitud de la prova diagnòstica (EPD) de la TEP amb 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol per detectar persones amb un DCL i que progressaran clínicament a una demència per malaltia d'Alzheimer (DMA), altres formes de demència no Alzheimer (no-DMA) o qualsevol forma de demència durant el seguiment.

Mètodes

Es van elaborar tres revisions sistemàtiques seguint els estàndards metodològics Cochrane, una per a cada un dels marcadors esmentats.

Cerques

Es van realitzar cerques a MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), BIOSIS Citation Index (Thomson Reuters Web of Science), Web of Science Core Collection, inclòs l'Science Citation Index (Thomson Reuters Web of Science) i el Conference

Proceedings Citation Index (Thomson Reuters Web of Science), LILACS (BIREME), CINAHL (EBSCOhost), ClinicalTrials.gov (https://clinicaltrials.gov) i el Registre de la Plataforma Internacional de Registre d'Assaigs Clínics de l'Organització Mundial de la Salut (ICTRP de l'OMS) (http://www.who.int/ictrp/search/en/). També es van realitzar cerques a ALOIS, el registre especialitzat d'estudis sobre demència del Grup Cochrane de Demència i Millora Cognitiva (http://www.medicine.ox.ac.uk/alois/). Es van verificar les llistes de referències de qualsevol estudi rellevant o revisió sistemàtica i es van realitzar un seguiment de cites mitjançant l'Science Citation Index per identificar estudis rellevants addicionals. No es van aplicar restriccions d'idioma o data a les cerques electròniques. Les cerques bibliogràfiques realitzades estan actualitzades fins a maig de 2017.

Criteri de Selecció

Es van incloure estudis que havien definit prospectivament cohorts amb qualsevol definició acceptada de DCL en el moment de realitzar la prova i l'ús de l'exploració amb 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol per avaluar la EPD en la progressió de DCL a DMA o altres formes de demència. A més, solament es van seleccionar estudis que van aplicar un estàndard de referència per al diagnòstic de la demència d'Alzheimer, per exemple, l'Institut Nacional de Trastorns Neurològics i Comunicatius i Accidents Vasculars Cerebrals i l'Associació de Malaltia d'Alzheimer i Trastorns Relacionats (NINCDS-ADRDA) o els criteris del Manual Diagnòstic i Estadístic de Trastorns Mentals IV (DSM-IV).

Recollida de dades i anàlisi

Es van examinar tots els títols i resums identificats en les cerques en les bases de dades electròniques. Dos revisors van seleccionar de forma independent els estudis per a la seva inclusió i van extreure les dades per crear taules de 2x2 per a les proves avaluades en forma visual i en forma quantitativa, mostrant els resultats de les proves binàries classificats de forma creuada amb l'estàndard de referència binari. Es van utilitzar aquestes dades per calcular la

sensibilitat, l'especificitat i els intervals de confiança del 95%. Dos avaluadors independents van realitzar l'avaluació de la qualitat mitjançant l'eina QUADAS-2 més alguns elements addicionals per avaluar la qualitat metodològica dels estudis inclosos.

Resultats

18F-Florbetapir: Es van incloure tres estudis en la respectiva revisió sistemàtica, dos dels quals van avaluar la progressió de DCL a DMA, i un va avaluar la progressió de DCL a qualsevol forma de demència.

En avaluar el risc de biaix, es va considerar que la selecció de pacients i l'estàndard de referència en els tres estudis va ser poc clar. Pel que fa al domini del flux de pacients, es va considerar que dos estudis tenien un alt risc de biaix.

La progressió de DCL a DMA en aquells amb un seguiment entre dos i menys de quatre anys va tenir una sensibilitat del 67% (IC 95%: 30 a 93) i una especificitat del 71% (IC 95%: 54 a 85) segons l'avaluació visual (n = 47, 1 estudi).

La progressió de DCL a DMA en aquells amb un seguiment entre un i menys de dos anys va tenir una sensibilitat del 89% (IC 95%: 78 a 95) i una especificitat del 58% (IC 95%: 53 a 64) per avaluació visual i una sensibilitat del 87% (IC 95%: 76 a 94) i una especificitat del 51% (IC 95%: 45 a 56) mitjançant l'avaluació quantitativa (n = 401, 1 estudi).

La progressió de DCL a qualsevol forma de demència en aquells amb un seguiment entre un i menys de dos anys va tenir una sensibilitat del 67% (IC 95%: 9 a 99) i una especificitat del 50% (IC 95%: 1 a 99) per avaluació visual (n = 5, 1 estudi).

18F-Florbetaben: Es va incloure un estudi que va avaluar la progressió des d'un DCL a una DMA, a qualsevol forma de demència no-DMA i a qualsevol forma de demència.

En avaluar el risc de biaix es va considerar que l'estudi tenia un alt risc de biaix en els dominis de l'estàndard de referència, el flux i el temps.

La progressió de DCL a DMA per avaluació visual va tenir una sensibilitat del 100% (IC 95%: 84 a 100) i una especificitat del 83% (IC 95%: 63 a 98). Analitzada quantitativament, la sensibilitat va ser del 100% (IC 95%: 84 a 100) i l'especificitat del 88% (IC 95%: 68 a 97) en el seguiment a quatre anys (n = 45, 1 estudi).

La progressió de DCL a qualsevol forma de demència no-DMA per avaluació visual va tenir una sensibilitat del 0% (IC 95%: 0 a 52) i una especificitat del 38% (IC 95%: 23 a 54). Analitzada quantitativament, la sensibilitat va ser del 0% (IC 95%: 0 a 52) i l'especificitat va ser del 40% (IC 95%: 25 a 57) per al diagnòstic de qualsevol forma de demència no-DMA en el seguiment (n = 45 , 1 estudi).

La progressió de DCL a qualsevol forma de demència per avaluació visual va tenir una sensibilitat del 81% (IC 95%: 61 a 93) i una especificitat del 79% (IC 95%: 54 a 94). Analitzat quantitativament, la sensibilitat va ser del 81% (IC 95: 61 a 93%) i l'especificitat va ser del 84% (IC 95%: 60 a 97) per al diagnòstic de qualsevol forma de demència en el seguiment (n = 45, 1 estudi).

18F-Flutemetamol: Es van incloure dos estudis que van avaluar la progressió de DCL a DMA. Es va considerar que tots dos estudis tenien un alt risc de biaix en els dominis de flux i temps.

La progressió de DCL a DMA al cap de dos anys de seguiment va tenir una sensibilitat del 89% (IC 95%: 52 a 100) i una especificitat del 80% (IC 95%: 44 a 97) segons l'avaluació quantitativa (n = 19, 1 estudi).

La progressió de DCL a DMA al cap de tres anys de seguiment va tenir una sensibilitat del 64% (IC 95%: 53 a 75) i una especificitat del 69% (IC 95%: 60 a 76) segons l'avaluació visual (n = 224, 1 estudi).

Conclusions

A causa de les sensibilitats i especificitats variables per predir la progressió de DCL a DMA i a les poques dades disponibles, no es pot recomanar l'ús rutinari de 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol en la pràctica clínica.

Els biomarcadors 18F-Florbetapir, 18F-Florbetaben i 18F-Flutemetamol són d'alt cost econòmic; per tant, és important demostrar amb suficient certesa la seva exactitud diagnòstica i estandarditzar les seves modalitats de procés abans de ser usats en forma àmplia.

1.3. Abstract

Background

18F-Florbetapir, 18F-Florbetaben or 18F-Flutemetamol uptake by brain tissue, measured by positron emission tomography (PET), is accepted by regulatory agencies like the Food and Drug Administration (FDA) and the European Medicine Agencies (EMA) for assessing amyloid load in people with dementia, one of the pathological hallmarks of Alzheimer's disease. Its added value is mainly demonstrated by excluding Alzheimer's pathology in an established dementia diagnosis. However, the National Institute on Aging and Alzheimer's Association (NIA-AA) revised the diagnostic criteria for Alzheimer's disease and established the diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease if the amyloid pathology is present when using some amyloid biomarkers tests. However, the DTA of 18F-Florbetapir, 18F-Florbetaben or 18F-Flutemetamol to predict the progression from MCI to Alzheimer's disease dementia (ADD) or other dementias has not yet been systematically evaluated.

Objectives

To determine the diagnostic test accuracy (DTA) of the 18F-Florbetapir, 18F-Florbetaben or 18F-Flutemetamol PET scan for detecting people with MCI at time of performing the test who will clinically progress to ADD, other forms of dementia (non-ADD), or any form of dementia at follow-up.

Methods

Three systematic reviews were performed following Cochrane methodological standards, one for each biomarker.

Search

We searched MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), BIOSIS Citation Index (Thomson Reuters Web of Science), Web of Science Core Collection, including the Science Citation Index (Thomson Reuters Web of Science) and the Conference Proceedings Citation Index (Thomson Reuters Web of Science), LILACS (BIREME), CINAHL (EBSCOhost), 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 also searched ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialised register of dementia studies (http://www.medicine.ox.ac.uk/alois/). We checked the reference lists of any relevant studies and systematic reviews, and performed citation tracking using the Science Citation Index to identify any additional relevant studies. No language or date restrictions were applied to electronic searches. The electronic searches were performed until May 2017.

Selection criteria

We included studies that had prospectively defined cohorts with any accepted definition of MCI at time of performing the test and the use of 18F-Florbetapir, 18F-Florbetaben or 18F-Flutemetamol scan to evaluate the DTA of the progression from MCI to ADD or other forms of dementia. In addition, we only selected studies that applied a reference standard for

Alzheimer's dementia diagnosis, for example, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS- ADRDA) or Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria.

Data collection and analysis

We screened all titles and abstracts identified in electronic-database searches. Two review authors independently selected studies for inclusion and extracted data to create two-by-two tables, showing the binary test results cross-classified with the binary reference standard. We used these data to calculate sensitivities, specificities, and their 95% confidence intervals. Two independent assessors performed quality assessment using the QUADAS-2 tool plus some additional items to assess the methodological quality of the included studies.

Results

18F-Florbetapir: Three studies were included, two of which evaluated the progression from MCI to ADD, and one evaluated the progression from MCI to any form of dementia.

Regarding the risk of bias, for the patient selection and reference standard domain, all three studies were considered to have an unclear risk of bias. Regarding the domains of flow and timing, two studies were considered at high risk of bias.

Progression from MCI to ADD in those with a follow-up between two to less than four years had a sensitivity of 67% (95% CI 30 to 93) and a specificity of 71% (95% CI 54 to 85) by visual assessment (n = 47, 1 study).

Progression from MCI to ADD in those with a follow-up between one to less than two years had a sensitivity of 89% (95% CI 78 to 95) and a specificity of 58% (95% CI 53 to 64) by

visual assessment, and a sensitivity of 87% (95% CI 76 to 94) and a specificity of 51% (95% CI 45 to 56) by quantitative assessment (n = 401, 1 study).

Progression from MCI to any form of dementia in those with a follow-up between one to less than two years had a sensitivity of 67% (95% CI 9 to 99) and a specificity of 50% (95% CI 1 to 99) by visual assessment (n = 5, 1 study).

18F-Florbetaben: One study was included and evaluated the progression from MCI to ADD, any other form of dementia, and any form of dementia.

We considered the study to be at high risk of bias in the domains of the reference standard, flow, and timing.

Progression from MCI to ADD had a sensitivity of 100% (95% CI 84 to 100) and a specificity of 83% (95% CI 63 to 98) by visual assessment, and a sensitivity of 100% (95% CI 84 to 100) and a specificity of 88% (95% CI 68 to 97) by quantitative assessment at four years of follow up (n = 45, 1 study).

Progression from MCI to any other form of dementia (non-ADD) had a sensitivity of 0% (95% CI 0 to 52) and a specificity of 38% (95% CI 23 to 54) by visual assessment, and a sensitivity of 0% (95% CI 0 to 52) and a specificity of 40% (95% CI 25 to 57) by quantitative assessment at follow-up (n = 45, 1 study).

Progression from MCI to any form of dementia had a sensitivity of 81% (95% CI 61 to 93) and a specificity of 79% (95% CI 54 to 94) by visual assessment, and a sensitivity of 81% (95% CI 61 to 93) and a specificity of 84% (95% CI 60 to 97) by quantitative assessment at follow-up (n = 45, 1 study).

18F-Flutemetamol: Two studies evaluated the progression from MCI to ADD. Regarding the domains of flow and timing, both studies were considered at high risk of bias.

Progression from MCI to ADD at two years of follow-up had a sensitivity of 89% (95% CI 52 to 100) and a specificity of 80% (95% CI 44 to 97) by quantitative assessment (n = 19, 1 study).

Progression from MCI to ADD at three years of follow-up had a sensitivity of 64% (95% CI 53 to 75) and a specificity of 69% (95% CI 60 to 76) by visual assessment (n = 224, 1 study).

Conclusion

Due to the varying sensitivity and specificity for predicting the progression from MCI to ADD and the limited data available, we cannot recommend routine use of 18F-Florbetapir, 18F-Florbetaben, and 18F-Flutemetamol in clinical practice.

18F-Florbetapir, 18F-Florbetaben, and 18F-Flutemetamol have high financial costs; therefore, clearly demonstrating the DTA and standardising the process modalities is important prior the wider use of these biomarkers.

2. Introducción

2.1 Introducción

Definición de demencia

No existe una definición universal para la demencia, pero dentro de las más aceptadas podemos encontrar las siguientes:

"La demencia es un síndrome que a menudo se diagnostica cuando los pacientes experimentan síntomas como deterioro cognitivo progresivo y disminución de las actividades de la vida diaria. Por lo general, el paciente, o sus familiares, expresarán el síntoma del "olvido", sin embargo, otras funciones corticales, como la orientación, el aprendizaje, la comprensión, el lenguaje y el juicio, también podrían verse afectadas. Además, los pacientes con demencia generalmente experimentan trastornos del comportamiento, como alucinaciones, agitación/agresión, delirios, irritabilidad/labilidad o desinhibición. La presencia y la gravedad de estos síntomas difieren entre las etapas de la demencia. En las primeras etapas, los síntomas suelen ser leves, sin embargo, la gravedad de los síntomas y el deterioro de la actividad funcional aumenta generalmente en las etapas más avanzadas" (McKhann 2011).

Otra definición aceptada es la de la Organización Mundial de la Salud (OMS), que define a la demencia como "un síndrome debido a una enfermedad cerebral, generalmente de naturaleza crónica o progresiva, en la cual hay una alteración de múltiples funciones corticales superiores, que incluyen memoria, pensamiento, orientación, comprensión, cálculo, capacidad de aprendizaje, lenguaje y juicio, donde la conciencia no se ve afectada. Los impedimentos de la función cognitiva suelen ir acompañados, y en ocasiones precedidos, por un deterioro del control emocional, el comportamiento social y la motivación, y el deterioro es suficiente para interferir con las actividades cotidianas" (WHO 2012).

Las dos definiciones previas dejan claramente establecido que la demencia va acompañada de una alteración de las actividades de la vida diaria. La afectación en las actividades de la vida diaria también es progresiva, afectando en un inicio actividades de la vida diaria tales como

conducir, manejo de dinero, salir de compras y conforme avanza la enfermedad, se afectan las actividades más básicas como bañarse, vestirse, transferirse y otras.

En el caso de que una persona se mantenga independiente en actividades de la vida diaria pese a objetivar un deterioro cognitivo, estamos ante la presencia de un deterioro cognitivo leve (DCL), condición muy frecuente de encontrar en personas mayores y que muchos consideran un paso previo al desarrollo de una demencia (Albert 2011).

Prevalencia

La demencia es un grave problema de salud pública mundial, afecta a un 5.2% de las personas mayores de 60 años (5.9% y 6.4% en Europa y América, respectivamente) (ADI 2015). Además, debido a que es una enfermedad asociada al envejecimiento y dado el envejecimiento poblacional, se espera que el número de personas con demencia se duplique cada 20 años. En consecuencia, en el año 2050 se espera un número cercano a 152 millones de personas con demencia (ADI 2018). Esta prevalencia implicará una alta carga económica para todos los países, carga que actualmente representa el 1% del Producto Interior Bruto mundial en costos directos e indirectos (WHO 2012) o al equivalente de 1 trillón de dólares y esto se duplicará en 10 años (ADI 2018).

Tipos de demencia

Existen diferentes subtipos de demencia que se distinguen por la patología subyacente. La demencia por enfermedad de Alzheimer (DEA) es el subtipo más común de demencia, representa aproximadamente el 60-70% de todos los casos de demencia. Otros subtipos importantes de demencia son la demencia vascular, la demencia con cuerpos de Lewy y la demencia frontotemporal (FTD) (WHO 2012).

La enfermedad de Alzheimer fue descrita el año 1906 por Alois Alzheimer, donde describía un caso de demencia en una persona joven con estudio post mortem donde se encontraron dos hallazgos histopatológicos principales, la presencia de placas neuríticas (o placas amiloides) y

de ovillos neurofibrilares. En estudios posteriores, se convino que esta patología era la predominante en la mayoría de las personas con demencia, por lo que, desde el punto de vista técnico, la presencia de placas neuríticas y ovillos neurofibrilares configuraban el diagnóstico histopatológico de la enfermedad de Alzheimer. El diagnóstico histopatológico de enfermedad de Alzheimer sólo se lograría post mortem o a través de biopsia, por lo que, la confirmación diagnóstica y diagnóstico diferencial ha sido principalmente clínico, a través del uso de criterios publicados por diferentes entidades o grupos de investigación durante las últimas décadas (APA 1987; APA 1994; McKhann 1984).

Una dificultad fundamental es que los criterios clínicos han tenido una exactitud diagnóstica variable con una sensibilidad entre 71% y 88% y una especificidad entre 44% y 71% cuando se comparan con el estándar histopatológico (Beach 2012).

Esto generó discrepancias respecto de lo que se entendía por enfermedad de Alzheimer. Desde el punto de vista de ciencias básicas, la enfermedad de Alzheimer es el hallazgo de evidencia histopatológica característica, en definitiva, un diagnóstico biológico (Jack 2018; Jack 2019).

Desde el punto de vista clínico, la enfermedad de Alzheimer es la condición donde se presentan ciertas características desde el punto de vista cognitivo, conductual y funcional, donde no se incluye la histopatología, ya que, no es una opción disponible en la práctica. Asociado a lo anterior, aún faltan estudios para evaluar la real exactitud diagnóstica de nuevos biomarcadores que pudieran ser incluidos en los criterios clínicos (CDCIG 2010).

Con los años y en estudios longitudinales, se ha logrado establecer que la patología Alzheimer, como forma única o mixta, está presente en el 84% de las personas con demencia (Schneider 2007) y se ha encontrado también en autopsias de personas con otros tipos de demencia clínica como la demencia vascular, la demencia con cuerpos de Lewy y la demencia frontotemporal (Jellinger 2006). Además, hasta un 88% de los pacientes diagnosticados con una DEA, tienen una forma de la patología de Alzheimer (Schneider 2009).

Pese a lo anterior, también es posible encontrar patología Alzheimer en personas mayores que viven en la comunidad o en estudios post mortem de personas que nunca manifestaron trastornos cognitivos en su vida (Schneider 2007). Esto ha generado controversias sobre la importancia de la presencia de la patología de Alzheimer. Por un lado, la patología estaría asociada con el envejecimiento y por otro, en personas mayores de 90 años no existe una relación significativa entre la carga de la placa amiloide y el deterioro cognitivo (Savva 2009). La presencia de patología amiloide en personas sin deterioro cognitivo, ha promovido el desarrollo de nuevas visiones respecto de la enfermedad, donde en un teórico continuo fisiopatológico, muchas personas pueden presentar patología Alzheimer hasta 20 años antes de la manifestación clínica, lo que explicaría que personas con patología Alzheimer en autopsias, no presentaban sintomatología cognitiva antes de fallecer. Por todo ello, se especula que si aquellas personas hubiesen vivido lo suficiente, habrían desarrollado la enfermedad en algún momento del transcurso de su vida. (Jack 2013).

Diagnóstico de la enfermedad de Alzheimer

En la última década, han surgido voces respaldadas por numerosos expertos acerca de que existe un continuo clínico en cuanto al desarrollo de la enfermedad y que va desde una persona sin quejas cognitivas hasta una persona con demencia clínica. Si se logra detectar patología, en este caso patología amiloidea, en teoría podríamos diagnosticar la enfermedad antes de que se manifieste clínicamente. En consecuencia, si se logra detectar patología amiloidea en una persona sin quejas cognitivas, estaríamos en presencia de una enfermedad de Alzheimer preclínica y si esta persona tiene un DCL asociado a amiloide cerebral, la condición sería un MCI por enfermedad de Alzheimer (Sperling 2011). Si la persona tiene una demencia clínica con biomarcador amiloideo positivo, se configura una demencia por enfermedad de Alzheimer (McKhann 2011).

En el ámbito terapéutico, el tratamiento de una demencia por enfermedad de Alzheimer ha logrado producir diferencias estadísticamente significativas en cuanto a cognición, pero el real impacto clínico de ello está en discusión. Incluso Francia, desde hace dos años, ya no dispensa los medicamentos aprobados hace más de una década en el sistema público, debido a dudas razonables de que logren un efecto clínicamente significativo (Ministère des Solidarités et de la Santé 2018).

En consecuencia, concentrarse en investigar en etapas más precoces de la enfermedad podría entregar mayores beneficios para la persona tanto desde el punto de vista diagnóstico, pronóstico y terapéutico.

Hoy en día, obtener un fármaco o desarrollar medidas no farmacológicas que desaceleren la progresión a una demencia es un objetivo común entre los investigadores, enfocándose dentro de este continuo en personas que tienen un DCL o incluso en personas asintomáticas para prevenir el desarrollo a una demencia clínica a través de los años. Modelos matemáticos han demostrado que medidas de intervención preventivas, como una reducción de 10% por década en la prevalencia de cada uno de factores de riesgo (como diabetes, hipertensión arterial en la edad media, obesidad en la edad media, inactividad física, depresión, tabaquismo y bajo nivel educacional) podría reducir la prevalencia de la demencia por enfermedad de Alzheimer un 8.5% a nivel mundial para el año 2050 (Norton 2014). Asimismo, con medidas que logren diferir en cinco años la conversión a una demencia desde una persona con un DCL, la prevalencia de la enfermedad podría disminuir hasta en un 43% en 2050 (Alzheimer's Association 2010).

Si bien el pensamiento tiene gran lógica, existe evidencia de que no todo DCL progresa a una demencia. Los estudios observacionales han demostrado que la progresión desde un DCL a una demencia puede variar desde un 5 a un 15% de los pacientes por año, pero datos de ensayos

clínicos han demostrado que esta tasa de conversión es altamente variable, e incluso muchas personas revierten su condición o se mantienen en el tiempo sin variación. Este hallazgo tiene múltiples explicaciones, una de ellas y al parecer la más importante es la variabilidad en los criterios diagnósticos de un DCL, edad, características amnésicas del DCL y otras (Roberts 2014; Overton 2019).

La disparidad en los criterios de diagnóstico y los diferentes escenarios de los pacientes estudiados (comunidad, primaria, secundaria y centro de investigación) son fuente importante de heterogeneidad de las tasas de conversión (Petersen 1999; Bruscoli 2004; Mattsson 2009; Petersen 2009). Existen muchos autores que han desarrollado criterios clínicos, tales como los Criterios de Petersen o los Criterios revisados de Petersen (Petersen 1999; Petersen 2004; Winblad 2004), la Escala de calificación de demencia cognitiva (CDR = 0.5) (Morris 1993), o las 16 diferentes clasificaciones de MCI encontradas por Matthews (Matthews 2008).

Determinar qué persona con un DCL va a desarrollar una demencia clínica es fundamental, con el fin de poder enfocarse en estas personas de alto riesgo y poder desarrollar terapias efectivas que retrasen o eviten la progresión. Ello no ha resultado fácil debido a la heterogeneidad entre las personas con DCL que progresan y no progresan a una demencia, lo que podría explicar el fracaso de las nuevas terapias que se han probado hasta hoy (Pandya 2016).

Históricamente el diagnóstico histopatológico se ha realizado post mortem, por lo que el diagnóstico ha sido eminentemente clínico, diagnóstico que muchas veces no ha sido del todo exactos (Beach 2012). Detectar patología Alzheimer como el amiloide in vivo es un acercamiento hacia un diagnóstico biológico de la enfermedad (Goedert 2006), lo que en la práctica llevaría a realizar diagnósticos exactos de enfermedad de Alzheimer y a descartar otros cuadros que podrían tener un fenotipo similar de trastornos cognitivos u alteración funcional pero que no necesariamente son una enfermedad de Alzheimer (Vandenberghe 2013).

Diagnóstico con biomarcador amiloideo

Diversas investigaciones en los últimos 15 años han logrado desarrollar moléculas que se unen con gran afinidad a la placa de beta amiloide. Estas moléculas fluorinadas se unen a la placa de beta amiloide y se logran visualizar a través de una tomografía por emisión de positrones (TEP). Dentro de estas moléculas o trazadores 18F existen principalmente tres que están disponibles comercialmente para su uso clínico; 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol.

18F-Florbetapir y 18F-Florbetaben demostraron tener una excelente cinética de absorción y lavado cerebral en estudios animales (Choi 2009; Zhang 2005), así como también 18F-Florbetapir tiene una excelente unión in vitro a placas Aβ en muestras de cerebro de personas con enfermedad de Alzheimer (Choi 2009; Lin 2010). Los tres biomarcadores se han evaluado a su vez en pacientes con una DEA y controles sanos (Wong 2010; Lin 2010; Barthel 2011; Nelissen 2009) y eventualmente podrían usarse para diferenciar entre diferentes tipos de demencia, específicamente entre una FTD y una DEA como con el 18F-Florbetapir (Kobylecki 2015) y el 18F-Florbetaben (Villemange 2011).

Entre 2012 y 2014, 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol fueron aprobados por la Administración de Medicamentos y Alimentos (FDA) y entre 2013 y 2014 por la Agencia Europea de Medicamentos (EMA). Una exploración TEP con 18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol negativa indica placas neuríticas escasas o nulas, lo que no es consistente con el diagnóstico de una demencia Alzheimer y una exploración TEP con 18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol positiva indica placas neuríticas amiloides moderadas a frecuentes. Sin embargo, también pueden estar positivas en personas con otros tipos de afecciones neurológicas, así como en personas mayores con cognición normal. Por lo tanto, deben combinarse con otras evaluaciones o instrumentos de diagnóstico y no se ha establecido que sirvan para predecir el desarrollo de la demencia u otras afecciones

neurológicas (EMA 2013; EMA 2014a; Cortes-Blanco 2014; EMA 2014b; FDA 2012; FDA 2013; FDA 2014).

Con base en la información mencionada anteriormente, aunque no está aprobada para este propósito por las agencias reguladoras, existe la presunción de que un paciente con un DCL con patología amiloidea detectada a través de alguno de estos tres biomarcadores desarrollará demencia clínica si la persona se sigue en el tiempo. Sin embargo, existe cierto grado de incertidumbre de la exactitud diagnóstica real de estos biomarcadores cuando son positivos en una persona con un DCL. Por lo tanto, una pregunta válida que se puede hacer la persona con un DCL, su entorno o el clínico es la siguiente: ¿cuál es el riesgo de desarrollar una DEA en el futuro si tengo amiloide cerebral medido por TEP con 18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol?.

Condición objetivo a ser diagnosticada

En este trabajo de tesis, las tomografías por emisión de positrones con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol fueron consideradas como nuestros marcadores diagnósticos de interés en cada una de las tres revisiones sistemáticas que se desarrollaron. En estas revisiones sistemáticas se evaluaron las EPDs para determinar la progresión desde un DCL a una DEA, a cualquier forma de demencia no-DEA o a cualquier forma de demencia.

Prueba (s) índice: **TEP con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol**

• La exploración TEP con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol es la prueba índice para la detección del depósito de Aβ en la región de interés (ROI). El ROI es un área anatómica del cerebro que es seleccionada para determinar el depósito de Aβ en ella. Normalmente se estudian varias ROI cerebrales, con el objetivo de definir la positividad del estudio o no.

- El 18F-Florbetapir es un biomarcador molecular para amiloide β, descrito como (E) - 4- (2- (6- (2- (2- (2- [2 [18F] fluoroetoxi) etoxi) etoxi) etoxi) piridina-3-il) vinilo) -N-metilbenzamina y también denominado 18F-AV-45 (Choi 2009).

- El 18F-Florbetaben es un biomarcador molecular para amiloide β, descrito como [^{18}F]BAY9172, trans-4-(N-metil-amino)-4'-2-[2-(2-[^{18}F]fluoro-etoxi)- etoxi]-etoxi-stilbeno y también conocido como BAY 94-9172 o ZK 6013443, que es un estilbeno derivado de polietilenglicol (Zhang 2005).

- El 18F-Flutemetamol es un biomarcador molecular para amiloide β, descrito como 6-benzotiazol, 2-[3-[^{18}F]fluoro-4-(metilamino)fenil], derivado de la tioflavina y también conocido como ^{18}F-3'-F-6-OH-BTA1, ^{18}F-GE067, AH110690 (Koole 2009; Nelissen 2009).

Interpretación de la imagen

La FDA y EMA han descrito los criterios para la positividad de la TEP con beta amiloide 18F-Florbetapir (EMA 2013; FDA 2012), 18F-Florbetaben (EMA 2014a; FDA 2014) y 18F-Flutemetamol (EMA 2014b; FDA 2013):

- 18F-Florbetapir: El diagnóstico se define como positivo o negativo al comparar la radiactividad en la materia gris cortical con la actividad en la materia blanca adyacente. Esta determinación se realiza solo en la corteza cerebral; la captación de señal en el cerebelo no contribuye a la interpretación de la exploración (por ejemplo, una exploración positiva puede mostrar retención del contraste cerebeloso gris-blanco incluso cuando se pierde el contraste gris-blanco cortical).

  Específicamente, una exploración positiva tendrá:

a) Dos o más áreas del cerebro (cada una más grande que una sola circunvolución cortical) en las que hay un contraste gris-blanco reducido o ausente. Esta es la visualización más común de una exploración positiva.

o

b) Una o más áreas en las cuales la radioactividad de la materia gris es intensa y claramente excede la radiactividad en la materia blanca adyacente.

- 18F-Florbetaben: El diagnóstico se define como positivo si el análisis muestra lo siguiente.

   a) Área (s) pequeñas o moderadas de captación del trazador igual o superior que la presentada en la sustancia blanca, extendiéndose más allá del borde de la sustancia blanca hasta el margen cortical externo que involucra la mayoría de los cortes dentro de la región respectiva.

   b) Depósitos pronunciados de Aβ (una gran área confluente de captación del trazador igual o superior a la que se presenta en la sustancia blanca que se extiende más allá del borde de la sustancia blanca hasta el margen cortical externo y que involucra a toda la región, incluida la mayoría de los cortes dentro de la región respectiva) en la materia gris de las siguientes cuatro regiones del cerebro: los lóbulos temporales, los lóbulos frontales, cingulado posterior / precuneus y los lóbulos parietales.

- 18F-Flutemetamol: El diagnóstico se define como positivo si el análisis muestra lo siguiente.

   a) Al menos una región cortical (lóbulos frontales, cingulado posterior y precuneus, lóbulos temporales laterales, lóbulos parietales inferolaterales, cuerpo estriado) con reducción o pérdida del contraste

de materia gris-blanca. Estas exploraciones tienen una o más regiones con un aumento de la señal de la sustancia gris cortical (por encima del 50% al 60% de intensidad máxima) o un contraste de la sustancia gris-blanca reducido (o ausente) (el patrón sulcal de la sustancia blanca es menos distintivo), o ambos.

b) Una exploración positiva puede tener una o más regiones en las que la radiactividad de la materia gris es tan intensa o supera la intensidad de la materia blanca adyacente.

Los encargados de interpretar e informar las imágenes a través de la tomografía por emisión de positrones con el 18F-Florbetapir, 18F-Florbetaben o 18F-flutemetamol deberían tener una capacitación específica para ello (EMA 2013; EMA 2014a; EMA 2014b; FDA 2012; FDA 2013; FDA 2014).

Antes de que la FDA y la EMA describieran los criterios para la positividad de la exploración con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol, el diagnóstico de demencia se realizaba utilizando diferentes umbrales. Por lo tanto, se planificó utilizar los criterios de la FDA o la EMA aplicados en cada estudio incluido para clasificar a los participantes como prueba positiva o negativa o, como alternativa, si la captación y retención de 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol Aβ excedía un cierto umbral.

Se consideró la medición de la retención de 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol (índice de retención): índice de volumen de distribución (DVR), índice de valor de captación estandarizado (SUVR) u otros índices. DVR se refiere a la relación entre el volumen de distribución de 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol en la región de interés seleccionada (ROI) y el volumen de distribución en el área de referencia. SUVR es la relación entre el valor de absorción estandarizado del ligando de 18F-Florbetapir, 18F-

Florbetaben o 18F-Flutemetamol en el área seleccionada (ROI) y el valor de absorción estandarizado en el área de referencia.

Instrucciones de administración y dosis recomendadas

- Dosis de inyección: la dosis recomendada para la tomografía por emisión de positrones con 18F-Florbetapir Aβ es de 370 MBq administrada como un solo bolo intravenoso (FDA 2012; EMA 2013).

- Dosis de inyección: la dosis recomendada para la tomografía por emisión de positrones con 18F-Florbetaben Aβ es de 300 MBq (8,1 mCi), dosis máxima de 30 mcg en masa (FDA 2014) o 300 MBq (240 a 360 MBq) como un único bolo intravenoso lento (6 s / ml) en un volumen total de hasta 10 ml (EMA 2014a; FDA 2014).

- Dosis de inyección: la dosis recomendada para la tomografía por emisión de positrones con 18F-Flutemetamol Aβ es de 185 MBq (5,0 mCi) administrada como un único bolo intravenoso lento (EMA 2014b; FDA 2013).

- Tiempo entre la inyección de 18F-Florbetapir y la adquisición de la TEP: las imágenes de la TEP deben adquirirse en 10 minutos, comenzando de 30 a 50 minutos después de la administración intravenosa (FDA 2012; EMA 2013).

- Tiempo entre la inyección de 18F-Florbetaben y la adquisición de la TEP: las imágenes se deben adquirir en 15 a 20 minutos a partir de 45 a 130 minutos después de la administración intravenosa (FDA 2014) o adquiridas en 20 minutos a partir de 90 minutos después de la administración intravenosa (EMA 2014a);

- Tiempo entre la inyección de 18F-Flutemetamol y la adquisición de la TEP: las imágenes se deben adquirir en 20 minutos a partir de los 90 minutos posteriores a la administración intravenosa (EMA 2014b; FDA 2013).

Aunque es inevitable que los estudios incluidos utilicen diferentes protocolos de imagen y parámetros variados, los datos de la tomografía por emisión de positrones en estos estudios deben ser técnicamente adecuados y adquiridos en una instalación totalmente calificada y certificada.

Circuito o ruta clínica

Si bien la patología de la enfermedad de Alzheimer incluye la presencia de placas beta amiloides y ovillos neurofibrilares que pueden detectarse en personas sin trastornos cognitivos, hoy en día se considera que estos pacientes tendrían Alzheimer preclínico, que solo se considera importante para el campo de investigación (Albert 2011). En este momento, la evaluación clínica frecuentemente tiene similitudes entre diferentes países (NICE 2018; Cordell 2013; Samsi 2014). A menudo comienza con personas que experimentan problemas de memoria, detectados por ellos mismos o sus familiares. Con frecuencia se consulta a médicos generales o médicos de familia y, frecuentemente, se realiza una evaluación médica, utilizando una prueba de detección del deterioro cognitivo. Cada vez que esta prueba de detección resulta positiva, se realiza una evaluación clínica con estudios de laboratorio que pueden descartar una causa secundaria de deterioro cognitivo (por ejemplo, hipotiroidismo, insuficiencia renal, insuficiencia hepática, déficit de vitamina B12 o folato, y otros). Además, los pacientes son remitidos a médicos especialistas en trastornos cognitivos (geriatras, psiquiatras o neurólogos) en un centro secundario o directamente a clínicas de memoria donde se pueden realizar más evaluaciones clínicas, estudios de laboratorio y estudios de imágenes cerebrales para confirmar el diagnóstico de un trastorno cognitivo leve o una demencia.

No es infrecuente que las personas con demencia, o sus familiares, consulten directamente a estos especialistas o en clínicas especializadas en el estudio de los trastornos cognitivos. Por lo tanto, las pruebas de diagnóstico realizadas probablemente variarán según sea una consulta

primaria o una derivación de la atención primaria o si los pacientes tienen un estadio clínico diferente de la enfermedad (DCL, demencia leve, moderada o grave).

Debido al circuito clínico anterior, el uso de la tomografía por emisión de positrones con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol se utilizará principalmente en consultas especializadas y clínicas de memoria como un complemento o add-on a una evaluación clínica u otra prueba realizada dado los lineamientos de la evidencia (Bossuyt 2006) y las indicaciones dadas por algunas organizaciones tanto gubernamentales o no gubernamentales (Cortes-Blanco 2014).

2.2. Justificación de la tesis

Razón fundamental

El diagnóstico válido, preciso y temprano de la enfermedad de Alzheimer es crucial para planificar los sistemas de salud, porque los costos de la demencia son en este momento al menos el 1% del producto bruto mundial (WHO 2012). Si somos capaces de retrasar el inicio de la enfermedad en 5 años a través de una intervención eficaz (farmacológica o con cambios en estilo de vida), la prevalencia de la demencia por enfermedad de Alzheimer disminuiría 43% en 2050 y reduciría los costos significativamente (Alzheimer's Association 2010).

Los biomarcadores amiloide-β comercialmente disponibles 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol están aprobados para su uso clínico en personas con una demencia clínica en donde el diagnóstico etiológico es incierto y si el test es negativo, se podría descartar la etiología Alzheimer como causa de la demencia. (EMA 2013; EMA 2014a; EMA 2014b; FDA 2012; FDA 2013; FDA 2014).

Aunque estos biomarcadores no están aprobados para este propósito, se están utilizando actualmente en el campo de la investigación para buscar la identificación precisa de personas con un DCL que progresarían a una DEA u otras formas de demencia. La TEP con los

trazadores β amiloide se han incluido en los nuevos criterios de diagnóstico en el estudio de personas con un DCL (Albert 2011; Dubois 2014). Además, han sido incluidos dentro de las recomendaciones de uso apropiado de la TEP con marcadores amiloideos. El uso clínico apropiado sería en aquellas personas con un DCL persistente o progresivo de etiología incierta o en aquellos donde el diagnóstico etiológico puede hacer cambiar el manejo de la persona, donde un test positivo para beta amiloide significaría que la persona tendría un DCL por enfermedad de Alzheimer (Johnson 2013; Arbizu 2015). Sin embargo, existen incertidumbres acerca de la generalización de estos resultados y de la exactitud diagnóstica de estas pruebas en entornos clínicos, especialmente en las personas mayores (Richard 2012).

En la actualidad no existe una "cura" para la demencia, pero hay algunos tratamientos que pueden retrasar el deterioro cognitivo y funcional en presencia de demencia, o reducir los síntomas conductuales y psiquiátricos asociados a la demencia (Birks 2018; McShane 2019). Sin embargo, todavía hay incertidumbres que ponen en duda su beneficio real (Qaseem 2008), incluso en países como Francia ya no son reembolsados dentro de la sanidad pública por falta de eficacia clínica (Ministère des Solidarités et de la Santé 2018).

Los biomarcadores actualmente deberían ser empleados para descartar la patología Alzheimer en personas con demencia y no para confirmar la etiología Alzheimer en personas con trastornos cognitivos (EMA 2013; EMA 2014a; EMA 2014b; FDA 2012; FDA 2013; FDA 2014). Sin embargo, si se lograra demostrar que estos biomarcadores pudiesen predecir qué personas tienen alto riesgo de conversión desde un DCL a una demencia, podríamos centrarnos en mejorar las oportunidades para una planificación adecuada tanto desde el punto de vista social como sanitario para estas personas. Además, el diagnóstico temprano y preciso de la demencia podría mejorar el reconocimiento de la enfermedad y evitar ingresos hospitalarios o institucionalizaciones inapropiadas y potencialmente dañinas para la persona o para el sistema

sanitario (NAO 2007). Asimismo, la detección precoz de aquellos que convertirán a una demencia clínica permitiría identificar a personas con mayor riesgo que sirva para enriquecer la muestra para ensayos clínicos de nuevas terapias para la enfermedad de Alzheimer, permitiría el desarrollo de nuevos tratamientos diseñados para retrasar o evitar la progresión a etapas más avanzadas de la enfermedad y probablemente demostraría un beneficio clínico real para pacientes, cuidadores y eventualmente, disminuiría los costos para el sistema de salud.

Este trabajo de tesis, evalúa la exactitud diagnóstica de la TEP con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol para diagnosticar (o predecir) la progresión a Alzheimer y otras demencias en pacientes con un DCL. Esta evaluación rigurosa es necesaria antes de incorporar estas pruebas a la práctica clínica rutinaria.

3. Objetivos

3. Objetivos

3.1. Objetivos generales

1. Determinar la exactitud diagnóstica del 18F-Florbetapir para la detección de personas con un deterioro cognitivo leve que pueden progresar a una demencia por enfermedad de Alzheimer u otros tipos de demencia no-demencia por enfermedad de Alzheimer o cualquier tipo de demencia.

2. Determinar la exactitud diagnóstica del 18F-Florbetaben para la detección de personas con un deterioro cognitivo leve que pueden progresar a una demencia por enfermedad de Alzheimer u otros tipos de demencia no demencia por enfermedad de Alzheimer o cualquier tipo de demencia.

3. Determinar la exactitud diagnóstica del 18F-Flutemetamol para la detección de personas con un deterioro cognitivo leve que pueden progresar a una demencia por enfermedad de Alzheimer u otros tipos de demencia no demencia por enfermedad de Alzheimer o cualquier tipo de demencia.

4. Métodos

4. Métodos

Como se mencionó al inicio del documento, esta tesis se conforma de tres diferentes revisiones sistemáticas, realizadas con la metodología Cochrane, que tiene los estándares de calidad más exigentes para responder a los objetivos previamente planteados.

4.1. Métodos de los tres estudios

4.1.1. Estrategia de Búsqueda

Se realizaron búsquedas en MEDLINE (Ovid SP) desde 1946 hasta mayo de 2017; Embase (Ovid SP) de 1974 a mayo de 2017; PsycINFO (Ovid SP) de 1806 a mayo de 2017; Índice de citas de BIOSIS (Thomson Reuters Web of Science) de 1922 a mayo de 2017; Web of Science Core Collection, que incluye el Science Citation Index (Thomson Reuters Web of Science) y el Conference Proceedings Citation Index (Thomson Reuters Web of Science) de 1946 a mayo de 2017; LILAS (Bireme); CINAHL (EBSCOhost) desde 1980 hasta mayo de 2017; ClinicalTrials.gov (https://clinicaltrials.gov); y la Plataforma Internacional de Registro de Ensayos Clínicos de la Organización Mundial de la Salud (ICTRP de la OMS) (http://www.who.int/ictrp/ search / en /). También se realizaron búsquedas en ALOIS, el registro especializado de estudios de demencia del Grupo Cochrane de Demencia y Mejora Cognitiva (http://www.medicine.ox.ac.uk/alois/).

Se utilizaron dos enfoques en el diseño de la búsqueda. Uno se centró únicamente en la prueba índice nombrada específicamente (incluyendo una variedad de sinónimos) y la segunda, ejecutada en paralelo, cubrió una búsqueda más general, vinculando términos más amplios para la prueba índice. Se centró en los términos que describen su uso diagnóstico y los términos de

la condición objetivo para tratar de capturar los estudios más difíciles de localizar de una naturaleza más general, donde estos radioligandos particulares se incluyeron en la investigación de exactitud diagnóstica.

No se aplicaron restricciones de idioma o fecha a las búsquedas electrónicas.

Búsqueda en otros recursos: Se examinaron las listas de referencias de todos los estudios relevantes para la búsqueda de estudios adicionales. También se buscó en la base de datos de resúmenes de Revisiones de Efectos (DARE) a través de la Biblioteca Cochrane (www.cochranelibrary.com), el Instituto Nacional de Investigación en Salud - Base de Datos de Evaluación de Tecnología en Salud (NIHR-HTA) (a través de la Biblioteca Cochrane: www.cochranelibrary.com), la Base de datos del Centro de Inteligencia de Investigación Agresiva (ARIF) (www.arif.bham.ac.uk) para otras revisiones sistemáticas relacionadas de exactitud diagnóstica, y la base de datos del Comité de la Federación Internacional de Química Clínica y Laboratorio de Medicina para el Laboratorio de Medicina Basado en Evidencia (C-EBLM) (http://www.ifcc.org/ifcc-education-division/emd-committees/ c-eblm / evidencia-basada-laboratorio-medicina-c-eblm-base).

Se verificaron las listas de referencias de cualquier estudio relevante y revisiones sistemáticas, y se realizó el seguimiento de citas utilizando el Science Citation Index para identificar cualquier estudio relevante adicional.

4.1.2. Criterios de elegibilidad

Tipos de estudios

Se incluyeron estudios longitudinales que tenían cohortes definidas prospectivamente con cualquier definición aceptada de deterioro cognitivo leve al momento de realizar la exploración

18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol y un estándar de referencia (ver Pruebas índice y Estándares de referencia a continuación). Se obtuvieron los resultados en el seguimiento de los estudios. Estos estudios tuvieron que emplear la verificación tardía de la progresión a la demencia y a veces se etiquetaron como "estudios transversales de verificación tardía" (Bossuyt 2008; Knottnerus 2002).

Participantes

Los participantes reclutados y clasificados clínicamente que tenían un DCL al momento de realizar la prueba fueron elegibles para su inclusión.

El diagnóstico de DCL se definió utilizando los siguientes criterios:

- Petersen o los criterios revisados de Petersen (Petersen 1999; Petersen 2004; Winblad 2004)
- criterios incluidos en el estudio Matthews (Matthews 2008)
- CDR = 0.5 (Clinical Dementia Rating o escala para evaluar la demencia clínica) (Morris 1993)
- criterios clínicos básicos del Instituto Nacional sobre el Envejecimiento-Alzheimer (NIA-AA) (Albert 2011),
- o una combinación de los criterios previos

Se excluyeron los estudios que incluyeron personas con un DCL posiblemente causado por cualquiera de las siguientes condiciones o patologías:

• Abuso de alcohol o drogas como antecedente o abuso actual.

• Trauma del sistema nervioso central (por ejemplo, hematoma subdural), tumor o infección.

• Otras afecciones neurológicas (por ejemplo, enfermedades de Parkinson o Huntington). Con respecto a la enfermedad de Parkinson, muchos de los estudios excluyeron específicamente a las personas con enfermedad de Parkinson del grupo con DCL. Este grupo específico de personas es complejo tanto en lo que respecta a la definición de neuropatología como a la determinación del deterioro funcional. Por estas razones, este grupo de personas debe abordarse en estudios específicos.

Prueba índice (Index test): TEP con 18F-Florbetapir, 18F-florbetaben o 18F-Flutemetamol

La prueba índice para estas revisiones sistemáticas fueron las pruebas de biomarcador 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol. Se utilizaron los criterios y valores de corte para la positividad de la prueba informados en los estudios incluidos. Se consideró la positividad para la captación y retención de la exploración con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol para Aβ si superaba cierto umbral.

El análisis de imágenes no fue preespecificado, por lo que se aceptaron todas las técnicas descritas en los estudios (por ejemplo, mapeo paramétrico estadístico (SPM) u otras técnicas de análisis de imágenes).

Condición clínica a diagnosticar

Se incluyeron tres condiciones objetivo en estas revisiones sistemáticas:

• Demencia por enfermedad de Alzheimer (DEA): progresión desde un DCL a una DEA

• Cualquier otra forma de demencia (demencia no-DEA): progresión desde un DCL a una demencia no-DEA

• Cualquier forma de demencia: progresión desde un DCL a cualquier forma de demencia.

Estándares de referencia

El estándar de referencia fue la progresión a las condiciones objetivo, evaluadas por un médico con experiencia en el campo de la demencia (preferiblemente geriatra, psiquiatra o neurólogo). Para este propósito, se aceptaron varias definiciones de una DEA y otras demencias. Se incluyeron estudios que aplicaron los siguientes criterios como definición:

- NINCDS-ADRDA: Instituto Nacional de Trastornos Neurológicos y de la Comunicación y Accidentes Cerebrovasculares y la Asociación de Enfermedad de Alzheimer y Trastornos Asociados (McKhann 1984),

- Manual Diagnóstico y Estadístico de Trastornos Mentales (DSM). (APA 1987; APA 1994),

- Clasificación Internacional de Enfermedades (CIE) (CIE-10) para una DEA,

- Se aceptaron diferentes definiciones clínicas de otras demencias. Para la demencia con cuerpos de Lewy, el estándares de referencia fueron los criterios de McKeith (McKeith 1996; McKeith 2005); para la demencia frontotemporal, los criterios de Lund (Boxer 2005; Brun 1994; Neary1998), los criterios DSM (APA 1987; APA 1994), los criterios CIE (CIE-10) o el Consorcio Internacional de Criterios de Demencia Frontotemporal Variante conductual (Rascovsky 2011); para la demencia vascular, los criterios del Instituto Nacional de Trastornos Neurológicos y Accidentes Cerebrovasculares y de la Asociación Internacional de Investigación y Educación en Neurociencias (NINDS-AIREN) (Román 1993), los criterios DSM (APA 1987; APA 1994), o los criterios de CIE (CIE-10); y, para la parálisis supranuclear progresiva (PSP), los criterios preliminares de NINDS (Hauw 1994).

El intervalo de tiempo durante el cual ocurre la progresión desde un DCL a una DEA (u otras formas de demencia) es muy importante. Se utilizó un año como el período mínimo de seguimiento para la verificación del diagnóstico (el tiempo entre la evaluación en la que se realiza un diagnóstico de un DCL y la evaluación en la que se realiza el diagnóstico de demencia).

Selección de estudios

Dos revisores seleccionaron de forma independiente los títulos y resúmenes obtenidos tras la búsqueda de los estudios potencialmente elegibles. Un tercer revisor resolvió cualquier desacuerdo entre los otros dos revisores. Los dos revisores evaluaron de forma independiente los artículos seleccionados en texto completo con los criterios de inclusión. Resolvieron cualquier desacuerdo mediante discusión o, cuando fue necesario, consultaron a un tercer revisor, que actuó como árbitro. Cuando un estudio no presentó todos los datos relevantes para crear una tabla 2×2, se contactaron a los autores del estudio directamente para solicitar información adicional. Cuando más de un artículo presentó datos sobre la misma población, se incluyó el artículo primario, que era el artículo con el mayor número de personas o con los datos más informativos (por ejemplo, el mayor tiempo de seguimiento en el resultado primario).

La unidad de análisis en nuestras revisiones sistemáticas fue el participante, por lo que no se incluyeron estudios que analizaran múltiples ROI por participante.

4.1.3. Extracción de datos

Se extrajeron los siguientes datos con respecto a las características del estudio.

• Detalles bibliográficos del trabajo primario:

    ◦ Autor, título de estudio, año y revista

• Detalles clínicos y demográficos básicos:

    ◦ Número de participantes

    ◦ Diagnóstico clínico

    ◦ Criterios clínicos de DCL

    ◦ Edad

    ◦ Sexo

    ◦ Fuentes de referencia

    ◦ Reclutamiento de participantes

    ◦ Procedimientos de muestreo

• Detalles de la prueba índice (TEP con 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol):

    ◦ Método de administración, incluida la información de quienes interpretaron la prueba

    ◦ Umbrales utilizados para definir pruebas positivas y negativas

    ◦ Otros aspectos técnicos que parecían relevantes para la revisión, por ejemplo; áreas del cerebro evaluadas

• Detalles del estándar de referencia:

◦ Definición de una DEA y otras demencias no-DEA utilizadas en el estándar de referencia

◦ Duración del seguimiento desde el momento de la prueba índice realizado para definir una DEA y otras demencias no-DEA por el estándar de referencia: un año a menos de dos años; dos años a menos de cuatro años; y cuatro años o más. Si los participantes habían sido seguidos durante períodos de tiempo variados, se registró un período de seguimiento medio para cada estudio incluido. Si es posible, se agruparon esos datos en períodos de seguimiento mínimos, máximos y medianos, para permitir análisis de subgrupos

◦ Prevalencia o proporción de población que desarrolla demencia por enfermedad de Alzheimer u otras demencias, con su gravedad, si se describe

Se crearon tablas 2×2 (resultados de pruebas índice de relación cruzada con los estándares de referencia).

Para los estudios incluidos, se registró el número de participantes perdidos durante el seguimiento. También se extrajeron los datos necesarios para la evaluación de la calidad, como se define a continuación. Dos revisores realizaron de forma independiente la extracción de datos. Se resolvió cualquier desacuerdo con respecto a la extracción de datos mediante discusión o consultando a un tercer autor de la revisión, cuando fue necesario.

4.1.4 Evaluación del riesgo de sesgo en los estudios incluidos

Se evaluó la calidad metodológica de los estudios incluidos mediante la herramienta Evaluación de la calidad de los estudios de exactitud diagnóstica 2 (QUADAS-2) (Whiting 2011), según lo recomendado por Cochrane (Davis 2013). Esta herramienta consta de cuatro

dominios: selección de pacientes, prueba índice, estándar de referencia y flujo de pacientes (Anexo 2).

Dos revisores, que no conocían los puntajes del otro, realizaron de forma independiente la evaluación QUADAS-2. Se resolvió cualquier desacuerdo mediante discusión y, de ser necesario, se consultó a un tercer revisor que actuó como árbitro. Se evaluó cada dominio en términos del riesgo de sesgo, y también se consideró los primeros tres dominios en términos de preocupaciones o dudas en la aplicabilidad de cada estudio primario a la revisión en cuestión.

Se incluyeron tres preguntas adicionales en la evaluación del riesgo de sesgo como parte de la adaptación del instrumento QUADAS-2 a estas revisiones: en la de evaluación del riesgo de sesgo:

• ¿La interpretación de la exploración a través de la tomografía por emisión de positrones fue realizada por un lector capacitado? ¿médico? (incluido en el dominio de "Prueba índice").

• ¿Hubo una definición clara de un resultado positivo? (incluido en el dominio "Prueba índice").

• ¿El estudio estuvo libre de financiamiento de origen comercial? (incluido en el dominio de "flujo y tiempo").

Se incluyó el ítem relacionado con la interpretación de la tomografía por emisión de positrones y la definición de resultados positivos para tener en cuenta la naturaleza subjetiva de la interpretación de la imagen del escaneo 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol, que puede basarse en una variedad de criterios diferentes, como la experiencia

clínica, los diferentes valores de captación estandarizados (SUV), las diferentes características morfológicas o una combinación de ellos.

Se incluyó el tercer elemento adicional para registrar cualquier sesgo potencial resultante del interés comercial en los resultados debido al riesgo potencial de que la empresa que produce el trazador pueda conducir a resultados y conclusiones más favorables comparado cuando el patrocinio proviene de otras fuentes (Lundh 2017).

No se utilizaron los datos de QUADAS-2 para calcular una puntuación global del riesgo de sesgo de cada estudio. En su lugar se realizó un resumen narrativo de este riesgo, incluido en cada revisión sistemática, que describió cada estudio incluido con una apreciación general de poseer un riesgo de sesgo alto, bajo o poco claro, así como las preocupaciones con respecto a la aplicabilidad de sus resultados.

4.1.5. Análisis de datos

Se extrajeron los datos del estudio en una tabla de 2x2, mostrando los resultados de la prueba en forma binaria con clasificación cruzada con el estándar de referencia en forma binaria. Se utilizaron datos de las tablas 2x2 extraídas de cada estudio incluido: verdadero positivo (TP), falso negativo (FN), falso positivo (FP), verdadero negativo (TN), y se ingresaron en el software Review Manager (Review Manager 2014) para calcular las sensibilidades, especificidades y sus intervalos de confianza al 95%. También se presentaron los resultados de cada estudio gráficamente al trazar estimaciones de sensibilidad y especificidad en un diagrama de bosque.

Debido a la falta de datos, no se realizó metanálisis en ninguna de las tres revisiones sistemáticas. Por lo tanto, se realizó una "tabla de resumen de hallazgos" para cada una de las revisiones sistemáticas.

La política editorial de Cochrane exige la actualización periódica de las revisiones sistemáticas publicadas. Esta actualización no está destinada exclusivamente a la actualización de las búsquedas para la inclusión de nuevas evidencias si no que puede suponer la reformulación de las preguntas de la revisión (objetivos) o la inclusión de nuevos objetivos. En el caso de las revisiones que conforman esta tesis, está programado realizar esta actualización el año 2021. En una decisión editorial conjunta del Grupo de Demencia y Mejora Cognitiva y del Grupo de Métodos de Pruebas de Cribado y Diagnóstico de la Colaboración Cochrane, se determinó que las tres revisiones sistemáticas se fusionarán y que la pregunta de la revisión será la evaluación de la exactitud diagnóstica de la TEP amiloide con trazadores 18F para determinar la progresión desde un DCL a una DEA y otras demencias.

4.1.6. Investigación de heterogeneidad

Dada la cantidad insuficiente de estudios, no se investigaron posibles fuentes de heterogeneidad.

4.1.7. Análisis de sensibilidad

Se encontraron datos insuficientes para realizar análisis de sensibilidad.

4.1.8. Evaluación del sesgo de publicación

No fue posible investigar el sesgo de publicación dado el número limitado de estudios primarios incluidos en la revisión.

4.2. Financiación

La realización de esta tesis doctoral fue posible gracias a:

5. Resultados

5. Resultados

Los resultados de esta tesis corresponden a los resultados reportados en cada una de las publicaciones incluidas.

5.1. Resultados de la primera publicación:

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

Gabriel Martínez, Robin WM Vernooij, Paulina Fuentes Padilla, Javier Zamora, Xavier Bonfill Cosp, Leon Flicker

Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD012216

Impact Factor 2017: 6.754

5.1.1. Resultado de las búsquedas

Las diferentes estrategias de búsqueda empleadas identificaron un total de 2502 referencias.

Al final del proceso de revisión, se incluyeron 3 referencias con un total de 453 participantes con deterioro cognitivo leve (Doraiswamy2014; Schreiber2015; Kawas2013) e identificamos diez referencias como estudios en curso, que serán incluidas en las siguientes actualizaciones de la revisión.

5.1.2. Características de los estudios incluidos

Selección de participantes y características:

Respecto a las características de los estudios analizados, el número de participantes analizados al final de los estudios fue de 453, con un rango de participantes por estudio de 5 a 401 participantes.

El estudio con más participantes incluyó participantes mixtos principalmente derivados de clínicas de memoria, llamados por avisos de radio y/o periódicos. En los otros dos estudios no se especificó la precedencia de los participantes. El promedio de edad fue mayor a los 70 años. Las participantes mujeres fueron entre un 45,4% a 69,2% de las personas incluidas en los estudios. En dos estudios el promedio de educación fue de al menos 14 años o más.

El seguimiento de las cohortes osciló entre 18 meses a 36 meses.

Prueba índice: TEP con 18F-Florbetapir

En un estudio se describen los modelos de tomógrafos usados (Discovery LS PET/CT (GE, Fairfield, CT, USA), Advance PET (GE), ECAT HR+ (Siemens, Washington DC, USA) y Biograph PET/CT (Siemens). En otro estudio se nombran sólo las compañías fabricantes (GE y Phillips) y en el tercer estudio, no están descritos ni la compañía que desarrolla el tomógrafo ni el modelo usado.

Respecto de la dosis utilizada, en los tres estudios la dosis fue la misma 10 mCi (370 MBq) y en 2 estudios la adquisición de imágenes se realizó 50 minutos después de la inyección del trazador 18F-Florbetapir y en el tercer estudio la adquisición fue entre 50 y 70 minutos post inyección del trazador.

En los tres estudios incluidos, se consideró una capacitación previa a los investigadores que interpretaron las imágenes de la tomografía por emisión de positrones con 18F-Florbetapir.

Los tres estudios utilizaron un método semicuantitativo visual para determinar la positividad de amiloide en el cerebro con la tomografía por emisión de positrones con 18-F-Florbetapir. Un estudio utilizó además un método cuantitativo con SUVR con un umbral de positividad descrito previamente para determinar la positividad o no a amiloide cerebral.

Condición clínica objetivo y estándar de referencia:

Dos estudios evaluaron la progresión a una DEA y el tercer estudio evaluó la progresión a cualquier tipo de demencia.

Respecto del estándar utilizado está claramente establecido que el criterio NINCDS-ADRDA (McKhann 1984) fue utilizado en un estudio y probablemente en otro. En el tercer estudio el estándar de referencia fue el criterio DSM-IV(APA1994).

Flujo y tiempo:

El promedio de seguimiento varió entre 18 meses y tres años, con una pérdida de 5 participantes (10%) en un estudio (Doraiswamy 2014) y en los otros dos el seguimiento fue completado por los 406 (100%) participantes (Schreiber 2015; Kawas 2013).

Se evaluó la positividad visualmente en 453 participantes del total, donde 216 (48%) participantes resultaron positivos y 237 (52%) participantes resultaron negativos para amiloide cerebral (Doraiswamy 2014; Kawas 2013; Schreiber 2015).

Cuando se usó la evaluación cuantitativa, 221 (55%) participantes resultaron positivos y 180 (45%) participantes resultaron negativos para amiloide cerebral (Schreiber 2015).

5.1.3 Evaluación del riesgo de sesgo y de la calidad metodológica de los estudios incluidos

Se realizó una evaluación del riesgo de sesgo y de la calidad metodológica de los estudios incluidos, a través del instrumento QUADAS-II (Whiting2011), donde se encontró lo siguiente:

Selección de participantes

Se consideró que los tres estudios incluidos tenían un riesgo poco claro de sesgo, ya que, si bien no son estudios con diseño de casos y controles, adolecen de falta de información sobre los procedimientos de muestreo y los criterios de exclusión.

Prueba índice

Se consideró que los tres estudios incluidos tenían un bajo riesgo de sesgo. Los tres estudios tenían un bajo riesgo de sesgo porque se estableció claramente el criterio de positividad en la evaluación visual, que fue utilizada en 2 estudios en forma exclusiva y en el tercer estudio que además de utilizar una evaluación visual, utilizó un criterio cuantitativo, donde el umbral de positividad SUVR >1.11 estaba previamente establecido. Se debe considerar además que la interpretación de la TEP 18F-Florbetapir se realizó sin conocer la condición clínica de los participantes.

En nuestras dos preguntas de alerta adicionales, hubo un riesgo bajo de que un médico no capacitado en lectura interpretara la prueba índice en los tres estudios incluidos, asociado a lo anterior, los criterios de positividad se establecieron claramente en dos estudios y, en uno, se consideró poco claro.

Estándar de referencia

Se consideró que los tres estudios incluidos tenían un riesgo poco claro de sesgo. Un estudio tuvo un poco claro riesgo de sesgo porque no se logró obtener la información sobre qué estándar de referencia había sido utilizado y en los otros 2 estudios a pesar del uso de los criterios DSM-IV para cualquier forma de demencia (APA 1994) y los criterios NINCDS-ADRDA (McKhann 1984) como estándares de referencia, respectivamente, no estaba claro si el médico estaba cegado a los resultados de la exploración TEP con 18F-Florbetapir para establecer el diagnóstico de demencia.

Flujo y el tiempo

Se consideró que un estudio tenía un riesgo poco claro de sesgo, ya que, no estaba explícito el uso del criterio para el diagnóstico de una DEA en el seguimiento de los participantes.

En nuestra pregunta de señalización adicional, hubo posibles conflictos de interés debido al apoyo financiero por parte de la compañía que produce los trazadores en dos estudios.

Aplicabilidad

Para la evaluación de la aplicabilidad, no hubo preocupación de que los participantes incluidos, el entorno, la realización e interpretación de la prueba de índice, no coincidieran con la pregunta de revisión. Sin embargo, la condición objetivo (como se define en el estándar de referencia) no estaba clara debido a la falta de información sobre qué estándar de referencia se aplicó en un estudio y si el investigador estaba cegado o no al resultado de la exploración TEP con 18F-Florbetapir para establecer el diagnóstico clínico de demencia por enfermedad de Alzheimer o cualquier demencia.

5.1.4. Exactitud diagnóstica de los estudios incluidos

La incidencia a una DEA durante el seguimiento, se presentó en 61 (15%) participantes de un total de 401 (Schreiber 2015) y en 9 (19%) participantes de un total de 47. La incidencia a cualquier forma de demencia se presentó en 3 (60%) de 5 participantes (Kawas 2013).

Progresión desde un DCL a una DEA

La progresión desde un DCL a una DEA en aquellos con un seguimiento de uno a menos de dos años tuvo una sensibilidad de 89% (IC 95%: 78 a 95) y una especificidad de 58% (IC 95%: 53 a 64) mediante evaluación visual y una sensibilidad de 87% (IC 95%: 76 a 94) y una especificidad de 51% (IC 95%: 45 a 56) mediante evaluación cuantitativa.

La progresión desde un DCL a una DEA en aquellos con un seguimiento entre dos y menos de cuatro años tuvo una sensibilidad de 67% (IC 95%: 30 a 93) y una especificidad de 71% (IC 95%: 54 a 85) mediante evaluación visual.

Progresión desde un DCL a una demencia no-DEA

No logramos encontrar estudios que evaluaran la progresión desde un DCL a cualquier otra forma de demencia no-DEA.

Progresión desde un DCL a cualquier forma de demencia

La progresión desde un DCL a cualquier forma de demencia en aquellos con un seguimiento de uno a menos de dos años tuvo una sensibilidad de 67% (IC 95%: 9 a 99) y una especificidad de 50% (IC 95%: 1 a 99) a través de la evaluación visual.

5.1.5. Publicación

Cochrane Library

Cochrane Database of Systematic Reviews

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

Martínez G, Vernooij RWM, Fuentes Padilla P, Zamora J, Bonfill Cosp X, Flicker L

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18F PET with florbetapir 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

[18]F-florbetapir uptake by brain tissue measured by positron emission tomography (PET) is accepted by regulatory agencies like the Food and Drug Administration (FDA) and the European Medicine Agencies (EMA) for assessing amyloid load in people with dementia. Its added value is mainly demonstrated by excluding Alzheimer's pathology in an established dementia diagnosis. However, the National Institute on Aging and Alzheimer's Association (NIA-AA) revised the diagnostic criteria for Alzheimer's disease and confidence in the diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease may be increased when using amyloid biomarkers tests like ^{18}F-florbetapir. These tests, added to the MCI core clinical criteria, might increase the diagnostic test accuracy (DTA) of a testing strategy. However, the DTA of ^{18}F-florbetapir to predict the progression from MCI to Alzheimer's disease dementia (ADD) or other dementias has not yet been systematically evaluated.

Objectives

To determine the DTA of the ^{18}F-florbetapir PET scan for detecting people with MCI at time of performing the test who will clinically progress to ADD, other forms of dementia (non-ADD), or any form of dementia at follow-up.

Search methods

This review is current to May 2017. We searched MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), BIOSIS Citation Index (Thomson Reuters Web of Science), Web of Science Core Collection, including the Science Citation Index (Thomson Reuters Web of Science) and the Conference Proceedings Citation Index (Thomson Reuters Web of Science), LILACS (BIREME), CINAHL (EBSCOhost), 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 also searched ALOIS, the Cochrane Dementia & Cognitive

Improvement Group's specialised register of dementia studies (http://www.medicine.ox.ac.uk/alois/). We checked the reference lists of any relevant studies and systematic reviews, and performed citation tracking using the Science Citation Index to identify any additional relevant studies. No language or date restrictions were applied to the electronic searches.

Selection criteria

We included studies that had prospectively defined cohorts with any accepted definition of MCI at time of performing the test and the use of ^{18}F-florbetapir scan to evaluate the DTA of the progression from MCI to ADD or other forms of dementia. In addition, we only selected studies that applied a reference standard for Alzheimer's dementia diagnosis, for example, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria.

Data collection and analysis

We screened all titles and abstracts identified in electronic-database searches. Two review authors independently selected studies for inclusion and extracted data to create two-by-two tables, showing the binary test results cross-classified with the binary reference standard. We used these data to calculate sensitivities, specificities, and their 95% confidence intervals. Two independent assessors performed quality assessment using the QUADAS-2 tool plus some additional items to assess the methodological quality of the included studies.

Main results

We included three studies, two of which evaluated the progression from MCI to ADD, and one evaluated the progression from MCI to any form of dementia.

Progression from MCI to ADD was evaluated in 448 participants. The studies reported data on 401 participants with 1.6 years of follow-up and in 47 participants with three years of follow-up. Sixty-one (15.2%) participants converted at 1.6 years follow-up; nine (19.1%) participants converted at three years of follow-up.

Progression from MCI to any form of dementia was evaluated in five participants with 1.5 years of follow-up, with three (60%) participants converting to any form of dementia.

There were concerns regarding applicability in the reference standard in all three studies. Regarding the domain of flow and timing, two studies were considered at high risk of bias.

MCI to ADD;

Progression from MCI to ADD in those with a follow-up between two to less than four years had a sensitivity of 67% (95% CI 30 to 93) and a specificity of 71% (95% CI 54 to 85) by visual assessment (n = 47, 1 study).

Progression from MCI to ADD in those with a follow-up between one to less than two years had a sensitivity of 89% (95% CI 78 to 95) and a specificity of 58% (95% CI 53 to 64) by visual assessment, and a sensitivity of 87% (95% CI 76 to 94) and a specificity of 51% (95% CI 45 to 56) by quantitative assessment by the standardised uptake value ratio (SUVR)(n = 401, 1 study).

MCI to any form of dementia;

Progression from MCI to any form of dementia in those with a follow-up between one to less than two years had a sensitivity of 67% (95% CI 9 to 99) and a specificity of 50% (95% CI 1 to 99) by visual assessment (n = 5, 1 study).

MCI to any other forms of dementia (non-ADD);

There was no information regarding the progression from MCI to any other form of dementia (non-ADD).

Authors' conclusions

Although sensitivity was good in one included study, considering the poor specificity and the limited data available in the literature, we cannot recommend routine use of ^{18}F-florbetapir PET in clinical practice to predict the progression from MCI to ADD.

Because of the poor sensitivity and specificity, limited number of included participants, and the limited data available in the literature, we cannot recommend its routine use in clinical practice to predict the progression from MCI to any form of dementia.

Because of the high financial costs of ^{18}F-florbetapir, clearly demonstrating the DTA and standardising the process of this modality are important prior to its wider use.

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

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PLAIN LANGUAGE SUMMARY

^{18}F-florbetapir PET scan for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment

Review question: In people with mild cognitive impairment (MCI), does using a ^{18}F PET scan with florbetapir predict the progression to Alzheimer's disease dementia (ADD) and other dementias?

Background

Due to global ageing, the number of people with dementia is expected to increase dramatically in the next few decades. Diagnosing dementia at an early stage is desirable, but there is no widespread agreement on the best approach. A range of simple pen and paper tests used by healthcare professionals can assess people with poor memory or cognitive impairment. Whether or not using special PET scans that detect amyloid -one of the hallmarks of Alzheimer's disease- improves our ability to predict the progression from MCI to ADD or other forms of dementia remains unclear. Since these tests are expensive, it is important that they provide additional benefits.

Aim

We aimed to evaluate the accuracy of the ^{18}F-florbetapir PET scan in identifying those people with MCI who clinically progress to ADD, other types of dementia, or any form of dementia over a period of time.

Study characteristics

The evidence is current to May 2017. We found three studies including 453 participants with MCI. Two studies evaluated the progression from MCI to ADD and one study evaluated the progression from MCI to any form of dementia.

Regarding the two studies that evaluated the progression from MCI to ADD, one study had 401 participants with a follow-up of 1.6 years and the mean age was 72 years. The other study had 47 participants with a follow-up of three years, and the mean age was 72 years.

The other study that looked at any form of dementia included 5 participants over 90 years old.

Two of the studies were funded by the test manufacturer.

Quality of the evidence

The main limitation of this review was that our findings were based on only three studies, with insufficient detail on how the people were selected, whether the information from the scan was assessed separately from the final diagnosis. The studies were considered to be at high risk of bias due to potential conflicts of interest detected.

Key findings

In this review, we found the following results based on the three studies.

At a follow-up of 1.6 years, using visual assessment, the scan correctly classified 89% of the participants who progressed to ADD but only 58% of the participants who did not progress to ADD. This means that in a group of 100 people with MCI, 15% of whom will develop ADD, we would expect 13 of 15 people to have a positive result and the other 2 participants to be falsely negative. Also 49 people who will not develop ADD would have a negative result, but 36 people who will not develop ADD would have a positive result (false positives).

In the study that followed up people for three years and used visual assessment, the scan correctly classified 67% of people who progressed to ADD and 71% who did not progress to ADD. This means that in a group of 100 people with MCI, 19 of whom will develop ADD, we would expect 13 people to have a positive result of the scan and 6 people to have a falsely negative result. In addition, 58 of 81 participants who will not progress to ADD would have a negative result, but 23 people who will not develop ADD would have a positive result (false positives). The small number of participants evaluated at three years lowered our confidence on these estimates of accuracy.

Regarding progression to any form of dementia, the extremely small number of participants meant that we were unable to provide meaningful estimates of accuracy.

We conclude that ^{18}F-florbetapir PET scans cannot be recommended for routine use in clinical practice to predict the progression from MCI to ADD or any form of dementia based on the currently available data. More studies are needed to demonstrate its usefulness.

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

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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. See the glossary in Appendix 1. 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 collection 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 number of 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 Revised 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 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 ($A\beta$) and neurofibrillary tangles (Goedert 2006). This pathology is present in approximately 84% of all people with dementia (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 ageing 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 for vascular damage (De la Torre 2004; Garcia-Alloza 2011). On the other hand, this controversy could be because our clinical diagnostic criteria have not enough accuracy to diagnose Alzheimer's disease that is detected by histopathology in postmortem studies (Hyman 2012). In addition, other researchers think that there is no real controversy about the amyloid hypothesis, because the amyloid cascade and the $A\beta$ deposition have a primary role in Alzheimer's disease (Selkoe 2016).

More recently, the development of $A\beta$ 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 $A\beta$ 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 an important initiative, 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 $A\beta$ ligands

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permits the in vivo detection of amyloid deposition in the brain. ^{18}F-florbetapir is a stilbene derivative and demonstrates a high binding affinity to $A\beta$ aggregates. ^{18}F-florbetapir has good uptake by brain tissue and washout kinetics in mice and monkeys (Choi 2009) and in vitro binding of $A\beta$ 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). ^{18}F-florbetapir could eventually be used to differentiate between different dementia types, specifically between FTD and ADD (Kobylecki 2015).

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved ^{18}F-florbetapir for $A\beta$ binding. 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-florbetapir scan indicates moderate to frequent or 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-florbetapir 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; FDA 2013).

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-florbetapir for $A\beta$, 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).

An assumption for some researchers, and one on which this systematic review (SR) is predicated, is 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 families, and clinicians involved in their care.

The ^{18}F-florbetapir PET scan is considered the diagnostic marker of interest and, in this SR, we assessed the DTA of ^{18}F-florbetapir $A\beta$ 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

This SR belongs to a series of SRs regarding PET biomarkers for amyloid β, including ^{18}F-florbetaben and ^{18}F-flutemetamol (Martínez 2016).

Target condition being diagnosed

This SR assessed 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 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 ^{18}F-florbetapir scan is an index test for the detection of $A\beta$ 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-florbetapir is a molecular biomarker, described as (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).
Image Interpretation
Both the FDA and EMA have described the criteria for ^{18}F-florbetapir for $A\beta$ positivity (EMA 2013; FDA 2013).
[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 exhibited 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.

Readers trained in PET images with ^{18}F-florbetapir, should interpret the Aβ PET image made with this ligand (EMA 2013; FDA 2013).

Before the FDA and EMA described the criteria for ^{18}F-florbetapir PET scan positivity, the diagnosis of dementia was made using different thresholds. Therefore, we planned 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 ^{18}F-florbetapir Aβ uptake and retention exceeded a certain threshold. We considered the measurement of the ^{18}F-florbetapir retention (retention ratio): distribution volume ratio (DVR), standardised uptake value ratio (SUVR), or other ratios. DVR refers to the ratio of the ^{18}F-florbetapir distribution volume in the selected area (ROI) to the distribution volume in the reference area. SUVR is the ratio of the ^{18}F-florbetapir ligand standardised uptake value in the selected area (ROI) to the standardised uptake value in the reference area.

The unit of analysis of our SR was the participant. We did not include studies that analysed multiple ROIs per person.

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

Administration Instructions and Recommended Dosing

- Time between ^{18}F-florbetapir injection and PET acquisition: images should be acquired in 10 minutes starting from 30 to 50 minutes after intravenous administration (EMA 2013; FDA 2013).

- 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).

Although it is inevitable that included studies 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 performance of the diagnostic tests will probably vary according to whether it is a primary consultation or a referral 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-florbetapir PET ligand 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 aetiology (e.g. FTD versus ADD). Otherwise, it might be used solely in the research field in people with MCI for the enrichment of clinical trials. For example, enrolling people with MCI and a positive PET scan to study preventive interventions before people develop dementia. However, in some memory clinics, the ^{18}F-florbetapir PET is used for clinical purposes in people with persistent or progressive unexplained MCI adopting the Johnson criteria (Johnson 2013), criteria without sufficient evidence. Therefore, if the ^{18}F-florbetapir PET is positive in a person with MCI, this positivity is considered as one of the core histopathological findings of Alzheimer's disease. The person will thus be catalogued as a patient with prodromal Alzheimer's disease or MCI due to Alzheimer's disease.

Alternative test(s)

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

- [18]F PET ligands for Aβ (^{18}F-florbetaben, ^{18}F-flutemetamol) (Martínez 2016).

- ^{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-florbetapir is 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-florbetapir is not approved for this purpose, this biomarker test is 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 of people with MCI (Albert 2011; Dubois 2014). However, some uncertainties exist about the generalisability of the DTA results 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.

This SR assessed the DTA of ^{18}F-florbetapir Aβ PET in people with MCI.

OBJECTIVES

To determine the diagnostic test accuracy (DTA) of ^{18}F-florbetapir as the index test for detecting participants with mild cognitive impairment (MCI) at time of performing the test 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, by evaluating the spectrum of people, referral centres, clinical criteria of MCI, ^{18}F-florbetapir 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 included longitudinal studies that had prospectively defined cohorts with any accepted definition of mild cognitive impairment (MCI), as outlined below, at time of performing the ^{18}F-florbetapir Aβ scan and a reference standard (see Index tests and Reference standards below). We obtained the results at the follow-up of the studies. These studies had to employ delayed verification of progression to dementia and were sometimes labelled as 'delayed verification cross-sectional studies' (Bossuyt 2008; Knottnerus 2002). We included case-control studies when they incorporated a delayed verification design. This occurred in the context of a cohort study, so these studies were invariably diagnostic-nested case-control studies.

Participants

Participants recruited and clinically classified as having MCI at time of performing the test were eligible for inclusion. We established the diagnosis of MCI using the Petersen criteria or revised Petersen criteria (Petersen 1999; Petersen 2004; Winblad 2004), the criteria included in the Matthews study (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 excluded 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). Regarding Parkinson's disease, many of the studies specifically excluded Parkison's disease patients from the group with mild cognitive impairment. This specific group of patients is complex in both regards to defining neuropathology and in determination of functional decline. For these reasons, this group of patients needs to be addressed in specific studies.

Index tests

The index test of this SR was the ^{18}F-florbetapir biomarker test. We used the criteria and cut-off values for test positivity as reported in the included studies. We considered positivity for ^{18}F-florbetapir $A\beta$ scan uptake and retention exceeding a certain threshold.

Target conditions

There were three target conditions in this SR:
- 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 was 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 this SR, we accepted several definitions of ADD. We included studies that applied the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) 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 considered all these issues when we interpreted the results.

Similarly, we accepted differing clinical definitions of other dementias. For Lewy body dementia, the reference standard is the McKeith criteria (McKeith 1996; McKeith 2005); for frontotemporal 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 Neu-

rosciences (NINDS-AIREN) criteria (Román 1993), the DSM criteria (APA 1987; APA 1994), or the ICD criteria (ICD-10). The time interval over which progression from MCI to ADD (or other forms of dementia) occurs is very important. We used 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 searched MEDLINE (Ovid SP) from 1946 to May 2017; Embase (Ovid SP) from 1974 to May 2017; PsycINFO (Ovid SP) from 1806 to May 2017; BIOSIS Citation Index (Thomson Reuters Web of Science) from 1922 to May 2017; Web of Science Core Collection, including the Science Citation Index (Thomson Reuters Web of Science) and the Conference Proceedings Citation Index (Thomson Reuters Web of Science) from 1946 to May 2017; LILACS (Bireme); CINAHL (EBSCOhost) from 1980 to May 2017; 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 also searched ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialized register of dementia studies (http://www.medicine.ox.ac.uk/alois/).

We used two approaches in designing the search. One focused solely on the specifically named index test (including a range of synonyms); the second, run in parallel, covered a more general search, linking broader terms for the index test, focused by terms describing its diagnostic use to terms for the target condition to try to capture the more difficult to locate studies of a more general nature, where these particular radioligands were included in diagnostic accuracy research but not named specifically in the parts of the electronic bibliographic record that are searchable and therefore would be missed.

See Appendix 2 for details of the sources and search strategies that we used. No language or date restrictions were applied to the electronic searches.

Searching other resources

We examined the reference lists of all relevant studies for additional studies. We also searched the Database of Abstracts of Reviews of Effects (DARE) via the Cochrane Library: www.cochranelibrary.com), the National Institute for Health Research - Health Technology Assessment Database (NIHR-HTA) (via the Cochrane Library: www.cochranelibrary.com), the Aggressive Research Intelligence Facility (ARIF) database (

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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 checked the reference lists of any relevant studies and systematic reviews, and performed citation tracking using the Science Citation Index to identify any additional relevant studies.

Data collection and analysis

Selection of studies

Two review authors (GM, RV) independently screened the retrieved titles and abstracts for potentially eligible studies. A third review author (PF) resolved any disagreements between the two review authors. The two review authors (GM, RV) then independently assessed the full-text articles of the selected studies with the inclusion criteria. They resolved any disagreements through discussion or, where necessary, consulted a third review author (PF) who acted as an arbitrator. When a study did not present all relevant data for creating a 2 × 2 table, we contacted the study authors directly to request further information. When more than one article presented data on the same population, we included the primary article, which was 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 planned 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-florbetapir test 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 the reference standard;
- duration of follow-up from time of index test performed to defining ADD and other dementias by the reference standard: one year to less than two years; two years to less than four years; and more than four years. If participants had been followed for varied amounts of time, we recorded a mean follow-up period for each included study. If possible, we grouped those data into minimum, maximum, and median follow-up periods, which could then become the subject of subgroup analyses;
- prevalence or proportion of population developing ADD and other dementias, with severity, if described.

We created 2 × 2 tables (cross-relating index test results of the reference standards) as shown in Appendix 3. For each included study, we recorded the number of people lost to follow-up. We also extracted data necessary for the assessment of quality, as defined below. Two review authors (GM, RV) independently performed data extraction. We resolved any disagreements regarding data extraction by discussion, or by consulting a third review author (PF).

Assessment of methodological quality

We assessed 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 (Davis 2013). This tool is comprised of four domains: participant selection, index test, reference standard, and participant flow.

Two review authors (GM, RV), who were blinded to each other's scores, independently performed the QUADAS-2 assessment. We resolved any disagreements by discussion or, if necessary, consulted a third review author (PF) who acted as an arbitrator. We assessed each domain in terms of risk of bias, and also considered the first three domains in terms of applicability concerns. In Appendix 4, we have detailed the components of each of these domains and provided a rubric that shows how we made judgements concerning risk of bias. Key areas important to quality assessment are participant selection, blinding, and missing data.

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

We included the item pertaining to the PET scan interpretation and the definition of positive results to take into account the subjective nature of ^{18}F-florbetapir Aβ scan image interpretation, which may be based on a variety of different criteria, such as extensive clinical experience, different standardised uptake values (SUV), different morphological features, or a combination of the

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aforementioned. We included the third additional item in order to record any potential bias resulting from commercial interest in the results due to the potential risk by the manufacturing company leading to more favourable results and conclusions than sponsorship by other sources (Lundh 2017).

We did not use QUADAS-2 data to form a summary quality score. We produced a narrative summary that described the numbers of included studies that were at high, low, or unclear risk of bias as well as concerns regarding applicability, which we have described in Appendix 5.

Statistical analysis and data synthesis

We applied the DTA framework for the analysis of a single test and extracted the data from each included study into a 2×2 table, showing the binary test results cross-classified with the binary reference standard, and we ignored any censoring that might have occurred. We acknowledge that such a reduction in the data may represent a significant oversimplification.

We used 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 these into Review Manager 5 (RevMan 5) (Review Manager 2014) to calculate the sensitivities, specificities, and their 95% confidence intervals. We also presented 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 published more than one threshold, we presented the graphical findings for all reported thresholds.

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. We planned to clearly note where the same included studies contributed to the analysis for more than one reference standard follow-up interval. However, due to lack of data, we conducted no meta-analyses, but we prepared a 'Summary of findings' table regardless.

Investigations of heterogeneity

We were able to include only three studies, therefore issues of heterogeneity did not arise.

Sensitivity analyses

We found insufficient data to conduct any sensitivity analyses.

Assessment of reporting bias

We did not investigate reporting bias.

RESULTS

Results of the search

The total number of records identified for this SR was 2502. The PRISMA diagram (Figure 1) shows the selection of records through the screening and selection processes. In total, we assessed 312 studies (74 full text papers, 81 conference publications, 86 registered studies in clinicaltrials.gov, and 71 registered studies in WHO ICTRP) for eligibility in the full-text screening. We excluded 299 studies. 115 studies were multiple publications or duplicates and 33 studies did not have extractable data for constructing 2×2 tables, and we received no reply when we contacted the authors. One study used an MCI definition not accepted in our protocol, and we excluded five studies with available data to extract due to duplication of participants or at high risk of duplication with the included studies (Characteristics of excluded studies). We excluded the remaining studies because they did not meet the inclusion criteria: i) not a longitudinal study (n = 44); ii) no MCI participants at time of performing the test (n = 35); iii) index test not a ^{18}F-florbetapir PET scan (n = 3); iv) discussion or review paper (n = 20); v) wrong design (n= 43). We included three studies and identified ten references as ongoing studies (Characteristics of ongoing studies).

Figure 1. Study flow diagram.

2 searches

TOTAL: 2502

May 2017: 1860

May 2017: 642

312 studies (74 full text, 81 conference publications, 86 registered studies in clinicaltrials.gov, and 71 studies registered in WHO portal) assessed for eligibility

May 2016: 244

May 2017: 68

2190 excluded after de-duplication and first assessment (based on title and abstract review)

May 2016: 1616

May 2017: 574

145 discarded upon reading full text, conference publications and studies registered in clinicaltrials.gov: i) not a longitudinal study (n = 44); ii) not MCI participants at baseline (n = 35); iii) index test not a ^{18}F-florbetapir PET scan (n = 3); iv) discussion or review paper (n = 20); v) wrong outcome or study design (n = 43)

115 duplicated or multiple publications

33 studies without data to create a 2 by 2 table

5 studies with data to create a 2 by 2 table, but with high risk of having duplicated participants from the included studies

1 study with no accepted definition of MCI according to our protocol

312 studies assessed for eligibility

N = 13

3 included studies

10 ongoing studies

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Included studies

See Characteristics of included studies.

Doraiswamy 2014 refers to one study reported previously with ADD, MCI, and healthy control (HC) participants and a longitudinal extension at 36 months follow-up of this cross-sectional study with the MCI participants. Participants were recruited from 21 sites in the United States of America as part of a cross-sectional study to determine the efficacy using both visual interpretation and quantitative interpretation to assess brain amyloid burden by ^{18}F-florbetapir PET scan to differentiate healthy controls (n = 79) from subjects with a clinical diagnosis of ADD (n = 45) or MCI (n = 60) study participants. The interim analysis of the longitudinal extension at 18 months reported baseline data of 51 MCI participants and the efficacy analysis included 46 participants. On the other hand, the baseline data described in Doraiswamy 2014 is of 47 MCI participants with at least one post-baseline measurement; however, there were 52 participants at baseline planned for efficacy participants.

MCI participants had a CDR score of 0.5; complaint of memory or cognitive decline corroborated by an informant; objective evidence of cognitive impairment or marginally normal cognition with a documented history of high cognitive performance; no obvious medical cause for the impairment; subject not demented and criteria for ADD not satisfied; normal score on the Alzheimer's Disease Clinical Studies Consortium Activities of Daily Living (ADCS ADL), 25 of 47 were female; participants with $A\beta$ (+) by ^{18}F-florbetapir PET scan had a mean age of 74.47 ± 7.72 years old, with 14.47 ± 2.18 mean years of education, their mean MMSE was 27.29 ± 2.14 points and 11 participants were APOE $\epsilon 4$ carrier positive, respectively. In those participants with $A\beta$ (-) by ^{18}F-florbetapir PET scan, they had a mean age of 70.40 ± 10.72 years old, with 15.27 ± 2.42 mean years of education and their mean MMSE was 27.53 ± 1.63 points. Four participants were APOE $\epsilon 4$ carrier positive, respectively. Of the 47 participants, 9 (19.1%) developed Alzheimer's dementia. 5 participants (9.6%) had no post-baseline measurement, therefore they were excluded from the analysis, and in those 47 with at least one post-baseline measurement, 37 completed the study at 36 months. The Reference standard at follow-up was not explicitly stated, although NINCDS-ADRDA criteria for ADD (McKhann 1984) were baseline diagnostic criteria.

Potential conflicts of interest were noted. The manufacturer of ^{18}F-florbetapir tracer provided financial support for the study and six authors were employees.

Kawas 2013 refers to a study with participants who were 90 years old or older who either lived at home or in institutions, evaluated in the United States of America. Those included were participants of a longitudinal, population-based study (90+ Study) and were also invited to participate in this study which was part of research to examine the relationship between measurements of brain amyloid and levels of amyloid burden measured by post-

mortem histopathological assessment (Clark 2011). Participants had normal cognition or cognitive or functional impairment resulting from cognition not severe enough to meet DSM-IV diagnostic criteria and they were classified as cognitively impaired, not demented (CIND). They agreed to postmortem brain donation. The purpose of the study was to examine cross-sectional and longitudinal associations between cognitive performance and beta amyloid load in non-demented oldest-old. Baseline characteristics was based on 13 non-demented oldest-old participants, eight were normal controls and five of them were classified as MCI at time of performing the test according to our MCI definitions (Matthews 2008), three MCI were considered as $A\beta$ (+), and two MCI were considered as $A\beta$ (-). In the total group (13 participants), the mean age was 94.1 years (range 90 to 99); for those considered as $A\beta$ (+), the mean age was 94.4 years (range 93 to 96) and 94.1 years (range 90 to 99) years old for those with $A\beta$ (-). Nine participants were women, two of whom were $A\beta$ (+), and two of four men were $A\beta$ (+) at baseline. Seven participants were reported as having been educated beyond high school age, two of them were $A\beta$ (+) and five were $A\beta$ (-), and for those six having been educated up to or less than high school age, two were $A\beta$ (+) and four were $A\beta$ (-), respectively. The mean MMSE was 28 (range 24 to 30); for those considered as $A\beta$ (+), the mean MMSE was 26.5 (range 24 to 29) and 28 (range 25 to 30) for those in the $A\beta$ (-) group; and no data regarding APOE $\epsilon 4$ carrier were reported.

All participants were followed for a mean period of 1.5 years; three of 13 participants developed dementia during follow-up, one in the $A\beta$ (-) group and two in the $A\beta$ (+) group, and it seemed that none of the participants were lost to follow-up. The reference standard used to classify participants at follow-up as dementia or not was DSM-IV (APA 1994).

Partial financial support was provided by and three authors were employees of the manufacturer of ^{18}F-florbetapir tracer.

Schreiber 2015 is a study with data from Alzheimer's Disease Neuroimaging Initiative (ADNI), a multicentre study, supported by the National Institute of Health, private companies, and non-profit organisations. This ADNI database recruited participants from nearly 50 different sites. All participants were aged between 55 and 90 years, had completed at least 6 years of education, and MCI participants were single-domain or multidomain amnestic, had subjective memory problems, had a MMSE score between 24 and 30, and had a CDR of 0.5.

The main objectives of this study were to investigate the concordance between visual and quantitative $A\beta$ PET with the ^{18}F-florbetapir PET scan and if these assessments agreed or not with CSF $A\beta_{1-42}$ in MCI participants, and also to examine the prediction of progression at follow-up according to their visual and quantitative categorization as $A\beta$ positive or negative at baseline with the ^{18}F-florbetapir PET scan (ADNI-GO; ADNI2).

The threshold used was a SUVR > 1.11 determined at baseline (Landau 2012, Landau 2013).

The study had 401 MCI participants. The mean age at baseline was 71.6 years (+ 7.5). There were 182 female participants, and 198 participants were APOE ∊ 4 carrier positive. The MMSE mean was 28.1 (+ 1.7) and the mean years of education was 16.2 (+ 2.7).

No potential conflicts of interest were noted.
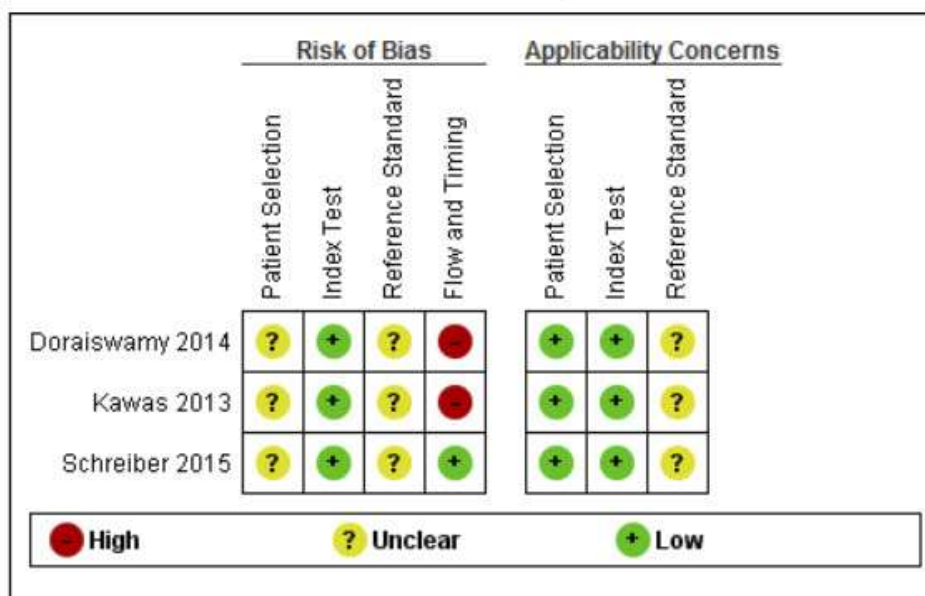
Excluded studies

120 studies were excluded since they did not meet the inclusion criteria for participants, index test, or target condition and 76 studies were duplicated or multiple publications. Additionally, 33 studies did not have data to create a 2 by 2 table, and three studies with data to create the 2 by 2 table were not included due to shared or high risk of shared participants with one included study (Characteristics of excluded studies).

Methodological quality of included studies

We assessed methodological quality 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 2.

Figure 2. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

In the participant selection domain, we considered all studies (Doraiswamy 2014; Kawas 2013; Schreiber 2015) to be at unclear risk of bias due to lack of reporting on sampling procedures and exclusion criteria. We stated that the included studies avoided a case-control design because we only considered data on performance of the index test to discriminate between people with MCI who converted to dementia and those who remained stable.

In the index test domain, we considered all three studies to have a low risk of bias (Doraiswamy 2014; Kawas 2013; Schreiber 2015). The three studies had low risk of bias because the visual assessment used in all three studies was established, the SUVR

used in the Schreiber study was described previously as a SUVR > 1.11 (Landau 2012), and in all three studies, the interpretation was made blinded to the clinical data. In our two additional signalling questions, there was low risk regarding whether the index test was interpreted by a trained reader physician in all three included studies, and the positivity criteria was clearly established in two studies and, in one, it was considered as unclear.

In the reference standard domain, we considered the three studies as at unclear risk of bias (Doraiswamy 2014; Kawas 2013; Schreiber 2015). The Doraiswamy study had an unclear risk of bias because we were not able to obtain the information about which reference standard was used. Regarding the Kawas and Schreiber studies, we considered the studies as unclear risk of bias because, despite the use of DSM-IV criteria for any form of dementia (APA 1994) and NINCDS-ADRDA criteria (McKhann 1984) as reference standards, respectively, it was unclear if the clinician was blinded to the results of the ^{18}F-florbetapir PET scan to establish the dementia diagnosis.

In the flow and timing domain, we judged the Doraiswamy study to have a high risk of bias because it was unclear if it used the same criterion to diagnose the ADD at follow-up. In our additional signalling question, there were potential conflicts of interest due to the financial support for the study and the fact that six authors were employees of the manufacturer of ^{18}F-Flobetapir tracer. Regarding the Kawas study, a high risk of bias was considered due to possible conflict of interest because of partial financial support and three authors were employees of the company producing ^{18}F-florbetapir. For assessment of applicability, there was no concern that the included participants and setting, and the conduct and interpretation of the index test, did not match the review question. However, the target condition (as defined by the reference standard)

was unclear due to lack to information about which reference standard(s) was applied (Doraiswamy 2014) and if the clinician was blinded or not to the ^{18}F-florbetapir PET scan result to establish the diagnosis (Kawas 2013; Schreiber 2015).
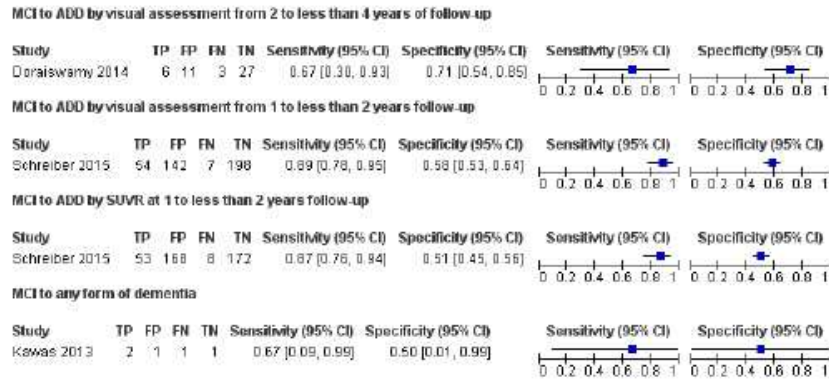
Findings

The results of the included studies are summarised in Data table 1 and Data table 2. Additionally, the summary of main results for the included studies are presented in the 'Summary of findings' table.

^{18}F-florbetapir to predict progression from MCI to Alzheimer's disease dementia (ADD)

Visual Assessment

Doraiswamy 2014 included data on 47 of the 52 eligible participants with MCI diagnosed with CDR = 0.5, and complaint of memory or cognitive decline corroborated by an informant; objective evidence of cognitive impairment or marginally normal cognition with a documented history of high cognitive performance; no obvious medical cause for the impairment; subject not demented and criteria for ADD not satisfied; normal score on the Alzheimer's Disease Clinical Studies Consortium Activities of Daily Living (ADCS ADL), using a nonspecified reference standard, probably NINCDS-ADRDA (McKhann 1984). They reported a sensitivity of 67% (95% CI 30 to 93) and a specificity of 71% (95% CI 54 to 85) to predict the progression from MCI to ADD at three years of follow up. Of the 52 participants who were given an initial clinical diagnosis of MCI, the study had data on 47 of them at the follow-up; 6 were true positive, 11 were false positives, 3 were false negative and 27 were true negative (Figure 3).

Figure 3. Forest plot of tests: 1 MCI to ADD by visual assessment from 2 to less than 4 years of follow-up, 2 MCI to ADD by visual assessment from 1 to less than 2 years follow-up, 3 MCI to ADD by SUVR at 1 to less than 2 years follow-up, 4 MCI to any form of dementia.

MCI to ADD by visual assessment from 2 to less than 4 years of follow-up

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Doraiswamy 2014	6	11	3	27	0.67 [0.30, 0.93]	0.71 [0.54, 0.85]

MCI to ADD by visual assessment from 1 to less than 2 years follow-up

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Schreiber 2015	54	142	7	198	0.89 [0.78, 0.95]	0.58 [0.53, 0.64]

MCI to ADD by SUVR at 1 to less than 2 years follow-up

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Schreiber 2015	53	168	8	172	0.87 [0.76, 0.94]	0.51 [0.45, 0.56]

MCI to any form of dementia

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kawas 2013	2	1	1	1	0.67 [0.09, 0.99]	0.50 [0.01, 0.99]

Schreiber 2015 included data on 401 participants with MCI defined as cases with single-domain or multidomain amnestic; having subjective memory concerns; MMSE score between 24 and 30 (inclusive); CDR = 0.5; Memory Box score had to be at least 0.5, and general cognition and functional performance sufficiently preserved such that a diagnosis of Alzheimer's disease could not be made at the screening visit. They reported a sensitivity of 89% (95% CI 78 to 95) and a specificity of 58% (95% CI 53 to 64) to predict the progression from MCI to ADD at 1.6 years of follow-up. Of the 401 participants who were given an initial clinical diagnosis of MCI, the study had data of all at follow-up; 54 were true positive, 142 were false positives, 7 were false negative, and 198 were true negative (Figure 3).

Quantitative Assessment by SUVR > 1.1

Schreiber 2015 included data on 401 participants with MCI defined as above and reported a sensitivity of 87% (95% CI 76 to 94) and a specificity of 51% (95% CI 45 to 56) to predict the progression from MCI to ADD at 1.6 years of follow up. Of 401 participants who were given an initial clinical diagnosis of MCI, the study had data of all at follow-up; 53 were true positive, 168 were false positives, 8 were false negative, and 172 were true negative (Figure 3).

¹⁸F-florbetapir to predict progression from MCI to any form of dementia

Visual Assessment

Kawas 2013 included data on five participants with MCI, defined as participants with a condition known as 'cognitive impairment non-demented (CIND)', where participants had either cognitive or functional impairment resulting from cognition not severe enough to meet DSM-IV criteria, and it was included in Matthews 2008 MCI definitions. This study had a sensitivity of 67% (95% CI 9 to 99) and a specificity of 50% (95% CI 1 to 99) to predict the progression from MCI to any form of dementia at 1.5 years of follow-up. Of five participants who were given an initial clinical diagnosis of MCI, the study had data on five of them at the follow-up; two were true positive, one was false positive, one was false negative and one was true negative (Figure 3).

No data were available regarding the other target condition in this Cochrane review; progression from MCI to another form of non-ADD.

Investigation of heterogeneity

The planned investigations were not possible due to the limited number of studies available for the analysis.

Sensitivity analyses

There were insufficient studies identified to permit any sensitivity analysis.

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Summary of findings

What is the diagnostic accuracy of ^{18}F-florbetapir PET amyloid biomarker for predict progression to ADD, any other form of dementia (non-ADD) or any form of dementia in people with MCI?	
Descriptive	
Patient population	Participants diagnosed with MCI at time of performing the test using any of the Petersen criteria or Winblad criteria or CDR = 0.5 or any 16 definitions included by Matthews (Matthews 2008).
Sources of referral	Not reported (n = 2) Mixed (memory clinics, newspaper ads, radio, and other public media campaigns) (n = 1)
MCI criteria	ADNI criteria, CDR0.5 criterion was included (n = 2) CIND (cognitive impairment not dementia) (Matthews 2008) (n = 1)
Sampling procedure	Unclear (n = 3)
Prior testing	The only testing prior to performing the ^{18}F-florbetapir PET amyloid biomarker was the application of diagnostic criteria for identifying participants with MCI
Settings	Community and institutionalised (n = 1) Not reported (n = 2)
Index test	^{18}F-florbetapir PET
Threshold prespecified at baseline	Yes (n = 3)
Threshold interpretation	Visual (n = 3) Quantitative (n = 1)
Threshold	Visual: • Increased tracer uptake reduced or absent white matter/ gray matter contrast in at least one cortical (frontal, parietal, temporal, occipital) region detectable on more than two adjacent scan slices (n = 1) • Amyloid burden based on successive levels of florbetapir retention from from 0 (no amyloid) to 4 (high levels of cortical amyloid). The median of the three visual scores was used to dichotomize participants into Aβ (-) (score, 0 to 1 point) and Aβ (+) (score, 2 to 4 points) (n = 2)

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SUVR (Standardised Uptake Volume ratio): • >1.11 (n=1)	
18F-florbetapir re-tention region	Global cortex (n=1)
Reference Standard	Alzheimer's disease dementia: NINCDS-ADRDA (n=1) Unclear (n=1); Any form of dementia: DSM-IV criteria for dementia (n=1)
Target condition	Progression from MCI to Alzheimer's disease dementia or any other forms of dementia (non-ADD) or any form of dementia
Included studies	Prospectively well-defined cohorts with any accepted definition of MCI (as above). Three studies (N = 458 participants) were included. Number of participants included in analysis: 453
Quality concerns	The participant selection and reference standard QUADAS-2 domain: unclear risk of bias. The index test domain: low risk of bias in all three included studies. The flow and timing domain: high risk of bias in the two included studies. Unclear concerns about applicability in the reference standard domain in all three included studies
Limitations	Limited investigation of heterogeneity and sensitivity analysis due to insufficient number of studies. We were unable to evaluate progression from MCI to any other form of dementia (non-ADD) due to lack of included studies

Test	Studies	Cases/Participants	Sensitivity	Specificity	Consequences in a cohort of 100		
					Proportion converting[1]	Missed cases[2]	Overdiagnosed[2]
Alzheimer's disease dementia							
18F-florbetapir by visual assessment from one to less than two years of follow-up	1	61/401	89% (95% CI 78% to 95%)	58% (95% CI 53% to 64%)		2	36

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(Schreiber 2015)	:	:	:	:	:
18F-florbetapir by 1 quantitative assessment from one to less than two years of follow-up (Schreiber 2015)	61/401	87% (95% CI 76% to 94%)	51% (95% CI 45% to 56%)	2	42
18F-florbetapir by 1 visual assessment from two to less than four years of follow-up (Doraiswamy 2014)	9/47	67% (95% CI 30% to 93%)	71% (95% CI 54% to 85%)	6	23
Any form of dementia	:	:	:	:	:
18F-florbetapir by 1 visual assessment from one to less than two years of follow-up (Kawas 2013)	3/5	67% (95% CI 9% to 99%)	50% (95% CI 1% to 99%)	20	20

Investigation of heterogeneity and sensitivity analysis: The planned investigations were not possible due to the limited number of studies available for each analysis

Conclusions: 18F-florbetapir PET scan is not an accurate test for detecting progression from MCI to Alzheimer's disease dementia or any form of dementia. The strength of the evidence was weak because of considerable variation in study methods, unclear methodological quality due to poor reporting, and high risk of bias due to possible conflict of interest. There is a need for conducting studies using standardised 18F-florbetapir PET scan methodology in larger populations.

1. Proportion concerting to ADD or any form of dementia across included study.

2. Misclassand overdiagnose number over accompanied using the proportion overting to the target condition.

ADD: Alzheimer' self accused dementia

ADNI: Alzheimer's Disease Neuroimaging Initiative
CDR: Clinical dementia rating
CIND: Cognitive impairment not dementia
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th ed.)

MCI: Mild cognitive impairment

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies

SUVR: Standardised uptake value ratio

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DISCUSSION

Summary of main results

The volume and quality of evidence regarding the DTA of ^{18}F-florbetapir for early diagnosis of ADD and other dementias in participants with MCI was limited. We identified three studies in this SR. However, we were not able to construct a meta-analysis because we planned to perform an analysis according to their 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. Neither of the two studies with the same target condition, progression from MCI to ADD, had the same follow-up period. We did not perform sensitivity analyses and were not able to analyse heterogeneity.

Two included studies (Doraiswamy 2014; Schreiber 2015) addressed the DTA of ^{18}F-florbetapir analysed by visual assessment for the prediction of progression from MCI to ADD at follow-up, and one also evaluated the progression from MCI to ADD at follow-up analysed quantitatively with a threshold of SUVR > 1.1 (Schreiber 2015). One study addressed the DTA of ^{18}F-florbetapir analysed by visual assessment for the prediction of progression from MCI to any form of dementia at follow-up (Kawas 2013). The results are summarised in the 'Summary of findings' table (Summary of findings). Two studies were evaluated as at high risk of bias, mainly due to the potential conflict of interest regarding financial support by the company who manufactured the ^{18}F-florbetapir tracer (Doraiswamy 2014; Kawas 2013). No other study had information about the progression to any other form of dementia (non-ADD).

Regarding the objectives of our SR, to determine the DTA of the ^{18}F-florbetapir PET scan for detecting participants with MCI at time of performing the test who would clinically progress to ADD, or to other forms of dementia or any form of dementia at follow-up, the results were as follows:

[18]F-florbetapir PET scan for Alzheimer's disease dementia (ADD)

Progression from MCI to ADD in those with a follow-up between two to less than four years had a sensitivity of 67% (95% CI 30 to 93) and a specificity of 71% (95% CI 54 to 85) by visual assessment (Figure 3).

Progression from MCI to ADD in those with a follow-up between one to less than two years had a sensitivity of 89% (95% CI 78 to 95) and a specificity of 58% (95% CI 53 to 64) by visual assessment and a sensitivity of 87% (95% CI 76 to 94) and a specificity of 51% (95% CI 45 to 56) by quantitative assessment by SUVR (Figure 3).

The DTA of ^{18}F-florbetapir included a wide range of low-to-moderate and good sensitivity and low-to-moderate specificity for predicting progression to ADD through visual or SUVR assessment

evaluation at different follow-up. In other words, the low-to-moderate or good sensitivity could be affected by a high false negative rate. One hypothesis that could explain false negatives is that some people with probable ADD diagnosis may have different and multiple brain pathologies, the most common being Alzheimer's disease pathology combined with microscopic infarcts or neocortical Lewy body disease. These heterogeneous pathological findings are similar in those with MCI (Schneider 2007; Schneider 2009). In addition, the soluble $A\beta$ oligomers are not detected by ^{18}F-florbetapir, and they have been playing a central role in Alzheimer's pathogenesis in the amyloid hypothesis (Heyden 2013), with the possibility of producing false negatives. Indeed, a study found two of 11 participants with an autopsy performed > one year after the ^{18}F-florbetapir PET scan as having a positive neuropathological diagnosis (probable or definite Alzheimer's disease), and they had a negative ^{18}F-florbetapir PET scan (Clark 2012).

Moreover, the presence of neurofibrillary tangles (NFTs), the other histopathologic core of Alzheimer's disease, is not detected by amyloid tracers. For example, the data from cohort studies indicated that plaques and tangles independently contributed to cognitive impairment in Alzheimer's disease pathology without any other primary neuropathologic diagnosis (Serrano-Pozo 2013). Furthermore, NFT formation might be either unrelated to amyloid plaques formation or a temporally distinct process, or both (Royall 2014).

In addition, the low-to-moderate specificity could be affected by a high false positive rate. A positive ^{18}F-florbetapir PET scan for $A\beta$, has been found in other neurological conditions. It was positive in seven of 11 cases of dementia with Lewy bodies, in one of five Parkinson's disease participants (Siderowf 2014), and in six of eight FTD participants evaluated with a SUVR > 1.11 (Kobylecki 2015). The latter could be explained due to the presence of mixed pathology in the same participant, however, in one study with a pathology diagnosis, in three cases with non-ADD by histopathology, the ^{18}F-florbetapir PET had a low likelihood of Alzheimer's disease by NIA/Reagan Institute criteria in all of them (Clark 2011). On the other hand, the false positive rate could be explained because it has affinity to amyloid in vessel walls, in particular, to cerebral amyloid angiopathy as this was shown in patients with intracerebral haemorrhage due to cerebral amyloid angiopathy (CAA)(Gurol 2016). The latter would indicate that some MCI participants have vascular MCI due to CAA. The other important option for a high false positive rate is that in many people without cognitive impairment, it is possible to find $A\beta$ deposits at autopsy (Gelber 2012) generating doubt about the pathophysiological relevance of the $A\beta$ hypothesis in Alzheimer's disease.

Duration of follow-up is also important in predicting the progression of MCI to ADD, because the reported progression rate of MCI to ADD is between 8% and 16% per year (Mitchell 2009). We took it for granted that, given a long follow-up period, a high percentage of people with MCI at time of performing the test would progress to Alzheimer's disease, thus affecting the predictive

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accuracy of the ^{18}F-florbetapir PET scan. This was found in a systematic review with PiB PET where the data were separated into short follow-up and longer than two years of follow-up (Ma 2014). The authors included five studies with 102 participants in total with a variable specificity between 58% to 100%. However, in this SR, the progression rate in both included studies was relatively similar despite the follow-up in one study being almost double the other (15.2% at 1.6 years and 19.1% at three years of follow-up). This difference is probably explained by the setting of recruitment or other characteristics of the MCI participants and other underlying factors affecting these progression rates (Doraiswamy 2014; Schreiber 2015). In consequence, due to the lack of data, we were not able to investigate the effect of the follow-up on the progression rate from MCI to ADD or any form of dementia.

The MCI subtypes have been studied regarding their relationship with the progression to ADD. In the largest longitudinal study to our knowledge, results from the follow-up of 550 MCI participants indicated that the MCI subtype, presence of storage memory impairment, multiple domain condition, and presence of APOE ε4 allele increased the risk of progression to dementia. Multivariate survival and Kaplan-Meier analyses showed that amnestic MCI with storage memory impairment had the most and closest risk of progression to dementia (Espinosa 2013). In our review, one study included only amnestic MCI, and this could explain the decrease in false negative rate with an increase in sensitivity. This may explain why the sensitivity was higher in this study (Schreiber 2015) than the study which included any type of MCI (Doraiswamy 2014). 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 progression rate to dementia. To support this, the Schreiber study showed different Cox proportional hazards regression models, where visual analysis adjusted by age, sex, and educational level had a higher hazard ratio to predict the progression than when analyses added APOE ε4 allele or ^{18}F-FDG-PET as covariates (Schreiber 2015). Another study using a multimodal approach to predict the progression including MRI, ^{18}F-florbetapir PET, and ^{18}F-FDG-PET had better predictive accuracy than the single modality (Xu 2016). In conclusion, further studies should include high-quality research with more detailed data about the characteristics of MCI, not only to explore the underlying mechanisms but also to elucidate the causal pathways that link ^{18}F-florbetapir PET scan positivity to diverse MCI subtypes and disease progression.

^{18}F-florbetapir PET scan for any other forms of dementia (non-Alzheimer's disease dementia (non-ADD))

Data for any other forms of dementia (non-Alzheimer's disease dementia) were limited in this SR. Although ^{18}F-florbetapir retention is a poor predictor of subsequent progression to Alzheimer's disease, the current available data suggested that ^{18}F-florbetapir may not play a role in any other forms of dementia (non-ADD).

^{18}F-florbetapir PET scan for any form of dementia

Progression from MCI to any form of dementia in those with a follow-up between one to less than two years had a sensitivity of 67% (95% CI 9 to 99) and a specificity of 50% (95% CI 1 to 99) by visual assessment (Figure 3).

Kawas 2013 had poor sensitivity and specificity to predict any form of dementia (Kawas 2013). This could be explained by the reasons stated before, specifically due to the small sample of the oldest-old participants of this study, and the high prevalence of Alzheimer's pathology in older people without a stated dementia (Savva 2009; Gelber 2012). The DTA may be different in those studies with a younger population.

Strengths and weaknesses of the review

We conducted an extensive, comprehensive, and sensitive literature search, using eleven different electronic databases without any limitation to language. However, we were able to include only three studies with 453 eligible participants, therefore our DTA estimates were relatively imprecise. This paucity of evidence reflected the very significant challenges inherent in conducting long-term prospective studies of well-characterised participants, followed up to the point of progression of clinical dementia. The methodological quality assessment and data syntheses were based on the recommended methods (Davis 2013). To increase the reliability of our findings, we included only studies that fulfilled delayed verification of progression from MCI to ADD or other form of dementia (non-ADD) or any form of dementia at follow-up.

The included studies did have significant methodological limitations that weakened confidence in the results of this SR. First, considerable uncertainty remained concerning the clinical diagnosis of ADD; the histopathological diagnosis would be the better way to define the diagnosis, but this is not a realistic option for a clinical trial. Second, the three studies lacked information regarding the selection of participants. It was not clear if the reference standard interpretation was made without knowledge of the ^{18}F-florbetapir PET scan results in two studies, and a major problem in two of the studies was a potential conflict of interest with the company that produced the tracer.

The selection of participants with MCI in these studies could be another weakness, because we did not have all the necessary baseline data to perform risk stratification to detect the MCI subgroup who would progress to ADD. However, this selection of participants such as type of MCI, age, presence of APOE ε4 allele, structural abnormality at MRI, hypometabolism at FDG-PET scan, and alteration in cerebrospinal fluid could help determine different subgroups of people at higher risk of developing dementia at follow-up, and could enable stratification that could help avoid biases, and develop more efficient studies in the future (Hampel 2012, Caroli 2015, Wolz 2016). In this way, Xu 2016 described a multimodal approach with a ^{18}F-florbetapir PET scan and ^{18}F-FDG- PET scan, Pascoal 2017 described the combination of p-

tau levels in cerebrospinal fluid with ^{18}F-florbetapir PET scan status, and in Schreiber 2015, age, sex, educational level, ADAS-cog at baseline, APOE ε4 allele, and ^{18}F-FDG-PET scan status were included in the Cox regression model.

Finally, an important weakness of this SR was the nonresponse from the majority of the authors about their studies. This has resulted in a lack of data for analysis in this review.

Applicability of findings to the review question

Regarding the question of this SR:

Could the ^{18}F-florbetapir PET scan identify those MCI participants who would progress to a clinical dementia at follow up?

There were concerns regarding the applicability of the included participants and setting and in the index test domain in all three studies. In addition, in all three studies, there were concerns regarding the applicability of the reference standard due to the lack of information about the knowledge or not of the index test result to make the diagnosis. There was also lack of information regarding which reference standard was used. In two studies, there were concerns regarding applicability because of potential conflicts of interest. Therefore, due to the limited number of included studies and levels of heterogeneity with respect to the domains mentioned above, it was difficult to determine to what extent the findings from this systematic review could be applied to clinical practice.

The DTA of the ^{18}F-florbetapir PET scan for identifying Alzheimer's disease pathology and identifying those people with MCI who would convert to ADD or any form of dementia could be affected by a number of factors that have not been determined so far. The most important, is the lack of a large study to evaluate this question; we included only three studies, two that addressed the progression from MCI to ADD with 448 participants and one that addressed the progression from MCI to any form of dementia with only five participants.

We have to wait for new longer-term longitudinal studies. The ^{18}F-florbetapir test is expensive, therefore, we believe it is important to clearly determine its DTA prior to recommending its adoption in clinical practice, because the actual sensitivity and especially the specificity are too low to have enough accuracy to be used in clinical practice to predict the progression from MCI to ADD.

AUTHORS' CONCLUSIONS

Implications for practice

Today, the use of ^{18}F-florbetapir has not been established for predicting development of Alzheimer's disease (FDA 2013, EMA 2013), and is not indicated in people 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 people with persistent or progressive unexplained MCI (Johnson 2013). The DTA of ^{18}F-florbetapir PET scans, as determined in this SR, has a variable sensitivity and low-to-moderate specificity to predict the progression from MCI to ADD, based on two studies with 448 participants at follow-up, and there were only five participants to predict the progression from MCI to any form of dementia in one study.

Due to the aforementioned, and the methodological limitations of the included studies, it is not possible to recommend the routine use of ^{18}F-florbetapir in clinical practice. The ^{18}F-florbetapir biomarker is expensive, therefore it is important to clearly determine its DTA prior to it being recommended for clinical practice.

Implications for research

The FDA and EMA have established the ^{18}F-florbetapir positivity criteria in order to use these in ADD patient evaluation and their use in MCI participants is accepted in research settings and clinical trials (Albert 2011). However, their use has also been proposed in clinical practice by the Nuclear Medicine Society and the Alzheimer's Association (Johnson 2013).

One problem found in the evaluation of the DTA of the ^{18}F-florbetapir PET scan is that many studies used different SUVR, visual assessment or both. This produces different accuracies for the tracer even in patients with ADD when compared with HC. Therefore, it is necessary to consider visual assessment as the option to interpret the ^{18}F-florbetapir PET scan, because this is the approach to the interpretation established by FDA and EMA (EMA 2013, FDA 2013)

On the other hand, clinical assessment in people with memory complaints is not always made with only one test; it could potentially use different tests like volumetric hyppocampal MRI, FDG-PET, SPECT, CSF, and others. This may be sensible as 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 progression 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 (Jack 2013). Based on this hypothesis, the combination of structural imaging, functional imaging, and cognitive tests may be better predictors of when an individual

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will convert. However, there is a lack of studies with ^{18}F-florbetapir combined with other tests. The only study combining MRI, ^{18}F-FDG PET, and ^{18}F-florbetapir PET suggests a better accuracy when these tests are using a multimodal approach rather than a single modality (Xu 2016), and one study combining a positive ^{18}F-florbetapir PET with a positive cerebrospinal fluid p-tau showed a sensitivity of 92% and a specificity of 55% (including as a negative index test all those with discordant results) to predict the progression to ADD at two years of follow-up (Pascoal 2017). However, when the analysis included the discordant results as a positive index test, the sensitivity increased to 97% and the specificity decreased to 18%.

Additionally, if we consider the hierarchical evidence needed for the level of efficacy of diagnostic imaging tests, we are currently in the second step of five according to Herscovitch (Herscovitch 2015): technical efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic impact, patient health outcomes, and, finally, societal efficacy. Therefore, we need further research about accuracy before progressing to the other steps with their specific studies before we can incorporate the ^{18}F-florbetapir PET scan into clinical practice.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Doraiswamy 2014

Study characteristics	
Patient sampling	• There were 52 MCI at time of performing the test planned as evaluable for efficacy participants. • The participants were 50 years old or older with memory complaint or cognitive impairment corroborated by an informant, CDR 0.5, and MMSE > 24, no episodic memory cut-off was required. • No further details of participant sampling and recruitment were reported
Patient characteristics and set-ting	• 52 MCI participants diagnosed by CDR 0.5, but the following data related to those reported in the study as the 'efficacy data set'. Therefore we reported data on 47 participants of 52 participants at baseline. • The mean age was 74.47 (+ 7.72) years for those with $A\beta$ (+) and 70.40 (+ 10.72) years old for those with $A\beta$ (-). • 25 of the 47 in the efficacy data set of participants were women. • APOE ϵ4 carrier: 11 of 17 participants in the $A\beta$ (+) group, and 4 of 30 in the $A\beta$ (-) were positive to APOE ϵ4. • MMSE: the mean MMSE for those in the $A\beta$ (+) group was 27.29 (+ 2.14) and 27.53 (+ 1.63) for those in $A\beta$ (-) group. • Years of education: the mean for those in $A\beta$ (+) group was 14.47 (+ 2.18) years and 15.27 (+ 2.42) years for those in $A\beta$ (-) group. • Sources of referral: not reported. • Setting: 21 sites in the United States of America, no data regarding the specific setting were reported.
Index tests	• Site PET scanners were qualified with a Hoffman brain phantom. • Time between the ^{18}F-florbetapir injection and PET acquisition: fifty minutes after injection and, a 10-min emission scan (acquired in 2 × 5 min frames) was obtained. • ^{18}F-florbetapir administration mCi (MBq) dose: 10 mCi (370 MBq). • PET scanners included Discovery LS PET/CT (GE, Fairfield, CT, USA), Advance PET (GE), ECAT HR+ (Siemens, Washington DC, USA) and Biograph PET/CT (Siemens) models. • Image reconstruction utilized an iterative algorithm (4 iterations, 16 subsets) and a post-reconstruction Gaussian filter of 5 mm. • Semiquantitative visual rating: After a training session, three nuclear medicine physicians with no access to clinical information, independently rated each PET image for amyloid burden based on successive levels of florbetapir retention from 0 to 4 as follows: (0) None: predominantly white matter tracer retention with no appreciable cortical gray matter retention above cerebellar grey matter levels; (1) Low: evidence of increased tracer retention above cerebellar grey levels in 1 or 2 cortical grey regions; (2) Low-moderate: either (a) predominantly white matter pattern, but at least 2 cortical regions with increased retention relative to cerebellar grey, or (b) predominantly a cortical gray matter pattern, with most cortical areas mildly positive relative to cerebellum;

Doraiswamy 2014 *(Continued)*

	(3) Moderate-high: specific cortical retention generally greater than or equal to white matter retention and at least one cortical area with greatly increased retention relative to cerebellar grey; (4) High: Specific cortical uptake greater than or equal to white matter background and multiple cortical areas with greatly increased retention relative to cerebellar grey • Binary Classification: The visual reads were used to classify each data set as either visually positive for $A\beta$ or visually negative for $A\beta$ Visual rating scores of 2 to 4 were considered positive and 0 to 1 were considered negative • Cerebellum was used as the reference region.		
Target condition and reference standard(s)	• Target condition: Alzheimer's disease dementia • Reference standard: not explicitly stated, although NINCDS-ADRDA criteria for ADD (McKhann 1984) were baseline diagnostic criteria, and clinical diagnoses were generated without knowledge of the ^{18}F-florbetapir scan results.		

Flow and timing	• Duration of follow-up: 3 years
	• Number included in analysis: 47 participants with at least one post baseline measurement; 17 ^{18}F-florbetapir (+) and 30 ^{18}F-florbetapir (-)
	• Progression from MCI to ADD:
	   o ^{18}F-florbetapir (+): 6 MCI converted to ADD and 11 MCI not converted to ADD; ^{18}F-florbetapir (-): 3 MCI converted to ADD and 27 MCI not converted to ADD
	   o TP = 6; FP = 11; FN = 3; TN = 27
	   o Loss to follow-up including those without any post-baseline measurement: 15 MCI participants. No further information was given on the MCI group reasons. There were data regarding all groups (ADD, MCI, normal controls) where it was described that the most common reasons for termination were withdrawal of consent (n = 38) and loss of follow-up (n = 8).
	• Financial support from the manufacturer of ^{18}F-florbetapir tracer and six authors were employees		

Comparative			
Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	Low

Doraiswamy 2014 *(Continued)*

DOMAIN 2: Index Test All tests			
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		
Was the PET scan interpretation done by a trained reader physician?	Yes		
Was there a clear definition of a positive result?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
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		
		Unclear	Unclear
DOMAIN 4: Flow and Timing			
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		
Was the study free of commercial funding?	No		
		High	

Kawas 2013

Study characteristics	
Patient sampling	• The participants were 90 years old or older. They were participants of a longitudinal, population-based study (90+ Study) and were invited to participate at this study. • The participants had normal cognition or with either cognitive or functional impairment resulting from cognition not severe enough to meet DSM-IV diagnostic criteria and they were classified as cognitively impaired not demented (CIND) and they agreed to postmortem brain donation. • There were 5 MCI at time of performing the test planned as evaluable for efficacy participants. • No further details of patient sampling and recruitment were reported.
Patient characteristics and setting	• 5 MCI participants diagnosed as CIND, three were considered as Aβ (+) and two were considered as Aβ (-). • The characteristics data of the participants included 13 participants: five of them were MCI participants and eight were normal controls; the mean age was 94.1 (range 90 to 99), for those considered as Aβ (+) the mean age was 94.4 (range 93 to 96) and 94.1 (range 90 to 99) years old for those with Aβ (-). Nine of the participants were women, two of them were Aβ (+), and two of four men were Aβ (+) at baseline APOE ϵ4 carrier: not reported MMSE: the mean MMSE was 28 (range 24 to 30); for those considered as in the Aβ (+) group, the mean was 26.5 (range 24 to 29) and 28 (range 25 to 30) for those in the Aβ (-) group Years of education: seven participants were reported having studied after high school: two of them were Aβ (+) and five were Aβ (-); for those six having studied at high school or with less education, two were Aβ (+) and four were Aβ (-), respectively • Sources of referral: not reported • Setting: participants lived at home as well as in institutions in the United States of America.
Index tests	• Participants were imaged using clinical PET and PET/computed tomographic scanners. • Time between the ^{18}F-florbetapir injection and PET acquisition: fifty minutes after injection and, a 10-min emission scan was obtained. • ^{18}F-florbetapir administration mCi (MBq) dose: 10 mCi (370 MBq) • Images were acquired with a 128 x 128 matrix (zoom x 2) and were reconstructed using iterative or row action maximization likelihood algorithms. • Semiquantitative visual rating: After a training session, three nuclear medicine physicians with no access to clinical information, independently rated each PET image for amyloid burden based on successive levels of florbetapir retention from from 0 (no amyloid) to 4 (high levels of cortical amyloid). The median of the three visual scores was used to dichotomize participants into Aβ (-) (score, 0 to 1 point) and Aβ (+) (score, 2 to 4 points)
Target condition and reference standard(s)	• Target condition: any form of dementia • Reference standard: DSM-IV criteria for dementia (APA 1994)
Flow and timing	• Duration of follow-up (median): 1.5 years (all participants, including those as control normals) • Number included in analysis: 5 participants; three ^{18}F-florbetapir (+) and two ^{18}F-florbetapir (-)

Kawas 2013 *(Continued)*

	• Progression from MCI to any form of dementia:
	  o ^{18}F-florbetapir (+): 2 MCI converted to any form of dementia and 1 MCI not converted to any form of dementia; ^{18}F-florbetapir (-): 1 MCI converted to any form of dementia and 1 MCI not converted to any form of dementia; TP = 2; FP = 1; FN = 1; TN = 1
	    o Loss to follow-up: none
	  • Partial financial support from the manufacturer of ^{18}F-florbetapir tracer and three authors were employees

Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	Low
DOMAIN 2: Index Test All tests			
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		
Was the PET scan interpretation done by a trained reader physician?	Yes		
Was there a clear definition of a positive result?	Unclear		
		Low	Low
DOMAIN 3: Reference Standard			

Kawas 2013 *(Continued)*

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		
		Unclear	Unclear

DOMAIN 4: Flow and Timing

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		
Was the study free of commercial funding?	No		
		High	

Schreiber 2015

Study characteristics

Patient sampling	• 401 amnestic MCI participants were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The study was performed from September 2010, to August 2014; data analysis was performed from September 2014, to May 2015. • The participants were between 55 to 90 (inclusive) years old with memory complaints or cognitive impairment corroborated by an informant, CDR 0.5, and MMSE > 24, Hachinski less than or equal to 4, Geriatric Depression Scale less than 6, without any significant neurologic disease other than suspected incipient Alzheimer's disease, had completed at least 6 years of education, were fluent in Spanish or English. • No sampling criteria was specified
Patient characteristics and setting	• 401 amnestic MCI participants diagnosed by CDR = 0.5 at time of performing the test, were recruited from ADNI data. • The mean age was 71.6 (+ 7.5) years for all participants. • Gender: 182 female in MCI group. • APOE $_c$ 4 carrier: 198 participants were positive in the MCI group.

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Schreiber 2015   *(Continued)*

	• MMSE: the mean MMSE in the MCI group was 28.1 (+ 1.7). • Years of education: the mean for those in the MCI group was 16.2 (+ 2.7) years. • Sources of referral mixed: memory clinics, newspaper ads, radio, and other public media campaigns. • Setting: multicentre, no other specific data regarding setting was reported.
Index tests	• Florbetapir image data were acquired from a variety of PET scanners (Siemens PET systems, GE, Phillips). • ^{18}F-florbetapir administration mCi (MBq) dose: approximately 10 mCi (370 MBq). • Time between the ^{18}F-florbetapir injection and PET acquisition: between 50 to 70 minutes after injection of approximately 10 mCi, a 20-min emission scan (acquired in 4 × 5 min frames) was obtained. • The four frames were coregistered to one another, averaged, interpolated to a uniform image and voxel size ($160 \times 106 \times 96$, $1.5mm^3$), and smoothed to a uniform resolution (8 mm full width half maximum) to account for differences between scanners. • **Visual analysis** was performed on axial, sagittal, and coronal slices, in an inverse gray scale, using software that permitted adjustment of image brightness and contrast to each reader's specifications. Florbetapir positivity was defined as increased tracer uptake in the cerebral cortex that was visually perceived as reduced or absent white matter/gray matter contrast in at least one cortical (frontal, parietal, temporal, occipital) region detectable on more than two adjacent scan slices. The reader was trained using an online electronic training tool produced by the company who produced the tracer, and the reader was blinded to all clinical data and any other imaging test of each participant • **Quantitative analysis**: To quantify cortical $A\beta$, preprocessed florbetapir image data and coregistered structural magnetic resonance images (MRI) were analysed using Freesurfer v4.5.0 MPRAGE scans of one structural 1.5T or 3T MRI scan within 2 months of florbetapir scans were segmented and parcellated into individual cortical regions, used to extract the mean florbetapir uptake from the gray matter of the ROI (lateral and medial frontal, anterior, and posterior cingulate, lateral parietal, and lateral temporal regions) relative to uptake in the whole cerebellum (white and gray matter). The threshold used was a SUVR > 1.11 determined at baseline.(Landau 2012, Landau 2013).
Target condition and reference standard(s)	• Target condition: Alzheimer's disease (progression from MCI to ADD) • Reference standard: NINCDS-ADRDA criteria Unclear whether clinicians conducting follow-up were aware of the ^{18}F-florbetapir PET scan results
Flow and timing	• Participants belonged to the ADNI database, the study was performed from September 2010 to August 2014. • All participants received the same reference standard. • Duration of follow-up: a median progression-free follow-up time of 1.6 years Number included in analysis: **MCI** • Visual assessment: 401 MCI: 196 MCI with ^{18}F-florbetapir positive test: 54 converted to ADD and 142 remained stable; 205 MCI with ^{18}F-florbetapir negative test: 7 converted to ADD and 198 remained stable. • TP = 54; FP = 142; FN = 7; TN = 198 • SUVR > 1.11: 401 MCI: 221 MCI with ^{18}F-florbetapir positive test; 53 converted to ADD and 168 remained stable; 180 MCI with ^{18}F-florbetapir negative test; 8 converted to ADD and

Schreiber 2015 *(Continued)*

	172 remained stable. • TP = 53; FP = 168; FN = 8; TN = 172 • Loss to follow-up: data appeared to have been reported for all 401 participants.
Comparative	
Notes	Dr Schreiber kindly sent the ADNI identification code for each MCI participant (mail received 04/07/2017)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	Low
DOMAIN 2: Index Test All tests			
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		
Was the PET scan interpretation done by a trained reader physician?	Yes		
Was there a clear definition of a positive result?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target	Yes		

Schreiber 2015 *(Continued)*

condition?			
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	Unclear
DOMAIN 4: Flow and Timing			
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		
Was the study free of commercial funding?	Yes		
		Low	

$^A β$: Amyloid Beta
ADD: Alzheimer's disease dementia
ADNI: Alzheimer's Disease Neuroimaging Initiative
APOE ε4: Apolipoprotein E4
CDR: Clinical dementia rating
CIND: Cognitive impairment not dementia
CT: Computed tomography
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th ed.)
FN: False negative
FP: False positive
MBq: Megabecquerel
MCI: Mild cognitive impairment
mCi: Millicurie
MMSE: Mini-mental state examination
MPRAGE: Magnetization-Prepared Rapid Gradient-Echo
NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PET: Positron emission tomography
ROI: Region of interest
SUVR: Standardised uptake value ratio
T:Tesla
TN: True negative
TP: True positive

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Altomare 2016	MCI diagnosis at baseline was not made with any of our accepted definitions by protocol for MCI participants Dr Altomare kindly responded to some questions regarding the method of his study (mail received 16/06/2017)
Apostolova 2016	Not having data for constructing a 2 x 2 table. The study was focused on the development of neuropsychiatric symptoms and not on Alzheimer's disease or dementia progression
Brendel 2014	Not having data for constructing a 2 x 2 table. The study was focused on longitudinal quantitative analyses of ^{18}F-florbetapir PET and their association with progression of dementia
Brendel 2015	Not having data for constructing a 2 x 2 table. The study was focused on testing the effects of different reference regions and atrophy-based partial volume effects on the discriminatory power and longitudinal performance of amyloid PET
Cheewakriengkrai 2014	Not having data for constructing a 2 x 2 table. The study was focused on the relationship between regional distributions of brain fibrillar amyloid deposition, neurodegenerative biomarkers in CSF (CSF Aβ 1-42, t-tau, p-tau) and cognitive function (ADAS-cog) at 24 months follow-up
Chen 2015a	Not having data for constructing a 2 x 2 table. The study compared the power of template-based cerebellar, pontine, and cerebral white matter reference regions to track 24-month florbetapir standardized uptake value (SUV) ratio (SUVR) changes; and to relate those changes to 24-month clinical declines
Chen 2015b	Not having data for constructing a 2 x 2 table. The study was focused in the diagnostic potential of FDG PET, florbetapir, PiB and CSF biomarkers in monitoring the progression from mild cognitive impairment (MCI) to Alzheimer's disease (ADD) and cognitively normal (NC) to MCI in a longitudinal study
Chincarini 2015	Not having data for constructing a 2 x 2 table. The study was focused on examining different approaches to amyloid-PET quantification and a longitudinal analyses of Aβ deposition
Chincarini 2016	The study focused on the evaluation of brain amyloidosis (ELBA) with a new method on imaging of the ^{18}F-florbetapir PET scan. We did not include this study because we preferred to include the Schreiber study for the following reasons: • There was a high risk of duplication of participants with the Schreiber study, due to both studies using the same ADNI database. • The Schreiber study had more participants: 401 MCI participants compared to 62 in the Chincarini study. • The reason why there were no participants with MCI at baseline who maintained their condition at the follow-up was not clear.
Durkanova 2015	Not having data for constructing a 2 x 2 table. The study was focused in evaluate five different test strategies for integrating use of florbetapir and FDG PET information to predict rates of cognitive and functional decline over 2 years

Fan 2015	Not having data for constructing a 2 x 2 table. The study was focused on investigating whether different translocator protein genotypes influenced cognitive function, amyloid load, and disease progression over time
Greenia 2014	Not having data for constructing a 2 x 2 table. The study was focused on evaluating the ^{18}F-florbetapir PET and the relationship with cognitive decline in the oldest-old
Hochstetler 2014	Not having data for constructing a 2 x 2 table. The study was focused on trying to define trajectories of cognitive and functional decline, and characteristics associated with distinct trajectories, using Growth Mixture Modeling
Joshi 2014	Not having data for constructing a 2 x 2 table. The study was focused on the estimation of longitudinal change in $A\beta$ burden over 2 years
Klein 2015	Not having data for constructing a 2 x 2 table. The study was focused on the evaluation of native space compared to SPM template methods and a variety of possible SUVR reference regions with highest longitudinal change in the SUVR at 24 months
Landau 2014	Not having data for constructing a 2 x 2 table. The study was focused on the ^{18}F-florbetapir PET longitudinal evaluation in cognitively normal, MCI, and ADD participants, examining characteristics of normal individuals with subthreshold florbetapir retention and the influence of reference region selection on estimated trajectories across the entire range of amyloid measurements
Landau 2016	This study was focused on comparing participants with amyloid beta negative MCI and participants with ADD enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with their $A\beta$ amyloid positive counterparts on a number of clinical, neuropsychological, and biomarker characteristics with an average available follow-up time for longitudinal cognitive measurements of 1.4 + 0.8 years. The conversion rate in those MCI participants with PET negative was 11% and the conversion in those with PET positive was 45% We did not include this study, and we preferred Schreiber 2015 to be included for the following reasons: • There was a high risk of duplication of participants with the Schreiber study, due to the use of the same ADNI database and Landau was the second author of the Schreiber study. • The Schreiber study had more participants: 401 MCI participants compared to 217 in the Landau study. • The follow-up was longer in the Schreiber study: 1.6 + 0.7 years and in the Landau study it was 1.4 + 0.8 years.
Lee 2015	Not having data for constructing a 2 x 2 table. This study was focused in the correlation between florbetapir and FDG PET and cognition measured by MMSE at follow-up
Lim 2014	Not having data for constructing a 2 x 2 table. This study was focused on evaluating the florbetapir status at baseline and different cognitive composite measures at 36 months
Manitsirikul 2015	Not having data for constructing a 2 x 2 table. The study was focused on the relationship between regional distributions of brain fibrillar amyloid deposition, neurodegenerative biomarkers in brain (FDG) and CSF (tau), brain structural change, and cognitive function at 24-month follow-up

Margolin 2013	Not having data for constructing a 2 x 2 table. The study was focused on evaluating the ^{18}F-florbetapir PET and the relationship with cognitive decline at follow-up
Mathotaarachchi 2015	Not having data for constructing a 2 x 2 table. The study was focused on the regional effects of amyloid retention measured by the ^{18}F-florbetapir PET scan on the rate of hypometabolism measured by FDG PET scan over the follow-up

Mattsson 2014a	This study was focused on comparing the diagnostic test accuracy with CSF Aβ42 and the ^{18}F-florbetapir PET scan in three different groups, healthy controls, Alzheimer's disease dementia, and MCI (progressive vs stable MCI) participants
	We did not include this study, as we preferred Schreiber 2015 to be included for the following reasons:
	   • There was a high risk of duplication of participants with the Schreiber study, due to both studies using the same ADNI database and two authors from the Schreiber study (Landau and Jagust) also worked in the Mattsson study.
	   • The Schreiber study had more participants, 401 MCI participants compared to 224 in the Mattson study.
	   • The follow-up was similar: Schreiber study: 1.6 + 0.7 years; Mattsson study: in those with stable MCI, the follow-up was 2.2 + 0.3 years and in those with progressive MCI, the follow-up was 1.7 + 0.6 years.

Mattsson 2014b	Not having data for constructing a 2 x 2 table. This study was focused in determine the extent to which CSF and ^{18}F-florbetapir PET contribute independent diagnostic information in AD studies, and to determine the nature and degree of pathology in discordantly classified individuals in healthy controls, ADD patients, and MCI participants
Mattsson 2015a	Not having data for constructing a 2 x 2 table. The study was focused on testing if CSF and amyloid beta PET scan biomarkers were independently related to other Alzheimer's disease markers, and to examine individuals who were discordantly classified by these two biomarker modalities with a follow-up for up to three years
Mattsson 2015b	Not having data for constructing a 2 x 2 table. The study was focused on relationships in a large number of brain regions in MCI participants with cognitive evaluations for up to three years with Logical Memory delayed recall and Rey Auditory Verbal Learning Test delayed recall
Ming 2015	Not having data for constructing a 2 x 2 table. The study was focused on MCI participants and ^{18}F-florbetapir at baseline and follow-up for up to three years with cognitive evaluations with MMSE, ADAS11 and CDR sum of boxes
Mohades 2014	Not having data for constructing a 2 x 2 table. The study was focused on comparing neurodegeneration in ^{18}F-florbetapir accumulators and nonaccumulators based on a 24-month assessment
Morbelli 2015	Not having data for constructing a 2 x 2 table. The study was focused on MCI participants that had longitudinal evaluation with the ^{18}F-florbetapir PET scan over two years and different methods to establish the PET positivity
Pascoal 2016	Not having data for constructing a 2 x 2 table. The study was focused on neuropsychological and clinical decline in participants with MCI and if they were associated with brain amyloid-beta deposition and tau hyperphosphorylation

Pascoal 2017	The study was focused on amnestic MCI individuals and whether the synergism between $A\beta$ aggregation and tau hyperphosphorylation could determine the progression from amnestic MCI to ADD dementia
	
	We did not include this study because we preferred the Schreiber study to be included for the following reasons:
	  • They used the same ADNI database and 279 of 314 MCI participants in Pascoal 2017 were also included in Schreiber 2015.
	  • The Schreiber study had more participants: 401 MCI participants compared to 314 in the Pascoal study.
	
	Dr Pascoal kindly responded to some questions regarding the method of his study and provided the ADNI identification code of the participants (mail received 16/06/2017)

Pontecorvo 2011	Not having data for constructing a 2 x 2 table. The study was focused on the evaluation of the correlation of florbetapir SUVR with cognitive change from baseline to month 24 in MCI and cognitively normal participants, PET PiB, and CSF amyloid and tau levels
Risacher 2014	Not having data for constructing a 2 x 2 table. The study was focused on the comparative assessment of two-year change in amyloid deposition, glucose metabolism, and hippocampal atrophy in healthy controls, MCI and ADD participants
Shokouhi 2016	Not having data for constructing a 2 x 2 table. The study was focused on evaluating the effect of reference tissue normalization in a test-retest ^{18}F-florbetapir SUVR study using different reference regions and evaluating the correlation between ^{18}F-florbetapir PET and concurrent CSF $A\beta1$-42 levels in a MCI cohort over the course of 2 years
Siderowf 2013	Not having data for constructing a 2 x 2 table. The study was focused on evaluating cognitive decline measured by ADAS-cog in participants with negative and positive ^{18}F-florbetapir PET scan imaging with a clinical follow-up of 18 months
Teipel 2015	Not having data for constructing a 2 x 2 table. The study was focused on comparing penalized regression analysis, with more classical unregularised regression models in respect to predicting conversion from MCI to ADD in 127 MCI subjects who had a clinical follow-up between 6 and 31 months
Toledo 2015	Not having data for constructing a 2 x 2 table. The study was focused on determining the association between CSF and PET amyloid biomarkers (cross-sectional and longitudinal measures) and comparing the cut-offs for these measures
Wisse 2015	Not having data for constructing a 2 x 2 table. The study was focused on characterising MCI participants separated into four groups according to their abnormal amyloid-beta 42 levels and abnormal hippocampal volume or hypometabolism using fluorodeoxyglucose PET and the conversion rate at 24 months

Xu 2016	The study was focused on exploring the contribution of different neuroimaging modalities in their predictive power and characterised the sensitive biomarkers from each modality
	
	We did not include this study, as we preferred the Schreiber study to be included for the following reasons:
	  • They used the same ADNI database and 70 of 110 MCI participants in Xu 2016 were also included in Schreiber 2015.
	  • Schreiber had more participants: 401 MCI participants compared to 110 in the Xu study.

$^A\beta$: Amyloid Beta

ADAS11: Alzheimer's disease assessment scale-11
ADAScog: Alzheimer's Disease Assessment Scale-Cognitive subscale
ADD: Alzheimer's disease dementia
ADNI: Alzheimer's Disease Neuroimaging Initiative
CDR: Clinical dementia rating
CSF: Cerebrospinal fluid
ELBA: Evaluation of brain amyloidosis
FDG: Fluorodeoxyglucose
MCI: Mild cognitive impairment
MMSE: Mini-mental state examination
PET: Positron emission tomography
PiB: Pittsburgh compound B
SPM: statistical parametric mapping
SUV: Standardised uptake value
SUVR: Standardised uptake value ratio

Characteristics of ongoing studies *[ordered by study ID]*

JPRN-UMIN000019926

Trial name or title	Clinical and neuroimaging study on preclinical Alzheimer's disease
Target condition and reference standard(s)	Estimation of progression rate at 36 months of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir, PET PiB, ^{18}F-flutemetamol
Starting date	2016
Contact information	Hiroshi Mori mori@med.osaka-cu.ac.jp
Notes	

NCT01325259

Trial name or title	FluoroAv45 Imaging Research-in Alzheimer's Disease (FAIR-AD)
Target condition and reference standard(s)	Cogitive decline after 2 years of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir
Starting date	2009
Contact information	vincent.camus@univ-tours.fr
Notes	

NCT01554202

Trial name or title	Multi-modal Neuroimaging in Alzheimer's Disease (IMAP)
Target condition and reference standard(s)	Cognitive decline over three years of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir
Starting date	2008
Contact information	Vincent de La Sayette, University Hospital, Caen
Notes	

NCT01638949

Trial name or title	Multi-modal Neuroimaging in Alzheimer's Disease (IMAP+)
Target condition and reference standard(s)	Cognitive decline over three years of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir
Starting date	2012
Contact information	Vincent de La Sayette, University Hospital, Caen
Notes	

NCT01687153

Trial name or title	A Study of Brain Aging in Vietnam War Veterans (DOD-ADNI)
Target condition and reference standard(s)	Cognitive decline over one year of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir
Starting date	2012
Contact information	Michael W. Weiner, University of California, San Francisco Paul Aisen, USC Alzheimer's Therapeutic Research Institute (ATRI) Ronald Petersen, Mayo Clinic
Notes	

NCT01746706

Trial name or title	Can the Assessment of the Subhippocampal Region Contribute to the Detection of Early Diagnosis of Alzheimer's Disease? A Validation Study Using PET With florbetapir (AV-45)
Target condition and reference standard(s)	Cognitive decline over two years of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir
Starting date	2011
Contact information	Bernard Belaiguesa, Assistance Publique Hopitaux De Marseille
Notes	

NCT02164643

Trial name or title	Longitudinal Study of Brain Amyloid imaGing in MEMENTO (MEMENTOAmy-Ging)
Target condition and reference standard(s)	Cognitive decline over two years of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir and ^{18}F-flutemetamol
Starting date	2014
Contact information	Genevieve Chene, CIC-EC7 - ISPED - CHU de Bodeaux
Notes	

NCT02330510

Trial name or title	Amyloid and Glucose PET Imaging in Alzheimer and Vascular Cognitive Impairment Patients With Significant White Matter Disease (MITNEC C6)
Target condition and reference standard(s)	Cognitive decline over two years of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir
Starting date	2014
Contact information	Maryam Niapour, maryam.niapour@sunnybrook.ca Christopher JM Scott, christopher.scott@sri.utoronto.ca
Notes	

NCT02343757

Trial name or title	Alzheimer's Disease Imaging With PET/MRI - Beta-amyloid
Target condition and reference standard(s)	Assessing the diagnosis of a participant at one year of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetapir
Starting date	2014
Contact information	James O'Donnell, Jamesk.ODonnell@UHhospitals.org
Notes	

NCT02854033

Trial name or title	Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Protocol
Target condition and reference standard(s)	Rate of progression to MCI or dementia due to ADD, reference standard not specified
Index and comparator tests	^{18}F-florbetapir and ^{18}F-florbetaben
Starting date	2016
Contact information	Paul Aisen, Director, Alzheimer's Therapeutic Research Institute, University of Southern California
Notes	

ADD: Alzheimer's disease dementia

MCI: Mild cognitive impairment
PET: Positron emission tomography
PiB: Pittsburgh Compound B

DATA

Presented below are all the data for all of the tests entered into the review.
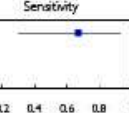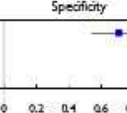
Tests. Data tables by test

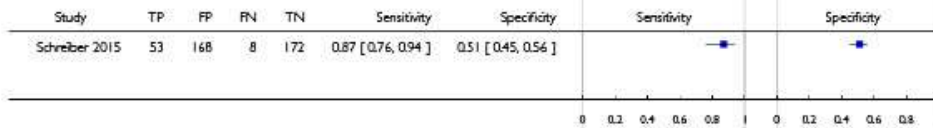| Test	No. of studies	No. of participants
1 MCI to ADD by visual assessment from 2 to less than 4 years of follow-up	1	47
2 MCI to ADD by visual assessment from 1 to less than 2 years follow-up	1	401
3 MCI to ADD by SUVR at 1 to less than 2 years follow-up	1	401
4 MCI to any form of dementia	1	5

Test 1. MCI to ADD by visual assessment from 2 to less than 4 years of follow-up.

Review: 18F PET with florbetapir for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)
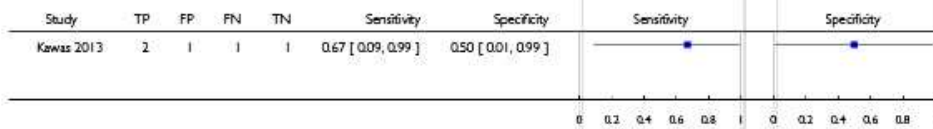
Test: 1 MCI to ADD by visual assessment from 2 to less than 4 years of follow-up

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Doraiswamy 2014	6	11	3	27	0.67 [0.30, 0.93]	0.71 [0.54, 0.85]		

Test 2. MCI to ADD by visual assessment from 1 to less than 2 years follow-up.

Review: 18F PET with florbetapir for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 2 MCI to ADD by visual assessment from 1 to less than 2 years follow-up
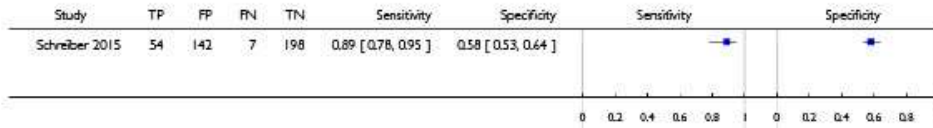
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Schreiber 2015	54	142	7	198	0.89 [0.78, 0.95]	0.58 [0.53, 0.64]		

0 0.2 0.4 0.6 0.8 1   0 0.2 0.4 0.6 0.8 1

Test 3. MCI to ADD by SUVR at 1 to less than 2 years follow-up.

Review: 18F PET with florbetapir for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 3 MCI to ADD by SUVR at 1 to less than 2 years follow-up

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Schreiber 2015	53	168	8	172	0.87 [0.76, 0.94]	0.51 [0.45, 0.56]		

0 0.2 0.4 0.6 0.8 1   0 0.2 0.4 0.6 0.8 1

Test 4. MCI to any form of dementia.

Review: 18F PET with florbetapir for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 4 MCI to any form of dementia

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Kawas 2013	2	1	1	1	0.67 [0.09, 0.99]	0.50 [0.01, 0.99]		

0 0.2 0.4 0.6 0.8 1   0 0.2 0.4 0.6 0.8 1

50

APPENDICES

Appendix I. Glossary

Aetiology: the cause, set of causes, or manner of causation of a disease or condition.

Amyloid beta (Aβ): an amyloid that is derived from a larger precursor protein and is the primary component of plaques characteristic of Alzheimer's disease.

Biomarker: measurable and quantifiable biological parameters (e.g., specific enzyme concentration, specific hormone concentration, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis; metabolic processes; etc.

Bolus: a single dose of a drug or other medicinal preparation given all at once.

Cingulate cortex: one of the convolutions on the medial surface of the cerebral hemispheres.

Cortical: the thin layer of grey matter on the surface of the cerebral hemispheres. It reaches its highest development in humans and is responsible for intellectual faculties and higher mental functions.

Epiphenomenon: A secondary effect or by-product. A secondary symptom or pathology, occurring simultaneously with a disease or condition but not directly related to it.

Frontotemporal: relating to the frontal and the temporal cerebral lobes.

Histopathology: the study of changes in tissues caused by disease.

Hypothyroidism: a syndrome that results from abnormally low secretion of thyroid hormones from the thyroid gland.

Index test: the test under evaluation.

In vivo: (of processes) performed or taking place in a living organism.

Ligand: a molecule that binds to another molecule, used especially to refer to a small molecule that binds specifically to a larger molecule, e.g., an antigen binding to an antibody, a hormone or neurotransmitter binding to a receptor, or a substrate or allosteric effector binding to an enzyme.

Neuritic plaques: accumulations of extracellularly deposited amyloid fibrils within tissues. Is one of the hallmarks of Alzheimer's disease.

Neurofibrillary tangles: abnormal structures located in various parts of the brain and composed of dense arrays of paired helical filaments (neurofilaments and microtubules). Are aggregates of hyperphosphorylated tau protein that are most commonly known as a primary marker of Alzheimer's disease.

Parietal lobe: upper central part of the cerebral hemisphere. It is located anterior to the occipital lobe, and superior to the temporal lobes.

Positron: an extremely small piece of matter with a positive electrical charge, having the same mass as an electron.

Precuneus: is a part of the parietal lobe of the brain, lying on the medial surface of the cerebral hemisphere.

Prodromal: relating to prodrome; indicating an early stage of a disease.

Radionuclide (sometimes called a radioisotope or isotope): is a chemical which emits a type of radioactivity called gamma rays. The radioactivity can be detected by special scanners.

Reference standard: the best available method for establishing the presence or absence of the target condition.

Sensitivity: a measure of a test's ability to correctly detect people with the disease. It is the proportion of diseased cases that are correctly identified by the test. It is calculated as follows: Sensitivity = Number with disease who have a positive test/Number with disease.

Specificity: a measure of a test's ability to correctly identify people who do not have the disease. It is the proportion of people without the target disease who are correctly identified by the test. It is calculated as follows: Specificity = Number without disease who have a negative test/Number without disease.

Stilbene: organic compounds that contain 1,2-diphenylethylene as a functional group.

Target condition: the disease or condition that the index test is expected to detect.

Temporal lobe: lower lateral part of the cerebral hemisphere responsible for auditory, olfactory, and semantic processing. It is located inferior to the lateral fissure and anterior to the occipital lobe.

Vascular: relating to, affecting, or consisting of a vessel or vessels, especially those which carry blood.

Appendix 2. Search strategy for ^{18}F-florbetapir Aβ scan

Source	Search strategy
MEDLINE In-process and other non-indexed citations and Medline® 1946 to May 2017(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. 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
Embase 1974 to May 2017 (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

(Continued)

PsycINFO 1806 to May 2017 (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
BIOSIS Citation Index (Thomson Reuters Web of Science) (1922 to May 2017)	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
Web of Science Core Collection, including the Science Citation Index and the Conference Proceedings Citation Index (Thomson Reuters Web of Science) (1946 to May 2017)	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
LILACS (BIREME)	Florbetapir OR AMYViD OR amyvid* OR "florbetapir-fluorine-18" OR "18F-AV-45" OR "[18F]Florbetapir" OR "florbetapir-PET" [Words]
CINAHL (EBSCOhost) (1980 to May 2017)	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
ClinicalTrials.gov (www.clinicaltrials.gov)	Florbetapir OR AMYViD OR amyvid* OR "florbetapir-fluorine-18" OR "18F-AV-45" OR "[18F]Florbetapir" OR "florbetapir-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"
ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialized register of dementia studies (http://www.medicine.ox.ac.uk/alois/).	Imaging AND PET

Appendix 3. 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-florbetapir PET ligand for Aβ (+) who progress to ADD (TP)	^{18}F-florbetapir PET ligand for Aβ (+) who remain MCI (FP) and ^{18}F-florbetapir PET ligand Aβ (+) who progress to non-ADD (FP)
Index test-negative	^{18}F-florbetapir PET ligand for Aβ (-) who progress to ADD (FN)	^{18}F-florbetapir PET ligand for Aβ (-) who remain MCI (TN) and ^{18}F-florbetapir PET ligand for Aβ (-) who progress to non-ADD (TN)

ADD: Alzheimer's disease dementia

FN: False negative
FP: False positive
MCI: Mild cognitive impairment
PET: Positron emission tomography

TN: True negative
TP: True positive

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

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

ADD: Alzheimer's disease dementia

FN: False negative
FP: False positive
MCI: Mild cognitive impairment
PET: Positron emission tomography

TN: True negative
TP: True positive

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-florbetapir PET ligand for Aβ (+) who progress to any form of dementia (TP)	^{18}F-florbetapir PET ligand for Aβ (+) who remain MCI (FP)
Index test-negative	^{18}F-florbetapir PET ligand for Aβ (-) who progress to any form of dementia (FN)	^{18}F-florbetapir PET ligand for Aβ (-) who remain MCI (TN)

FN: False negative

FP: False positive

MCI: Mild cognitive impairment

PET: Positron emission tomography

TN: True negative

TP: True positive

Appendix 4. 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 participants (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 patient 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
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	Did all patients receive a reference standard?

	Did the study avoid inappropriate exclusions?		test?	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 participants did 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 5. Anchoring statements for quality assessment of ¹⁸F-florbetapir Aβ scan 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	¹⁸F-florbetapir PET ligand for Aβ biomarker	¹⁸F-florbetapir PET ligand for Aβ biomarker
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 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)

ADD: Alzheimer's disease dementia

DSM: Diagnostic and Statistical Manual of Mental Disorders

FTD: Frontotemporal dementia

ICD: International Classification of Diseases

MCI: Mild cognitive impairment

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences

PET: Positron emission tomography

Anchoring statements for quality assessment ^{18}F-florbetapir PET ligand 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-florbetapir PET ligand for Aβ biomarker 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 contacted the relevant study teams for additional information. Whenever we scored one question as high risk of bias, we considered the study as 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 automatically graded the study as unclear if the study authors did not detail exclusions (pending contact with study authors) Where a study details exclusions, we graded the study as 'low risk' if we considered exclusions to be appropriate. Certain exclusions common to many studies of dementia are: medical instability; terminal disease; alcohol/substance misuse; concomitant psy-

		chiatric diagnosis; other neurodegenerative conditions
		Exclusions are not appropriate if they comprise 'difficult to diagnose' patients
		We labelled post-hoc and inappropriate exclusions as at 'high risk' of bias

Index test

Was the ^{18}F-florbetapir PET ligand for Aβ 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 the 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 the reference standard should not influence the 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
Was the ^{18}F-florbetapir PET ligand for Aβ biomarker's threshold 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 the threshold, clinical cut-off, or dichotomisation point. A study is classified at 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
Was the ^{18}F-florbetapir PET ligand for Aβ 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 scored this item as 'yes' If no definition of trained reader was done, we scored this item as 'unclear'

		If a nontrained reader physician performed the scan interpretation, we scored this item as 'no'
Did the study provide a clear definition of what was considered to be a ^{18}F-florbetapir PET ligand for Aβ biomarker's positive result?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	If the study clearly stated the definition of a positive result (e.g. SUV), we scored this item as 'yes' If the study did not give a definition of what it considered a positive result or the definition of a positive result varied between the participants, we scored this item as 'no' If the study gave insufficient information to permit judgement, we scored 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 included those detailed in DSM-IV and ICD-10. Criteria specific to dementia subtypes included but were 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 were not familiar to the review authors or the Cochrane Dementia and Cognitive Improvement group ('unclear'), we classified this item as 'high risk of bias'
Were clinical assessments for dementia performed without knowledge of the ^{18}F-florbetapir PET ligand for Aβ 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' were sufficient and full details of the blinding procedure were not required. Interpretation of the results of the reference standard may be influenced by knowledge of the results of the index test

Patient flow

Was there an appropriate interval between ^{18}F-florbetapir PET ligand for Aβ 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 ^{18}F-florbetapir PET ligand for Aβ biomarker for MCI progression to dementia, there will always be a delay between the index test and

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

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(Continued)

		the reference standard assessments. The time between the reference standard and the index test will influence the accuracy (Geslani 2005; Okello 2007; Visser 2006), and therefore we noted 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 was scored 'no'
Did all subjects get the same assessment for dementia regardless ^{18}F-florbetapir PET ligand for Aβ biomarker?	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 the 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-florbetapir PET ligand for Aβ 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 dropouts differ systematically from those who remain, then estimates of test performance may differ. If there are dropouts, these should be accounted for; a maximum proportion of dropouts for a study to remain at low risk of bias has been specified as 20%
Were missing ^{18}F-florbetapir PET ligand for Aβ 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 did not report these results, we scored this as 'unclear' and we contacted the study authors
Was the study with ^{18}F-florbetapir PET ligand for Aβ 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' 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

(Continued)

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; pretesting; 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 ^{18}F-florbetapir PET ligand for Aβ 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-florbetapir PET ligand for Aβ 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 'Risk of bias' assessments will already have assessed the dementia diagnosis. For certain reviews, an applicability statement relating to the 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

FTD: Frontotemporal dementia

ICD: International Classification of Diseases

MCI: Mild cognitive impairment

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences

PET: Positron emission tomography

CONTRIBUTIONS OF AUTHORS

- Gabriel Martínez, Robin WM Vernooij, and Paulina Fuentes Padilla: contributed to the conception, design, and draft of the protocol; overall responsibility of study selection; data extraction; contact of the authors; draft of discussion; and authors' conclusion sections.

- Leon Flicker: contributed to the conception, and designed and reviewed the draft protocol and final manuscript.

- Xavier Bonfill Cosp: reviewed the draft protocol and final manuscript.

- Javier Zamora: designed and drafted the protocol, performed statistical analyses, updated the statistical methods section and final manuscript.

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

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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.

Xavier Bonfill Cosp has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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5.2. Resultados de la segunda publicación

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

Gabriel Martínez, Robin WM Vernooij, Paulina Fuentes Padilla, Javier Zamora, Leon Flicker, Xavier Bonfill Cosp

5.2.1. Resultado de las búsquedas

Las diferentes estrategias de búsqueda empleadas identificaron un total 1382 referencias.

Al final del proceso de revisión, se incluyó una referencia con un total de 45 participantes con deterioro cognitivo leve e identificamos cinco referencias como estudios en curso, que serán incluidas en las siguientes actualizaciones de la revisión.

5.2.2. Características del estudio incluido

Selección de participantes y características:

Respecto de la selección y características de los participantes, el número de participantes fue de 45 personas en total, derivados de clínicas de memoria locales en Australia. No se informaron más detalles sobre el muestreo y el reclutamiento de pacientes. El estudio tuvo un seguimiento de cuatro años de duración.

Se informaron sólo los datos demográficos de los participantes con DCL y con una clasificación de positividad por la evaluación cuantitativa (SUVR), en donde 24 participantes fueron catalogados como positivos para amiloide cerebral y 21 como negativos para amiloide cerebral a través del 18F-Florbetaben.

No se describe el porcentaje de mujeres en el estudio, la media de edad para aquellos considerados como 18F-Florbetaben (+) fue de 73,5 años (DS 6,9) y un promedio de educación de 13,8 (SD 4,2) años y para aquellos considerados como 18F-Florbetaben (-), el promedio de edad fue de 71,8 años (DS 6,1) y el promedio de educación fue de 13,5 (SD 3,0) años.

Prueba índice: TEP con 18F-Florbetaben

Se inyectó 18F-Florbetaben por vía intravenosa durante 38 ± 17 segundos. Cada participante recibió en promedio 286 ± 19 MBq de 18F-Florbetaben.

Se analizaron las imágenes obtenidas entre 90 y 110 minutos después de la inyección.

Las imágenes de la TEP con 18F-Florbetaben fueron evaluadas por cinco médicos nucleares, cegados a los datos clínicos de los participantes. Los evaluadores tenían una experiencia previa limitada o nula para la interpretación visual de la TEP amiloide y fueron capacitados con una herramienta electrónica de formación.

Se utilizó el sistema de puntuación de la captación regional cortical del trazador (RCTU) para evaluar el depósito de beta-amiloide en las siguientes regiones cerebrales: corteza frontal, cingulado / precuneo posterior, corteza temporal y corteza parietal. Se asignó un valor de 1, 2 o 3 de acuerdo a la captación observada, desde una observación sin absorción del marcador, hasta una absorción de marcador pronunciada.

El enfoque de lectura mayoritaria entre los cinco evaluadores estableció el resultado final.

La carga cuantitativa de Aβ neocortical se expresó como la SUVR promedio de la media ponderada por área para las siguientes regiones de interés: frontal (que consiste en regiones dorsolateral prefrontal, ventrolateral prefrontal y orbitofrontal), parietal superior, temporal lateral, occipital lateral y cingulado anterior y posterior. El SUVR preespecificado utilizado fue ≥ 1,45 para considerar la TEP como positiva.

Condición clínica objetivo y estándar de referencia:

Para la condición objetivo, demencia por enfermedad de Alzheimer, se utilizó el estándar de referencia dado por los criterios NINCDS-ADRDA (McKhann 1984). Para los otros tipos de demencia, se utilizaron como estándar de referencia los siguientes criterios diagnósticos: McKeith 1996 para demencia con cuerpos de Lewy, criterios de Lund para demencia frontotemporal (Neary 1998) y criterios NINDS (Hauw 1994) para PSP.

Flujo y tiempo:

El seguimiento de los 45 participantes incluidos en el estudio fue de cuatro años en total. El seguimiento fue logrado en los 45 participantes (100%).

Se evaluó la positividad visualmente para amiloide con el 18F-Florbetaben, donde 25 (56%) participantes resultaron positivos y 20 (44%) participantes negativos para carga amiloidea cerebral.

Cuando se usó la evaluación cuantitativa, 24 (53%) participantes resultaron positivos para amiloide con el 18F-Florbetaben y 21 (47%) participantes fueron considerados negativos para carga amiloidea cerebral.

5.2.3 Evaluación de calidad metodológica del estudio incluido

Se realizó una evaluación de la calidad metodológica al estudio incluido, a través del instrumento QUADAS-II (Whiting2011), donde se encontró lo siguiente:

Selección de participantes

Se consideró que el estudio incluido tenía un riesgo poco claro de sesgo, ya que, adolece de falta de información sobre los procedimientos de muestreo ni tampoco es posible determinar si existieron exclusiones inapropiadas de participantes.

Prueba índice

En el dominio de prueba del índice, consideramos que el estudio tenía un bajo riesgo de sesgo porque el umbral positivo utilizado en la evaluación visual y cuantitativa estaba preespecificado (Ong 2015). Además, los resultados de la prueba índice se interpretaron sin conocer los resultados del estándar de referencia. En nuestras dos preguntas de alerta adicionales, el riesgo relacionado con la prueba de índice fue considerado bajo.

Estándar de referencia

Si bien, los estándares de referencia se establecieron claramente (McKhann 1984; McKeith 1996; Neary 1998; Hauw 1994), se consideró que el estudio tenía un alto riesgo de sesgo porque se informó que el neurólogo tenía acceso a todos los resultados del estudio y a los registros médicos personales para hacer el diagnóstico (Ong 2015).

Flujo y el tiempo

Se consideró que el estudio incluido tenía un alto riesgo de sesgo, ya que, en nuestra pregunta de alerta adicional se detectaron posibles conflictos de interés debido al apoyo financiero para

el estudio y, además, tres autores eran empleados del fabricante original del trazador y tres autores eran empleados del actual fabricante del trazador.

Aplicabilidad

Para la evaluación de la aplicabilidad, no hubo preocupación de que los pacientes incluidos, el entorno, y la realización e interpretación de la prueba de índice no coincidieran con la pregunta de revisión. Sin embargo, la condición objetivo (como se define en el estándar de referencia) fue motivo de gran preocupación debido al hecho de que el diagnóstico se realizó con pleno acceso a los resultados del estudio y los registros médicos a los cuatro años.

5.2.4. Exactitud diagnóstica del estudio incluido

Al final del seguimiento de 4 años, 21 (47%) participantes presentaron una DEA, 5 (11%) participantes presentaron una demencia no-DEA y finalmente, 26 participantes (58%) presentaron cualquier forma de demencia.

Progresión desde un DCL a una DEA

La progresión tuvo una sensibilidad de 100% (IC 95%: 84 a 100) y una especificidad de 83% (IC 95%: 63 a 95) mediante evaluación visual.

La progresión tuvo una sensibilidad de 100% (IC 95%: 84 a 100) y una especificidad de 88% (IC 95%: 68 a 97) mediante evaluación cuantitativa.

Progresión desde un DCL a una demencia no-DEA

La progresión tuvo una sensibilidad de 0% (IC 95%: 0 a 52) y una especificidad de 38% (IC 95%: 23 a 54) mediante evaluación visual.

La progresión tuvo una sensibilidad de 0% (IC 95%: 0 a 52) y una especificidad de 40% (IC 95%: 25 a 57) mediante la evaluación cuantitativa.

Progresión desde un DCL a cualquier forma de demencia

La progresión tuvo una sensibilidad de 81% (IC 95%: 61 a 93) y una especificidad de 79% (IC 95%: 54 a 94) mediante evaluación visual.

La progresión tuvo una sensibilidad de 81% (IC 95%:61 a 93) y una especificidad de 84% (IC 95%: 64 a 97) mediante evaluación cuantitativa.

5.2.5 Publicación

Cochrane Database of Systematic Reviews

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

Martínez G, Vernooij RWM, Fuentes Padilla P, Zamora J, Flicker L, Bonfill Cosp X

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[Diagnostic Test Accuracy Review]

18F PET with florbetaben 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

[18]F-florbetaben uptake by brain tissue, measured by positron emission tomography (PET), is accepted by regulatory agencies like the Food and Drug Administration (FDA) and the European Medicine Agencies (EMA) for assessing amyloid load in people with dementia. Its added value is mainly demonstrated by excluding Alzheimer's pathology in an established dementia diagnosis. However, the National Institute on Aging and Alzheimer's Association (NIA-AA) revised the diagnostic criteria for Alzheimer's disease and confidence in the diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease may be increased when using some amyloid biomarkers tests like ^{18}F-florbetaben. These tests, added to the MCI core clinical criteria, might increase the diagnostic test accuracy (DTA) of a testing strategy. However, the DTA of ^{18}F-florbetaben to predict the progression from MCI to Alzheimer's disease dementia (ADD) or other dementias has not yet been systematically evaluated.

Objectives

To determine the DTA of the ^{18}F-florbetaben PET scan for detecting people with MCI at time of performing the test who will clinically progress to ADD, other forms of dementia (non-ADD), or any form of dementia at follow-up.

Search methods

The most recent search for this review was performed in May 2017. We searched MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), BIOSIS Citation Index (Thomson Reuters Web of Science), Web of Science Core Collection, including the Science Citation Index (Thomson Reuters Web of Science) and the Conference Proceedings Citation Index (Thomson Reuters Web of Science), LILACS (BIREME), CINAHL (EBSCOhost), 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 also searched ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialised register of dementia studies (http://www.medicine.ox.ac.uk/alois/). We checked

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

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the reference lists of any relevant studies and systematic reviews, and performed citation tracking using the Science Citation Index to identify any additional relevant studies. No language or date restrictions were applied to electronic searches.

Selection criteria

We included studies that had prospectively defined cohorts with any accepted definition of MCI at time of performing the test and the use of ^{18}F-florbetaben scan to evaluate the DTA of the progression from MCI to ADD or other forms of dementia. In addition, we only selected studies that applied a reference standard for Alzheimer's dementia diagnosis, for example, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria.

Data collection and analysis

We screened all titles and abstracts identified in electronic-database searches. Two review authors independently selected studies for inclusion and extracted data to create two-by-two tables, showing the binary test results cross-classified with the binary reference standard. We used these data to calculate sensitivities, specificities, and their 95% confidence intervals. Two independent assessors performed quality assessment using the QUADAS-2 tool plus some additional items to assess the methodological quality of the included studies.

Main results

Progression from MCI to ADD, any other form of dementia, and any form of dementia was evaluated in one study (Ong 2015). It reported data on 45 participants at four years of follow-up; 21 participants met NINCDS-ADRDA criteria for Alzheimer's disease dementia at four years of follow-up, the proportion converting to ADD was 47% of the 45 participants, and 11% of the 45 participants met criteria for other types of dementias (three cases of FrontoTemporal Dementia (FTD), one of Dementia with Lewy body (DLB), and one of Progressive Supranuclear Palsy (PSP)). We considered the study to be at high risk of bias in the domains of the reference standard, flow, and timing (QUADAS-2).

MCI to ADD; ^{18}F-florbetaben PET scan analysed visually: the sensitivity was 100% (95% confidence interval (CI) 84% to 100%) and the specificity was 83% (95% CI 63% to 98%) (n = 45, 1 study). Analysed quantitatively: the sensitivity was 100% (95% CI 84% to 100%) and the specificity was 88% (95% CI 68% to 97%) for the diagnosis of ADD at follow-up (n = 45, 1 study).

MCI to any other form of dementia (non-ADD); ^{18}F-florbetaben PET scan analysed visually: the sensitivity was 0% (95% CI 0% to 52%) and the specificity was 38% (95% CI 23% to 54%) (n = 45, 1 study). Analysed quantitatively: the sensitivity was 0% (95% CI 0% to 52%) and the specificity was 40% (95% CI 25% to 57%) for the diagnosis of any other form of dementia at follow-up (n = 45, 1 study).

MCI to any form of dementia; ^{18}F-florbetaben PET scan analysed visually: the sensitivity was 81% (95% CI 61% to 93%) and the specificity was 79% (95% CI 54% to 94%) (n = 45, 1 study). Analysed quantitatively: the sensitivity was 81% (95% CI 61% to 93%) and the specificity was 84% (95% CI 60% to 97%) for the diagnosis of any form of dementia at follow-up (n = 45, 1 study).

Authors' conclusions

Although we were able to calculate one estimation of DTA in, especially, the prediction of progression from MCI to ADD at four years follow-up, the small number of participants implies imprecision of sensitivity and specificity estimates. We cannot make any recommendation regarding the routine use of ^{18}F-florbetaben in clinical practice based on one single study with 45 participants. ^{18}F-florbetaben has high financial costs, therefore, clearly demonstrating its DTA and standardising the process of the ^{18}F-florbetaben modality are important prior to its wider use.

PLAIN LANGUAGE SUMMARY

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

Review question: In people with mild cognitive impairment (MCI), does using a ^{18}F PET scan with florbetaben predict progression to Alzheimer's disease dementia (ADD) and other dementias?

Background

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

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Due to global ageing, the number of people with dementia is expected to increase dramatically in the next few decades. Diagnosing dementia at an early stage is desirable, but there is no widespread agreement on the best approach. A range of simple pen and paper tests used by healthcare professionals can assess people with poor memory or cognitive impairment. Whether or not using special PET scans that detect amyloid -one of the hallmarks of Alzheimer's disease- improves our ability to predict the progression from MCI to ADD or other forms of dementia remains unclear. Since these tests are expensive, it is important that they provide additional benefits.

Aim

We aimed to evaluate the accuracy of the ^{18}F-florbetaben PET scan in identifying those people with MCI who clinically progress to ADD, other types of dementia, or any form of dementia over a period of time.

Study characteristics

The evidence is current to May 2017. We found 1 study including 45 participants with MCI with a follow-up of 4 years; gender was not reported and the median age for those with a PET-positive scan by quantitative assessment was 73.5 years old. For those with a PET-negative scan the mean age was 71.8 years old. Participants were mainly recruited from local memory clinics.

Study funding sources: the study was funded by the test manufacturer.

Quality of the evidence

The main limitation of this review was that our findings were based on only one study, with not enough details on how the participants were selected. The study was considered to be at high risk of bias, since the final ADD diagnosis was not established separately from the scan results, and due to potential conflicts of interest detected.

Key findings

In this review, based on only one study, we found that the ^{18}F-florbetaben PET scan, as a single test with visual assessment, correctly classified 100% of the participants who will progress to ADD and 83% of the participants who did not progress to ADD at four years follow-up. This means that in a cohort with 100 participants with MCI, 47 of whom will progress to ADD, we would expect that all those 47 MCI participants would test positive with the ^{18}F-florbetaben scan and that 0 participants would be falsely negative (i.e. none of the 47 participants would have a negative test and yet progress to ADD). In addition, we would expect 44 of 53 participants who did not progress to ADD to be ^{18}F-florbetaben-negative and 9 to be falsely positive (i.e. 9 of the 53 participants would have a positive test but not progress to ADD).

The small size of the included study lowered our confidence on these estimates of accuracy and it is still possible that the test is considerably less accurate than these results suggest.

We conclude that ^{18}F-florbetaben imaging is a promising test to predict the progression from MCI to ADD; however, we need more studies to clearly demonstrate its accuracy.

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. See the glossary in Appendix 1. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by a deterioration in emotional control, social behaviour, and motivation, and the impairment is sufficient to interfere with everyday activities.

Dementia is a collection of different subtypes distinguished by the underlying pathology. 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 number of 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 Revised Criteria (Petersen 1999; Petersen 2004; Winblad 2004), Clinical Dementia Rating (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 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 ($A\beta$) and neurofibrillary tangles (Goedert 2006). This pathology is present in approximately 84% of all people with dementia (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). On the other hand, this controversy could be because our clinical diagnostic criteria have not had enough accuracy to diagnose Alzheimer's disease that is detected by histopathology in postmortem studies (Hyman 2012). In addition, other researchers think that there is not a real controversy about the amyloid hypothesis, because the amyloid cascade and the $A\beta$ deposition have a primary role in Alzheimer's disease (Selkoe 2016).

More recently, the development of $A\beta$ 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 $A\beta$ 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 an important initiative, 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 $A\beta$ ligands permits the in vivo detection of amyloid deposition in the brain. ^{18}F-florbetaben is a stilbene derivative, which was first described 12 years ago, and is characterised by a high affinity for $A\beta$. ^{18}F-florbetaben has excellent uptake by brain tissue and washout kinetics in mice (Zhang 2005). ^{18}F-florbetaben was evaluated in people with ADD, healthy people without ADD (Barthel 2011), and people with other dementias (Villemagne 2011).

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved ^{18}F-florbetaben for $A\beta$ binding. 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-florbetaben scan indicates moderate to frequent presence of neuritic amyloid plaques. However, this might also occur in people with other neurological conditions and in older adults with normal cognition. Therefore, it should be combined with other diagnostic evaluations or instruments and cannot be used solely to assess the risk of progression to ADD. Therefore, a positive result of an ^{18}F-florbetaben 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 effective-

ness 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 2014; FDA 2014).

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-florbetaben for Aβ, increase the risk of developing dementia over time. The evidence for this is uncertain. For this and other reasons, the 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).

An assumption for some researchers, and one on which this systematic review (SR) is predicated, is 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 families, and clinicians involved in their care.

[18]F-florbetaben PET scan is considered the diagnostic marker of interest, and in this SR we assessed the DTA of ^{18}F-florbetaben 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

This SR belongs to a series of SRs regarding PET biomarkers for Aβ, including ^{18}F-florbetapir and ^{18}F-flutemetamol (Martínez 2016).

Target condition being diagnosed

This SR assessed 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 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 ^{18}F-florbetaben scan is an index test 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-florbetaben is a molecular biomarker, described as
[^{18}F]BAY   94-9172, trans-4-(N-methyl-amino)-4'-2-[2-(2-^{18}F]fluoro-ethoxy)-ethoxy]-ethoxy-stilbene and also referred to as BAY 94-9172 or ZK 6013443, which is a polyethylene glycol stilbene derivative (Zhang 2005).

Image Interpretation

Both the FDA and EMA have described the criteria for ^{18}F-florbetaben Aβ positivity (EMA 2014; FDA 2014).
[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 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.

Readers trained in PET images with the ^{18}F-florbetaben should interpret the Aβ PET images made with this ligand (EMA 2014; FDA 2014).
Before the FDA and EMA described the criteria for ^{18}F-florbetaben scan positivity, the diagnosis of dementia was made using different thresholds. Therefore, we planned 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 ^{18}F-florbetaben Aβ uptake and retention exceeded a certain threshold. We considered the measurement of the ^{18}F-florbetaben retention (retention ratio): distribution volume ratio (DVR), standardised

uptake value ratio (SUVR), or other ratios. DVR refers to the ratio of the ^{18}F-florbetaben distribution volume in the selected area (ROI) to the distribution volume in the reference area. SUVR is the ratio of the ^{18}F-florbetaben ligand standardised uptake value in the selected area (ROI) to the standardised uptake value in the reference area.

The unit of analysis of our SR was the participant. We did not include studies that analysed multiple ROIs per person.

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

Administration Instructions and Recommended Dosing

- Time between ^{18}F-florbetaben injection and PET acquisition: images should be acquired in 15 to 20 minutes starting from 45 to 130 minutes after intravenous administration (FDA 2014) or acquired in 20 minutes starting from 90 minutes after intravenous administration (EMA 2014);

- Injection dose: the recommended dose for ^{18}F-florbetaben Aβ PET is 300 MBq (8.1 mCi), maximum 30 mcg mass dose (FDA 2014) or 300 MBq (240 to 360 MBq) as a single slow intravenous bolus (6 sec/mL) in a total volume of up to 10 mL (EMA 2014).

Although it was inevitable that included studies had 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 performance of the diagnostic tests will probably vary according to whether it is a primary consultation or referral 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-

florbetaben PET ligand for Aβ is 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 aetiology (e.g. FTD versus ADD). Otherwise, it might be used solely in the research field in people with MCI for the enrichment of clinical trials, for example, enrolling people with MCI and a positive PET scan to study preventive interventions before people develop dementia.

However, in some memory clinics the ^{18}F-florbetaben PET is used for clinical purposes in people with persistent or progressive unexplained MCI adopting the Johnson criteria (Johnson 2013), criteria without sufficient evidence. Therefore, if the ^{18}F-florbetaben PET is positive in a person with MCI, this positivity is considered as one of the core histopathological findings of Alzheimer's disease. The person will thus be catalogued as a patient with prodromal Alzheimer's disease or MCI due to Alzheimer's disease.

Alternative test(s)

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

- [18]F PET ligands for Aβ (^{18}F-florbetapir, ^{18}F-flutemetamol) (Martínez 2016).

- ^{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

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

[18]F-florbetaben is 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-florbetaben is not approved for this purpose, this biomarker test is currently being used in the research field to search for the accurate identification of people with MCI who would progress to ADD 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 the generalisability of the DTA results 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.

This SR assesses the DTA with ^{18}F-florbetaben $A\beta$ PET in people with MCI.

OBJECTIVES

To determine the diagnostic test accuracy (DTA) of ^{18}F-florbetaben as the index test for detecting people with mild cognitive impairment (MCI) at time of performing the test 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, by evaluating the spectrum of people, referral centres, clinical criteria of MCI, ^{18}F-florbetaben 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 included longitudinal studies that had prospectively defined cohorts with any accepted definition of mild cognitive impairment (MCI), as outlined below, at time of performing the ^{18}F-florbetaben $A\beta$ scan and a reference standard (see Index tests and Reference standards below). We obtained the results at the follow-up of the studies. These studies had to employ delayed verification of progression to dementia and were sometimes labelled as 'delayed verification cross-sectional studies' (Bossuyt 2008; Knottnerus 2002). We included case-control studies when they incorporate a delayed verification design. This occurred in the context of a cohort study, so these studies were invariably diagnostic-nested case-control studies.

Participants

Participants recruited and clinically classified as having MCI at time of performing the test were eligible for inclusion. We established the diagnosis of MCI using the Petersen criteria or revised Petersen criteria (Petersen 1999; Petersen 2004; Winblad 2004), the criteria included in Matthews study (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 excluded 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). Regarding Parkinson's disease, many of the studies specifically excluded people with Parkinson's disease from the group with mild cognitive impairment. This specific group of people is complex in both regards to defining neuropathology and in determination of functional decline. For these reasons, this group of people needs to be addressed in specific studies.

Index tests

The index test of this SR was ^{18}F-florbetaben biomarker test. We used the criteria and cut-off values for test positivity, as reported in the included studies. We considered positivity for ^{18}F-florbetaben $A\beta$ scan uptake and retention exceeding a certain threshold.

Target conditions

Three target conditions were included in this SR:

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- 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 was 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 this SR, we accepted several definitions of ADD. We included 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 considered all these issues when we interpreted the results.

Similarly, we accepted differing clinical definitions of other dementias. For Lewy body dementia, the reference standard is the McKeith criteria (McKeith 1996; McKeith 2005); for frontotemporal 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); 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); and, for progressive supranuclear palsy (PSP), the preliminary NINDS criteria (Hauw 1994).

The time interval over which the progression from MCI to ADD (or other forms of dementia) occurs is very important. We used 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 searched MEDLINE (Ovid SP) from 1946 to May 2017; Embase (Ovid SP) from 1974 to May 2017; PsycINFO (Ovid SP) from 1806 to May 2017; BIOSIS Citation Index (Thomson Reuters Web of Science) from 1922 to May 2017; Web of Science Core Collection, including the Science Citation Index (Thomson Reuters Web of Science) and the Conference Proceedings Citation Index (Thomson Reuters Web of Science) from 1946 to May 2017; LILACS (Bireme); CINAHL (EBSCOhost) from 1980 to May 2017; 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 also searched ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialized register of dementia studies (http://www.medicine.ox.ac.uk/alois/).

We used two approaches in designing the search. One focused solely on the specifically named index test (including a range of synonyms) and the second, run in parallel covered a more general search, linking broader terms for the index test. It focused on terms describing its diagnostic use and terms for the target condition to try to capture the more difficult to locate studies of a more general nature, where these particular radioligands were included in diagnostic accuracy research but not named specifically in the parts of the electronic bibliographic record that are searchable and therefore would be missed.

See Appendix 2 for details of the sources and search strategies that we used. No language or date restrictions were applied to the electronic searches.

Searching other resources

We examined the reference lists of all relevant studies for additional studies. We also searched the Database of Abstracts of Reviews of Effects (DARE) via the Cochrane Library (www.cochranelibrary.com), the National Institute for Health Research - Health Technology Assessment Database (NIHR-HTA) (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 checked the reference lists of any relevant studies and SRs, and performed citation tracking using the Science Citation Index to identify any additional relevant studies.

Data collection and analysis

Selection of studies

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Two review authors (GM, RV) independently screened the retrieved titles and abstracts for potentially eligible studies. A third review author (PF) resolved any disagreements between the two review authors. The two review authors (GM, RV) then independently assessed the full-text articles of the selected studies with the inclusion criteria. They resolved any disagreements through discussion or, where necessary, consulted a third review author (PF) who acted as an arbitrator. When a study did not present all relevant data for creating 2 × 2 table, we contacted the study authors directly to request further information. When more than one article presented data on the same population, we included the primary article, which was 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 planned 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-florbetaben 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 the reference standard;
  - duration of follow-up from time of the index test performed to defining ADD and other dementias by the reference standard: one year to less than two years; two years to less than four years; and four years or more. If participants had been followed for varied amounts of time, we recorded a mean follow-up period for each included study. If possible, we grouped those data into minimum, maximum, and median follow-up periods, to enable subgroup analyses;
  - prevalence or proportion of population developing ADD and other dementias, with severity, if described.

We created 2 × 2 tables (cross-relating index test results of the reference standards) as shown in Appendix 3. For the included study, we recorded the number of participants lost to follow-up. We also extracted data necessary for the quality assessment, as defined below. Two review authors (GM, RV) independently performed data extraction. We resolved any disagreements regarding data extraction by discussion, or by consulting a third review author (PF), if it was necessary.

Assessment of methodological quality

We assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2) (Whiting 2011), as recommended by Cochrane (Davis 2013). This tool is comprised of four domains: patient selection, index test, reference standard, and patient flow.

Two review authors (GM, RV), who were blinded to each other's scores, independently performed the QUADAS-2 assessment. We resolved any disagreements by discussion or, if necessary, consulted a third review author (PF) who acted as an arbitrator. We assessed each domain in terms of risk of bias, and also considered the first three domains in terms of applicability concerns. In Appendix 4, we have detailed the components of each of these domains and provided a rubric that shows how we made judgements concerning risk of bias. Key areas important to quality assessment were participant selection, blinding, and missing data.

We included three additional signalling questions on our checklist.

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

We included the item pertaining to the PET scan interpretation and the definition of positive results to take into account the subjective nature of the ^{18}F-florbetaben Aβ scan image interpretation, which may be based on a variety of different criteria, such as extensive clinical experience, different standardised uptake values (SUV), different morphological features, or a combination of the aforementioned. We included the third additional item in order to record any potential bias resulting from commercial interest in the results due to the potential risk by the manufacturing company leading to more favourable results and conclusions than sponsorship by other sources (Lundh 2017).

We did not use QUADAS-2 data to form a summary quality score. We produced a narrative summary that described each included study as at high, low, or unclear risk of bias, as well as concerns regarding applicability, which we have described in Appendix 5.

Statistical analysis and data synthesis

We applied the DTA framework for the analysis of a single test and extracted the data from the study into a 2 x 2 table, showing the binary test results cross-classified with the binary refer-

ence standard. We used data from the 2 x 2 tables abstracted from the included study: true positive (TP), false negative (FN), false positive (FP), true negative (TN), and entered these into Review Manager (RevMan) Review Manager 2014 to calculate the sensitivities, specificities, and their 95% confidence intervals. We also presented the study results graphically by plotting estimates of sensitivities and specificities in a forest plot.

However, due to lack of data, we conducted no meta-analyses. However, we prepared a 'summary of findings table'.

Investigations of heterogeneity

We were able to include only one study, therefore issues of heterogeneity did not arise.

Sensitivity analyses

We found insufficient data to conduct any sensitivity analyses.

Assessment of reporting bias

We did not investigate reporting bias.

RESULTS

Results of the search

The total number of records identified through all databases for this SR was 1382. The PRISMA diagram shows the selection of records through the screening and selection processes (Figure 1). In total, we assessed 79 studies (42 full text papers, 16 conference publications, 9 registered studies in clinicaltrials.gov, and 12 registered in WHO ICTRP) for eligibility in the full-text screening. We included one study (Ong 2015). Additionally, five references were identified as ongoing studies (EUCTR2013-004671-12-BE; EUCTR2014-000562-21-NL; EUCTR2014-004244-35-IT; NCT01222351, NCT02854033). We excluded 73 studies: 19 studies were multiple publications or duplicated, and the remaining 53 studies were excluded as they did not meet the inclusion criteria: i) not a longitudinal study (n = 13); ii) not MCI participants at baseline (n = 14); iii) index test not a ^{18}F-florbetaben PET scan (n = 5); iv) discussion or review paper (n = 19); v) wrong outcome or study design (n = 2). One study did not have data suitable for analysis (Characteristics of excluded studies).

Figure 1. Flow diagram.

2 searches:

TOTAL: 1382 studies

May 2017: 1077 studies

May 2016: 305 studies

79 studies (42 full-text, 16 conference publications, 9 registered in clinicaltrials.gov, and 12 registered in WHO ICTRP)

May 2016: 65

May 2017: 14

1303 discarded after de-duplication and first assessment (based on title and abstract review)

May 2016: 1012

May 2017: 291

Discarded upon reading full text, conference publications and studies registered in clinicaltrials.gov and WHO ICTRP (n=53):

i) not a longitudinal study (n = 13);

ii) not MCI participants at baseline (n= 14);

iii) index test not a ^{18}F-florbetaben PET scan (n = 5);

iv) discussion or review paper (n = 19);

v) wrong outcome or study design (n = 2);

Duplicated or multiple publications (n = 19);

Data not suitable for analysis (Characteristics of excluded studies) (n = 1).

79 references assessed for eligibility

N = 6

1 included study

5 ongoing studies

Included Study

See Characteristics of included studies.

The study of Ong 2015 was conducted in Australia (Ong 2015). This study included older adult participants who were referred from local memory clinics and who met consensus criteria for MCI at baseline, and were recruited as part of a study to evaluate the ¹⁸F-florbetaben PET positivity scan at baseline and progression from MCI to ADD, and compare an SUVR assessment with visually assessed scans in determining a positive or negative scan. The other objective of this study was to examine whether progressive Aβ accumulation was detectable using the ¹⁸F-florbetaben PET scan at follow-up.

Ong 2015 included 45 MCI participants and performed follow-up at two and four years, evaluating progression from MCI to probable ADD. The authors described their ¹⁸F-florbetaben status as positive or negative, using a visual assessment by five readers trained on an electronic training tool and their SUVR > 1.45 as described previously (Ong 2015). We included the data at four years of follow-up, because, according to the methodology, we included the longest time of follow-up in the primary outcome. MCI participants fulfilled the Petersen 2004 and Winblad 2004 criteria for MCI. Participants had to be at least 60 years old and to have had at least seven years of formal schooling. They were also required to communicate fluently in English, to have no contraindications to undergoing an MRI scan, and to have a MMSE of > 23 points. There were 21 participants with ¹⁸F-florbetaben with an SUVR value < 1.45 and 24 participants with a ¹⁸F-florbetaben SUVR value > 1.45; using the visual assessment, there were 20 participants with ¹⁸F-florbetaben negative and 25 participants with ¹⁸F-florbetaben positive. The demographic data provided was based on those classified as positive or negative by SUVR. The age of the participants was 71.8 ± 6.1 and 73.5 ± 6.9 years, years of education 13.5 ± 3.0, and 13.8 ± 4.2, and MMSE was 27.9 ± 1.4 and 26.7 ± 1.9 for those with ¹⁸F-florbetaben < 1.45 or > 1.45, respectively. No demographic data was available for those classified by visual assessment. Of the 45 participants classified with SUVR, at four years follow-up, 21 of 45 participants (46.7%) had developed ADD, and 5 of 45 (11.1%) had developed another form of dementia. Of the 45 participants classified with visual assessment, at four years follow-up, 21 of 45 participants (46.7%) had developed ADD, and 5 of 45 (11.1%) had developed another form of dementia. At four years follow-up, the diagnosis was performed by a neurologist with access to all study results and personal medical records. The reference standard was the NINCDS-ADRDA criteria for ADD (McKhann 1984) and, for other forms of dementia, the reference standards were McKeith 1996 for Lewy body dementia, Lund criteria for frontotemporal dementia Neary 1998, and Hauw 1994 for PSP.

Potential conflicts of interest were noted. Financial support for the study was provided by the previous and current manufacturer of the test; three authors were employees from the previous manufacturer of ¹⁸F-florbetaben tracer and another three authors were employees from the actual manufacturer of ¹⁸F-florbetaben (Ong 2015).

Ongoing studies

Two studies were found as ongoing studies in clinicaltrials.gov. The first study, NCT01222351, included a sub-study of the Washington Heights-Inwood Community Aging Project focused on cognitively normal older adults, older adults with MCI, and older adults with Alzheimer's disease. Participants were selected on the basis of change in plasma amyloid beta levels over prior assessment intervals. The purpose of the study was to examine whether brain amyloid plaque load, which was to be measured with ¹⁸F-florbetaben PET scan, varied as a function of change in plasma levels of amyloid beta and the risk and progression of late onset Alzheimer's disease, MCI, and cognitive decline after three years follow-up. No further details were provided regarding index test and reference standard(s). This study has been recruiting participants since December 2010 in the United States. No expected date of publication was provided in this record. The second study, NCT02854033, was focused on cognitively normal, mild cognitive impairment, and mild ADD participants. The main objective was to determine the relationships among the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics and the evolution of the entire spectrum of ADD and try to identify diagnostic and prognostic markers among others. The clinical follow-up will be five years. No further details were provided regarding the reference standard(s). This study has been recruiting participants since October 2016. No expected date of publication was provided in this record.

Three studies were found as ongoing studies in WHO ICTRP and they belong to the European Union Clinical Trials Register. EUCTR2014-004244-35-IT is a study focused on amnestic MCI participants with long disease duration (range 2 to 10 years) and imaging studies (MRI and/or ¹⁸F-FDG-PET) suggestive of involvement of the limbic/mesial temporal lobe, with the main objective to define the value of the load of amyloid protein. The secondary outcome was the correlation of the amyloid load with neuropsychological measures, the clinical indices, the values of Aβ42, total tau, and phospho-tau and with data from MRI and ¹⁸F-FDG-PET previously acquired for diagnostic purposes and with a clinical follow-up for at least two years in order to assess the possible clinical progression with basal ¹⁸F-florbetaben. No further details were provided regarding the participants, index test, and reference standard(s). This study has been ongoing since March 2015. No expected date of publication was provided in this record.

One additional Dutch ongoing study has been found that focuses on an unselected patient population of subjects visiting the memory clinic of the VUmc Alzheimer Center (EUCTR2014-000562-21-NL). Its main objective was change after ^{18}F-florbetaben in diagnosis, change in level of confidence of diagnosis, and the impact on patient healthcare management, and the secondary outcome in those with MCI was the clinical progression to dementia during annual follow-up (based on follow-up visits to neurologist and neuropsychologist). No further details were provided regarding the participants, index test, and reference standard(s) and the length of follow-up. This study has been ongoing since January 2015. Similarly, no expected date of publication was provided in this record.

One additional Belgian ongoing study has been found that focuses on the predictive value of baseline ^{18}F-florbetaben capture for longitudinal change in amyloid load measured using PET in MCI cases (EUCTR2013-004671-12-BE). A secondary outcome was the comparison of CSF Aß42 and amyloid PET for classification of amyloid-positive and amyloid-negative cases, and the comparison of the predictive value of CSF biomarkers Aß42, T-tau and P-tau181P with that of amyloid imaging for MCI cases that progressed to Alzheimer's disease dementia. No further details were provided regarding the index test, and reference standard(s). This study has been ongoing since June 2014 and no expected date of publication has been provided.

Methodological quality of included studies

We assessed methodological quality using the QUADAS-2 tool (Whiting 2011). Review authors' judgements about each methodological quality item for the included study are presented in the Characteristics of included studies and in Figure 2.

Figure 2.   Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study
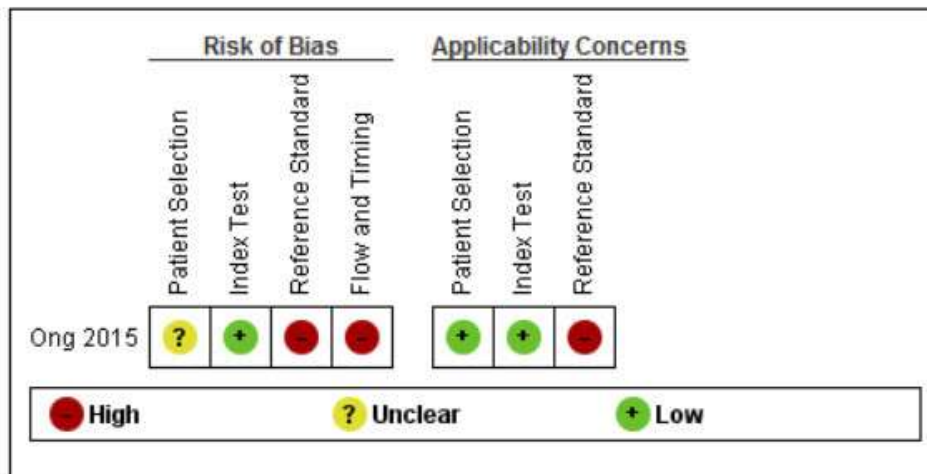
In the patient selection domain, we considered the study of Ong 2015 to be at unclear risk of bias due to lack of reporting on sampling procedures and exclusion criteria (Ong 2015). We stated that the included study avoided a case-control design because we only considered data on performance of the index test to discriminate between people with MCI who converted to dementia and those who remained stable.

In the index test domain, we considered the study of Ong 2015 at low risk of bias because the positive threshold used in both visual and quantitative assessment was prespecified (Ong 2015). Moreover, the index test results were interpreted without knowledge of the results of the reference standard. In our two additional signalling questions, the risk concerning the index test being inter-

preted by a trained reader physician was low, because they were trained on an electronic training tool to do the amyloid PET visual interpretation. The other signalling question was rated as low risk, because there was a clear definition of a positive result.

In the reference standard domain, we considered the study to be at high risk of bias because it was reported that the neurologist had access to all study results and personal medical records to make the diagnosis (Ong 2015). However, the reference standard(s) were clearly established (McKhann 1984, McKeith 1996 Neary 1998; Hauw 1994).

In the flow and timing domain, we judged the study to be at high risk of bias because in our additional signalling question there were potential conflicts of interest due to the financial support for the study and, in addition, three authors were employees of the previous manufacturer of ^{18}F-florbetaben tracer and the other three authors were employees of the actual manufacturer of ^{18}F-florbetaben (Ong 2015). However, the four years of interval between the index test and the reference standard was considered an appropriate interval, all participants received the same reference standard(s), and all 45 participants were accounted for in the analysis.

For assessment of applicability, there was no concern that the included patients and setting, and the conduct and interpretation of the index test, did not match the review question (Ong 2015). However, the target condition (as defined by the reference standard) was of high concern due to the fact that diagnosis was made with full access to study results and medical records at four years follow-up.

Findings

The key characteristics of the study are summarised in Characteristics of included studies. The summary of main results for the only included study is presented in the 'Summary of findings' table (Summary of findings).

Ong 2015 included data on 45 participants with MCI diagnosed with Petersen criteria (Petersen 2004), and Winblad 2004. The study used two different assessments to evaluate the PET: visual assessment PET positive if increased tracer uptake was visible in any of four different cerebral regions (frontal, parietal, temporal, and posterior cingulate/precuneus cortices) and quantitative assessment with a SUVR $\geq$ 1.45 for a positive ^{18}F-florbetaben. At four years follow-up, the diagnosis of ADD was made using NINCDS-ADRDA criteria (McKhann 1984). Lewy Body dementia was made using McKeith 1996 criteria, FTD diagnosis was made using Lund criteria (Neary 1998) and PSP diagnosis was made using (Hauw 1994) criteria.

^{18}F-florbetaben for Alzheimer's disease dementia (ADD)

- **Visual Assessment:** ^{18}F-florbetaben PET scan had a sensitivity of 100% (95% CI 84% to 100%) and a specificity of 83% (95% CI 63% to 95%) to predict the progression from MCI to ADD at four years follow-up. Of 45 participants who were given an initial clinical diagnosis of MCI, 21 were true positive, 4 were false positives, 0 were false negative, and 20 were true negative (Figure 3).

Figure 3. Forest plot of tests: 1 18F-florbetaben visual assessment and progression to ADD, 2 18F-florbetaben SUVR and progression to ADD, 3 18F-florbetaben visual assessment and progression to any other form of non-ADD, 4 18F-florbetaben SUVR and progression to any other form of non-ADD, 5 18F-florbetaben visual assessment and progression to any form of dementia, 6 18F-florbetaben SUVR and progression to any form of dementia.

18F-florbetaben visual assessment and progression to ADD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ong 2015	21	4	0	20	1.00 [0.84, 1.00]	0.83 [0.63, 0.95]

18F-florbetaben SUVR and progression to ADD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ong 2015	21	3	0	21	1.00 [0.84, 1.00]	0.88 [0.68, 0.97]

18F-florbetaben visual assessment and progression to any other form of non-ADD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ong 2015	0	25	5	15	0.00 [0.00, 0.52]	0.38 [0.23, 0.54]

18F-florbetaben SUVR and progression to any other form of non-ADD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ong 2015	0	24	5	16	0.00 [0.00, 0.52]	0.40 [0.25, 0.57]

18F-florbetaben visual assessment and progression to any form of dementia

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ong 2015	21	4	5	15	0.81 [0.61, 0.93]	0.79 [0.54, 0.94]

18F-florbetaben SUVR and progression to any form of dementia

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ong 2015	21	3	5	16	0.81 [0.61, 0.93]	0.84 [0.60, 0.97]

• SUVR: 18F-florbetaben PET scan had a sensitivity of 100% (95% CI 84% to 100%) and a specificity of 88% (95% CI 68% to 97%) to predict the progression from MCI to ADD at four years follow-up. Of 45 participants who were given an initial clinical diagnosis of MCI, 21 were true positive, 3 were false positives, 0 were false negative, and 21 were true negative (Figure 3).

18F-florbetaben for any other form of dementia (non-ADD)

• Visual Assessment: 18F-florbetaben PET scan had a sensitivity of 0.0% (95% CI 0.0% to 52%) and a specificity of 38% (95% CI 23% to 54%) to predict the progression from MCI to any other form of dementia (non-ADD) at four years follow-up. Of 45 participants who were given an initial clinical diagnosis of MCI, 0 were true positive; 25 were false positives, 5 were false negative (3 FTD, 1 Lewy body dementia, and 1 PSP), and 15 were true negative (Figure 3).

• SUVR: 18F-florbetaben PET scan had a sensitivity of 0.0% (95% CI 0.0% to 52%) and a specificity of 40% (95% CI 25% to 57%) to predict the progression from MCI to any other form of dementia (non-ADD) at four years follow-up. Of 45 participants who were given an initial clinical diagnosis of MCI, 0 were true positive, 24 were false positives, 5 were false negative (3 FTD, 1 Lewy body dementia and 1 PSP), and 16 were true negative (Figure 3).

18F-florbetaben for any form of dementia

• Visual Assessment: 18F-florbetaben PET scan had a sensitivity of 81% (95% CI 61% to 93%) and a specificity of 79% (95% CI 54% to 94%) to predict the progression from

MCI to any form of dementia at four years follow-up. Of 45 participants who were given an initial clinical diagnosis of MCI; 21 were true positive, 4 were false positives, 5 were false negative (3 FTD, 1 Lewy body dementia, and 1 PSP) and 15 were true negative (Figure 3).

- SUVR_r ^{18}F-florbetaben PET scan had a sensitivity of 81% (95% CI 61% to 93%) and a specificity of 84% (95% CI 60% to 97%) to predict the progression from MCI to any form of dementia at four years follow-up. Of 45 participants who were

given an initial clinical diagnosis of MCI, 21 were true positive, 3 were false positives, 5 were false negative (3 FTD, 1 Lewy body dementia, and 1 PSP), and 16 were true negative (Figure 3).

Investigation of heterogeneity

We were able to include only one study, therefore, issues of heterogeneity did not arise.

Sensitivity analyses

There were insufficient data to permit any sensitivity analyses.

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Summary of findings

What is the diagnostic accuracy of ^{18}F-florbetaben PET amyloid biomarker for predict progression to ADD or any other form of dementia (non-ADD) or any form of dementia in people with MCI?	
Descriptive	
Patient population	Participants diagnosed with MCI at baseline using any of the Petersen criteria or Winblad criteria or CDR= 0.5 or any 16 definitions included by Matthews (Matthews 2008)
Sources of referral	Memory clinic
MCI criteria	Petersen criteria 2004 and Winblad 2004 (Petersen 2004; Winblad 2004)
Sampling procedure	unclear
Prior testing	The only testing prior performing the ^{18}F-florbetaben PET amyloid biomarker was the application of diagnostic criteria for identifying participants with MCI
Settings	Secondary care
Index test	^{18}F-florbetaben PET
Threshold prespecified at baseline	Yes
Threshold interpretation	Visual and quantitative
Threshold	Visual: if any tracer uptake was visible in any of the frontal, parietal, temporal, and posterior cingulate/ precuneus cortices SUVR (Standardised Uptake Volume ratio) of ROI: > 1.45
^{18}F-florbetaben retention region	Visual: frontal, parietal, temporal, and posterior cingulate/precuneus cortices Global cortex (SUVR) SUVR: Global cortex

Reference Standard	For Alzheimer's disease dementia: NINCDS-ADRDA (McKhann 1984) For Lewy body dementia: McKeith criteria (McKeith 2005) For frontotemporal dementia: Lund criteria (Brun 1994) For progressive supranuclear palsy: Preliminary NINDS criteria (Hauw 1994)
Target condition	Progression from MCI to Alzheimer's disease dementia or any other forms of dementia or any form of dementia
Included studies	Prospectively well-defined cohorts with any accepted definition of MCI (as above). One study (N = 45 participants) was included. Number of participants included in analysis: 45
Quality concerns	Patient characteristics were poorly reported. Reference standard diagnosis was made with knowledge of the index test. Applicability concerns were high in reference standard
Limitations	We were not able to calculate a summary of sensitivity and specificity due to insufficient number of studies. Investigation of heterogeneity and sensitivity analysis were not done due to insufficient number of studies

Test	Studies	Cases/Participants	Sensitivity	Specificity	Consequences in a cohort of 100		
					Proportion converting[1]	Missed cases[2]	Overdiagnosed
Alzheimer's disease dementia							
18F-florbetaben (visual assessment)	1	21/45	100% (95% CI 84% to 100%)	83% (95% CI 63% to 95%)	47	0	9
18F-florbetaben (SUVR)	1	21/45	100% (95% CI 84% to 100%)	88% (95% CI 68% to 97%)	47	0	6
Any other form of dementia (non-ADD)							

18F-florbetaben (visual assessment)	5/45 1	0% (95% CI 0% to 52%)	38% (95% CI 23% to 54%)	11	55
18F-florbetaben (SUVR)	5/45 1	0% (95% CI 0% to 52%)	40% (95% CI 25% to 57%)	11	53
Any form of dementia				
18F-florbetaben (visual assessment)	26/45 1	81% (95% CI 61% to 93%)	79% (95% CI 54% to 94%)	11	9
18F-florbetaben (SUVR)	26/45 1	81% (95% CI 61% to 93%)	84% (95% CI 60% to 97%)	11	7

Investigation of heterogeneity and sensitivity analysis: The planned investigations of heterogeneity or sensitivity analyses were not possible due to a limited number of studies available for each analysis

Conclusions: 18F-florbetaben PET scan has a good sensitivity achieved especially in predicting the progression from MCI to ADD. The quality of evidence was weak because it was based on only one study (45 participants) and there was high risk of bias due to the knowledge of the reference standard to do the diagnosis at four-year follow-up and due to possible conflict of interest detected. There is a need for conducting studies using standardised 18F-florbetaben PET scan methodology in larger populations. Regarding the aforementioned we do not recommend the use in clinical practice until the DTA performance will be clearly demonstrated

1. Proportion converting to ADD or any other form of dementia (non-ADD) over any of dementia/the related included study

2. MI: as at one sided/ age as a denominator accompanied at using the group proportion converting to the target condition.

ADD: Alzheimer's disease dementia

CDR: Clinical Dementia Rating
MCI: Mild cognitive impairment
NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and
Related Disorders Association
NINDS: National Institute of Neurological Disorder and Stroke
PET: Positron emission tomography
ROI: Region of interest
SUVR: Standardised uptake value ratio

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DISCUSSION

Summary of main results

The volume and quality of evidence regarding the DTA of ^{18}F-florbetaben for early diagnosis of ADD and other dementias in people with MCI is very limited. We identified only one study in this systematic review and for that reason we were not able to conduct a meta-analysis, sensitivity analysis, or heterogeneity analyses (Ong 2015). The results are summarised in a 'Summary of findings' table (Summary of findings). The study was evaluated as at high risk of bias, mainly due to the potential conflicts of interest (financial support of the study and also because three authors were employees of the previous company who manufactured the ^{18}F-florbetaben tracer and three authors were employees of the current company that manufactures the ^{18}F-florbetaben tracer (Characteristics of included studies)).

Regarding our objectives: to determine the DTA of the ^{18}F-florbetaben PET scan for detecting people with MCI at baseline who will clinically progress to ADD, or to other forms of dementia or any form of dementia at follow-up, the results were the following:

[18]F-florbetaben PET scan for Alzheimer's disease dementia (ADD)

Progression from MCI to ADD analysed by visual assessment: sensitivity of 100% (95% CI 84% to 100%) and a specificity of 83% (95% CI 63% to 95%).

Progression from MCI to ADD analysed by SUVR > 1.45: sensitivity of 100% (95% CI 84% to 100%) and a specificity of 88% (95% CI 68% to 97%).

[18]F-florbetaben has a close to perfect sensitivity and a good specificity for predicting progression to ADD through visual assessment evaluation or SUVR (Ong 2015). However, a positive ^{18}F-florbetaben PET scan for $A\beta$, has been found in other neurological conditions clinically diagnosed, and it was positive in vascular dementia, frontotemporal dementia and dementia with Lewy bodies (Villemagne 2011). Nevertheless, in one study with 12 cases with non-ADD at autopsy, the ^{18}F-florbetaben PET scan was negative in all of them (Sabbagh 2017). On the other hand, in other amyloid biomarkers like PET PiB, the false positive rate could be explained because it has affinity to amyloid in vessel walls, in particular, to cerebral amyloid angiopathy (CAA) (Zhang 2014). We would think that the pathological diagnosis of some patients with clinically probable ADD may be vascular dementia secondary to CAA and some people with MCI may be have vascular MCI due to CAA.

As other amyloid tracers, ^{18}F-florbetaben has probed the detection of amyloid plaques that are composed of insoluble $A\beta$ peptides (EMA 2014, FDA 2014), however, the soluble $A\beta$ oligomers have been playing a central role in Alzheimer's pathogenesis in the amyloid hypothesis (Heyden 2013), with the possibility of producing false negatives. In addition, amyloid tracers do not bind to the other histopathologic core of Alzheimer's disease, the neurofibrillary tangles (NFTs). There is evidence that indicates that plaques and tangles independently contribute to cognitive impairment over the clinical course of Alzheimer's disease (Serrano-Pozo 2013). Moreover, in another cohort study, the NFT formation might be either unrelated to amyloid plaques formation or a temporally distinct process, or both(Royall 2014). The latest could explain why, in 44 participants with ADD and positive $A\beta$ histopathology, one had a negative ^{18}F-florbetaben PET scan (Sabri 2015).

Another important factor to be considered in predicting the progression to ADD is the duration of follow-up, because the reported progression rate of MCI to ADD is between 8% and 16% per year (Mitchell 2009). Therefore, a high percentage of people with baseline MCI would progress to Alzheimer's disease dementia if we could include a longer follow-up period, which would consequently affect the predictive accuracy of the ^{18}F-florbetaben PET scan. However the progression rate at two years was 44% (including two participants who at four years follow-up reverted to MCI or converted to another form of dementia (non-ADD)) and at four years was 47%. This is more than normal and probably can be explained by the setting of recruitment or demographic or MCI characteristics and maybe other underlying factors that can increase the progression rate. In addition, in one systematic review regarding the progression from MCI to ADD with PiB PETp-u, a correlation between longer follow-up and higher specificities was found (Ma 2014). However, due to the lack of data, we were not able to investigate the effect of the follow-up on the progression rate from MCI to ADD, or any form of dementia.

On the other hand, MCI subtypes have been related to progression to dementia. In a large longitudinal study with 550 MCI participants, evidence were found that the MCI subtype, presence of storage memory impairment, multiple domain condition, and presence of APOE ϵ4 allele increased the risk of progression to dementia. Multivariate survival and Kaplan-Meier analyses showed that amnestic MCI with storage memory impairment had the most and closest risk of progression to dementia (Espinosa 2013). Specifically, in our systematic review, the study of Ong 2015 (Ong 2015), included amnestic and non-amnestic MCI, and after adjusting for both ^{18}F-florbetaben PET scan positive status and hippocampal atrophy, the hazard ratio for the development of ADD from amnestic MCI was not significant. Additionally, some other risk factors like family history of dementia, APOE ϵ4 allele presence, and $A\beta$ and tau protein levels in cerebrospinal fluid may contribute to a faster progression rate to dementia. In conclusion, further updated systematic reviews should include high quality research with more detailed data about the characteristics of MCI that are required to not only explore the underlying mechanisms but also to elucidate the causal pathways that link ^{18}F-florbetaben PET scan positivity of diverse MCI subtypes and disease progression.

[18]F-florbetaben PET scan for any other forms of dementia (non-Alzheimer's disease dementia (non-ADD))

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

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Progression to any other form of non-ADD analysed by visual assessment: sensitivity of 0.0% (95% CI 0.0% to 52%) and a specificity of 38% (95% CI 23% to 54%).

Progression to any other form of non-ADD analysed by SUVR ≥ 1.45: sensitivity of 0.0% (95% CI 0.0% to 52%) and a specificity of 40% (95% CI 25% to 57%).

The study reported only 5 people converting to non-ADD at four years follow-up: frontotemporal dementia (3), Lewy body dementia (1) and progressive supranuclear palsy (1); all of them were ^{18}F-florbetaben negative (Ong 2015).

[18]F-florbetaben PET scan cortical binding has been observed in non-ADD; 9% (1/11) of FTLD, 25% (1/4) of VaD, 29% (2/7) of DLB in a study from Australia (Villemagne 2011) and in 11% (3/27) in those with confirmed non-Alzheimer's disease neurodegenerative pathologies at autopsy (Sabri 2015). However, in this study none of the five converters to non-ADD at four years follow-up were ^{18}F-florbetaben positive; the latest could explain the sensitivity of 0% and specificity of 38% with visual assessment in the included study. Nevertheless, according to histopathological studies, we would expect that studies with more participants, or participants with positive PET scans that progress to non-ADD, could potentially increase the DTA to predict progression to other forms of dementia and decrease the DTA to predict the progression to ADD.

The latest data suggested the test was insufficient to evaluate the early diagnostic value for progression from MCI to any form of non-ADD.

[18]F-florbetaben PET scan for any form of dementia

Progression to any form of dementia analysed by visual assessment: sensitivity of 81% (95% CI 61% to 93%) and a specificity of 79% (95% CI 54% to 94%).

Progression to any form of dementia analysed by SUVR ≥ 1.45: sensitivity of 81% (95% CI 61% to 93%) and a specificity of 84% (95% CI 60% to 97%).

Ong 2015 reported lower sensitivity and specificity for prediction of any form of dementia other than ADD (Ong 2015). This is explained because the test has a close to perfect sensitivity and good specificity to predict the progression to ADD and if we add the data with those that are PET negative with other types of non-ADD, the sensitivity decreased to 81% and the specificity to 79%. According to the aforementioned, in the cases of ^{18}F-florbetaben PET scans for any other forms of dementia, there are cases that are PET positive with other neurological conditions in the literature, but not in this study; and this paucity of data with this type of participant, could be explained due to the small sample of participants of this study. For that reason, we would expect that in other studies where we would check the progression to any form of dementia, the DTA would be higher because it is probable to find participants with DBL, FTD and others with a PET positive result, and also we would expect an decrease in the DTA to predict the progression to ADD.

Strengths and weaknesses of the review

We conducted an extensive, comprehensive, and sensitive literature search using 11 different electronic databases without any limitation to language or publication status. However, we only identified one study with 45 eligible participants, therefore our DTA estimates are relatively imprecise. This paucity of evidence reflects the very significant challenges inherent in conducting long term prospective studies of well characterised participants, followed up to the point of progression of a clinical dementia. The 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 progression from MCI to ADD or any other form of dementia (non-ADD) or any form of dementia at follow-up.

The included study did have significant methodological limitations that weakened confidence in the findings of the review. The study lacked information about the selection of the participants, the reference standard was made with knowledge of the medical studies and medical records, and the major problem was a potential conflict of interest due to the relationship with the companies who produced and produce the tracer. On the other hand, considerable uncertainty remained concerning the clinical diagnosis of ADD; the histopathological diagnosis would be the better way to probe the diagnosis, however, this option is not realistic for a clinical trial.

Applicability of findings to the review question

Regarding the question of this review:

Could the ^{18}F-florbetaben PET scan identify those people with MCI who would progress to clinical dementia at follow-up?. There was no applicability concern that the included patients, the setting, the conduct, and interpretation of the index test in the included study did not match the review question. However, there was a high applicability concern about the target condition (as defined by the reference standard) because the diagnosis at follow-up was made with access to the study tests and medical records for all participants and, therefore, due to the one study included, it was difficult to extend the findings into clinical practice without a meta-analysis.

The diagnostic utility of ^{18}F-florbetaben PET scan for identifying Alzheimer's disease pathology and identifying those people with MCI who would convert to ADD could be affected by a number of factors that have not been determined so far. The most important was the lack of a large study to evaluate this question, as we included one study that addressed the question with only 45 participants at follow-up. Conducting a ^{18}F-florbetaben test is expensive, therefore it is important to clearly demonstrate its accuracy prior to recommending its adoption in clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

Today, the use of ^{18}F-florbetaben is not indicated in people with MCI (FDA and EMA) except in clinical trials and research studies. 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 people with persistent or progressive unexplained MCI (Johnson 2013). The DTA of ^{18}F-florbetaben PET scans, as determined in this SR, suggests a limited use due to a lack of information based only on one study with 45 participants to predict the progression from MCI to ADD and any form of dementia. Despite this, in the sole study, the sensitivity was 100% and the specificity was 83% for visual assessment analysis to predict the progression to ADD and the sensitivity was 81% and the sensitivity was 79% to predict the progression to any form of dementia. The prediction to other forms of dementia (non-ADD) was poor, however, this could be explained because the pathology of the other neurodegenerative conditions is not based on the $A\beta$ plaques. Finally, we have to consider the risk of bias due to the access to medical tests and medical records by the neurologist who made the diagnosis at four years follow-up, because this could overestimate the DTA of ^{18}F-florbetaben (Lijmer 1999). Due to the aforementioned and the methodological limitations of the included study, it is not possible to recommend the routine use of ^{18}F-florbetaben in clinical practice. The ^{18}F-florbetaben biomarker is expensive, therefore, it is important to clearly demonstrate its DTA and to standardise the process for the diagnostic modality prior to it being widely used.

Implications for research

The FDA and EMA had established the ^{18}F-florbetaben positivity criteria in order that the use in ADD patients' evaluation and use in people with MCI is accepted in research settings and clinical trials (Albert 2011). On the other hand, it has been proposed for use in clinical practice by the Nuclear Medicine Society and the Alzheimer's Association (Johnson 2013).

The interpretation of the results of the ^{18}F-florbetaben PET scan studies could be difficult due to the use of different methods to define the result of the test. It is still used in many studies with different SUVR, visual assessment or both, and this promotes different accuracies for the tracer, even in people with ADD when they are compared with healthy people without ADD. Therefore, it is necessary to consider that visual assessment is the most important option to interpret the ^{18}F-florbetaben PET scan, because this is the approach to the interpretation established by FDA and EMA (FDA 2014, EMA 2014).

Moreover, clinical assessment in people with memory complaints is not always undertaken with only one test, as clinical assessment could use different tests, like volumetric hippocampal MRI, FDG-PET, SPECT, CSF, and others. This makes sense because neurodegenerative diseases are complex disorders with occasionally multiple and overlapping pathophysiological processes, and 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 dementia. In future, various PET imaging modalities are needed to evaluate the usefulness of the various PET tracers as predictors of progression to Alzheimer's disease dementia 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 (Jack 2010). Based on this hypothesis, the combination of structural imaging, functional imaging, and cognitive tests may be better predictors of when an individual will convert. However, in this way, the Ong 2015 study showed that a ^{18}F-florbetaben PET positive result predicted progression after adjusting for both aMCI status and hippocampal atrophy evaluated with sMRI (Ong 2015). Nevertheless, there is a lack of studies with ^{18}F-florbetaben combined with other tests.

Additionally, if we consider the hierarchical evidence needed for the level of efficacy of diagnostic imaging tests, we are currently in the second step of six according to Herscovitch (Herscovitch 2015): technical efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic impact, patient health outcomes, and, finally, societal efficacy. Therefore, we need further research about accuracy before progressing to the other steps with their specific studies before we can incorporate the ^{18}F-florbetaben PET scan into clinical practice.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ong 2015

Study characteristics	
Patient sampling	Forty-five older adults who were referred from local memory clinics in Australia. No further details of patient sampling and recruitment were reported Participants had to be at least 60 years old and to have had at least 7 years of formal schooling. They were also required to communicate fluently in English Exclusion criteria included the presence of dementia, a score lower than 23 on the MMSE, the presence of other conditions that may impair their cognition and independence, including other neurological (stroke, multiple sclerosis, epilepsy, moderate-severe traumatic brain injury), psychiatric (psychotic symptoms, bipolar disorder), or substance use conditions (e.g. drug and alcohol dependence, use of acetylcholinesterase inhibitors and memantine
Patient characteristics and setting	45 MCI participants diagnosed by the Petersen 2004 and Winblad 2004 criteria Demographic data were reported for 45 MCI participants (with SUVR); demographic data were not available for those classified by visual assessment ^{18}F-florbetaben positive: 24, ^{18}F-florbetaben negative: 21 Gender: not described Age Mean (SD): ^{18}F-florbetaben positive: 73.5 (6.9), ^{18}F-florbetaben negative: 71.8 (6.1) years APOE ϵ4 carrier: not reported MMSE Mean (SD) ^{18}F-florbetaben positive: 26.7 (1.9), ^{18}F-florbetaben negative: 27.9 (1.4) Years of education Mean (SD): ^{18}F-florbetaben positive: 13.8 (4.2), ^{18}F-florbetaben negative: 13.5 (3.0) Sources of referral: not reported Setting: secondary care (memory clinic)
Index tests	**Administration instructions and tracer dose** ^{18}F-florbetaben was injected intravenously over 38 ± 17 s, with a mean specific activity at the time of injection of 60 ± 29 GBq/μmol. Each participant received on average 286 ± 19 MBq of ^{18}F-florbetaben. PET imaging was conducted using a 3D GSO Phillips Allegro PET camera. A 2-min transmission scan using a rotating 137Cs source was done for attenuation correction immediately prior to scanning. Images obtained between 90 to 110 min post injection were analysed. Images were reconstructed using a 3D RAMLA **Image interpretation** PET images were processed with a semiautomatic volume of interest (VOI) method. This method used a preset template of narrow cortical VOI that was applied to either the spatially normalized ^{18}F-florbetaben scan or via placement on the subject's spatially normalized coregistered MRI by a single operator who was blinded to the subject's clinical status. Minor manual adjustments on the MRI were made to ensure that overlap with white matter and cerebrospinal fluid was minimized Spatial normalization and coregistration of the PET and MRI images was performed using SPM8 Mean radioactivity values were obtained from VOI for cortical, subcortical, and cerebellar regions. The cerebellar cortical VOI was placed taking care to avoid cerebellar white matter. No correction for partial volume effect was applied to the PET data • **Visual assessment**

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Ong 2015 *(Continued)*

Baseline ^{18}F-florbetaben PET images underwent visual assessment by five independent nuclear medicine physicians blinded to clinical data. Readers had limited or no prior experience with amyloid PET visual interpretation and were trained on an electronic training tool

The image assessment was performed on axial slices, in a grey scale. The regional cortical tracer uptake (RCTU) scoring system was used to assess the beta-amyloid deposition in the following four regions: frontal cortex, posterior cingulate/precuneus, lateral temporal cortex, and parietal cortex. A RCTU value of 1, 2, or 3 was assigned if either no, moderate, or pronounced tracer uptake was observed respectively as described below:

1 No tracer uptake: Tracer uptake (i.e. signal intensity) in grey matter in the region is lower than in white matter

2 Moderate tracer uptake: Smaller area(s) of tracer uptake equal to or higher than that present in white matter;

- extending beyond the white matter rim to the outer cortical margin
- involving the majority of the slices within the respective region

3 Pronounced tracer uptake: A large confluent area of tracer uptake equal to or higher than that present in white matter;

- extending beyond the white matter rim to the outer cortical margin
- and involving the entire region including the majority of the slices within the respective region

The RCTU scores for the four brain regions were condensed into a binary brain amyloid plaque load (BAPL) score with positive or negative interpretation as described below:

[18]F-florbetaben PET scan negative: scan without β-amyloid deposition (RCTU score 1 in each of the 4 brain regions 1, 2, 3, and 4)

[18]F-florbetaben PET scan positive: scan with moderate β-amyloid deposition (RCTU score 2 in any or all of the 4 brain regions 1, 2, 3, and 4 and no score 3 in these 4 regions) or scan with pronounced β-amyloid deposition (RCTU score 3 at least in one of the brain regions 1, 2, 3, and 4)

The majority read approach established the final result.

- **Quantitative assessment (SUVR):**

PET images were processed with a semiautomatic volume of interest (VOI) method. This method used a preset template of narrow cortical VOI that was applied to either the spatially normalized ^{18}F-florbetaben scan or via placement on the subject's spatially normalised coregistered MRI by a single operator who was blinded to the subject's clinical status. Minor manual adjustments on the MRI were made to ensure that overlap with white matter and cerebrospinal fluid was minimized. Spatial normalization and coregistration of the PET and MRI images was performed using SPM8. Mean radioactivity values were obtained from VOI for cortical, subcortical, and cerebellar regions. The cerebellar cortical VOI were placed taking care to avoid cerebellar white matter. No correction for partial volume effect was applied to the PET data

The standardised uptake value (SUV), defined as the decay-corrected brain radioactivity concentration normalised for injected dose and body weight, was calculated for all regions. These were then used to derive the SUV ratio (SUVR), which was referenced to cerebellar cortex. Neocortical Aβ burden was expressed as the average SUVR of the area-weighted mean for the following cortical ROIs: frontal (consisting of dorsolateral prefrontal, ventrolateral prefrontal, and orbitofrontal regions), superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate. The prespecified SUVR used was ≥ 1.45

Target condition and reference standard(s)	Target condition as ADD with NINCDS-ADRDA criteria were established with access to all study results and personal medical records

Ong 2015 *(Continued)*

Flow and timing	Duration of follow-up: 4 years
	Number included in analysis: 45 participants
	Visual Assessment: 25 ^{18}F-florbetaben (+) and 20 ^{18}F-florbetaben (-)
	Progression from MCI to ADD by visual assessment:
	^{18}F-florbetaben (+): 21 MCI to ADD and 4 MCI-MCI; ^{18}F-florbetaben (-): 0 MCI to ADD and 20 MCI-MCI
	TP = 21; FP = 4; FN = 0; TN = 20
	Progression from MCI to any other form of dementia (non-ADD) by visual assessment:
	^{18}F-florbetaben (+): 0 MCI to non-ADD and 25 MCI-MCI; ^{18}F-florbetaben (-): 5 MCI to non-ADD and 15 MCI-MCI
	TP = 0; FP = 25; FN = 5; TN = 15
	Progression from MCI to any form of dementia by visual assessment:
	^{18}F-florbetaben (+): 21 MCI to any dementia and 4 MCI-MCI; ^{18}F-florbetaben (-): 5 MCI to any dementia and 15 MCI-MCI
	TP = 21; FP = 4; FN = 5; TN = 15
	SUVR: 24 ^{18}F-florbetaben (+) and 21 ^{18}F-florbetaben (-)
	Progression from MCI to ADD by SUVR:
	^{18}F-florbetaben (+): 21 MCI to ADD and 3 MCI-MCI; ^{18}F-florbetaben (-): 0 MCI to ADD and 21 MCI-MCI
	TP = 21; FP = 3; FN= 0; TN = 21
	Progression from MCI to any other form of dementia (non-ADD) by SUVR:
	^{18}F-florbetaben (+): 0 MCI to non-ADD and 24 MCI-MCI or ADD; ^{18}F-florbetaben (-): 5 MCI to non-ADD and 16 MCI-MCI or ADD
	TP = 0; FP = 24; FN = 5; TN = 16
	Progression from MCI to any form of dementia by SUVR:
	^{18}F-florbetaben (+): 21 MCI to any dementia and 3 MCI-MCI; ^{18}F-florbetaben (-): 5 MCI to any dementia and 16 MCI-MCI
	TP = 21; FP = 3; FN = 5; TN = 16
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	Low

Ong 2015 *(Continued)*

DOMAIN 2: Index Test All tests			
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		
Was the PET scan interpretation done by a trained reader physician?	Yes		
Was there a clear definition of a positive result?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
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?	No		
		High	High
DOMAIN 4: Flow and Timing			
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		
Was the study free of commercial funding?	No		
		High	

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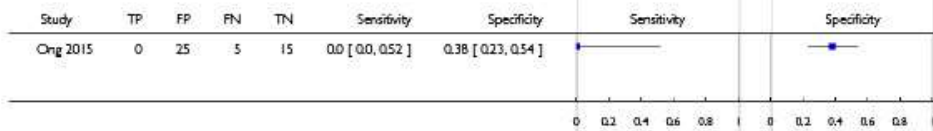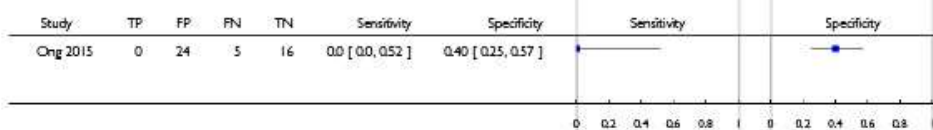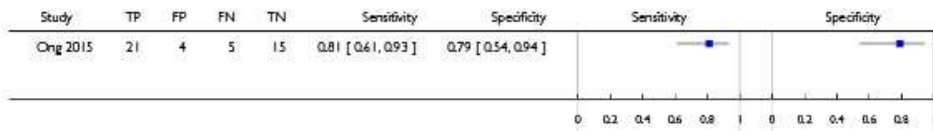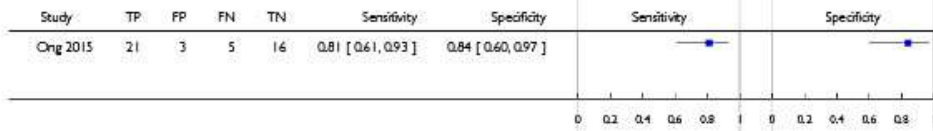
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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kim 2017	No data for constructing a 2 x 2 table was provided. The study focused on different cortical thickness subgroups and the progression to dementia in aMCI participants whom were evaluated at baseline with PiB PET or ^{18}F-florbetaben. We emailed the authors to resolve this issue, however, no response from the lead author was received

ADD: Alzheimer' sdiseasedementia
APOE: Apolipoprotein E
BAPL: Brain amyloid plaque load
FN: False negative
FP: False positive
MCI: Mild cognitive impairment
MMSE: Mini Mental State Examination
MRI: Magnetic resonance imaging
NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PET: Positron emission tomography
RCTU: Regional cortical tracer uptake
RAMLA: Row action maximum likelihood algorithm
ROI: Region of interest
SD: Standard deviation
SPM8: Statistical parametric mapping 8
SUV: Standardised uptake value
SUVR: Standardised uptake value ratio
TN: True negative
TP: True positive
VOI: Volume of interest

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2013-004671-12-BE

Trial name or title	Predictive value of biomarkers in patients with amnestic mild cognitive impairment
Target condition and reference standard(s)	Cognitive decline after two years of follow-up, reference standard not specified
Index and comparator tests	^{18}F-florbetaben
Starting date	June 2014
Contact information	rik.vandenberghe@uzleuven.be University of Leuven

EUCTR2013-004671-12-BE (*Continued*)

Notes	Dr. Vandenberghe was contacted; he provided requested information regarding the tracer used; email from Dr. Vandenberghe on 23/01/17

EUCTR2014-000562-21-NL

Trial name or title	Amyloid-PET as a diagnostic marker in daily practice
Target condition and reference standard(s)	Progression to dementia, reference standard not specified
Index and comparator tests	^{18}F-florbetaben
Starting date	January 2015
Contact information	Alzheimer Center, VU University Medical Center Alzheimer Center alzheimercentrum@vumc.nl
Notes	

EUCTR2014-004244-35-IT

Trial name or title	Amyloid load in prodromal ADD with limbic-predominant phenotype
Target condition and reference standard(s)	Clinical 'indices', reference standard not specified
Index and comparator tests	^{18}F-florbetaben
Starting date	March 2015
Contact information	Medicina Nucleare, IRCCS Ospedale San Raffaele perani.daniela@hsr.it
Notes	

NCT01222351

Trial name or title	BAY 94-9172 PET/CT in cognitively normal older adults, older adults with mild cognitive impairment, and older adults with Alzheimer's disease
Target condition and reference standard(s)	Alzheimer's disease, reference standard not specified
Index and comparator tests	^{18}F-florbetaben
Starting date	2010
Contact information	Oksana Taterina, ot2004@columbia.edu Yaakov Stern, ys11@columbia.edu

NCT01222351 *(Continued)*

Notes	

NCT02854033

Trial name or title	Alzheimer's disease neuroimaging initiative 3 (ADNI3) protocol
Target condition and reference standard(s)	Rate of progression to dementia due to ADD, reference standard not specified
Index and comparator tests	^{18}F-florberaben, ^{18}F-florbetapir
Starting date	October 2016
Contact information	Dr. Paul Aisen, Director, Alzheimer's Therapeutic Research Institute, University of Southern California
Notes	

ADD:Alzheimer'sdiseasedementia

ADNI3: Alzheimer's disease neuroimaging initiative 3
CT: Computed tomography
PET: Positron emission tomography

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

Test	No. of studies	No. of participants
1 ^{18}F-florbetaben visual assessment and progression to ADD	1	45
2 ^{18}F-florbetaben SUVR and progression to ADD	1	45
3 ^{18}F-florbetaben visual assessment and progression to any other form of non-ADD	1	45
4 ^{18}F-florbetaben SUVR and progression to any other form of non-ADD	1	45
5 ^{18}F-florbetaben visual assessment and progression to any form of dementia	1	45
6 ^{18}F-florbetaben SUVR and progression to any form of dementia	1	45

Test 1. 18F-florbetaben visual assessment and progression to ADD.

Review: 18F PET with florbetaben for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 1 ^{18}F-florbetaben visual assessment and progression to ADD

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Ong 2015	21	4	0	20	1.00 [0.84, 1.00]	0.83 [0.63, 0.95]		

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Test 2. 18F-florbetaben SUVR and progression to ADD.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Ong 2015	21	3	0	21	1.00 [0.84, 1.00]	0.88 [0.68, 0.97]		

Test 3. 18F-florbetaben visual assessment and progression to any other form of non-ADD.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Ong 2015	0	25	5	15	0.0 [0.0, 0.52]	0.38 [0.23, 0.54]		

Test 4. 18F-florbetaben SUVR and progression to any other form of non-ADD.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Ong 2015	0	24	5	16	0.0 [0.0, 0.52]	0.40 [0.25, 0.57]		

Test 5. 18F-florbetaben visual assessment and progression to any form of dementia.

Review: 18F PET with florbetaben for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 5 18F-florbetaben visual assessment and progression to any form of dementia

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Ong 2015	21	4	5	15	0.81 [0.61, 0.93]	0.79 [0.54, 0.94]		

Test 6. 18F-florbetaben SUVR and progression to any form of dementia.

Review: 18F PET with florbetaben for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 6 18F-florbetaben SUVR and progression to any form of dementia

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Ong 2015	21	3	5	16	0.81 [0.61, 0.93]	0.84 [0.60, 0.97]		

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APPENDICES

Appendix 1. Glossary

Aetiology: the cause, set of causes, or manner of causation of a disease or condition.

Amyloid beta ($A\beta$): an amyloid that is derived from a larger precursor protein and is the primary component of plaques characteristic of Alzheimer's disease.

Biomarker: measurable and quantifiable biological parameters (e.g., specific enzyme concentration, specific hormone concentration, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis; metabolic processes; etc.

Bolus: a single dose of a drug or other medicinal preparation given all at once.

Cingulate cortex: one of the convolutions on the medial surface of the cerebral hemispheres.

Cortical: the thin layer of grey matter on the surface of the cerebral hemispheres. It reaches its highest development in humans and is responsible for intellectual faculties and higher mental functions.

Epiphenomenon: A secondary effect or by-product. A secondary symptom or pathology, occurring simultaneously with a disease or condition but not directly related to it.

Frontotemporal: relating to the frontal and the temporal cerebral lobes.

Histopathology: the study of changes in tissues caused by disease.

Hypothyroidism: a syndrome that results from abnormally low secretion of thyroid hormones from the thyroid gland.

Index test: the test under evaluation.

In vivo: (of processes) performed or taking place in a living organism.

Ligand: a molecule that binds to another molecule, used especially to refer to a small molecule that binds specifically to a larger molecule, e.g., an antigen binding to an antibody, a hormone or neurotransmitter binding to a receptor, or a substrate or allosteric effector binding to an enzyme.

Neuritic plaques: accumulations of extracellularly deposited amyloid fibrils within tissues. Is one of the hallmarks of Alzheimer's disease.

Neurofibrillary tangles: abnormal structures located in various parts of the brain and composed of dense arrays of paired helical filaments (neurofilaments and microtubules). Are aggregates of hyperphosphorylated tau protein that are most commonly known as a primary marker of Alzheimer's disease.

Parietal lobe: upper central part of the cerebral hemisphere. It is located anterior to the occipital lobe, and superior to the temporal lobes.

Positron: an extremely small piece of matter with a positive electrical charge, having the same mass as an electron.

Precuneus: is a part of the parietal lobe of the brain, lying on the medial surface of the cerebral hemisphere.

Prodromal: Relating to prodrome; indicating an early stage of a disease.

Radionuclide (sometimes called a radioisotope or isotope): is a chemical which emits a type of radioactivity called gamma rays. The radioactivity can be detected by special scanners.

Reference standard: the best available method for establishing the presence or absence of the target condition.

Sensitivity: a measure of a test's ability to correctly detect people with the disease. It is the proportion of diseased cases that are correctly identified by the test. It is calculated as follows: Sensitivity = Number with disease who have a positive test/Number with disease.

Specificity: a measure of a test's ability to correctly identify people who do not have the disease. It is the proportion of people without the target disease who are correctly identified by the test. It is calculated as follows: Specificity = Number without disease who have a negative test/Number without disease.

Stilbene: organic compounds that contain 1,2-diphenylethylene as a functional group.

Target condition: the disease or condition that the index test is expected to detect.

Temporal lobe: lower lateral part of the cerebral hemisphere responsible for auditory, olfactory, and semantic processing. It is located inferior to the lateral fissure and anterior to the occipital lobe.

Vascular: relating to, affecting, or consisting of a vessel or vessels, especially those which carry blood.

Appendix 2. Search strategy for ¹⁸F-florbetaben PET ligand

Source	Search strategy
MEDLINE In-process and other non-indexed citations and Medline® 1946 to May 2017 (Ovid SP)	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
Embase 1974 to May 2017 (Ovid SP)	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
PsycINFO 1806 to May 2017 (Ovid SP)	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

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BIOSIS Citation Index (Thomson Reuters Web of Science) (1922 to May 2017)	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
Web of Science Core Collection, including the Science Citation Index and the Conference Proceedings Citation Index (Thomson Reuters Web of Science) (1946 to May 2017)	Topic=(Florbetaben OR NEURACEQ 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-EX-PANDED, IC
LILACS (BIREME)	Florbetaben OR NEURACEQ OR neuraceq* OR "florbetaben-fluorine-18" OR "18F-BAY94-9172" OR "[18F]Florbetaben" OR "florbetaben-PET" [Words]
CINAHL (EBSCOhost) (1980 to May 2017)	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
ClinicalTrials.gov (www.clinicaltrials.gov)	Florbetaben OR NEURACEQ OR neuraceq* OR "florbetaben-fluorine-18" OR "18F-BAY94-9172" OR "[18F]Florbetaben" OR "florbetaben-PET"
World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (http://apps.who.int/trialsearch)	Florbetaben OR NEURACEQ OR neuraceq OR "florbetaben-fluorine-18" OR "18F-BAY94-9172" OR "[18F]Florbetaben" OR "florbetaben-PET"
ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialized register of dementia studies (http://www.medicine.ox.ac.uk/alois/)	Imaging AND PET

Appendix 3. 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**

(Continued)

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

ADD: Alzheimer's disease dementia

FN: false negative

FP: false positive

MCI: mild cognitive impairment

PET: positron emission tomography

TN: true negative

TP: true positive

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

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

ADD: Alzheimer's disease dementia

FN: false negative

FP: false positive

MCI: mild cognitive impairment

PET: positron emission tomography

TN: true negative

TP: true positive

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-florbetaben PET ligand for $A\beta$ (+) who progress to any form of dementia (TP)	^{18}F-florbetaben PET ligand for $A\beta$ (+) who remain MCI (FP)
Index test-negative	^{18}F-florbetaben PET ligand for $A\beta$ (-) who progress to any form of dementia (FN)	^{18}F-florbetaben PET ligand for $A\beta$ (-) who remain MCI (TN)

FN: false negative

FP: false positive

MCI: mild cognitive impairment

PET: positron emission tomography

TN: true negative

TP: true positive

Appendix 4. 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
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?

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	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 5. Anchoring statements for quality assessment of ^{18}F-florbetaben PET ligand for Aβ 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-florbetaben PET ligand for Aβ biomarker	^{18}F-florbetaben PET ligand for Aβ biomarker
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 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)

ADD: Alzheimer's disease dementia

DSM: Diagnostic and Statistical Manual of Mental Disorders
FTD: Frontotemporal dementia

ICD: International Classification of Diseases

MCI: Mild cognitive impairment

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences

PET: Positron emission tomography

Anchoring statements for quality assessment ¹⁸F-florbetaben PET ligand for Aβ diagnostic studies

We have provided some core anchoring statements for quality assessment in the diagnostic test accuracy (DTA) review of the ¹⁸F-florbetaben PET ligand for Aβ biomarker 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 contacted the relevant study teams for additional information. Whenever we scored one question as high risk of bias, we considered the study as 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 automatically graded the study as unclear if the study authors did not detail exclusions (pending contact with study authors) Where a study details exclusions, we graded the study as 'low risk' if we considered 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 labelled post-hoc and inappropriate exclusions as at 'high risk' of bias
Index test		
Was the ^{18}F-florbetaben PET ligand for $A\beta$ 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 the 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 the reference standard should not influence the 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
Was the ^{18}F-florbetaben PET ligand for $A\beta$ biomarker's threshold 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 the threshold, clinical cut-off, or dichotomisation point. A study is classified at 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
Was the ^{18}F-florbetaben PET ligand for $A\beta$ 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 scored this item as 'yes' If no definition of trained reader was done, we scored this item as 'unclear' If a nontrained reader physician performed the scan interpretation, we scored this item

		as 'no'
Did the study provide a clear definition of what was considered to be a ^{18}F-florbetaben PET ligand for Aβ biomarker's positive result?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	If the study clearly stated the definition of a positive result (e.g. SUV), we scored this item as 'yes' If the study did not give a definition of what it considered a positive result or the definition of a positive result varied between the participants, we scored this item as 'no' If the study gave insufficient information to permit judgement, we scored 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 included those detailed in DSM-IV and ICD-10. Criteria specific to dementia subtypes included but were 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 were not familiar to the review authors or the Cochrane Dementia and Cognitive Improvement group ('unclear'), we classified this item as 'high risk of bias'
Were clinical assessments for dementia performed without knowledge of the ^{18}F-florbetaben PET ligand for Aβ 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' were sufficient and full details of the blinding procedure were not required. Interpretation of the results of the reference standard may be influenced by knowledge of the results of the index test

Patient flow

Was there an appropriate interval between ^{18}F-florbetaben PET ligand for Aβ 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 ^{18}F-florbetaben PET ligand for Aβ biomarker for MCI progression to dementia, there will always be a delay between the index test and the reference standard assessments. The time between the reference standard and

		the index test will influence the accuracy (Geslani 2005; Okello 2007; Visser 2006) , and therefore we noted 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 was scored 'no'
Did all subjects get the same assessment for dementia regardless ^{18}F-florbetaben PET ligand for Aβ biomarker?	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 the 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-florbetaben PET ligand for Aβ 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 dropouts differ systematically from those who remain, then estimates of test performance may differ. If there are dropouts, these should be accounted for; a maximum proportion of dropouts for a study to remain at low risk of bias has been specified as 20%
Were missing ^{18}F-florbetaben PET ligand for Aβ 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 did not report these results, we scored this as 'unclear' and we contacted the study authors
Was the study with ^{18}F-florbetaben PET ligand for Aβ 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' 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; pretesting; 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 ^{18}F-florbetaben PET ligand for Aβ 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-florbetaben PET ligand for Aβ 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 'Risk of bias' assessments will already have assessed the dementia diagnosis. For certain reviews, an applicability statement relating to the 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

FTD: Frontotemporal dementia

ICD: International Classification of Diseases

MCI: Mild cognitive impairment

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences

PET: Positron emission tomography

CONTRIBUTIONS OF AUTHORS

Gabriel Martínez, Robin WM Vernooij, and Paulina Fuentes Padilla: contributed to conception, design, and draft of the protocol; overall responsibility of study selection; data extraction; contacted the authors; draft of discussion and authors' conclusion sections.

Javier Zamora: reviewed draft protocol, updated statistical methods section, performed statistical analyses and final manuscript.

Leon Flicker: contributed to conception, and designed and reviewed draft protocol and final manuscript.

Xavier Bonfill Cosp: reviewed draft protocol and final manuscript.

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

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DECLARATIONS OF INTEREST

Gabriel Martínez 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.

Leon Flicker has no known conflicts of interest.

Xavier Bonfill Cosp has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We added as the reference standard the definition of progressive supranuclear palsy (PSP) (Hauw 1994).

5.3. *Resultados de la tercera publicación*

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

Gabriel Martínez, Robin WM Vernooij, Paulina Fuentes Padilla, Javier Zamora, Leon Flicker, Xavier Bonfill Cosp

5.3.1. Resultado de las búsquedas

Las diferentes estrategias de búsqueda empleadas identificaron un total de 1333 referencias.

Al final del proceso de revisión, se incluyeron dos referencias con un total de 252 participantes con un DCL, de ellos un estudio corresponde a un estudio con datos sólo en las plataformas de registro de estudios clínicos (en los Estados Unidos registrado como NCT01028053 y en Europa como EUCTR 2009-010227-62) e identificamos siete referencias como estudios en curso, que serán incluidas en las siguientes actualizaciones de la revisión.

5.3.2. Características de los estudios incluidos

Selección de participantes y características:

Respecto a las características de los estudios analizados, el número de participantes al inicio de los estudios fue de 252, un estudio incluyó 232 participantes (NCT01028053) y el segundo estudio incluyó 20 participantes al inicio del seguimiento (Thurfjell 2012).

El estudio con más participantes (NCT01028053) no proporciona información de cómo se realizó el muestreo o reclutamiento de los participantes, aunque según la información proporcionada en la plataforma de registro, los participantes fueron reclutados en seis países, principalmente Estados Unidos y Reino Unido. En el otro estudio, los participantes provenían de siete diferentes clínicas de memoria sin especificación de continente o país.

El promedio de edad en un estudio fue de 72,7 años y en el segundo estudio fue de 71,1 años de edad. Las participantes mujeres fueron entre un 45% y un 50,9% de los participantes de los estudios. Sólo en un estudio se entrega información acerca del nivel educacional de los participantes, con 14,4 años de educación en promedio.

El seguimiento de las cohortes osciló entre 24 y 36 meses.

Prueba índice: TEP con 18F-Flutemetamol

Sólo en un estudio se describen los modelos de tomógrafos usados (Biograph PET / CT de 16 cortes de Siemens, ECAT EXACT HR de Siemens y un escáner Advance de General Electric).

Respecto de la dosis usada, en los dos estudios tenían una dosis objetivo de 185 MBq de 18F-Flutemetamol inyectada en bolo lento dentro de 40 segundos. En un estudio la adquisición de las imágenes fue 90 minutos post punción y en el otro estudio entre 85 y 115 minutos post punción, la adquisición de imágenes se realizó durante al menos 30 minutos.

Solo en un estudio está establecido que los investigadores habían sido entrenados en la interpretación de la TEP con 18F-Flutemetamol.

Respecto del método para determinar la positividad del 18F-Flutemetamol, un estudio utilizó un medio cuantitativo, con un umbral que según los autores estaba predeterminado en >1.5 SUVR, pero según el estudio referenciado por los investigadores para establecer el SUVR, el

SUVR fue >1.56. El otro estudio utilizó un método visual para determinar positividad o no a amiloide cerebral donde las imágenes fueron evaluadas visualmente por cinco lectores cegados, independientes, la forma en cómo se determinó en forma grupal la positividad o no del test, no está descrita.

Condición clínica objetivo y estándar de referencia:

Los dos estudios evaluaron la progresión a una DEA en el seguimiento.

Respecto del estándar utilizado está establecido que el criterio NINCDS-ADRDA fue utilizado en un estudio y probablemente en el otro estudio fue utilizado NINCDS-ADRDA o APA 1994.

Flujo y tiempo:

El seguimiento varió entre 24 meses con una pérdida de un participante (5%) de 20 participantes en total (Thurfjell 2012) y 36 meses, con una pérdida de 8 (3%) participantes de 232 participantes en total al inicio del estudio (NCT01028053).

Se evaluó la positividad visualmente en 224 participantes, donde 97 (43%) participantes resultaron positivos y 127 (57%) participantes fueron negativos para carga amiloidea cerebral (NCT01028053).

La valoración cuantitativa se realizó en 19 participantes, donde 10 (53%) participantes resultaron positivos y 9 (47%) participantes fueron negativos para carga amiloidea cerebral (Thurfjell 2012).

5.3.3 Evaluación de calidad metodológica de los estudios incluidos

Se realizó una evaluación de la calidad metodológica a los estudios incluidos, a través del instrumento QUADAS-II (Whiting2011), donde se encontró lo siguiente:

Selección de participantes

Se consideró que los dos estudios incluidos tenían un riesgo poco claro de sesgo, por falta de información sobre los procedimientos de muestreo y los criterios de exclusión.

Prueba índice

Se consideró que un estudio tenía un bajo riesgo de sesgo y el otro estudio tenía un riesgo poco claro de sesgo.

Respecto del estudio con riesgo incierto, el umbral no estaba claramente establecido y en la interpretación de la prueba índice positiva, su definición no estaba claramente establecida.

Estándar de Referencia

Se consideró que un estudio tenía un bajo riesgo de sesgo y el otro estudio un riesgo poco claro porque no se informó si los médicos que realizaban el seguimiento estaban al tanto del resultado inicial de 18F-Flutemetamol, tampoco se pudo obtener la información sobre qué estándar de referencia se usó, ni cómo y por quién se obtuvo este estándar de referencia.

Flujo y el tiempo

Se consideró que los dos estudios incluidos tenían un alto riesgo de sesgo porque en ambos estudios existían posibles conflictos de intereses debido al apoyo financiero por parte de la compañía productora del trazador y en un estudio, dos de sus autores eran empleados de la misma compañía productora del trazador.

Aplicabilidad

Para la evaluación de la aplicabilidad, no hubo preocupación de que los pacientes incluidos, el entorno, o la realización e interpretación de la prueba índice, no coincidieran con la pregunta de revisión; sin embargo, la condición objetivo (como se define en el estándar de referencia) no estaba clara debido a la falta de información sobre qué estándar(es) de referencia se aplicaron y también acerca de la metodología utilizada en el estudio (Thurfjell 2012). Por otro lado, en NCT01028053, había preocupación con respecto a la prueba índice debido a la falta de información sobre el umbral y su definición.

5.3.4. Exactitud diagnóstica de los estudios incluidos

Progresión desde un DCL a una DEA

La progresión desde un DCL a una DEA en el estudio con un seguimiento de tres años tuvo una sensibilidad de 64% (IC 95%: 53 a 75) y una especificidad de 69% (IC 95%: 60 a 76) mediante evaluación visual de la TEP con 18F-Flutemetamol.

La progresión en aquellos con un seguimiento a dos años tuvo una sensibilidad de 89% (IC 95%:52 a 100) y una especificidad de 80% (IC 95%: 44 a 97) mediante una evaluación cuantitativa del 18F-Flutemetamol.

Progresión desde un DCL a una demencia no-DEA o cualquier forma de demencia

No se encontraron estudios que evaluaran la progresión desde un DCL a cualquier forma de demencia o cualquier forma de demencia no-DEA.

5.3.5. Publicación

Cochrane Database of Systematic Reviews

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

Martínez G, Vernooij RWM, Fuentes Padilla P, Zamora J, Flicker L, Bonfill Cosp X

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[Diagnostic Test Accuracy Review]

18F PET with flutemetamol 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

[18]F-flutemetamol uptake by brain tissue, measured by positron emission tomography (PET), is accepted by regulatory agencies like the Food and Drug Administration (FDA) and the European Medicine Agencies (EMA) for assessing amyloid load in people with dementia. Its added value is mainly demonstrated by excluding Alzheimer's pathology in an established dementia diagnosis. However, the National Institute on Aging and Alzheimer's Association (NIA-AA) revised the diagnostic criteria for Alzheimer's disease and the confidence in the diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease may be increased when using some amyloid biomarkers tests like ^{18}F-flutemetamol. These tests, added to the MCI core clinical criteria, might increase the diagnostic test accuracy (DTA) of a testing strategy. However, the DTA of ^{18}F-flutemetamol to predict the progression from MCI to Alzheimer's disease dementia (ADD) or other dementias has not yet been systematically evaluated.

Objectives

To determine the DTA of the ^{18}F-flutemetamol PET scan for detecting people with MCI at time of performing the test who will clinically progress to ADD, other forms of dementia (non-ADD) or any form of dementia at follow-up.

Search methods

The most recent search for this review was performed in May 2017. We searched MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), BIOSIS Citation Index (Thomson Reuters Web of Science), Web of Science Core Collection, including the Science Citation Index (Thomson Reuters Web of Science) and the Conference Proceedings Citation Index (Thomson Reuters Web of Science), LILACS (BIREME), CINAHL (EBSCOhost), 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 also searched ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialised register of dementia studies (http://www.medicine.ox.ac.uk/alois/). We checked

the reference lists of any relevant studies and systematic reviews, and performed citation tracking using the Science Citation Index to identify any additional relevant studies. No language or date restrictions were applied to the electronic searches.

Selection criteria

We included studies that had prospectively defined cohorts with any accepted definition of MCI at time of performing the test and the use of ^{18}F-flutemetamol scan to evaluate the DTA of the progression from MCI to ADD or other forms of dementia. In addition, we only selected studies that applied a reference standard for Alzheimer's dementia diagnosis, for example, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria.

Data collection and analysis

We screened all titles and abstracts identified in electronic-database searches. Two review authors independently selected studies for inclusion and extracted data to create two-by-two tables, showing the binary test results cross-classified with the binary reference standard. We used these data to calculate sensitivities, specificities, and their 95% confidence intervals. Two independent assessors performed quality assessment using the QUADAS-2 tool plus some additional items to assess the methodological quality of the included studies.

Main results

Progression from MCI to ADD was evaluated in 243 participants from two studies. The studies reported data on 19 participants with two years of follow-up and on 224 participants with three years of follow-up. Nine (47.4%) participants converted at two years follow-up and 81 (36.2%) converted at three years of follow-up.

There were concerns about participant selection and sampling in both studies. The index test domain in one study was considered unclear and in the second study it was considered at low risk of bias. For the reference standard domain, one study was considered at low risk and the second study was considered to have an unclear risk of bias. Regarding the domains of flow and timing, both studies were considered at high risk of bias.

MCI to ADD;

Progression from MCI to ADD at two years of follow-up had a sensitivity of 89% (95% CI 52 to 100) and a specificity of 80% (95% CI 44 to 97) by quantitative assessment by SUVR (n = 19, 1 study).

Progression from MCI to ADD at three years of follow-up had a sensitivity of 64% (95% CI 53 to 75) and a specificity of 69% (95% CI 60 to 76) by visual assessment (n = 224, 1 study).

There was no information regarding the other two objectives in this systematic review (SR): progression from MCI to other forms of dementia and progression to any form of dementia at follow-up.

Authors' conclusions

Due to the varying sensitivity and specificity for predicting the progression from MCI to ADD and the limited data available, we cannot recommend routine use of ^{18}F-flutemetamol in clinical practice. ^{18}F-flutemetamol has high financial costs; therefore, clearly demonstrating its DTA and standardising the process of the ^{18}F-flutemetamol modality is important prior to its wider use.

PLAIN LANGUAGE SUMMARY

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

Review question: In people with mild cognitive impairment (MCI), does using a ^{18}F PET scan with flutemetamol predict the progression to Alzheimer's disease dementia (ADD) and other dementias?

Background

Due to global ageing, the number of people with dementia is expected to increase dramatically in the next few decades. Diagnosing dementia at an early stage is desirable, but there is no widespread agreement on the best approach. A range of simple pen and paper tests used by healthcare professionals can assess people with poor memory or cognitive impairment. Whether or not using special PET

scans that detect amyloid -one of the hallmarks of Alzheimer's disease- improves our ability to predict the progression from MCI to ADD or other forms of dementia remains unclear. Since these tests are expensive, it is important that they provide additional benefits.

Aim

We aimed to evaluate the accuracy of the ^{18}F-flutemetamol PET scan in identifying those people with MCI who clinically progress to ADD, other types of dementia, or any form of dementia over a period of time.

Study characteristics

The evidence is current to May 2017. We found two studies evaluating the progression from MCI to ADD. The studies included 252 MCI eligible participants, with 243 participants that had follow-up. Of these, 127 were women. The average age in one study with two years of follow-up was 72.7 ± 7.09 years. In the other study with three years of follow-up, the average age was 71.1 ± 8.62 years. The setting in one study was memory clinics.

Study funding sources: both studies were funded by the test manufacturer.

Quality of the evidence

The main limitation of this review was that our findings were based on only two studies, with not enough details on how the people were selected, how the interpretation of the PET scan was made in one study, how the clinical diagnosis of dementia was established in the other study. The studies were considered to be at high risk of bias due to potential conflicts of interest detected.

Key findings

In this review, we found that the ^{18}F-flutemetamol PET scan, as a single test, in one study with 19 participants included with 2 years of follow-up, had a sensitivity of 89% and a specificity of 80%. This means that in a cohort with 100 participants with MCI and a proportion of progression in this study of 47%, we would expect 42 of 47 MCI participants with a positive result for ^{18}F-flutemetamol scan to progress to ADD, and 5 participants to be falsely positive. In addition, we would expect 42 of 53 participants who will not progress to ADD to have a negative result for ^{18}F-flutemetamol, and 11 to be falsely negative.

In the other study with 224 participants included in the analysis with 3 years follow-up, the sensitivity was 64% and the specificity was 69%. This means that in a cohort with 100 participants with MCI and a proportion of progression in this study of 36%, we would expect 23 of 36 MCI participants with a positive result for ^{18}F-flutemetamol to progress to ADD, and 13 participants to be falsely positive. In addition, we would expect 44 of 64 participants who will not progress to ADD to have a negative result for ^{18}F-flutemetamol, and 20 to be falsely negative.

There was no information regarding the progression from MCI to other forms of dementia and progression to any form of dementia at follow-up.

We conclude that ^{18}F-flutemetamol PET imaging cannot be recommended for routine use in clinical practice to predict the progression from MCI to ADD based on the currently available data. More studies are needed to clearly demonstrate its usefulness.

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. See the glossary in Appendix 1. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by a dete-

rioration in emotional control, social behaviour, motivation, and the impairment is sufficient to interfere with everyday activities. Dementia is a collection of different subtypes distinguished by the underlying pathology. 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 number of 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 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 people with dementia (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). On the other hand, this controversy could be because our clinical diagnostic criteria have not had enough accuracy to diagnose Alzheimer's disease that is detected by histopathology in postmortem studies (Hyman 2012). In addition, other researchers think that there is not a real controversy about the amyloid hypothesis, because the amyloid cascade and the Aβ deposition have a primary role in Alzheimer's disease (Selkoe 2016).

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 an important initiative, 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-flutemetamol, is a fluorinated tracer, derived from the Pittsburgh Compound B (the first tracer developed), and it is characterised by a higher median life of 110 minutes than the Pittsburgh Compound B and a high affinity for amyloid β. The performance of the ^{18}F-flutemetamol PET scan was probed in vivo with healthy people and ADD (Nelissen 2009) and also in people with MCI (Vandenberghe 2010) and it has been considered that it could eventually be used to differentiate between different dementia types, specifically between FTD and ADD like other fluorinated tracers such as ^{18}F-florbetaben (Villemagne 2011) or ^{18}F-florbetapir (Kobylecki 2015).

In 2013, ^{18}F-flutemetamol was approved by the Food and Drug Administration (FDA) and, in 2014, by the European Medicines Agency (EMA). A positive scan indicates moderate to frequent presence of neuritic amyloid plaques. However, this might also occur in people with other neurological conditions and in older

adults with normal cognition. Therefore, the safety and effectiveness of ^{18}F-flutemetamol have not been established for predicting development of dementia or other neurological conditions and it should be combined with other diagnostic evaluations or instruments (EMA 2014; FDA 2014).

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-flutemetamol for Aβ, increase the risk of developing dementia over time. The evidence for this is uncertain. For this and other reasons, the 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).

An assumption for some researchers, and one on which this systematic review (SR) is predicated, is 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 families, and clinicians involved in their care.

[18]F-flutemetamol PET scan is considered the diagnostic marker of interest, and in this SR we assessed the DTA of ^{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.

This SR belongs to a series of SRs regarding PET biomarkers for Aβ, including ^{18}F-florbetaben and ^{18}F-florbetapir (Martínez 2016).

Target condition being diagnosed

This SR assessed 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 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 ^{18}F-flutemetamol scan is an index test 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-flutemetamol is a molecular biomarker, described as follows.

- ^{18}F-flutemetamol Aβ is described as 6-benzothiazolol, 2-[3-[18F]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).

- ^{18}F-flutemetamol has been evaluated in people with ADD, MCI, and healthy controls in a clinical field in order to identify a valid, simple, and reliable PET quantitation method for the routine measure of brain amyloid retention in vivo (Vandenberghe 2010).

Image Interpretation

Both the FDA and EMA have described the criteria for ^{18}F-flutemetamol for Aβ positivity (EMA 2014; FDA 2014). ^{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 ^{18}F-flutemetamol should interpret the Aβ PET images made with this ligand (EMA 2014; FDA 2014).

Before the FDA and EMA described the criteria for ^{18}F-flutemetamol scan positivity, the diagnosis of dementia was made using different thresholds. Therefore, we planned 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 [18]F-

flutemetamol Aβ uptake and retention exceeded a certain threshold.

We considered the measurement of the ^{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-flutemetamol distribution volume in the selected area (ROI) to the distribution volume in the reference area. SUVR is the ratio of the ^{18}F-flutemetamol ligand standardised uptake value in the selected area (ROI) to the standardised uptake value in the reference area.

The unit of analysis of our SR was the participant. We did not include studies that analysed multiple ROIs per participant.

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

Administration Instructions and Recommended Dosing

- Time between ^{18}F-flutemetamol injection and PET acquisition: images should be acquired in 20 minutes starting from 90 minutes after intravenous administration (EMA 2014; FDA 2014).

- Injection dose: the recommended dose for ^{18}F-flutemetamol Aβ PET is 185 MBq (5.0 mCi) administered as a single slow intravenous bolus (EMA 2014; FDA 2014).

Although it was inevitable that included studies had 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 performance of the diagnostic tests will probably vary according to whether it is a primary consultation or referral 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-flutemetamol PET ligand for Aβ is 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 aetiology (e.g. FTD versus ADD). Otherwise, it might be used solely in the research field in people with MCI for the enrichment of clinical trials, for example, enrolling people with MCI and a positive PET scan to study preventive interventions before people develop dementia.

However, in some memory clinics the ^{18}F-flutemetamol PET is used for clinical purposes in people with persistent or progressive unexplained MCI adopting the Johnson criteria (Johnson 2013), criteria without sufficient evidence. Therefore, if the ^{18}F-flutemetamol PET is positive in a person with MCI, this positivity is considered as one of the core histopathological findings of Alzheimer's disease. The person will thus be catalogued as a patient with prodromal Alzheimer's disease or MCI due to Alzheimer's disease.

Alternative test(s)

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

- [18]F PET ligands for Aβ (^{18}F-florbetapir, ^{18}F-florbetaben) (Martinez 2016).

- ^{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 in healthcare systems, because the costs of dementia are currently at least 1% of the world's GNP (WHO 2012).

[18]F-flutemetamol is 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-flutemetamol is not approved for this purpose, this biomarker test is currently being used in the research field to search for the accurate identification of people with MCI who would progress to ADD 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 the generalisability of the DTA results 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.

This SR assesses the DTA with ^{18}F-flutemetamol Aβ PET in people with MCI.

OBJECTIVES

To determine the diagnostic test accuracy (DTA) of ^{18}F-flutemetamol as the index test for detecting people with mild cognitive impairment (MCI) at time of performing the test 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, by evaluating the spectrum of people, referral centres, clinical criteria of MCI, ^{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 included longitudinal studies that had prospectively defined cohorts with any accepted definition of mild cognitive impairment (MCI), as outlined below, at time of performing the ^{18}F-flutemetamol Aβ scan and a reference standard (see Index tests and Reference standards below). We obtained the results at the follow-up of the studies. These studies had to employ delayed verification of progression to dementia and were sometimes labelled as 'delayed verification cross sectional studies' (Bossuyt 2008; Knottnerus 2002). We included case-control studies when they incorporate a delayed verification design. This occurred in the context of a cohort study, so these studies were invariably diagnostic-nested case-control studies.

Participants

Participants recruited and clinically classified as having MCI at time of performing the test were eligible for inclusion. We established the diagnosis of MCI using the Petersen criteria or revised Petersen criteria (Petersen 1999; Petersen 2004; Winblad 2004), the criteria included in Matthews study (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 excluded 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). Regarding Parkinson's disease, many of the studies specifically excluded people with Parkinson's disease from the group with mild cognitive impairment. This specific group of people is complex in both regards to defining neuropathology and in determination of functional decline. For these reasons this group of people needs to be addressed in specific studies

Index tests

The index test of this SR was ^{18}F-flutemetamol biomarker test. We used the criteria and cut-off values for test positivity, as reported in the included studies. We considered positivity for ^{18}F-flutemetamol Aβ scan uptake and retention exceeding a certain threshold.

Target conditions

Three target conditions were included in this SR:

- 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 was 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 this SR, we accepted several definitions of ADD. We included 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 considered all these issues when we interpreted the results.

Similarly, we accepted differing clinical definitions of other dementias. For Lewy Body Dementia the reference standard is the McKeith criteria (McKeith 1996; McKeith 2005); for frontotemporal 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 (Roman 1993), the DSM criteria (APA 1987; APA 1994), or the ICD criteria (ICD-10).

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

We searched MEDLINE (Ovid SP) from 1946 to May 2017; Embase (Ovid SP) from 1974 to May 2017; PsycINFO (Ovid SP) from 1806 to May 2017; BIOSIS Citation Index (Thomson Reuters Web of Science) from 1922 to May 2017; Web of Science Core Collection, including the Science Citation Index (Thomson Reuters Web of Science) and the Conference Proceedings Citation Index (Thomson Reuters Web of Science) from 1946 to May 2017; LILACS (Bireme); CINAHL (EBSCOhost) from 1980 to May 2017; 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 also searched ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialized register of dementia studies (http://www.medicine.ox.ac.uk/alois/).

We used two approaches in designing the search. One focused solely on the specifically named index test (including a range of synonyms) and the second, run in parallel covered a more general search, linking broader terms for the index test. It focused on terms describing its diagnostic use and terms for the target condition to try to capture the more difficult to locate studies of a more general nature, where these particular radioligands were included in diagnostic accuracy research but not named specifically in the parts of the electronic bibliographic record that are searchable and therefore would be missed.

See Appendix 2 for details of the sources and search strategies that we used. No language or date restrictions were applied to the electronic searches.

Searching other resources

We examined the reference lists of all relevant studies for additional studies. We also searched the Database of Abstracts of Reviews of Effects (DARE) via the Cochrane Library (www.cochranelibrary.com)), the National Institute for Health Research - Health Technology Assessment Database (NIHR-HTA) (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 checked the reference lists of any relevant studies and SRs, and performed citation tracking using the Science Citation Index to identify any additional relevant studies.

Search methods for identification of studies

Data collection and analysis

Electronic searches

Selection of studies

Two review authors (GM, RV) independently screened the retrieved titles and abstracts for potentially eligible studies. A third review author (PF) resolved any disagreements between the two review authors. The two review authors (GM, RV) then independently assessed the full-text articles of the selected studies with the inclusion criteria. They resolved any disagreements through discussion or, where necessary, consulted a third review author (PF) who acted as an arbitrator. When a study did not present all relevant data for creating 2 × 2 table, we contacted the study authors directly to request further information. When more than one article presented data on the same population, we included the primary article, which was 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 planned 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-flutemetamol test administration, including those who administered the test;
  - thresholds used to define positive and negative test;
  - 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 the index test performed to defining ADD and other dementias by the reference standard: one year to less than two years; two years to less than four years; and four years or more. If participants had been followed for varied amounts of time we recorded a mean follow-up period for each included study. If possible, we grouped those data into minimum, maximum, and median follow-up periods, to enable subgroup analyses;
  - prevalence or proportion of population developing ADD and other dementias, with severity if described.

We created 2 × 2 tables (cross-relating index test results of the reference standards) as shown in Appendix 3. For each included study, we recorded the number of participants lost to follow-up.

We also extracted data necessary for the quality assessment, as defined below. Two review authors (GM, RV) independently performed data extraction. We resolved any disagreements regarding data extraction by discussion, or consulting a third review author (PF), if it was necessary.

Assessment of methodological quality

We assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2) (Whiting 2011), as recommended by Cochrane (Davis 2013). This tool is comprised of four domains: patient selection, index test, reference standard, and patient flow.

Two review authors (GM, RV), who were blinded to each other's scores, independently performed the QUADAS-2 assessment. We resolved any disagreements by discussion or, if necessary, consulted a third review author (PF) who acted as an arbitrator. We assessed each domain in terms of risk of bias, and also considered the first three domains in terms of applicability concerns. In Appendix 4, we have detailed the components of each of these domains and provided a rubric that shows how we made judgements concerning risk of bias. Key areas important to quality assessment were participant selection, blinding, and missing data.

We included three additional signalling questions on our checklist.

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

We included the item pertaining to the PET scan interpretation and the definition of positive results to take into account the subjective nature of the ^{18}F-flutemetamol Aβ scan image interpretation, which may be based on a variety of different criteria, such as extensive clinical experience, different standardised uptake values (SUV), different morphological features, or a combination of the aforementioned. We included the third additional item in order to record any potential bias resulting from commercial interest in the results due to the potential risk by the manufacturing company leading to more favourable results and conclusions than sponsorship by other sources (Lundh 2017).

We did not use QUADAS-2 data to form a summary quality score. We produced a narrative summary that described each included study as at high, low, or unclear risk of bias, as well as concerns regarding applicability, which we have described in Appendix 5.

Statistical analysis and data synthesis

We applied the DTA framework for the analysis of a single test and extracted the data from each included study into a 2×2 table,

showing the binary test results cross-classified with the binary reference standard, and we ignored any censoring that might have occurred. We acknowledge that such a reduction in the data may represent a significant oversimplification. We used 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 these into Review Manager (RevMan) (Review Manager 2014) to calculate the sensitivities, specificities, and their 95% confidence intervals. We also presented individual study results graphically by plotting estimates of sensitivities and specificities in both a forest plot. If an individual included study published more than one threshold, we presented the graphical findings for all reported thresholds.

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 we planned to clearly note where the same included studies contributed to the analysis for more than one reference standard follow-up interval.

However, due to lack of data, we conducted no meta-analyses. However, we prepared a 'summary of findings table'.

Investigations of heterogeneity

We were able to include only two studies, therefore issues of heterogeneity did not arise.

Sensitivity analyses

We found insufficient data to conduct any sensitivity analyses.

Assessment of reporting bias

We did not investigate reporting bias.

RESULTS

Results of the search

The total number of records identified for this SR was 1333. The PRISMA diagram (Figure 1) shows the selection of records through the screening and selection processes. In total, we assessed 81 studies (23 full-text papers, 22 conference publications, 11 registered studies in clinicaltrials.gov, and 25 registered studies in WHO ICTRP) for eligibility in the full-text screening. We excluded 72 studies. Ten studies were multiple publications or duplicated and 4 studies did not have extractable data for constructing 2 x 2 tables, and we received no reply when we contacted the authors (Goukasian 2015; Rowe 2015a; Rowe 2015b; Rowe 2015c) (Characteristics of excluded studies). We excluded the remaining 58 studies because they did not meet the inclusion criteria: i) not a longitudinal study (n = 23); ii) no MCI participants at time of performing the test (n = 21); iii) index test not a ^{18}F-flutemetamol PET scan (n = 4); iv) discussion or review paper (n = 6); v) wrong outcomes or design (n = 4). We included two studies and identified seven references as ongoing studies.

Figure 1. Flow diagram.

Included studies

See Characteristics of included studies.

Thurfjell 2012 refers to a study with baseline data that had been published 2 years earlier with ADD, MCI and healthy controls (HC) participants. MCI participants were recruited from secondary care (7 memory clinics). Participants were recruited as part of a study to evaluate the ^{18}F-flutemetamol PET scan in people with ADD (n = 27), amnestic MCI (n = 20) and healthy controls (n = 20) as a cross-sectional study to determine the efficacy of blinded visual assessment of images of ^{18}F-flutemetamol uptake for separating subjects with clinically probable ADD from healthy controls, the SUVRs of subjects with probable ADD and HC, the concordance between (11)C-labelled Pittsburgh Compound-B ((11)C-PIB) and ^{18}F-flutemetamol scans, regarding visual assessment and quantitative SUVR in ADD and MCI participants, and the assignation of a raised or low amyloid group category through visual or quantitative assessment in MCI participants (Vandenberghe 2010).

The study of Thurfjell 2012 included 20 MCI participants with a follow-up of two years to evaluate the progression from amnestic MCI to probable ADD according to their ^{18}F-flutemetamol status as positive or negative, using a SUVR > 1.5 (Thurfjell 2012). The SUVR established in the previous study with ADD and HC participants was 1.56. The other objective of this study was to compute the hippocampus volume from MRI and investigate its accuracy performance alone and combined with the ^{18}F-flutemetamol PET scan at follow-up. MCI participants fulfilled Petersen 1999 criteria for amnestic MCI, 11 were male, they had a mean age of 72.7 $\pm$ 7.09 years, with 14.4 $\pm$ 2.97 mean years of education, and their mean MMSE was 28.0 $\pm$ 0.94 points.

Of the 20 participants, 9 (45%) developed Alzheimer's dementia. One participant (5%) was reported as lost to follow-up without further information about the cause.

The reference standard was not explicitly stated, although NINCDS-ADRDA criteria for ADD (McKhann 1984) and APA 1994 were baseline diagnostic criteria in the Vandenberghe study (Vandenberghe 2010).

Potential conflicts of interest were noted. Financial support for the baseline study (Vandenberghe 2010) was from the manufacturer of ^{18}F-flutemetamol tracer and two authors were employees of this company.

NCT01028053 refers to an international and multicentric study in the United States and Europe (also known as EUCTR2009-010227-62-GB in Europe) and with a common sponsor's protocol code number, GE-067-005.

The main objective of this study was to evaluate the 'hazard ratio by PET scan readers for conversion to probable Alzheimer's disease based on visual image Interpretation' in amnestic MCI participants with normal and abnormal patterns of ^{18}F-flutemetamol uptake, based on the visual assessment of a ^{18}F-flutemetamol

PET scan. This unpublished study had no information regarding the participants' recruitment. There were 230 planned evaluable participants. The participants were 60 years old or older (US inclusion criteria in clinicaltrials.gov) or over 55 years old (Europe in EUDRACT), they met the Petersen criteria for amnestic MCI (not provided which of the different Petersen criteria published were used), had a score of less than or equal to 4 on the Modified Hachinski Ischemic Scale, a MMSE score of 24 to 30, and a non-contrast MRI examination as part of the screening visit that excluded amnestic MCI arising from structural causes, and they had no significant neurologic disease other than suspected amnestic MCI. The mean age was 71.1 ($\pm$ 8.62) years, 63 participants were less than 65 years, and 118 were women.

Participants were assessed clinically on-site every six months until progression to probable ADD (as determined by an independent Clinical Adjudication Committee (CAC)); or completion of 36 months of follow-up, whichever came first. Clinical assessments were performed by a trained on-site clinician who collected the results of a battery of tests, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria for probable ADD, and clinical assessment: this clinician was blinded to the subjects' PET images and interpretations until the study was complete. The follow-up data were regularly submitted to the CAC (which consisted of four experts in the diagnosis of memory disorders), which determined whether or not the subject had converted to probable ADD. The CAC reviewed all study data (excluding the investigator's progression assessment, the ^{18}F-flutemetamol PET scan results and any other amyloid imaging data) for each subject to determine whether or not the subject had converted to probable ADD. The decision rules to be used in defining a progression to probable ADD were established by the CAC before reviewing any subject's data.

The study analysed 224 participants of the original 232 participants at 36 months of follow-up, because 8 participants withdrew before the first assessment at the follow-up.

Potential conflicts of interest were noted. Total financial support was provided from the manufacturer of ^{18}F-flutemetamol tracer.

Excluded studies

We excluded four studies since they did not meet the inclusion criteria for participants, index test, or target condition (Characteristics of excluded studies).

The Goukasian 2015 study was focused on neuropsychiatric symptoms with a probable follow-up in 38 MCI participants with a SUVR > 1.27 for brain amyloidosis. In Rowe 2015a, there were 59 participants with MCI at the time of performing the test and at the end of 18 months of follow-up, there were 16 participants to be evaluated. In Rowe 2015b, there were 50 MCI participants and at the end of 18 months of follow-up, there were seven par-

ticipants to be evaluated. In Rowe 2015c, there were 17 participants with MCI evaluated at 18 months of follow-up. All of these three studies were focused on change of ¹⁸F-flutemetamol PET scan retention over time and probably shared participants, so it is possible that these reports referred to the same study.

None of the authors answered our email inquiries for additional information.

Ongoing studies

We

found two ongoing studies in clinicaltrials.gov. NCT02164643 is a study that focused on participants with different cognitive spectrums, from isolated cognitive complaints to MCI with a basal ¹⁸F-flutemetamol or ¹⁸F-florbetapir PET scan and the progression to a clinical dementia stage according to DSM-IV and NINCDS-ADRDA as reference standards for up 24 months follow-up. This study has been recruiting participants since July 2014 in France. The second study, NCT02196116, is focused on the amyloid load in three different participants in a cross-sectional study: controls, MCI without memory complaints, and MCI with memory complaints. However, they also considered a longer term clinical follow-up of study participants to investigate the prognosis value of amyloid load for improving the prediction of cognitive decline and disease progression. No further information about the follow-up was detailed.

We found five ongoing studies in the WHO ICTRP register. EUCTR2011-001756-12-BE is a study focused on cognitively healthy older people and MCI participants. The main objective is to evaluate, with a multimarker approach, the amnestic MCI participants by quantitative analysis of each biomarker by comparison to a normal database of recruited healthy volunteers and a clinical follow-up from one to three years with basal ¹⁸F-flutemetamol. No further details were provided regarding the participants, index test, and reference standard(s). This study has been ongoing since April 2012. The second study, EUCTR2011-006195-39-SE, is focused on MCI participants and the main objective is to examine the efficacy of raised ¹⁸F-flutemetamol brain uptake for dif-

ferentiating people with mild cognitive impairment (MCI), who subsequently will develop ADD, from people with MCI who will be cognitively stable or develop other dementias than ADD. No further details were provided regarding the participants, index test, and reference standard(s). This study has been ongoing since January 2012. The third study is JPRN-UMIN000019926, which is focused on preclinical Alzheimer's disease and MCI participants. Their main objective is to discriminate between MCI individuals at risk of development of Alzheimer dementia over an established follow-up of 36 months. The index test will be 11C-PiB, ¹⁸F-florbetapir, or ¹⁸F-flutemetamol PET scan. No further details were given regarding index test, and reference standard(s). This study has been ongoing since January 2016. The fourth study, EUCTR2017-000094-36-SE, is focused on MCI, dementia, and healthy elderly people and the main objective is to study the diagnostic accuracy of Tau PET ¹⁸F-RO6958948 and ¹⁸F-flutemetamol for identifying healthy elderly individuals and people with subjective or objective mild cognitive symptoms who are at high risk of subsequent development of ADD or other neurodegenerative disorders. The follow-up was not clearly stated. This study has been ongoing since March 2017. The fifth study, EUCTR2016-002635-15-NL, is focused on people aged 90 or older. The main objectives are to understand how clinical markers and biomarkers previously identified in younger and older ADD cohorts apply to the extremely old, to identify novel biomarkers linked with resilience to developing ADD in extremely old subjects and the generation of normative data for the oldest, and measure the concordance between amyloid pathology as assessed in CSF and by PET. This study has been ongoing since July 2016.

Methodological quality of included studies

We assessed methodological quality 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. The overall methodological quality of the studies is summarised in Figure 2.

Figure 2. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

In the patient selection domain, we considered both studies (Thurfjell 2012; NCT01028053) to be at unclear risk of bias due to lack of reporting on sampling procedures and exclusion criteria. We stated that the included studies avoided a case-control design because we only considered data on performance of the index test to discriminate between people with MCI who converted to dementia and those who remained stable.

In the index test domain, we considered one study to have a low risk of bias and the other study to be at unclear risk of bias. The Thurfjell study had low risk of bias because the threshold used, according to Thurfjell 2012 references, was established in the previous study in ADD and HC participants as a SUVR > 1.56 (Vandenberghe 2010), however, the SUVR used in this study was 1.5 and the index test results were interpreted without knowledge of the results of the reference standard. Regarding NCT01028053, the interpretation was made without knowledge of the reference standard, however the threshold was not clearly prespecified. In our two additional signalling questions, in the question on whether the index test was interpreted by a trained reader physician, this risk was unclear due to lack of information in the Thurfjell study, but no risk was identified in the NCT01028053 study. On the other hand, the other signalling question was rated as low risk in the Thurfjell study because there was a clear definition of a positive result, and unclear in NCT01028053 due to lack of information.

In the reference standard domain, we considered the Thurfjell study to have an unclear risk of bias because it was not reported if the clinicians conducting follow-up were aware of the initial ^{18}F-flutemetamol result. We were not able to obtain the information about which reference standard was used, or how and by whom this reference standard was obtained, due to poor reporting (Thurfjell 2012). We judged NCT01028053, to be at a low risk of bias, because the reference standard used was NINCDS-ADRDA (McKhann 1984) and the CAC were blinded to the ^{18}F-flutemetamol PET scan to established the reference standard.

In the flow and timing domain, we judged the Thurfjell study to have a high risk of bias because, in our additional signalling question, there were potential conflicts of interest due to financial support for the study (Vandenberghe 2010) and two authors of Thurfjell 2012 were employees from the manufacturer of the ^{18}F-flutemetamol tracer. We judged the NCT01028053 study as having a high risk of bias due to possible conflict of interest due to financial support by the ^{18}F-flutemetamol producer company. For assessment of applicability, there was no concern that the included patients and setting, or the conduct and interpretation of the index test, did not match the review question; however, the target condition (as defined by the reference standard) was unclear due to lack to information about which reference standard(s)

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were applied and also the methodology used in the Thurfjell study (Thurfjell 2012). On the other hand, in NCT01028053, there was concern regarding the index test due to lack to information about the threshold and its definition.

Findings

The results of the included studies are summarised in Data table 1. Additionally, the summary of main results for the included studies are presented in the Summary of findings.

18F-flutemetamol for Alzheimer's disease dementia (ADD)

NCT01028053 data on 224 of 232 eligible participants with amnestic MCI (diagnosed with Petersen criteria (not clear which of them were used), using NINCDS-ADRDA (McKhann 1984)) had a sensitivity of 64% (95% CI 53 to 75) and a specificity of 69% (95% CI 60 to 76) to predict the progression from amnestic MCI to ADD at three years follow-up. Of 232 participants who were given an initial clinical diagnosis of amnestic MCI, the study had data on 224 of them at the follow-up: 52 were true positive, 45 were false positive, 29 were false negative, and 98 were true negative (Figure 3).

Figure 3. Forest plot of 18F-flutemetamol.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
NCT01028053	52	45	29	98	0.64 [0.53, 0.75]	0.69 [0.60, 0.76]		
Thurfjell 2012	8	2	1	8	0.89 [0.52, 1.00]	0.80 [0.44, 0.97]		
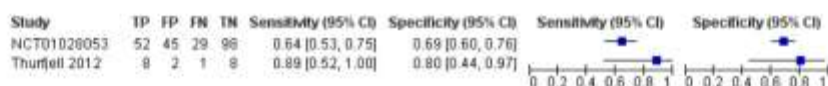
The criteria for 18F-flutemetamol PET scan positivity was a visual assessment done by five blinded and trained readers, and they established the positivity or negativity of the PET scan according to the majority readings.

Thurfjell 2012 data on 19 of 20 eligible participants with amnestic MCI (diagnosed with Petersen criteria (Petersen 1999), using a nonspecified reference standard, probably NINCDS-ADRDA (McKhann 1984) and APA 1994) had a sensitivity of 89% (95% CI 52 to 100) and a specificity of 80% (95% CI 44 to 97) to predict the progression from amnestic MCI to ADD at two years follow-up. Of 20 participants who were given an initial clinical diagnosis of amnestic MCI, the study had data on 19 of them at the follow-up; 8 were true positive, 2 were false positive, 1 was false negative and 8 were true negative (Figure 3).

The criterion for 18F-flutemetamol PET scan positivity was a quantitative threshold with a SUVR > 1.5 and the measures of 18F-flutemetamol amyloid retention were;; lateral frontal cortex (FRO), lateral temporal cortex (LTC), lateral parietal cortex (PAR), anterior cingulate (ANC), occipital cortex (OCC), and pons (PON); a cerebellar ROI served as the reference region.

No data were available regarding the other two target conditions in this Cochrane review: progression from MCI to another form of dementia (non-ADD) or progression from MCI to any form of dementia.

Investigation of heterogeneity

The planned investigations were not possible due to the limited number of studies available for the analysis.

Sensitivity analyses

There were insufficient studies identified to permit any sensitivity analyses.

Summary of findings

What is the diagnostic accuracy of ^{18}F-flutemetamol PET amyloid biomarker for predict progression to ADD in people with MCI?

Descriptive	
Patient population	Participants diagnosed with MCI at the time of performing the test using any of the Petersen criteria or Winblad criteria or CDR = 0.5 or any of the 16 definitions included by Matthews (Matthews 2008).
Sources of referral	Not reported (n = 2)
MCI criteria	Petersen criteria (n = 2)
Sampling procedure	Unclear (n = 2)
Prior testing	The only testing prior to performing the ^{18}F-flutemetamol PET amyloid biomarker was the application of diagnostic criteria for identifying participants with MCI
Settings	Secondary care (n = 1) Not reported (n = 1)
Index test	^{18}F-flutemetamol PET
Threshold pre-specified at baseline	Yes (n=1) Unclear (n=1)
Threshold interpretation	Visual (n = 1) Quantitative (n = 1)
Threshold	SUVR (Standardised Uptake Volume ratio) of ROI: > 1.5 (n = 1) Not specified: analytical visual approach of ROI: (n = 1)
^{18}F-flutemetamol retention region	Global cortex (n = 1) Not reported (n = 1)

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Reference Standard	For Alzheimer's disease dementia: NINCDS-ADRDA (n = 1) Unclear (n = 1)
Target condition	Progression from MCI to Alzheimer's disease dementia or any other forms of dementia (non-ADD) or any form of dementia
Included studies	Prospectively well-defined cohorts with any accepted definition of MCI (as above). Two studies (N = 252 participants) were included. Number of participants included in analysis: 243
Quality concerns	NCT01028053: Patient selection and index test QUADAS-2 domain: unclear risk of bias Reference standard domain: low risk of bias Flow and timing domain: high risk of bias There were unclear concerns about applicability in the patient selection and index test domain. Thurfjell 2012: Patient selection and index test QUADAS-2 domain: unclear risk of bias Reference standard domain: unclear risk of bias Flow and timing domain: high risk of bias. There was unclear concern about applicability in the reference standard domain
Limitations	Limited investigation of heterogeneity and sensitivity analysis due to an insufficient number of studies We were unable to evaluate progression from MCI to any other form of dementia (non-ADD) or any form of dementia due to lack of included studies

Test	Studies	Cases/Participants	Sensitivity	Specificity	Consequences in a cohort of 100		
					Proportion converting [1]	Missed cases [2]	Overdiagnosed [2]
Alzheimer's disease dementia							
18F-flutemetamol with visual assessment	1	81/224	64% (95% CI 53% to 75%)	69% (95% CI 60% to 76%)	36	13	20
18F-flutemetamol with SUVR	1	9/19	89% (95% CI 52% to 100%)	80% (95% CI 44% to 97%)	47	5	11

Investigation of heterogeneity and sensitivity analysis: The planned investigations were not possible due to the limited number of studies available for each analysis

Conclusions: ^{18}F-flutemetamol PET scan is not an accurate test for detecting progression from MCI to Alzheimer's disease dementia. The strength of the evidence was weak because of considerable variation in study methods, unclear methodological quality due to poor reporting, and high risk of bias due to possible conflict of interest. There is a need for conducting studies using standardised ^{18}F-flutemetamol PET scan methodology in larger populations.

1. *Proportion converting to AD Dementia who did study*

2. *Mixed and mixed diagnoses and numbers reviews not indicating the proportion as reviewing with no specific condition.*

AD D: Alzheimer's disease dementia

CDR: Clinical Dementia Rating
MCI: Mild cognitive impairment
NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PET: Positron emission tomography
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies—2
RO I: Region of interest
SUVR: Standardised uptake value ratio

DISCUSSION

Summary of main results

The volume and quality of evidence regarding the DTA of ^{18}F-flutemetamol for early diagnosis of ADD and other dementias in people with MCI is limited. We identified two studies in this SR. However, we were not able to construct a meta-analysis. We did not perform sensitivity analyses and were not able to analyse the heterogeneity.

The two included studies addressed the DTA of ^{18}F-flutemetamol analysed quantitatively with a threshold of SUVR > 1.5 (Thurfjell 2012) or by visual assessment (NCT01028053) for the prediction of progression from MCI to ADD at follow-up. The results are summarised in the 'Summary of findings' table (Summary of findings). The studies were evaluated as at high risk of bias mainly due to the potential conflict of interest because of the financial support of the company that manufactured the ^{18}F-flutemetamol tracer. The study had no information about the progression to any form of dementia or any other form of dementia (non-ADD). Regarding our objectives, to determine the DTA of the ^{18}F-flutemetamol PET scan for detecting participants with MCI at the time of performing the test who would clinically progress to ADD, or to other forms of dementia or any form of dementia at follow-up, the results were the following:

[18]F-flutemetamol PET scan for Alzheimer's disease dementia (ADD)

Progression from MCI to ADD at three years of follow-up by visual assessment had a sensitivity of 64% (95% CI 53 to 75) and a specificity of 69% (95% CI 60 to 76) respectively (n = 224) (Figure 3).

Progression from MCI to ADD at two years of follow-up by quantitative assessment by SUVR had a sensitivity of 89% (95% CI 52 to 100) and a specificity of 80% (95% CI 44 to 97) respectively (n = 19) (Figure 3).

The DTA of ^{18}F-flutemetamol includes a wide range of low-to-moderate and good sensitivity and specificity for predicting progression to ADD through visual or SUVR assessment evaluation at different follow-up. In other words, the low-to-moderate or good sensitivity could be affected by a relatively high false negative rate, admittedly from only one study. As with other amyloid tracers, ^{18}F-flutemetamol probes the detection of amyloid plaques that are composed of insoluble Aβ peptides (EMA 2014; FDA 2014). However, the soluble Aβ oligomers play a central role in Alzheimer's pathogenesis in the amyloid hypothesis (Heyden 2013), with the possibility of producing false negatives. In addition, amyloid tracers are not be able to bind to the other histopathologic core of Alzheimer's disease - the neurofibrillary tangles (NFTs). There is evidence that suggests that plaques and tangles independently contribute to cognitive impairment over the clinical course of Alzheimer's disease (Serrano-Pozo 2013). Moreover, in another cohort study, the NFT formation might be either unrelated to amyloid plaques formation or a temporally distinct process, or both(Royall 2014). Another reason that could explain false negative results is that those with probable ADD may have multiple brain pathologies, most commonly Alzheimer's disease with macroscopic infarcts, followed by Alzheimer's disease with neocortical Lewy body disease, and, like ADD, MCI pathology could be heterogeneous (Schneider 2007; Schneider 2009).

In addition, the low-to-moderate or good specificity could be affected by a high false positive rate. A positive ^{18}F-flutemetamol PET scan for Aβ, has been found in other neurological conditions. It was positive in pure vascular dementia and Lewy body dementia cases confirmed by autopsy (Thal 2015). On the other hand, in other amyloid biomarkers like PET PiB, and closer to the ^{18}F-flutemetamol chemical composition, the false positive rate could be explained because it has affinity to amyloid in vessel walls, in particular to cerebral amyloid angiopathy (CAA) (Zhang 2014). We would think that the pathological diagnosis of some people with clinical probable ADD may be vascular dementia secondary to CAA and some MCI participants may have vascular MCI due to CAA. The other important option for a high false positive rate is that in many people without cognitive impairment it is possible to find Aβ deposits at their autopsies (Gelber 2012), generating some doubts about the real pathophysiological relevance of the Aβ hypothesis in Alzheimer's disease.

Another important factor to be considered in predicting the progression to ADD and the number of false positives is the duration of follow-up, because the reported progression rate of MCI to ADD is between 8% and 16% per year (Mitchell 2009). Therefore, a high percentage of people with MCI at the time of performing the test would progress to Alzheimer's disease if we had included a longer follow-up period, and this would affect the predictive DTA of the ^{18}F-flutemetamol PET scan. However, the progression rate at two years was 47.4% and 36.2% at three years of follow-up in the included studies. The latest was found in a systematic review with PiB PET where the data were separated into short follow-up and longer than two years of follow-up. They included five studies with 102 participants in total, with a specificity between 58% to 100% (Ma 2014). However, in our study, the follow-up time and percentage of progression were discordant: the progression rate at two years was 47.4% and 36.2% at three years of follow-up in the included studies. This difference is probably explained by the setting of recruitment or demographic or MCI characteristics and possibly other underlying factors that were affecting the data (Thurfjell 2012; NCT01028053). As a consequence, due to the lack of data, we were not able to investigate the effect of the follow-up on the progression rate from MCI to ADD or any form of dementia.

On the other hand, MCI subtypes have been related to progression to dementia. A large longitudinal study with 550 MCI participants indicated that the MCI subtype, presence of storage memory impairment, multiple domain condition, and presence of APOE ϵ4 allele increased the risk of progression to dementia. Multivariate

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

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survival and Kaplan-Meier analyses showed that amnestic MCI with storage memory impairment had the most and closest risk of progression to dementia (Espinosa 2013). In our review, both studies included only amnestic participants, therefore, we could predict a worse accuracy if non-amnestic MCI were included. Additionally, some other risk factors like family history of dementia, APOE ε4 allele presence, and Aβ and tau protein levels in cerebrospinal fluid may contribute to a faster progression rate to dementia. In conclusion, further reviews that include high quality research with 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 ^{18}F-flutemetamol PET scan positivity of diverse MCI subtypes and disease progression.

Strengths and weaknesses of the review

We conducted an extensive, comprehensive, and sensitive literature search, using eleven different electronic databases without any limit to language or date. However, we were only able to include two studies with 243 participants, therefore, our DTA estimates are relatively imprecise. This paucity of evidence reflects the very significant challenges inherent in conducting long term prospective studies of well-characterised participants, followed up to the point of progression to clinical dementia. The methodological quality assessment and data syntheses were based on the recommended methods (Davis 2013). To increase the reliability of our findings, we included only studies that fulfilled delayed verification of progression from MCI to ADD or other form of dementia (non-ADD) or any form of dementia at follow up.

The included studies had significant methodological limitations that weakened confidence in the results of this SR. First, considerable uncertainty remains concerning the clinical diagnosis of ADD; the anatomopathological diagnosis would be the better way to probe the diagnosis, but there was not a clear definition of a positive index test in one study, the reference standard in one study was not explicitly described, and the major problem was the potential conflict of interest with the company that produced the tracer in both studies.

The selection of participants with MCI in these studies could be another weakness, because we did not have all the necessary baseline data in the ClinicalTrials.gov registered study included in this SR (NCT01028053), and what would happen in those with non-amnestic MCI in the future. However, this selection of participants, such as type of MCI, age, presence of the APOE ε4 allele, structural abnormality at MRI, hypometabolism at FDG-PET scan, and alteration in cerebrospinal fluid could help determine different subgroups of people at higher risk of developing dementia at follow-up, and perform a stratification that could help avoid biases, and develop more efficient studies in the future (Caroli 2015; Hampel 2012; Wolz 2016). NCT01028053 had some information about age, presence of the APOE ε4 allele, and

amnestic MCI stage (early/late) in a Cox regression, but without useable data for this DTA review. The Thurfjell study tried to correlate SUVR and hippocampus volume (Thurfjell 2012).

Finally, an important weakness of this SR was the nonresponse of the authors about their studies. This has resulted in a lack of data for analysis in this review.

Applicability of findings to the review question

Regarding the question of this review: Could the ^{18}F-flutemetamol PET scan identify those MCI participants who would progress to clinical dementia at follow up? There were applicability concerns in the index test in one study that did not provide a clear definition of what was considered a ^{18}F-flutemetamol positive result. There were also applicability concerns in the reference standard in one study, mainly due to lack of information regarding how the clinical progression to ADD was made. However, due to the limited number of included studies and levels of heterogeneity with respect to the two domains mentioned above, it was difficult to determine to what extent the findings from this review could be applied to clinical practice.

The DTA of the ^{18}F-flutemetamol PET scan for identifying Alzheimer's disease pathology and identifying those people with MCI who would convert to ADD could be affected by a number of factors that have not been determined so far. First, and most important, is the lack of a large study to evaluate this question. We included only two studies that addressed the question with 243 participants at follow-up. Second, the quantitative criterion used for several studies is not the actually approved criterion of FDA and EMA, because they approved the visual assessment interpretation. However, in this SR we included one study with quantitative evaluation and the other with visual assessment, with lack of information regarding how that visual assessment was made.

We await new studies using the FDA and EMA approval visual assessment criteria in longitudinal studies. The ^{18}F-flutemetamol test is expensive, therefore, we believe it is important to clearly determine its DTA prior to recommending its adoption in clinical practice. The actual sensitivity and specificity are too low to have enough accuracy to be used in clinical practice to predict the progression from MCI to ADD.

AUTHORS' CONCLUSIONS

Implications for practice

As of today, the use of ^{18}F-flutemetamol has not been established for predicting development of Alzheimer's disease (FDA 2014; EMA 2014), and is not indicated in people 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 people with persistent or progressive unexplained MCI (Johnson 2013). The DTA of ^{18}F-flutemetamol PET scans, as determined in this SR, has a variable sensitivity and specificity based on two studies with 243 participants at follow-up to predict the progression from MCI to ADD.

Due to the aforementioned and the methodological limitations of the included studies, it is not possible to recommend the routine use of ^{18}F-flutemetamol in clinical practice. The ^{18}F-flutemetamol biomarker is expensive, therefore it is important to clearly determine its DTA and to standardise the process for the diagnostic modality prior to it being recommended for clinical practice.

Implications for research

FDA and EMA have established the ^{18}F-flutemetamol criteria positivity in order to use these in ADD patient evaluation and their use in MCI participants is accepted in research settings and clinical trials (Albert 2011). However, their use has also been proposed in clinical practice to evaluate people with MCI by the Nuclear Medicine Society and the Alzheimer's Association (Johnson 2013). It is still used in many studies with different ^{18}F-flutemetamol SUVRs, visual assessment, or both. This promotes different accuracies for the tracer even in people with ADD when are compared with HC. Therefore, it is necessary to consider visual assessment as the most important option to interpret the ^{18}F-flutemetamol PET scan, because this is the approach to the interpretation established by FDA and EMA (EMA 2014; FDA 2014).

On the other hand, clinical assessment in people with memory complaints is not always made with only one test: one could add different tests such as volumetric hyppocampal MRI, FDG-PET, SPECT, CSF, and others. This suggestion has face validity because 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 progression 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 (Jack 2010). Based on this hypothesis, the combination of structural imaging, functional imaging, and cognitive tests may be better predictors of when an individual will convert. However, there is a lack of studies with ^{18}F-flutemetamol combined with other tests to predict the progression from MCI to ADD or any form of dementia.

Additionally, if we consider the hierarchical evidence needed for level of efficacy of diagnostic imaging tests, we are currently in the second step of six according to Herscovitch (Herscovitch 2015): technical efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic impact, patient health outcomes, and finally societal efficacy. Therefore, we need further research about accuracy before progressing to the other steps with their specific studies before we can incorporate the ^{18}F-flutemetamol PET scan into clinical practice.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

NCT01028053

Study characteristics	
Patient sampling	• There were 230 amnestic MCI participants that were evaluable for efficacy. • The participants were 60 years old or older (US inclusion criteria in clinicaltrials.gov) or over 55 years old (Europe in EUDRACT). • All participants met the Petersen criteria for amnestic MCI (details of the criteria not provided), had a score of less than or equal to 4 on the Modified Hachinski Ischemic Scale, a MMSE score of 24 to 30, and non-contrast MRI examination as part of the screening visit that excluded amnestic MCI arising from structural causes, and had not any significant neurologic disease other than suspected amnestic MCI. • No further details of participant sampling and recruitment were reported.
Patient characteristics and set-ting	• 232 amnestic MCI participants diagnosed by Petersen criteria (not reported which one of Petersen criteria was used) • Gender: 114 male, 118 female • Mean ± SD age:71.1 + 8.62 years, 63 participants were less than 65 years old • APOE ε4 carrier: not reported • MMSE: not reported • Years of education: not reported • Sources of referral: not reported • Setting: not reported
Index tests	• No data were given regarding the PET/CT scanner used in the different centres. Each participant received one 185 MBq intravenous dose of ^{18}F-flutemetamol Injection ($\leq$ 10 mcg total flutemetamol) injected within 40 seconds. A 185 MBq dose exposes the subject to an effective dose of 5.92 mSv of radiation. • PET imaging started approximately 90 minutes after dosing. Imaging data were collected for 30 minutes in six 5-minute frames. Images were assessed visually by 5 blinded, independent, and trained readers. Based on the blinded image evaluation, each of 5 independent readers separately categorized each subject as having either 'normal' (negative for Aβ) or 'abnormal' (positive for Aβ uptake) based on the PET image pattern. • No further details were given regarding the index test.
Target condition and reference standard(s)	• Target condition: Alzheimer's disease dementia • Reference standard: NINCDS-ADRDA criteria for ADD (McKhann 1984), and a CAC (consisted of 4 experts in the diagnosis of memory disorders) determined if the participant progressed or not to probable ADD, blinded to the investigator's progression assessment, flutemetamol and any other amyloid imaging data.
Flow and timing	• Duration of follow-up: 3 years • Number included in analysis: 224 participants: 97 ^{18}F-flutemetamol (+) and 127 ^{18}F-flutemetamol (-) • Progression from MCI to ADD: ○ 97 ^{18}F-flutemetamol (+): 52 MCI-converted to ADD and 45 MCI-not converted to ADD; 127 ^{18}F-flutemetamol (-): 29 MCI-converted to ADD and 98 MCI-not converted to ADD

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NCT01028053 *(Continued)*

	○ TP = 52; FP = 45; FN = 29; TN = 98 • 8 participants withdrew prior to the first Clinical Adjudication Committee (CAC) evaluation • Full financial support from the manufacturer of ^{18}F-flutemetamol tracer		
Comparative			
Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	Low
DOMAIN 2: Index Test All tests			
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		
Was the 18F-flutemetamol PET scan interpretation done by a trained reader physician?	Yes		
Did the study provide a clear definition of what was considered to be a 18F-flutemetamol positive result?	Unclear		
		Unclear	Unclear
DOMAIN 3: Reference Standard			

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		
		Low	Low

DOMAIN 4: Flow and Timing

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		
Was the study with 18F-flutemetamol free of commercial funding?	No		
		High	

Thurfjell 2012

Study characteristics

Patient sampling	• Participants with MCI and Alzheimer's disease were included from 7 academic memory clinics and healthy volunteers were recruited by advertisement or they were the spouses of Alzheimer's disease patients or MCI participants. • We only included data on the performance of the index test to discriminate between people with MCI who converted to dementia and those who remained stable. • Among those participants, there were 20 MCI participants. No further details of participant sampling and recruitment were reported. • Inclusion criteria: MMSE 27 to 30 and older than 55 years (Vandenberghe 2010).
Patient characteristics and setting	• 20 MCI participants diagnosed by the Petersen 1999 criteria. Demographic data were reported for 20 MCI participants and they were classified as having amnestic MCI. • Gender: 11 male, 9 female. • Mean ± SD age: 72.7 ± 7.09 years (Vandenberghe 2010) • APOE ε4 carrier: not reported • MMSE: 28.0 ± 0.94 (Vandenberghe 2010)

Thurfjell 2012 *(Continued)*

	• Mean ± SD years of education: 14.8 ± 2.97 (Vandenberghe 2010) • Sources of referral: not reported • Setting: secondary care (memory clinic)
Index tests	• PET imaging was conducted at 3 different scanning centres using a 16-slice Biograph PET/CT scanner (Siemens, Er- langen, Germany), an ECAT EXACT HR scanner (Siemens), and a GE Advance scanner, respectively. • All PET time frames were realigned using an automated method and a PET sum image was created. The PET sum image was spatially normalised into Montreal Neurologic Institute space where a volume of interest (VOI) template was used to extract counts in VOIs for frontal, lateral temporal and parietal cortices as well as for the anterior and posterior cingulate. In addition, a reference region corresponding to the cerebellar cortex was defined. • Standard uptake value ratios (SUVRs) were computed by dividing counts in the target regions with counts in the reference region. The authors computed a composite neocortical SUVR value as an average of the above mentioned cortical VOIs. • ^{18}F-flutemetamol was injected intravenously as a slow bolus (< 40 seconds) in an antecubital vein (target activity set at 185 MBq maximally (max), equivalent to an effective dose of approximately 6 mSv). • ^{18}F-flutemetamol administration mean MBq dose: 173.3 (SD 13.3). • Time between ^{18}F-flutemetamol injection and PET acquisition: from 85 to 115 minutes (6 x 5-minute frames). • All PET time frames were realigned using an automated method and a PET sum image was created. The PET sum image was spatially normalized into Montreal Neurologic Institute space where a volume of interest (VOI) template was used to extract counts in VOIs for frontal, lateral temporal and parietal cortices as well as for the anterior and posterior cingulate. In addition, a reference region corresponding to the cerebellar cortex was defined. • Standard uptake value ratios (SUVRs) were computed by dividing counts in the target regions with counts in the reference region. The authors computed a composite neocortical SUVR value as an average of the above mentioned cortical VOIs. • Threshold: > 1.5 determined at baseline, based in Vandenberghe study with a threshold > 1. 56 (Vandenberghe 2010). • ROIs included lateral frontal cortex (FRO), lateral temporal cortex (LTC), lateral parietal cortex (PAR), anterior cingulate (ANC), occipital cortex (OCC), and pons (PON). • A cerebellar ROI served as reference region.
Target condition and reference standard(s)	• Target condition: Alzheimer's disease dementia. • Reference standard: not explicitly stated, although NINCDS-ADRDA criteria for ADD (McKhann 1984) and APA 1994 were baseline diagnostic criteria.

Flow and timing	• Duration of follow-up: 2 years.
	• Number included in analysis: 19 participants: 10 ^{18}F-flutemetamol (+) and 9 ^{18}F-flutemetamol (-)
	• Progression from MCI to ADD:
	  ○ 10 ^{18}F-flutemetamol (+): 8 MCI-ADD and 2 MCI-MCI; 9 ^{18}F-flutemetamol (-): 1 MCI-ADD and 8 MCI-MCI
	  ○ TP = 8; FP = 2; FN = 1; TN = 8
	• Loss to follow-up: 1 MCI participant
	• No further information was given
	• Financial support for the baseline study (Vandenberghe 2010) was provided by the

Thurfjell 2012 *(Continued)*

	manufacturer of ^{18}F-flutemetamol tracer and two authors of Thurfjell 2012 were employees		
Comparative			
Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	Low
DOMAIN 2: Index Test All tests			
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		
Was the 18F-flutemetamol PET scan interpretation done by a trained reader physician?	Unclear		
Did the study provide a clear definition of what was considered to be a 18F-flutemetamol positive result?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target	Unclear		

Thurfjell 2012 *(Continued)*

condition?			
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	Unclear

DOMAIN 4: Flow and Timing

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		
Was the study with 18F-flutemetamol free of commercial funding?	No		
		High	

$^4\beta$: Amyloid Beta
$^{APOE}\epsilon 4$: Apolipoprotein E4
ADD: Alzheimer's disease dementia
ANC: Anterior cingulate
CAC: Clinical Adjudication Committee
CT: Computed tomography
EUDRACT: European Union Drug Regulating Authorities Clinical Trials
FN:False negative
FP: False positive
FRO: Frontal cortex
LTC: Lateral temporal cortex
MBq: Megabecquerel
mcg: Microgramme
MCI: Mild cognitive impairment
MMSE: Mini-mental state examination
mSv: Millisievert
NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
OCC: Occipital cortex
PAR: Lateral parietal cortex
PET: Positron emission tomography

PON: Pons
ROI: Region of interest
SD: Standard deviation
SUVR: Standardised uptake value ratio
TN:True negative
TP: True positive
VOI: Volume of interest

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Goukasian 2015	Target condition: not looking at progression from MCI to dementia. The focus of the study was the association of Aβ deposition and neuropsychiatric symptoms
Rowe 2015a	Target condition: not looking at progression from MCI to dementia. The focus of the study was the change in ^{18}F-flutemetamol PET scan retention over time.
Rowe 2015b	Target condition: not looking at progression from MCI to dementia. The focus of the study was the change in ^{18}F-flutemetamol PET scan retention over time.
Rowe 2015c	Target condition: not looking at progression from MCI to dementia. The focus of the study was the change in ^{18}F-flutemetamol retention over time.

^{A}β: Amyloid beta
MCI: Mild cognitive impairment
PET: Positron emission tomography

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2011-001756-12-BE

Trial name or title	Surrogate markers evaluation in pre-demented Alzheimer's disease patients and healthy elderly controls
Target condition and reference standard(s)	Progression to Alzheimer's disease at the end of the clinical follow-up period (from 1 to 3 years); no further details were given regarding the target condition(s) and the reference standard
Index and comparator tests	^{18}F-flutemetamol
Starting date	April 2012
Contact information	Cliniques Universitaires Saint Luc, Nuclear Medicine Department, Dr R.Lhommel, renaud.lhommel@uclouvain.be

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EUCTR2011-001756-12-BE *(Continued)*

Notes	

EUCTR2011-006195-39-SE

Trial name or title	An open-label study to compare the prognostic value of ^{18}F-flutemetamol PET scan imaging with longitudinal biomarker data in healthy volunteers and patients with mild cognitive impairment
Target condition and reference standard(s)	Progression to Alzheimer's disease and other dementias. No further details were given regarding the target condition and the reference standard(s) used. Included subjects will be followed clinically over at least four years
Index and comparator tests	^{18}F-flutemetamol
Starting date	February 2012
Contact information	Skånes universitetssjukhus, Minneskliniken, oskar.hansson@med.lu.se
Notes	

EUCTR2016-002635-15-NL

Trial name or title	Study to Identify factors associated with resilience to clinical dementia at old age - 90+ study
Target condition and reference standard(s)	Developing ADD in extremely elderly subjects: no further details were given regarding the reference standard(s) used
Index and comparator tests	^{18}F-flutemetamol
Starting date	July 2016
Contact information	Alzheimer Center, VU Medical Center n.legdeur@vumc.nl
Notes	

EUCTR2017-000094-36-SE

Trial name or title	The BioFINDER 2 study - improved diagnostics and increased understanding of the pathophysiology of cognitive disorders
Target condition and reference standard(s)	Progression from subjective cognitive decline and MCI to ADD or other neurodegenerative disorders: no further details were given regarding the reference standard(s) used

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Index and comparator tests	^{18}F-flutemetamol
Starting date	January 2017
Contact information	Minneskliniken, Skåne University Hospital Oskar.Hansson@med.lu.se
Notes	

JPRN-UMIN000019926

Trial name or title	Clinical and neuroimaging study on preclinical Alzheimer's disease
Target condition and reference standard(s)	Progression rate from asymptomatic preclinical ADD to MCI and further to AD dementia at 36 months of follow-up; no further details were given regarding the reference standard(s) used
Index and comparator tests	11C-PiB, ^{18}F-florbetapir or ^{18}F-flutemetamol
Starting date	January 2016
Contact information	Graduate School of medicine, Osaka City University, Center for Clinical study on dementia, Hiroshi Mori, mori@med.osaka-cu.ac.jp
Notes	

NCT02164643

Trial name or title	Longitudinal study of brain amyloid imaging in MEMENTO (MEMENTOAmyGing)
Target condition and reference standard(s)	Progression to clinical dementia stage according to standardized classifications (DSM-IV and NINCDS-ADRDA) at 2 years follow-up
Index and comparator tests	^{18}F-flutemetamol and ^{18}F-florbetapir at baseline
Starting date	June 2014
Contact information	University Hospital, Bordeaux Prof. Geneviève Chene: genevieve.chene@isped.u-bordeaux2.fr Carole Dufouil: carole.dufouil@isped.u-bordeaux2.fr
Notes	

Trial name or title	Amyloïd load in elderly population: effect of cognitive reserve (EDUMA)
Target condition and reference standard(s)	Prediction of cognitive decline and disease progression; no target condition or reference were prespecified
Index and comparator tests	^{18}F-flutemetamol
Starting date	July 2014
Contact information	University Hospital, Bordeaux Michele Allard: michele.allard@chu-bordeaux.fr
Notes	

ADD:Alzheimer's disease/dementia

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th ed.)

MCI: Mild cognitive impairment

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

Test	No. of studies	No. of participants
1 18F-flutemetamol	2	243

Test 1. 18F-flutemetamol.

Review: 18F PET with flutemetamol for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI)

Test: 1 18F-flutemetamol

Study	TP	FP	FN	TN	Sensitivity	Specificity
NCT01028053	52	45	29	98	0.64 [0.53, 0.75]	0.69 [0.60, 0.76]
Thurfjell 2012	8	2	1	8	0.89 [0.52, 1.00]	0.80 [0.44, 0.97]

APPENDICES

Appendix 1. Glossary

Aetiology: the cause, set of causes, or manner of causation of a disease or condition.

Amyloid beta (Aβ): an amyloid that is derived from a larger precursor protein and is the primary component of plaques characteristic of Alzheimer's disease.

Biomarker: measurable and quantifiable biological parameters (e.g., specific enzyme concentration, specific hormone concentration, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis; metabolic processes; etc.

Bolus: a single dose of a drug or other medicinal preparation given all at once.

Cingulate cortex: one of the convolutions on the medial surface of the cerebral hemispheres.

Cortical: the thin layer of grey matter on the surface of the cerebral hemispheres. It reaches its highest development in humans and is responsible for intellectual faculties and higher mental functions.

Epiphenomenon: A secondary effect or by-product. A secondary symptom or pathology, occurring simultaneously with a disease or condition but not directly related to it.

Frontotemporal: relating to the frontal and the temporal cerebral lobes.

Histopathology: the study of changes in tissues caused by disease.

Hypothyroidism: a syndrome that results from abnormally low secretion of thyroid hormones from the thyroid gland.

Index test: the test under evaluation.

In vivo: (of processes) performed or taking place in a living organism.

Ligand: a molecule that binds to another molecule, used especially to refer to a small molecule that binds specifically to a larger molecule, e.g., an antigen binding to an antibody, a hormone or neurotransmitter binding to a receptor, or a substrate or allosteric effector binding to an enzyme.

Neuritic plaques: accumulations of extracellularly deposited amyloid fibrils within tissues. Is one of the hallmarks of Alzheimer's disease.

Neurofibrillary tangles: abnormal structures located in various parts of the brain and composed of dense arrays of paired helical filaments (neurofilaments and microtubules). Are aggregates of hyperphosphorylated tau protein that are most commonly known as a primary marker of Alzheimer's disease.

Parietal lobe: upper central part of the cerebral hemisphere. It is located anterior to the occipital lobe, and superior to the temporal lobes.

Positron: an extremely small piece of matter with a positive electrical charge, having the same mass as an electron.

Precuneus: is a part of the parietal lobe of the brain, lying on the medial surface of the cerebral hemisphere.

Prodromal: Relating to prodrome; indicating an early stage of a disease.

Radionuclide (sometimes called a radioisotope or isotope): is a chemical which emits a type of radioactivity called gamma rays. The radioactivity can be detected by special scanners.

Reference standard: the best available method for establishing the presence or absence of the target condition.

Sensitivity: a measure of a test's ability to correctly detect people with the disease. It is the proportion of diseased cases that are correctly identified by the test. It is calculated as follows: Sensitivity = Number with disease who have a positive test/Number with disease.

Specificity: a measure of a test's ability to correctly identify people who do not have the disease. It is the proportion of people without the target disease who are correctly identified by the test. It is calculated as follows: Specificity = Number without disease who have a negative test/Number without disease.

Stilbene: organic compounds that contain 1,2-diphenylethylene as a functional group.

Target condition: the disease or condition that the index test is expected to detect.

Temporal lobe: lower lateral part of the cerebral hemisphere responsible for auditory, olfactory, and semantic processing. It is located inferior to the lateral fissure and anterior to the occipital lobe.

Vascular: relating to, affecting, or consisting of a vessel or vessels, especially those which carry blood.

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Appendix 2. Search strategy for ^{18}F-flutemetamol PET ligand

Source	Search strategy
MEDLINE In-process and other non-indexed citations and MEDLINE® 1946 to May 2017 (Ovid SP)	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] 16. Plaque, Amyloid/ri [Radionuclide Imaging] 17. or/15-16 18. 14 and 17 19. 7 or 18
Embase 1974 to May 2017 (Ovid SP)	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. 12. amyloid plaque/di [Diagnosis] 13. mild cognitive impairment/ 14. or/10-13 15. 9 and 14 16. 8 or 15
PsycINFO 1806 to May 2017 (Ovid SP)	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 Science) (1922 to May 2017)	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 Science) (1946 to May 2017)	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)	Flutemetamol OR VIZAMYL OR vizamyl* OR "flutemetamol-fluorine-18" OR "18F-GE067" OR "[18F]Flutemetamol" OR "flutemetamol-PET" [Words]
CINAHL (EBSCOhost) (1980 to May 2017)	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)	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)	Flutemetamol OR VIZAMYL OR vizamyl OR "flutemetamol-fluorine-18" OR "18F-GE067" OR "[18F]Flutemetamol" OR "flutemetamol-PET"
ALOIS, the Cochrane Dementia & Cognitive Improvement Group's specialized register of dementia studies (http://www.medicine.ox.ac.uk/alois/)	Imaging AND PET

Appendix 3. 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	Reference standards information	
	ADD present	ADD absent
Index test-positive	^{18}F-flutemetamol PET ligand for Aβ (+) who progress to ADD (TP)	^{18}F-flutemetamol PET ligand for Aβ (+) who remain MCI (FP) and ^{18}F-flutemetamol PET ligand for Aβ (+) who progress to non-ADD (FP)
Index test-negative	^{18}F-flutemetamol PET ligand for Aβ (-) who progress to ADD (FN)	^{18}F-flutemetamol PET ligand for Aβ (-) who remain MCI (TN) and ^{18}F-flutemetamol PET ligand for Aβ (-) who progress to non-ADD (TN)

ADD: Alzheimer's disease dementia
FN: False negative
FP: False positive
MCI: Mild cognitive impairment
PET: Positron emission tomography
TN: True negative
TP: True positive
Table 2. Progression from mild cognitive impairment (MCI) to non-Alzheimer's disease dementia (non-ADD)

Index test information	Reference standards information	
	Non-ADD present	Non-ADD absent
Index test-positive	^{18}F-flutemetamol PET ligand for Aβ (+) who progress to non-ADD (TP)	^{18}F-flutemetamol PET ligand for Aβ (+) who remain MCI (FP) and ^{18}F-flutemetamol PET ligand Aβ (+) who progress to ADD (FP)
Index test-negative	^{18}F-flutemetamol PET ligand for Aβ (-) who progress to non-ADD (FN)	^{18}F-flutemetamol PET ligand for Aβ (-) who remain MCI (TN) and ^{18}F-flutemetamol PET ligand for Aβ (-) who progress to ADD (TN)

ADD: Alzheimer's disease dementia
FN: False negative
FP: False positive
MCI: Mild cognitive impairment
PET: Positron emission tomography
TN: True negative
TP: True positive
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-flutemetamol PET ligand for Aβ (+) who progress to any form of dementia (TP)	^{18}F-flutemetamol PET ligand for Aβ (+) who remain MCI (FP)
Index test-negative	^{18}F-flutemetamol PET ligand for Aβ (-) who progress to any form of dementia (FN)	^{18}F-flutemetamol PET ligand for Aβ (-) who remain MCI (TN)

FN: False negative
FP: False positive
MCI: Mild cognitive impairment
PET: Positron emission tomography
TN: True negative
TP: True positive

Appendix 4. 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
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	Did all patients receive a reference standard?

	Did the study avoid in-appropriate exclusions?		test?	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 5. Anchoring statements for quality assessment of ^{18}F-flutemetamol PET scan for Aβ 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-flutemetamol PET ligand for Aβ biomarker	^{18}F-flutemetamol PET ligand for Aβ biomarker
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 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)

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ADD: Alzheimer's disease dementia

DSM: Diagnostic and Statistical Manual of Mental Disorders

FTD: Frontotemporal dementia

ICD: International Classification of Diseases

MCI: Mild cognitive impairment

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences

PET: Positron emission tomography

Anchoring statements for quality assessment ^{18}F-flutemetamol PET ligand 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-flutemetamol PET ligand for Aβ biomarker 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 contacted the relevant study teams for additional information. Whenever we scored one question as high risk of bias, we considered the study as 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 automatically graded the study as unclear if the study authors did not detail exclusions (pending contact with study authors) Where a study details exclusions, we graded the study as 'low risk' if we considered 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 labelled post-hoc and inappropriate exclusions as at 'high risk' of bias

Index test

Was the ^{18}F-flutemetamol PET ligand for Aβ 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 the 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 the reference standard should not influence the 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
Was the ^{18}F-flutemetamol PET ligand for Aβ biomarker's threshold 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 the threshold, clinical cut-off, or dichotomisation point. A study is classified at 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
Was the ^{18}F-flutemetamol PET ligand for Aβ 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 scored this item as 'yes'

		If no definition of trained reader was done, we scored this item as 'unclear'. If a nontrained reader physician performed the scan interpretation, we scored this item as 'no'
Did the study provide a clear definition of what was considered to be a ^{18}F-flutemetamol PET ligand for Aβ biomarker's positive result?	No = high risk of bias Yes = low risk of bias Unclear = unclear risk of bias	If the study clearly stated the definition of a positive result (e.g. SUV), we scored this item as 'yes'. If the study did not give a definition of what it considered a positive result or the definition of a positive result varied between the participants, we scored this item as 'no'. If the study gave insufficient information to permit judgement, we scored 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 included those detailed in DSM-IV and ICD-10. Criteria specific to dementia subtypes included but were 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 were not familiar to the review authors or the Cochrane Dementia and Cognitive Improvement group ('unclear'), we classified this item as 'high risk of bias'
Were clinical assessments for dementia performed without knowledge of the ^{18}F-flutemetamol PET ligand for Aβ 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' were sufficient and full details of the blinding procedure were not required. Interpretation of the results of the reference standard may be influenced by knowledge of the results of the index test

Patient flow

(*Continued*)

Was there an appropriate interval between ^{18}F-flutemetamol PET ligand for Aβ 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 ^{18}F-flutemetamol PET ligand for Aβ biomarker for MCI progression to dementia, there will always be a delay between the index test and the reference standard assessments. The time between the reference standard and the index test will influence the accuracy (Geslani 2005; Okello 2007; Visser 2006), and therefore we noted 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 was scored 'no'
Did all subjects get the same assessment for dementia regardless ^{18}F-flutemetamol PET ligand for Aβ biomarker?	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 the 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-flutemetamol PET ligand for Aβ 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 dropouts differ systematically from those who remain, then estimates of test performance may differ. If there are dropouts, these should be accounted for; a maximum proportion of dropouts for a study to remain at low risk of bias has been specified as 20%
Were missing ^{18}F-flutemetamol PET ligand for Aβ 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 did not report these results, we scored this as 'unclear' and we contacted the study authors
Was the study with ^{18}F-flutemetamol PET ligand for Aβ 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'

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		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; pretesting; 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 ^{18}F-flutemetamol PET ligand for Aβ 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-flutemetamol PET ligand for Aβ 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 'Risk of bias' assessments will already have assessed the dementia diagnosis. For certain reviews, an applicability statement relating to the 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

FTD: Frontotemporal dementia

ICD: International Classification of Diseases

MCI: Mild cognitive impairment

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences

PET: Positron emission tomography

CONTRIBUTIONS OF AUTHORS

- Gabriel Martínez, Robin WM Vernooij, and Paulina Fuentes Padilla: contributed to conception, design, and draft of the protocol; overall responsibility of study selection; data extraction; contacted the authors; draft of discussion; and authors' conclusion sections.

- Leon Flicker: contributed to conception, and designed and reviewed the draft protocol and final manuscript.

- Xavier Bonfill Cosp: reviewed the draft protocol and final manuscript.

- Javier Zamora: designed and drafted the protocol, performed statistical analyses, updated the statistical methods section and finalised the manuscript.

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.

- Xavier Bonfill Cosp has no known conflicts of interest.

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6. Discusión

6. Discusión

6.1. Principales resultados derivados de las publicaciones y breve discusión específica acerca de los mismos.

El volumen y la calidad de la evidencia con respecto a la exactitud diagnóstica de 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol para el diagnóstico temprano de enfermedad de Alzheimer y otras demencias en personas con un DCL es muy limitado. Identificamos tres estudios en la revisión sistemática de 18F-Florbetapir, un estudio en la revisión sistemática de 18F-Florbetaben y dos estudios en la revisión sistemática de 18F-Flutemetamol y, por ese motivo, no fue posible realizar un metanálisis, análisis de sensibilidad o análisis de heterogeneidad.

En cuanto a la primera revisión sistemática de la literatura, esta detectó tres estudios. Dos de ellos (Doraiswamy 2014; Schreiber 2015) abordaron la exactitud diagnóstica del 18F-Florbetapir analizado por evaluación visual para la predicción de la progresión desde un DCL a una DEA en el seguimiento, y uno de ellos también evaluó la progresión desde un DCL a una DEA de forma cuantitativa con un umbral SUVR> 1,1 para la positividad (Schreiber 2015).

Un tercer estudio abordó la exactitud diagnóstica del 18F-Florbetapir analizado mediante evaluación visual para la predicción de la progresión desde un DCL a cualquier forma de demencia durante el seguimiento (Kawas 2013).

Ningún estudio tuvo información sobre la progresión a cualquier otra forma de demencia no-DEA.

Dos estudios se clasificaron como de alto riesgo de sesgo, principalmente debido al posible conflicto de interés con respecto al apoyo financiero de la empresa que fabricó el trazador 18F-Florbetapir (Doraiswamy 2014; Kawas 2013).

La segunda revisión sistemática de la literatura detectó un estudio (Ong2015) que evaluó la exactitud diagnóstica del 18F-Florbetaben analizado por evaluación visual y cuantitativa para la predicción de la progresión desde un DCL a una DEA en el seguimiento. También en el mismo estudio, se logró tener información para evaluar la exactitud diagnóstica del 18F-Florbetaben para predecir la progresión a cualquier otra forma de demencia no-DEA y cualquier forma de demencia en el seguimiento.

El estudio incluido se clasificó como de alto riesgo de sesgo, principalmente debido a los posibles conflictos de interés (apoyo financiero del estudio) y también porque tres autores eran empleados de la empresa que fabricaba el trazador 18F-Florbetaben previamente y tres autores eran empleados de la actual empresa que fabrica el trazador 18F-Florbetaben.

La tercera revisión sistemática de la literatura detectó dos estudios que abordaron la exactitud diagnóstica del 18F-Flutemetamol analizado cuantitativamente con un umbral de SUVR> 1,5 (Thurfjell 2012) o mediante evaluación visual (NCT01028053) para la predicción de la progresión desde un DCL a una DEA durante el seguimiento.

Ningún estudio tuvo información sobre la progresión a cualquier otra forma de demencia no-DEA o a cualquier forma de demencia.

Los estudios incluidos se clasificaron como de alto riesgo de sesgo principalmente por el posible conflicto de interés debido al apoyo financiero de la empresa que fabricó el trazador 18F-Flutemetamol.

Exactitud diagnóstica para predecir la progresión desde un DCL a una DEA

La exactitud diagnóstica de los tres biomarcadores fue variable en cuanto a su sensibilidad y especificidad dentro de las tres revisiones sistemáticas.

18F-Florbetapir:

Para la evaluación visual, la sensibilidad varió desde un 67% a un 89% y la especificidad desde un 58% a un 71% y para la evaluación cuantitativa, la sensibilidad fue de un 87% y la especificidad de un 51% para predecir la progresión desde un DCL a una DEA.

18F-Florbetaben:

Para la evaluación visual, la sensibilidad fue de un 100% y la especificidad fue de un 83% y para la evaluación cuantitativa, la sensibilidad fue de un 100% y la especificidad de un 88% para predecir la progresión desde un DCL a una DEA.

18F-Flutemetamol:

Para la evaluación visual, la sensibilidad fue de un 64% y la especificidad de un 69% y para la evaluación cuantitativa, la sensibilidad fue de un 89% y la especificidad de un 80% para predecir la progresión desde un DCL a una DEA.

Una sensibilidad variable detectada tanto en el 18F-Florbetapir como para el 18F-Flutemetamol puede ser explicada por una alta tasa de falsos negativos. Una hipótesis que podría explicar los falsos negativos es que algunas personas con probable diagnóstico de DEA pueden tener otro u otros tipos de patología cerebral, siendo la más común la patología de la enfermedad de Alzheimer combinada con infartos microscópicos o cuerpos de Lewy, heterogeneidad histopatológica frecuente en una DEA y que también se presenta en un DCL (Schneider 2007; Schneider 2009). Por otro lado, los oligómeros solubles Aβ no son detectados por estos biomarcadores, y se sabe que los oligómeros solubles desempeñan una función central en la patogénesis de la enfermedad de Alzheimer en la hipótesis amiloide (Heyden 2013), con la posibilidad de producir falsos negativos. De hecho, un estudio encontró que dos de los 11 participantes con autopsia realizada más de un año después de la tomografía por emisión de positrones con 18F-Florbetapir tenían un diagnóstico neuropatológico positivo (enfermedad de

Alzheimer probable o definitiva) pese a que tenían previamente un test con 18F-Florbetapir negativo (Clark 2012).

Además, los trazadores amiloideos no detectan la presencia de ovillos neurofibrilares (NFT), el otro hallazgo histopatológico de la enfermedad de Alzheimer. Algunos estudios de cohortes han mostrado que las placas y los ovillos contribuyen de forma independiente al deterioro cognitivo en la patología de la enfermedad de Alzheimer sin ningún otro diagnóstico neuropatológico primario (Serrano - Pozo 2013). Además, la formación de NFT podría no estar relacionada con la formación de placas amiloides o ser un proceso temporalmente distinto (Royall 2014).

En cuanto a la especificidades variables encontradas en los estudios con 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol, estas se ven afectadas por una alta tasa de falsos positivos. Se ha encontrado una TEP positiva en demencia con cuerpos de Lewy, enfermedad de Parkinson (Siderowf 2014) y demencia frontotemporal (Kobylecki 2015) con 18F-Florbetapir, también en demencia vascular, demencia frontotemporal y demencia con cuerpos de Lewy con 18F-Florbetaben (Villemange 2011) y en demencia vascular y demencia con cuerpos de Lewy con 18F-Flutemetamol (Thal 2015). Lo anterior podría ser explicado por una posible etiología mixta de las condiciones descritas, pero muchos casos fueron confirmados con estudios anatomopatológicos que descartaron la presencia de patología amiloidea.

Otra explicación de la presencia de falsos positivos es que los biomarcadores amiloideos se unan al amiloide que está presente en los vasos sanguíneos cerebrales, en especial en la angiopatía cerebral amiloidea como se ha visto con el 18F-Florbetapir (Gurol 2016) y con un biomarcador cercano al flutemetamol como la TEP con PiB (Zhang 2014).

Finalmente, otra razón importante para explicar falsos positivos es que muchas personas sin deterioro cognitivo presentan patología amiloidea cerebral en sus autopsias (Gelber 2012), lo que genera dudas respecto de la real relevancia de la teoría amiloidea cerebral como agente causal del deterioro cognitivo.

La duración del seguimiento también es importante para predecir la progresión desde un DCL a una DEA. La tasa de progresión anual desde un DCL a una DEA está entre el 8% y el 16% (Mitchell 2009). Por lo tanto, un alto porcentaje de personas con un DCL basal progresaría a una DEA si pudiéramos incluir un período de seguimiento más largo, lo que en consecuencia afectaría la capacidad predictiva de la tomografía por emisión de positrones con marcadores amiloideos. Esto se evidenció en una revisión sistemática con la TEP con PiB en la que los datos se dividieron en un seguimiento a corto plazo y un seguimiento de más de dos años, donde la tasa de conversión a corto plazo varió entre un 6% y un 31% y a largo plazo entre un 32% y un 90%, pese a lo anterior, la sensibilidad se mantuvo estable entre los seguimientos, pero la especificidad varió a corto plazo entre un 42% y un 83% y a largo plazo entre un 58% y un 100% (Ma 2014).

Sin embargo, en estas revisiones sistemáticas las tasas de conversión desde un DCL a una DEA fueron bastante similares en los estudios incluidos, pese a la diferencia en seguimiento. En la revisión con 18F-Florbetapir las tasas fueron similares, pese a que un estudio tenía casi el doble de tiempo de seguimiento que el otro (15,2% a los 1,6 años y 19,1% a los tres años de seguimiento). En la revisión de 18F-Florbetaben el único estudio incluido tenía una tasa de conversión de 47% a 4 años y en el caso de los estudios incluidos en la revisión de 18F-flutemetamol, las tasas de conversión desde un DCL a una DEA a dos años fueron de 47% y de 36% a tres años de seguimiento, respectivamente. Estas diferencias probablemente se

explican por el contexto del reclutamiento u otras características de los participantes con un DCL y otros factores subyacentes que afectan estas tasas de progresión.

Además, los subtipos de DCL también se han estudiado con respecto a su relación con la progresión a una DEA. En un estudio longitudinal, los resultados del seguimiento de 550 participantes con un DCL indicaron que el subtipo de DCL con presencia de deterioro de la memoria de almacenamiento, dominio múltiple y la presencia del alelo APOE ϵ4 aumentaron el riesgo de progresión a la demencia. Los análisis de supervivencia multivariado y de Kaplan Meier mostraron que el DCL amnésico con deterioro de la memoria de almacenamiento tenía el mayor riesgo de progresión a la demencia (Espinosa 2013).

En nuestra revisión con 18F-Florbetapir, un estudio de los tres incluyó solo DCL amnésico, en la revisión con 18F-Florbetaben, se incluyeron personas con un DCL amnésico y no amnésico y en la revisión con 18F-Flutemetamol los dos estudios incluyeron sólo personas con un DCL amnésico. Esto podría explicar las diferentes tasas de progresión a una demencia y también pudiera explicar las diferencias en sensibilidad; por ejemplo en la revisión de 18F-Florbetapir, la sensibilidad en el estudio de Schreiber que sólo incluyó personas con un DCL amnésico es más alta que el estudio de Doraiswamy, que incluyó personas con un DCL amnésico y no amnésico. Ello nos hace suponer que al incluir en los estudios personas con un DCL amnésico y no amnésico las sensibilidades pudieran ser más bajas, algo que no se cumple en el estudio con 18F-Florbetaben que tuvo una alta sensibilidad pese a tener personas con ambos tipos de DCL (Ong 2015).

En conclusión, existe una falta de estudios primarios independientes, de alta calidad metodológica, con un adecuado número de participantes y un seguimiento apropiado. Además, se requieren datos más detallados sobre las características de los diversos subtipos de DCL, no solo para explorar los mecanismos subyacentes, sino también para dilucidar las vías causales

que vinculan la positividad de la exploración con 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol y la progresión de la enfermedad, y que luego podrán ser incorporados en las actualizaciones de estas revisiones sistemáticas.

Exactitud diagnóstica para predecir la progresión desde un DCL a una demencia no-DEA

En cuanto a nuestro objetivo de determinar la exactitud diagnóstica de la TEP con 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol para detectar personas con un DCL al inicio del estudio que progresarán clínicamente a cualquier otra forma de demencia no-DEA en el seguimiento, los resultados fueron los siguientes:

18F-Florbetapir y 18F-Flutemetamol:

En la revisiones sistemáticas, no se pudieron incluir datos para cualquier otra demencia no Alzheimer. Los datos disponibles sugieren que el 18F-Florbetapir o el 18F-Flutemetamol no jugarían un rol en la evaluación de la progresión desde un DCL a cualquier otra forma de demencia no-DEA.

18F-Florbetaben:

La progresión desde un DCL a cualquier otra forma de demencia no-DEA tuvo una sensibilidad de 0% (IC 95%: 0 a 52) y una especificidad de 38% (IC 95%: 23 a 54) analizada mediante evaluación visual.

La progresión desde un DCL a cualquier otra forma de demencia no-DEA tuvo una sensibilidad de 0% (IC 95%: 0 a 52) y una especificidad de 40% (IC 95%: 25 a 57) por evaluación cuantitativa con SUVR> 1,45.

El estudio informó que sólo cinco personas progresaron a una demencia no-DEA en el seguimiento (tres casos de demencia frontotemporal, un caso de demencia con cuerpos de Lewy y un caso de parálisis supranuclear progresiva) y todos ellos fueron negativos para 18F-Florbetaben (Ong 2015).

Si bien no fue algo observado en el estudio incluido, otros estudios han observado unión cortical con el 18F-Florbetaben en personas sin una DEA; 9% (1/11) en personas con demencia frontotempotal, 25% (1/4) en personas con demencia vascular, 29% (2/7) en personas con demencia con cuerpos de Lewy (Villemagne 2011) y en 11% (3/27) en aquellos con patologías neurodegenerativas distintas de la enfermedad de Alzheimer confirmadas en la autopsia (Sabri 2015). En el estudio de Ong, ninguna de las cinco personas que progresaron a una demencia no-DEA a los cuatro años de seguimiento fue positiva para 18F-Florbetaben; lo último podría explicar la sensibilidad del 0% y la especificidad del 38% a través de la evaluación visual. Sin embargo, de acuerdo a los estudios histopatológicos, esperaríamos que, en los estudios con más participantes, se encontrarían personas con tomografías por emisión de positrones positivas que progresan a una demencia no-DEA, por lo que podrían potencialmente aumentar la exactitud diagnóstica a otras formas de demencia y disminuir la exactitud diagnóstica a una DEA.

Exactitud diagnóstica para predecir la progresión desde un DCL a cualquier forma de demencia

En cuanto a nuestro objetivo de determinar la exactitud diagnóstica de la TEP con 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol para detectar personas con un DCL al inicio del estudio que progresarán clínicamente a cualquier forma de demencia en el seguimiento, los resultados fueron los siguientes:

18F-Florbetapir:

La progresión desde un DCL a cualquier forma de demencia en aquellos con un año o menos de seguimiento tuvo una sensibilidad de 67% (IC 95%: 9 a 99) y una especificidad de 50% (IC 95%: 1 a 99) analizada mediante evaluación visual.

18F-Florbetaben:

La progresión desde un DCL a cualquier forma de demencia a cuatro años de seguimiento tuvo una sensibilidad de 81% (IC 95%: 61 a 93) y una especificidad de 79% (IC 95%: 54 a 94) analizada mediante evaluación visual.

La progresión desde un DCL a cualquier forma de demencia a cuatro años de seguimiento tuvo una sensibilidad de 81% (IC 95%: 61 a 93) y una especificidad de 84% (IC 95%: 60 a 97) por evaluación cuantitativa con SUVR> 1,45.

18F-Flutemetamol:

En la revisión sistemática, no se pudo incluir datos para cualquier forma de demencia.

Respecto del 18F-Florbetapir, el único estudio incluido tiene una sensibilidad de 67% y una especificidad de 50%, lo cual puede ser explicado principalmente por el escaso número de personas muy mayores incluidas y a la alta prevalencia de patología Alzheimer encontrada en personas mayores sin una demencia establecida (Savva 2009; Gelber 2012). La exactitud diagnóstica puede ser diferente en aquellos estudios con una población más joven.

En cuanto a la revisión que evaluó al 18F-Florbetaben, se informó una menor sensibilidad y especificidad para la predicción de cualquier forma de demencia en comparación con la exactitud diagnóstica para una DEA (Ong 2015). Esto se explica porque la prueba tiene una sensibilidad de 100% y una especificidad entre 83% y 88% para predecir la progresión a una DEA y si sumamos los datos con los que son TEP negativas que progresaron a otro tipo de demencia no Alzheimer, la sensibilidad disminuyó al 81% y la especificidad al 79%.

De acuerdo a lo expresado previamente, hay casos en la literatura donde personas con demencia no-DEA, presentan una TEP con 18F-Florbetaben positiva (Villemange 2011; Sabri 2015),

pero no en este estudio. Esto puede ser explicado por el pequeño tamaño de la muestra. Por esa razón, se podría esperar que en otros estudios donde se evalúe la progresión a cualquier forma de demencia, la exactitud diagnóstica sería mayor, disminuyendo la exactitud diagnóstica para predecir la progresión de personas con un DCL a una DEA.

6.2. Discusión de los aspectos generales. Comparación con el contexto actual

En base a nuestro conocimiento y después de hacer la correspondiente revisión bibliográfica, podemos afirmar que estas son las primeras revisiones sistemáticas que evalúan la exactitud diagnóstica de los biomarcadores amiloideos 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol para determinar la progresión desde un DCL a una DEA, a otro tipo de demencia no-DEA o a cualquier tipo de demencia. Por lo tanto, no existen estudios similares que se hayan realizado con estos objetivos.

Pese a lo anterior y dada la escasa evidencia disponible en la actualidad respecto de la exactitud diagnóstica de los biomarcadores amiloideos estudiados, la impresión actual de los clínicos y de los investigadores es que la exactitud ya está demostrada para poder predecir la progresión desde un DCL a una DEA, por lo que los estudios han migrado a otros objetivos, enfocándose actualmente en el potencial beneficio que podría tener el paciente y la confianza del médico con el diagnóstico clínico al acceder a un estudio con un marcador amiloideo como con la 18F-TEP positiva y a una posible disminución del costo económico al realizar el estudio (Boccardi 2016; Zwan 2017; de Wilde 2018; Spallazzi 2019; Rabinovici 2019; Wittenberg 2019). Lo anterior es de suma importancia y potencialmente grave, ya que los investigadores y clínicos parten de la premisa de que la exactitud está demostrada y ante esta supuesta exactitud, se están realizando diagnósticos, cambiando terapias farmacológicas y entregando información a pacientes y familiares potencialmente erróneas. Todo ello puede impactar no solo en distintos manejos clínicos, o en costos económicos para el paciente o el sistema de salud, sino que

también puede provocar impactos profundos en familias y personas a las que se les puede estar dando un pronóstico erróneo y que deben tomar decisiones ante este nuevo escenario (Bunnik 2018).

Con el objetivo de disminuir o resolver el problema expuesto, es necesaria la adquisición por todo clínico de competencias en la evaluación crítica de estudios de exactitud diagnóstica, la promoción de estudios independientes que no tengan conflictos evidentes de interés económico, con un diseño adecuado y principalmente con un mayor número de participantes.

6.3. *Fortalezas y limitaciones*

6.3.1. Fortalezas

Realizamos tres estudios con los más altos estándares que exige la literatura para desarrollar una revisión sistemática, basada en un protocolo publicado previamente y siguiendo la metodología Cochrane, con revisiones por pares de dos grupos de investigación, el Grupo de Demencias y de Mejora Cognitiva basado en la Universidad de Oxford y del Grupo de Métodos de Pruebas de Cribado y Diagnóstico de la Colaboración Cochrane basado en la Universidad de Birmingham, quienes realizaron revisiones por pares tanto del registro del título, del diseño del protocolo y de las posteriores revisiones sistemáticas.

Realizamos una búsqueda de literatura extensa, completa y sensible, utilizando 11 bases de datos electrónicas diferentes sin límite de idioma o fecha. Pese a lo anterior, solo pudimos incluir seis estudios en total en las tres revisiones sistemáticas; por lo tanto, nuestras estimaciones de exactitud diagnósticas son relativamente imprecisas. Ello se puede considerar una limitación pero en este caso es una fortaleza, ya que con una exhaustiva búsqueda en la literatura nosotros sólo logramos detectar estos seis trabajos publicados. Ello nos da la confianza de que probablemente no existían más trabajos publicados al respecto hasta la fecha

de la búsqueda y que nuestros resultados son los que deberían esperarse para la exactitud diagnóstica de cada uno de los biomarcadores estudiados.

Esta escasez de evidencia refleja los desafíos más importantes inherentes a la realización de estudios prospectivos a largo plazo, tener participantes bien caracterizados y seguidos hasta el punto de progresión a la demencia clínica.

6.3.2. Limitaciones

Muchos de los estudios incluidos tuvieron limitaciones metodológicas significativas que debilitaron la confianza en los resultados de estas revisiones sistemáticas. Primero, persiste una considerable incertidumbre con respecto al diagnóstico clínico de una DEA en algunos estudios; no hubo una definición clara en las pruebas índice en otros, el estándar de referencia no se describió explícitamente en algunos y el principal problema fue el potencial conflicto de interés con la compañía que produjo el marcador en cinco de los seis estudios incluidos.

La selección de participantes con un DCL en algunos estudios podría ser otra debilidad, ya que no se obtuvo información de cómo habían sido referidos los participantes en varios estudios. Tener claridad respecto de la selección de participantes, tipo de DCL, edad, presencia del alelo APOE4, anormalidad estructural en la RM, hipometabolismo en la exploración TEP con FDG y alteración en el líquido cefalorraquídeo podrían ayudar a determinar diferentes subgrupos de personas con mayor riesgo de desarrollar demencia en el seguimiento, y realizar una estratificación que podría ayudar a evitar sesgos, y desarrollar estudios más eficientes en el futuro (Caroli 2015; Hampel 2012; Wolz 2016).

Una debilidad y común para estas tres revisiones sistemáticas fue la falta de respuesta de los autores sobre sus estudios cuando así se les requirió. Esto ha resultado en una falta de datos para el análisis en esta revisión.

Finalmente, un aspecto que puede ser considerado como una debilidad es que la búsqueda de la literatura en las tres revisiones sistemáticas fue realizada hasta fines de mayo de 2017, por

lo que la búsqueda tiene 3 años 6 meses de antigüedad. Pese a ello, las referencias incluidas en las revisiones como "en marcha" no tienen información o publicaciones relacionadas con datos que puedan ser incluidos en una actualización de las revisiones. Sólo tenemos conocimiento de un estudio con 18F-Florbetaben en 41 personas con un DCL y un seguimiento a 13 meses, que claramente podría ser incluido en una actualización de las revisiones (Ciarmiello 2019).

6.4. Implicaciones para la práctica

Hasta el día de hoy, el uso de un biomarcador amiloideo cerebral a través de la realización de una tomografía por emisión de positrones con 18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol está aprobado por la FDA y EMA dentro del estudio de una demencia por enfermedad de Alzheimer. Su principal valor se materializa cuando la imagen es negativa para amiloide cerebral, lo que permitiría descartar patología Alzheimer dentro del cuadro clínico demencial que presenta el paciente (por ejemplo: para diferenciar una DEA de una demencia frontotemporal) (EMA 2013; EMA 2014a; EMA 2014b; FDA 2012; FDA 2013; FDA 2014), y no está indicado en personas con un DCL, excepto en ensayos clínicos y estudios de investigación (Albert 2011).

Sin embargo, la Task Force de Imágenes Amiloidea, la Sociedad de Medicina Nuclear e Imágenes Moleculares y la Asociación de Alzheimer han propuesto el uso de una TEP amiloide en personas con un DCL inexplicable, persistente o progresivo (Johnson 2013).

La exactitud diagnóstica de las exploraciones con tomografía por emisión de positrones con los trazadores disponibles comercialmente hoy en día (18F-Florbetapir, 18F-Florbetaben, 18F-Flutemetamol), según lo determinado en estas revisiones sistemáticas, tienen una sensibilidad y especificidad variables basadas en escasos estudios, con pocos participantes y principalmente un alto riesgo de sesgo en la mayoría de los estudios por potenciales conflictos de interés comerciales.

Debido a las limitaciones metodológicas mencionadas anteriormente de los estudios incluidos, no es posible recomendar el uso rutinario de 18F-Florbetapir, 18F-Florbetaben o 18F-Flutemetamol en la práctica clínica. Los biomarcadores amiloideos con 18F-Florbetapir, 18F-Florbetaben, 18F-Flutemetamol son costosos, por lo tanto es importante determinar claramente su exactitud diagnóstica, su impacto en el pensamiento diagnóstico, su impacto clínico evaluado en resultados de salud medibles y estandarizar el proceso para la modalidad de diagnóstico antes de recomendarlo para la práctica clínica.

6.5. Implicaciones para la investigación

La FDA y la EMA han establecido los criterios de positividad de 18F-Florbetapir, 18F-Florbetaben, 18F-Flutemetamol para usarlos en la evaluación de pacientes con demencia por enfermedad de Alzheimer y su uso en participantes con un DCL es aceptado en entornos de investigación y ensayos clínicos (Albert 2011). Sin embargo, su uso también ha sido propuesto en la práctica clínica para evaluar a las personas con un DCL por la Sociedad de Medicina Nuclear y la Asociación de Alzheimer (Johnson 2013). Además, existen diferentes estudios de exactitud diagnóstica de los diferentes biomarcadores, que utilizan diferentes criterios de positividad, con diferentes SUVR, escalas de valoración visual o ambos. Esto provoca diferentes exactitudes para los distintos biomarcadores, incluso en personas con una DEA en comparación con controles sin demencia. Por lo anterior, creemos que es necesario unificar los criterios de positividad y para ello, se debe considerar la evaluación visual como la opción más importante para interpretar la exploración con biomarcador amiloideo cerebral por TEP, porque este es el enfoque de la interpretación establecido por la FDA (FDA 2012; FDA 2013; FDA 2014) y la EMA (EMA 2013; EMA 2014a; EMA 2014b).

Por otro lado, la evaluación clínica en personas con problemas de memoria no siempre se realiza con una sola prueba; se podrían asociar delimitado por el uso de pruebas, de diferentes

pruebas (add-on) (Bossuyt 2006), de acuerdo al perfil de la persona, como resonancia magnética volumétrica del hipocampo, TEP con FDG, SPECT, CSF y otras, y así determinar quién se beneficiará más con el uso de estas técnicas más sofisticadas . Esta sugerencia tiene validez porque las enfermedades neurodegenerativas son trastornos complejos con procesos fisiopatológicos potencialmente múltiples y superpuestos. Las imágenes con múltiples trazadores pueden ser útiles al combinar marcadores metabólicos, de inflamación o de apoptosis con aquellos que marcan las agregaciones de proteínas típicas observadas en la progresión desde un DCL a la enfermedad de Alzheimer. Existe la hipótesis de que el depósito de amiloide es un evento temprano en la enfermedad de Alzheimer y que alcanza una meseta relativa incluso en la etapa de DCL, mientras que los biomarcadores posteriores miden la pérdida y disfunción neuronal, siendo las medidas cognitivas mucho más tardías y dinámicas en la etapa de enfermedad sintomática (Jack 2010). En base a esta hipótesis, la combinación de imágenes estructurales, imágenes funcionales y pruebas cognitivas pueden ser mejores predictores de cuándo un individuo progresará a una demencia. Sólo en los últimos años, se han publicado estudios con biomarcadores amiloideos cerebrales por tomografía computada de cerebro combinado con otras pruebas para predecir la progresión desde un DCL a una DEA o cualquier forma de demencia, pero que requieren ser reproducidos y validados en otras poblaciones (Jang 2019; Ottoy 2019, Choi 2018, Varatharajah 2019).

Además, si consideramos la jerarquía de la evidencia necesaria para el nivel de eficacia de las pruebas de diagnóstico por imagen, actualmente estamos en el segundo paso de seis según Herscovitch: eficacia técnica, eficacia de exactitud diagnóstica, pensamiento diagnóstico de eficacia, impacto terapéutico, objetivos en salud del paciente y finalmente eficacia social (Herscovitch 2015). Por lo tanto, dado los resultados de estas investigaciones, necesitamos más estudios que evalúen la exactitud diagnóstica de los biomarcadores amiloideos por tomografía

por emisión de positrones, antes de avanzar a los siguientes pasos dentro de la jerarquía de la

evidencia diagnóstica y de incorporarlos en la práctica clínica rutinaria.

7. Conclusiones

7.1 Conclusiones

Pese al amplio uso actual de la tomografía por emisión de positrones con biomarcadores amiloideos, particularmente en personas con un DCL para eventualmente predecir la progresión a una DEA, la evidencia recogida en estas tres revisiones sistemáticas Cochrane sobre la exactitud de los biomarcadores con 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol es escasa, con pocos estudios y con un riesgo de sesgo establecidos, lo que limita la certidumbre sobre el rendimiento diagnóstico de estas pruebas.

Los resultados de estas revisiones sistemáticas no apoyan por el momento el uso en el ámbito clínico de estos biomarcadores para predecir la progresión desde un DCL a una DEA y la investigación debe centrarse nuevamente en establecer con certeza la exactitud diagnóstica de la tomografía por emisión de positrones con 18F-Florbetapir, 18F-Florbetaben y 18F-Flutemetamol.

8. Bibliografía

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9. Anexos

9. Anexos

9.1. Anexo 1: Resultados de pruebas índices de relación cruzada con los estándares de referencia

Progresión desde un deterioro cognitivo leve (DCL) a una demencia por enfermedad de Alzheimer (DEA)

Información de la prueba índice	Información del estándar de referencia	
	DEA presente	**DEA ausente**
Prueba índice positiva	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol positivo que progresa a una DEA (VP)	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol positivo que no progresa a una DEA (FP)
Prueba índice negativa	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol negativo que progresa a una DEA (FN)	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol negativo que no progresa a una DEA (VN)

VP: verdadero positivo
FP: falso positivo
FN: falso negativo
VN: verdadero negativo

Progresión desde un deterioro cognitivo leve (DCL) a una demencia no Alzheimer (no-DEA)

Información de la prueba índice	Información del estándar de referencia	
	No-DEA presente	**No-DEA ausente**
Prueba índice positiva	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol positivo que progresa a una no-DEA (VP)	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol positivo que no progresa a una no-DEA (FP)
Prueba índice negativa	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol negativo que progresa a una no-DEA (FN)	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol negativo que no progresa a una no-DEA (VN)

VP: verdadero positivo
FP: falso positivo
FN: falso negativo
VN: verdadero negativo

Progresión desde un deterioro cognitivo leve (DCL) a cualquier forma de demencia

Información de la prueba índice	Información del estándar de referencia	
	Cualquier forma de demencia presente	Cualquier forma de demencia ausente
Prueba índice positiva	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol positivo que progresa a cualquier forma de demencia (VP)	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol positivo que no progresa cualquier forma de demencia
Prueba índice negativa	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol negativo que progresa a cualquier forma de demencia (FN)	18F-Florbetapir o 18F-Florbetaben o 18F-Flutemetamol negativo que no progresa a cualquier forma de demencia (VN)

VP: verdadero positivo
FP: falso positivo
FN: falso negativo
VN: verdadero negativo

9.2. Anexo 2. Tabla de evaluación de calidad metodológica: Herramienta de evaluación de calidad de estudios de exactitud diagnóstica 2 (QUADAS-2)

Dominio	Selección de pacientes	Prueba índice	Estándar de referencia	Flujo y tiempo
Descripción	¿Describe los métodos de selección de pacientes? Describe los pacientes incluidos (pruebas previas, presentación, intención de uso de la prueba índice y ámbito?	¿Describe la prueba índice y cómo se realizó y se interpretó?	¿Describe el estándar de referencia y cómo fue realizado e interpretado?	¿Describe a los pacientes que no recibieron la prueba índice o el estándar de referencia o quienes fueron excluidos de la tabla 2x2? ¿Describe el intervalo y cualquier intervención entre la realización de la prueba índice y el estándar de referencia?
Preguntas de señalización (Sí, No, o poco claro)	¿La muestra de pacientes fue enrolada en forma	¿Fue la prueba índice interpretada sin conocer los resultados del	¿El estándar de referencia clasifica correctamente a	¿Existió un adecuado intervalo entre la prueba índice

	consecutiva o aleatorizada? ¿Se evitó el diseño de casos y controles? ¿El estudio evitó exclusiones inapropiadas?	estándar de referencia? Si se utilizó un umbral, ¿éste estaba pre-especificado?	la condición objetivo? ¿Fue el estándar de referencia interpretado sin conocer los resultados de la prueba índice?	y el estándar de referencia? ¿Todos los pacientes recibieron el estándar de referencia? ¿Todos los pacientes recibieron el mismo estándar de referencia? ¿Todos los pacientes fueron incluidos en el análisis?
Riesgo de sesgo (alto, bajo o poco claro)	¿Pudo la selección de pacientes haber introducido sesgo?	¿Pudo la realización o interpretación de la prueba índice haber introducido sesgo?	¿Pudo la realización o interpretación del estándar de referencia haber introducido sesgo?	¿Pudo el flujo y tiempo del paciente haber introducido sesgo?
Preocupaciones acerca de la aplicabilidad (alto, bajo o poco claro)	¿Hay preocupaciones de que los pacientes incluidos no coincidan con la pregunta de la revisión?	¿Hay preocupaciones de que la prueba índice, su realización o su interpretación no coincida con la pregunta de la revisión?	¿Hay preocupaciones de que la condición objetivo, definida por el estándar de referencia no coincida con la pregunta de la revisión?	

9.3. Anexo 3 Publicaciones relacionadas

Quinn TJ, Elliott E, Hietamies TM, **Martínez G**, Tieges Z, Mc Ardle R.
Diagnostic test accuracy of remote, multidomain cognitive assessment (telephone and video call) for dementia

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Diagnostic test accuracy of remote, multidomain cognitive assessment (telephone and video call) for dementia (Protocol)

Quinn TJ, Elliott E, Hietamies TM, Martínez G, Tieges Z, Mc Ardle R

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Rodriguez-Gomez O, Sanabria A, Perez-Cordon A, Sanchez-Ruiz D, Abdelnour C, Valero S, Hernandez I, Rosende-Roca M, Mauleon A, Vargas L, Alegret M, Espinosa A, Ortega G, Guitart M, Gailhajanet A, Sotolongo-Grau O, Moreno-Grau S, Ruiz S, Tarragona M, Serra J, Martin E, Peleja E, Lomeña F, Campos F, Vivas A, Gomez-Chiari M, Tejero MA, Giménez J, Pesini P, Sarasa M, **Martinez G**, Ruiz A, Tarraga L, Boada M. FACEHBI: A prospective study of risk factors, biomarkers and cognition in a cohort in a cohort of individuals with subjective cognitive decline. Study rationale and research protocols. J Prev Alz Dis 2017;4(2):100-108

FACEHBI: A Prospective Study of Risk Factors, Biomarkers and Cognition in a Cohort of Individuals with Subjective Cognitive Decline. Study Rationale and Research Protocols

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Abstract

BACKGROUND: Long-term longitudinal studies with multimodal biomarkers are needed to delve into the knowledge of preclinical AD. Subjective cognitive decline has been proposed as a risk factor for the development of cognitive impairment. Thus, including individuals with SCD in observational studies may be a cost-effective strategy to increase the prevalence of preclinical AD in the sample.

OBJECTIVES: To describe the rationale, research protocols and baseline characteristics of participants in the Fundació ACE Healthy Brain Initiative (FACEHBI).

DESIGN: FACEHBI is a clinical trial (EudraCT: 2014-000798-38) embedded within a long-term observational study of individuals with SCD.

SETTING: Participants have been recruited at the memory clinic of Fundació ACE (Barcelona) from two different sources: patients referred by a general practitioner and individuals from an Open House Initiative.

PARTICIPANTS: 200 individuals diagnosed with SCD with a strictly normal performance in a comprehensive neuropsychological battery.

MEASUREMENTS: Individuals will undergo an extensive neuropsychological protocol, risk factor assessment and a set of multimodal biomarkers including florbetaben PET, structural and functional MRI, diffusion tensor imaging, determination of amyloid species in plasma and neurophthalmologic assessment with optical coherence tomography.

RESULTS: Two hundred individuals have been recruited in 15 months. Mean age was 65.9 years; mean MMSE was 29.2 with a mean of 14.8 years of education.

CONCLUSIONS: FACEHBI is a long-term study of cognition, biomarkers and lifestyle that has been designed upon an innovative symptom-based approach using SCD as target population. It will shed light on the pathophysiology of preclinical AD and the role of SCD as a risk marker for the development of cognitive impairment.

Key words: Subjective cognitive decline, biomarkers, preclinical AD, longitudinal study.
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Introduction

The prevalence of dementia is increasing in developed societies due to social and demographic changes, and this trend is expected to worsen within the next decades. This epidemic progression could pose a threat to public health, to such an extent that the World Health Organization has declared dementia control a global health prority (1). The disappointing results of the clinical trials in patients with Alzheimer´s disease (AD) dementia (2) or even mild cognitive impairment (MCI) have highlighted the necessity to act earlier (3). In this context, the earliest stages of AD are becoming a topic of major scientific interest. Nowadays, advancing research has provided a large amount of knowledge of the phenomena involved in the transition from mild cognitive impairment to dementia, but much less is known about the events that lead individuals that are strictly normal from a cognitive viewpoint to develop cognitive impairment (4). In this regard, strong evidence exists that the pathophysiological process of Alzheimer´s disease (AD) begins many years before the onset of the clinical symptoms, leading to the formulation of the biomarker-defined construct of preclinical AD (5). Deep knowledge of this process is essential to develop diagnostic and prognostic markers. Additionally, it will allow a better selection of individuals at risk for preventive trials and monitorization of the efficacy of treatments intended to modify the course of the disease. However, our present understanding of preclinical AD is far from complete and the very definition of the concept is controversial to date

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Sánchez D, Castilla-Marti M, Rodríguez-Gómez O, Valero S, Piferrer A, **Martínez G**, Martínez J, Serra J, Moreno-Grau S, Hernández-Olasagarre B, De Rojas I, Hernández I, Abdelnour C, Rosende-Roca M, Vargas L, Mauleón A, Santos-Santos MA, Alegret M, Ortega G, Espinosa A, Pérez-Cordón A, Sanabria A, Ciudin A, Simó R, Hernández C, Villoslada P, Ruiz A, Tàrraga Ll, Boada M.
Usefulness of peripapillary nerve fiber layer thickness assessed by optical coherence tomography as a biomarker for Alzheimer's disease. Scientific Reports. 2018; 8: 16345.
DOI: 10.1038/s41598-018-34577-3

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Usefulness of peripapillary nerve fiber layer thickness assessed by optical coherence tomography as a biomarker for Alzheimer's disease

Domingo Sánchez[1], Miguel Castilla-Marti[2,3], Octavio Rodríguez-Gómez[1], Sergi Valero[1,4], Albert Piferrer[5], Gabriel Martínez[6,7], Joan Martínez[1], Judit Serra[1], Sonia Moreno-Grau[1], Begoña Hernández-Olasagarre[1], Itziar De Rojas[1], Isabel Hernández[1], Carla Abdelnour[1], Maitée Rosende-Roca[1], Liliana Vargas[1], Ana Mauleón[1], Miguel A. Santos-Santos[1], Montserrat Alegret[1], Gemma Ortega[1], Ana Espinosa[1], Alba Pérez-Cordón[1], Ángela Sanabria[1], Andrea Ciudin[8], Rafael Simó[8], Cristina Hernández[8], Pablo Villaoslada[9], Agustín Ruiz[1], Lluís Tàrraga[1] & Mercè Boada[1]

The use of optical coherence tomography (OCT) has been suggested as a potential biomarker for Alzheimer's Disease based on previously reported thinning of the retinal nerve fiber layer (RNFL) in Alzheimer's disease's (AD) and Mild Cognitive Impairment (MCI). However, other studies have not shown such results. 930 individuals (414 cognitively healthy individuals, 192 probable amnestic MCI and 324 probable AD) attending a memory clinic were consecutively included and underwent spectral domain OCT (Maestro, Topcon) examinations to assess differences in peripapillary RNFL thickness, using a design of high ecological validity. Adjustment by age, education, sex and OCT image quality was performed. We found a non-significant decrease in mean RNFL thickness as follows: control group: $100,20 \pm 14,60\,\mu m$, MCI group: $98,54 \pm 14,43\,\mu m$ and AD group: $96,61 \pm 15,27\,\mu m$. The multivariate adjusted analysis revealed no significant differences in mean overall ($p = 0.352$), temporal ($p = 0,119$), nasal ($p = 0,151$), superior ($p = 0,435$) or inferior ($p = 0,825$) quadrants between AD, MCI and control groups. These results do not support the usefulness of peripapillary RNFL analysis as a marker of cognitive impairment or in discriminating between cognitive groups. The analysis of other OCT measurements in other retinal areas and layers as biomarkers for AD should be tested further.

Alzheimer's disease (AD) is a complex neurodegenerative disease and the most common cause of dementia[1]. Clinical diagnostic criteria for AD do not discriminate with accuracy between different dementing etiologies[2]. Before the onset of dementia, cognitive disorders progress slowly with minor cognitive impairment and without significant interference in daily activities. This prodromal phase is known as mild cognitive impairment (MCI), a clinically heterogeneous syndrome whose definition has evolved in last years[3–5] and can be due to many different etiologies (AD, vascular damage, depression,…). Although some MCI patients can remain stable for decades or even return to cognitive normality, it is well established that amnestic and multi-domain MCI condition increases the risk of progressing to AD[6,7]. Given the fact that diagnosis of AD is still complicated especially in the MCI

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Sánchez D, Castilla-Marti M, Marquié M,Valero S, Moreno-Grau S, Rodríguez-Gómez O, Piferrer A, **Martínez G**, Martínez J, Rojas I, Hernández I, Abdelnour C, Rosende-Roca M, Vargas L, Mauleón A, Gil S, Alegret M, Ortega G, Espinosa A, Pérez-Cordón A, Sanabria A, Roberto N, Ciudin A, Simó R, Hernández C, Tárraga Ll, Boada M, Ruiz A.Evaluation of macular thickness and volume tested by optical coherence tomography as biomarkers for Alzheimer's disease in a memory clinic. Scientific Reports 2020;10: 1580

SCIENTIFIC REPORTS

natureresearch

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Evaluation of macular thickness and volume tested by optical coherence tomography as biomarkers for Alzheimer's disease in a memory clinic

Domingo Sánchez [1*], Miguel Castilla-Marti [3,4], Marta Marquié [1,2], Sergi Valero[1,2], Sonia Moreno-Grau[1,2], Octavio Rodríguez-Gómez[1,2], Albert Piferrer[5], Gabriel Martínez[6,7], Joan Martínez[1], Itziar De Rojas [1], Isabel Hernández[1,2], Carla Abdelnour[1,2], Maitée Rosende-Roca[1], Liliana Vargas[1], Ana Mauleón[1], Silvia Gil[1,2], Montserrat Alegret[1,2], Gemma Ortega[1,2], Ana Espinosa[1,2], Alba Pérez-Cordón[1], Ángela Sanabria[1,2], Natalia Roberto[1], Andreea Ciudin[8], Rafael Simó[8], Cristina Hernández[8], Lluís Tárraga[1,2], Mercè Boada[1,2] & Agustín Ruiz [1,2]

Building on previous studies that report thinning of the macula in Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients, the use of optical coherence tomography (OCT) has been proposed as a potential biomarker for AD. However, other studies contradict these results. A total of 930 participants (414 cognitively healthy people, 192 with probable amnestic MCI, and 324 probable AD patients) from a memory clinic were consecutively included in this study and underwent a spectral domain OCT scan (Maestro, Topcon) to assess total macular volume and thickness. Macular width measurements were also taken in several subregions (central, inner, and outer rings) and in layers such as the retinal nerve fiber (RNFL) and ganglion cell (CGL). The study employed a design of high ecological validity, with adjustment by age, education, sex, and OCT image quality. AD, MCI, and control groups did not significantly vary with regard to volume and retinal thickness in different layers. When these groups were compared, multivariate-adjusted analysis disclosed no significant differences in total ($p = 0.564$), CGL ($p = 0.267$), RNFL ($p = 0.574$), and macular thickness and volume ($p = 0.380$). The only macular regions showing significant differences were the superior ($p = 0.040$) and nasal ($p = 0.040$) sectors of the inner macular ring. However, adjustment for multiple comparisons nullified this significance. These results are not supporting existing claims for the usefulness of macular thickness as a biomarker of cognitive impairment in a memory unit. OCT biomarkers for AD should be subject to further longitudinal testing.

The diagnosis of Alzheimer's disease (AD), the most frequent neurodegenerative disease, requires clinical diagnostic criteria which do not get to differentiate this disease accurately from other causes of dementia[1].

Before dementia phase is established, cognition problems develop in a slow but progressive way, and can interfere limitedly in daily activities. This prodromal stage, called mild cognitive impairment (MCI), is a clinically heterogeneous syndrome and a consequence of different etiologies. Its definition has expanded in recent years[2–4].

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Rutjes AWS, Denton DA, Di Nisio M, Chong LY, Abraham RP, Al-Assaf AS, Anderson JL, Malik MA, Vernooij RWM, **Martínez G**, Tabet N, McCleery J.

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Rutjes AWS, Denton DA, Di Nisio M, Chong LY, Abraham RP, Al-Assaf AS, Anderson JL, Malik MA, Vernooij RWM, Martínez G, Tabet N, McCleery J

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Areosa Sastre A, Vernooij RWM, González-Colaço Harmand M, Martínez G

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McCleery J, Abraham RP, Denton DA, Rutjes AWS, Chong LY, Al-Assaf AS, Griffith DJ, Rafeeq S, Yaman H,
Malik MA, Di Nisio M, **Martínez G**, Vernooij RWM, Tabet N.
Vitamin and mineral supplementation for preventing dementia or delaying cognitive decline in people with mild
cognitive impairment. *Cochrane Database of Systematic Reviews* 2018, Issue 11. Art. No.: CD011905. DOI:
10.1002/14651858.CD011905.pub2.

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Cañabate P, **Martínez G**, Rosende-Roca M, Moreno M, Preckler S, Valero S, Sotolongo O, Hernandez I, Alegret M, Ortega G, Espinosa A, Mauleón A, Vargas L, Rodriguez O, Abdelnour C, Sánchez D, Martín E, Ruíz A, Tárraga Ll, Boada M.
Social Representation of Dementia: An Analysis of 5,792 Consecutive Cases Evaluated in a Memory Clinic. *J Alzheimers Dis*. 2017; 58(4):1099-1108

Social Representation of Dementia: An Analysis of 5,792 Consecutive Cases Evaluated in a Memory Clinic

Pilar Cañabate[a,*], Gabriel Martínez[a,b,c], Maitée Rosende-Roca[a], Mariola Moreno[a], Silvia Preckler[a], Sergi Valero[a,d], Oscar Sotolongo[a], Isabel Hernández[a], Montserrat Alegret[a], Gemma Ortega[a], Ana Espinosa[a], Ana Mauleón[a], Liliana Vargas[a], Octavio Rodríguez[a], Carla Abdelnour[a], Domingo Sánchez[a], Elvira Martín[a], Agustín Ruiz[a], Lluís Tárraga[a] and Mercè Boada[a]
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Abstract.
Background: Different interpretations of cognitive impairment and dementia due to differences in health structures, such as cultural differences could affect the diagnosis and treatment of the condition. it is reasonable to expect that the social and family impact of the disease and coping strategies will differ among societies.
Objective: The general aim of this study is to understand the social representations of dementia, its associated practices, and the effects they imply.
Methods: People diagnosed with clinical dementia and their families were assessed from 2005 to 2015 in the memory clinic of the Fundació ACE, Institut Català de Neurociències Aplicades in Barcelona, Spain.
Results: 9,898 people were examined and 5,792 were diagnosed with dementia. For those with a caregiver (71%), the decision-making fell on the person with dementia in 16.2% of the cases; and for those without a caregiver, in 26.4% of the cases the family did not perceive the deficits as a disease, which led to multiple risk situations (74.6%).
Conclusions: The recognition of dementia as part of aging is common among families. Consequently, risk situations may arise and diagnosis and access to treatment may be delayed. The incorporation of a social appraisal to the diagnostic process is a necessity to evaluate these situations.

Keywords: Alzheimer's disease, beliefs, caregiver, dementia, social perception, social representation, social-cultural

INTRODUCTION

The aging population is a worldwide reality. In 2015, approximately 12.2% of the world population was older than 60 years, and it is expected to grow up to 21.2% by 2050 [1]. In Spain, it is estimated that the age group over 60 years will constitute 43%

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Information, support and training for informal caregivers of people with dementia (Protocol)

González-Fraile E, Solà I, Ballesteros J, Rueda JR, Martinez G, Santos B

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