Universitat Autònoma de Barcelona

TESIS DOCTORAL

DEMENCIA ASOCIADA A ENFERMEDAD DE ALZHEIMER Y OTRAS DEMENCIAS: EVIDENCIAS DIAGNÓSTICAS

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BARCELONA, MAYO 2015

UNIVERSITAT AUTÒNOMA DE BARCELONA

DEPARTAMENT DE PEDIATRIA, d´OBSTETRICIA I GINECOLOGIA, I DE MEDICINA PREVENTIVA

Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI).

Arevalo-Rodriguez I, Smailagic N, Roqué i Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, Pedraza OL, Bonfill Cosp X, Cullum S.

Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD010783.

DOI:10.1002/14651858.CD010783.pub2.

Factor de impacto: 5.93

RESUMEN DE RESULTADOS

Las diferentes estrategias de búsqueda empleadas recuperaron un total de 24.357 referencias, de las cuales 17.513 fueron excluidas en una primera etapa por no evaluar al MMSE como una prueba diagnóstica. En un segundo momento los autores de la revisión eliminaron 6.611 referencias, evaluando en profundidad un total de 233. Al final del proceso de revisión del texto completo, se incluyeron 12 referencias que representaron 11 estudios con un total de 1569 participantes con DCL (Mediana= 109, RIQ: 105 a 140).

Respecto a las características de las muestras analizadas, más de la mitad de los estudios fue desarrollado en pacientes derivados de Clínicas de Memoria, con un promedio de edad superior a los 60 años. Un porcentaje entre 36.3 a 70% de los participantes de los estudios fueron mujeres. El promedio de seguimiento de las cohortes osciló desde 15 meses a siete años. Para el total de las muestras se calculó una incidencia mediana de demencia general (por cualquier causa) de 36.5% (RIQ= 32.9 a 37.8), con una incidencia mediana de demencia por EA de 39.4 % (RIQ= 13.3 a 54.2). Las sensibilidades y especificidades del MMSE en los estudios identificados oscilaron entre 23-88% y 32-94%, respectivamente.

Respecto a la evaluación de la calidad metodológica de los estudios incluidos por medio de la herramienta QUADAS-II, se encontró que:

- En el dominio de selección de la muestra, tres estudios fueron catalogados como de alto riesgo de sesgo debido al reporte deficiente de la inclusión de los pacientes y de los

criterios de exclusión empleados. Asimismo, en cuatro estudios no se pudo determinar los métodos para la inclusión de pacientes y fueron catalogados como de riesgo no-claro.

- En el dominio de la prueba evaluada, ocho estudios fueron catalogados como de alto riesgo de sesgo debido a que el punto de corte para definir conversión a demencia no fue establecido previo al inicio del estudio.
- En el dominio del estándar de referencia, dos estudios fueron catalogados como de alto riesgo y dos adicionales como de riesgo no-claro, debido a deficiencias en el reporte de la independencia en la evaluación del MMSE y el diagnóstico final de demencia. Los dos últimos estudios mencionados tampoco presentaron los criterios para definir la conversión a demencia de los pacientes con DCL.
- En el dominio de flujo de la información, dos estudios fueron considerados como de alto riesgo de sesgo debido a pérdidas al seguimiento entre 5 a 15% de los pacientes incluidos en el estudio, así como un reporte poco claro de las razones de estas pérdidas.

Respecto a las características operativas del MMSE para la conversión del DCL a demencia por cualquier causa, se encontraron tres estudios con cuatro cohortes de pacientes con DCL, para un total de 792 pacientes. La sensibilidad en dichos estudios osciló entre 23 a 76%, mientras que la especificidad osciló entre 40 a 94%. Cuando estos resultados se presentaron en el espacio ROC, se encontró una amplia falta de precisión, representada en el posible intervalo de confianza de la estimación conjunta de las características operativas, así como una amplia región de predicción alrededor de dichas cifras, lo cual es indicativo de una alta presencia de heterogeneidad en dichas estimaciones. Bajo estas condiciones, los autores de la revisión no realizaron adicionales por obtener estimaciones conjuntas de la exactitud diagnóstica del MMSE en este caso. Una situación similar se encontró en la evaluación de las características operativas del MMSE para la conversión del DCL a demencia por EA. La evaluación de las diferentes fuentes de heterogeneidad no pudo ser realizada de manera completa, debido al bajo número de estudios incluido para cada comparación; sin embargo, con los resultados descriptivos se pudo apreciar que el punto de corte representa una de las principales fuentes de variación de los resultados del MMSE.

Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI) (Review)

Arevalo-Rodriguez I, Smailagic N, Roqué i Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, Pedraza OL, Bonfill Cosp X, Cullum S

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TABLE OF CONTENTS

[Diagnostic Test Accuracy Review]

Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI)

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Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: New, published in Issue 3, 2015.
Review content assessed as up-to-date: 20 May 2014.

Citation: Arevalo-Rodriguez I, Smailagic N, Roqué i Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, Pedraza OL, Bonfill Cosp X, Cullum S. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD010783. DOI: 10.1002/14651858.CD010783.pub2.

ABSTRACT

Background

Dementia is a progressive global cognitive impairment syndrome. In 2010, more than 35 million people worldwide were estimated to be living with dementia. Some people with mild cognitive impairment (MCI) will progress to dementia but others remain stable or recover full function. There is great interest in finding good predictors of dementia in people with MCI. The Mini-Mental State Examination (MMSE) is the best-known and the most often used short screening tool for providing an overall measure of cognitive impairment in clinical, research and community settings.

Objectives

To determine the diagnostic accuracy of the MMSE at various thresholds for detecting individuals with baseline MCI who would clinically convert to dementia in general, Alzheimer's disease dementia or other forms of dementia at follow-up.

Search methods

We searched ALOIS (Cochrane Dementia and Cognitive Improvement Specialized Register of diagnostic and intervention studies (inception to May 2014); MEDLINE (OvidSP) (1946 to May 2014); EMBASE (OvidSP) (1980 to May 2014); BIOSIS (Web of Science) (inception to May 2014); Web of Science Core Collection, including the Conference Proceedings Citation Index (ISI Web of Science) (inception to May 2014); PsycINFO (OvidSP) (inception to May 2014), and LILACS (BIREME) (1982 to May 2014). We

also searched specialized sources of diagnostic test accuracy studies and reviews, most recently in May 2014: MEDION (Universities of Maastricht and Leuven, www.mediondatabase.nl), DARE (Database of Abstracts of Reviews of Effects, via the Cochrane Library), HTA Database (Health Technology Assessment Database, via the Cochrane Library), and ARIF (University of Birmingham, UK, www.arif.bham.ac.uk). No language or date restrictions were applied to the electronic searches and methodological filters were not used as a method to restrict the search overall so as to maximize sensitivity. We also checked reference lists of relevant studies and reviews, tracked citations in Scopus and Science Citation Index, used searches of known relevant studies in PubMed to track related articles, and contacted research groups conducting work on MMSE for dementia diagnosis to try to locate possibly relevant but unpublished data.

Selection criteria

We considered longitudinal studies in which results of the MMSE administered to MCI participants at baseline were obtained and the reference standard was obtained by follow-up over time. We included participants recruited and clinically classified as individuals with MCI under Petersen and revised Petersen criteria, Matthews criteria, or a Clinical Dementia Rating = 0.5. We used acceptable and commonly used reference standards for dementia in general, Alzheimer's dementia, Lewy body dementia, vascular dementia and frontotemporal dementia.

Data collection and analysis

We screened all titles generated by the electronic database searches. Two review authors independently assessed the abstracts of all potentially relevant studies. We assessed the identified full papers for eligibility and extracted data to create two by two tables for dementia in general and other dementias. Two authors independently performed quality assessment using the QUADAS-2 tool. Due to high heterogeneity and scarcity of data, we derived estimates of sensitivity at fixed values of specificity from the model we fitted to produce the summary receiver operating characteristic curve.

Main results

In this review, we included 11 heterogeneous studies with a total number of 1569 MCI patients followed for conversion to dementia. Four studies assessed the role of baseline scores of the MMSE in conversion from MCI to all-cause dementia and eight studies assessed this test in conversion from MCI to Alzheimer´s disease dementia. Only one study provided information about the MMSE and conversion from MCI to vascular dementia. For conversion from MCI to dementia in general, the accuracy of baseline MMSE scores ranged from sensitivities of 23% to 76% and specificities from 40% to 94%. In relationship to conversion from MCI to Alzheimer's disease dementia, the accuracy of baseline MMSE scores ranged from sensitivities of 27% to 89% and specificities from 32% to 90%. Only one study provided information about conversion from MCI to vascular dementia, presenting a sensitivity of 36% and a specificity of 80% with an incidence of vascular dementia of 6.2%. Although we had planned to explore possible sources of heterogeneity, this was not undertaken due to the scarcity of studies included in our analysis.

Authors' conclusions

Our review did not find evidence supporting a substantial role of MMSE as a stand-alone single-administration test in the identification of MCI patients who could develop dementia. Clinicians could prefer to request additional and extensive tests to be sure about the management of these patients. An important aspect to assess in future updates is if conversion to dementia from MCI stages could be predicted better by MMSE changes over time instead of single measurements. It is also important to assess if a set of tests, rather than an isolated one, may be more successful in predicting conversion from MCI to dementia.

PLAIN LANGUAGE SUMMARY

Baseline scores of Mini-Mental State examination (MMSE) for early prediction of developing dementia in people with mild cognitive impairments (MCI)

Patients with MCI should be evaluated and monitored due to their increased risk of progression to dementia. At present there are no agreements about what the best approach is to register the progression to dementia. Several cognitive function tests have been proposed for this task because most of them are easy to administer, take no longer than 10 minutes to complete, involve major executive functions, and yield an objective score. Our review assessed the current evidence related to one of those brief tests, the Mini-Mental State Examination (MMSE), in the prediction of decline to dementia in people with cognitive impairments. After an extensive search and analysis of available information, we did not find evidence supporting a substantial role of MMSE as a stand-alone single-administration test in the identification of patients who will convert to dementia in the future.

BACKGROUND

Dementia is a progressive global cognitive impairment syndrome. In 2010, more than 35 million people worldwide were estimated to be living with dementia, a number that will increase to more than 115 million by 2050 (Ferri 2005; Prince 2013; Wimo 2010). Dementia encompasses a group of neurodegenerative disorders that are characterised by progressive loss of both cognitive function and the ability to perform daily living activities. It can be accompanied by neuropsychiatric symptoms and challenging behaviours of varying type and severity. Its underlying pathology is usually degenerative, and subtypes of dementia include Alzheimer's disease dementia (ADD), vascular dementia, dementia with Lewy bodies and frontotemporal dementia, among others. Considerable overlap may be noted in the clinical and pathological presentations of dementia (MRC CFAS 2001), and ADD and vascular dementia often coexist (Matthews 2009; Savva 2009).

Recently a new type of cognitive function stage called mild cognitive impairment (MCI) has been proposed. MCI refers to a heterogeneous condition and currently 16 different classifications are used to define it (Matthews 2008; Petersen 1999; Petersen 2004; Winblad 2004). Prevalence of MCI varies widely (between 0.1% and 42%) according to the criteria applied, with most systems including memory impairment and absence of cognitive decline as basic conditions for diagnosis (Stephan 2007). As part of the Aging, Demographics, and Memory Study (ADAMS) assessment, Plassman et al estimated the prevalence of cognitive impairment without dementia as 22% in people aged 71 years or older (Plassman 2008). MCI may be classified as amnestic or non-amnestic, according to the presence of clinically significant memory impairment that does not meet the criteria for dementia, or a subtle decline in other functions not related to memory (Petersen 2011).

Over time, people with MCI may experience a gradually progressive cognitive decline and changes in personality and behaviour. When the cognitive impairment in memory, reasoning, language and visuospatial abilities interferes with daily function, individuals are diagnosed with dementia. Research studies indicate that an annual average of 10% to 15% of individuals with MCI may progress to dementia, in particular ADD, but with wide variation depending upon the source of study participants, with self-selected clinic attendees having the highest conversion rates (Bruscoli 2004; Mitchell 2008). Information on long-term cohorts suggests that annual conversion rates range from 4.2% (95% confidence interval (CI) 3.9% to 4.6%) for all-cause dementia to 5.8% (95% CI 5.5% to 6.5%) for ADD (Mitchell 2008).

Establishing a definitive diagnosis of MCI in the presence of subtle symptoms can be challenging. In these cases, it is necessary to document the cognitive decline from the patient's medical history and corroborate it by means of neuropsychological testing, among other suggested tools (Petersen 2001). The American Academy of Neurology recommended in 2001 that patients with MCI should be evaluated and monitored in accordance with their risk of progression to dementia by means of general or brief cognitive screening tools (Petersen 2001). Likewise, the National Institute on Aging and the Alzheimer's Association remarked in 2011 that longitudinal evidence of progressive decline in cognition could support the diagnosis of MCI due to ADD and could allow assessment of the potential benefits of early treatment (Albert 2011).

Usually recognition and assessment of people with suspected dementia in any setting (community, primary care or secondary care) requires a brief test of cognitive function or the use of informant questionnaires, or both (Arevalo-Rodriguez 2013; Moyer 2014). The brief cognitive evaluations needed are usually paper-and-pencil tests that are easy to administer, take no longer than 10 minutes to complete, involve major executive functions and yield an objective score. This final score is useful in determining which individuals need a more comprehensive evaluation (usually identified by low scores) (Boustani 2003). One of these brief cognitive tests is the Mini-Mental State Examination (MMSE) (Folstein 1975), which has become the best-known and the most often used short screening tool for providing an overall measure of cognitive impairment in clinical, research and community settings, although it is now the subject of copyright issues (Nieuwenhuis-Mark 2010).

Systematic assessments of the diagnostic accuracy of brief cognitive tests such as MMSE are scarce (Arevalo-Rodriguez 2014). In 1992, Tombaugh et al presented a narrative review of MMSE studies that emphasised psychometric properties such as reliability and construct validity without evaluating the quality of the included evidence (Tombaugh 1992). Later, Mitchell published a meta-analysis of cross-sectional studies of MMSE and reported different estimations of sensitivity and specificity according to the setting and population (Mitchell 2009). Until now, the relationship between MMSE scores and conversion from MCI to ADD or other dementias has not been evaluated in a systematic fashion.

It is thus the aim of this DTA review for diagnostic test accuracy in dementia to evaluate the ability of the MMSE in such settings as community residences, primary care facilities and memory clinics to identify those people with MCI who will progress to the full clinical syndrome of dementia.

Target condition being diagnosed

In general, dementia as diagnosed is defined by a deficit in more than two cognitive domains that is of sufficient degree to impair functional activities. Symptoms are usually progressive over a period of at least several months and should not be attributable to any other brain disease (American Psychiatric Association 1994). Dementia develops over a trajectory of several years, and it is presumed that during some portion of this time people are asymptomatic and pathology is accumulating (Jack 2011). Individuals or their

relatives may notice subtle impairments of recent memory during this time. Gradually, more cognitive domains become involved and difficulty planning complex tasks becomes increasingly apparent. Subtypes of dementia include Alzheimer's disease dementia (ADD) (McKhann 1984; McKhann 2011), vascular dementia (Roman 1993), frontotemporal dementia (Lund and Manchester Groups 1994) and Lewy body dementia (McKeith 1996), among others. Some dementia subtypes are related to other neurological diseases such as Parkinson's disease (Goetz 2008).

This review focused on conversion from MCI to all-cause dementia, ADD, as well as conversion from MCI to other forms of dementia, which were assessed at follow-up. As was previously noted, several studies have shown that most patients with MCI are at increased risk of developing dementia (Petersen 2011). Several medications have been evaluated for use in reducing or delaying the risk of progression, but none have been adopted for extended clinical use (Farina 2012; Russ 2012; Yue 2012).

Index test(s)

The Folstein Mini-Mental State Examination (MMSE) is a 30-question assessment of cognitive function that evaluates attention and orientation, memory, registration, recall, calculation, language and ability to draw a complex polygon (Folstein 1975). The MMSE has recently been subject to copyright restrictions (de Silva 2010). In its inception, the MMSE was not conceived to identify early stages of dementia, distinguish between different types of dementia or to predict the development of dementia in the long term.

Advantages of the MMSE include rapid administration, availability of multiple language translations and high levels of acceptance as a diagnostic instrument amongst health professionals and researchers (Nieuwenhuis-Mark 2010). The presence of cognitive decline is determined by the total score. Traditionally, a 23/24 cut-off has been used to select patients with suspected cognitive impairment or dementia (Tombaugh 1992). However, several studies have shown that sociocultural variables, age and education, among other factors, could affect individual scores (Bleecker 1988; Brayne 1990; Crum 1993); therefore local standards must be developed for each population and setting evaluated (Diniz 2007; Kulisevsky 2009; Shiroky 2007; Trenkle 2007).

Clinical pathway

Dementia develops over a trajectory of several years. It is presumed that during some portion of this time people are asymptomatic and pathology is accumulating. Individuals or their relatives may notice subtle impairments of recent memory during this time. Gradually, more cognitive domains become involved and difficulty planning complex tasks becomes increasingly apparent. People with memory complaints usually present to their general practitioner (primary care), who may administer one or more brief cognitive tests and potentially refer the individual to a memory clinic (secondary care). However, many people with dementia do not present until much later in the course of the disease and follow a different pathway to diagnosis. In community settings, screening tests are usually administered to estimate the epidemiological figures of dementia, identify cases to be included in clinical trials or even establish a follow-up to detect incident cases or changes in cognitive performance (Brayne 2011). In all cases, a follow-up period is mandatory to detect cognitive changes in populations and conversion of mild cases to dementia (delayed verification).

Standard assessment of dementia includes a history and clinical examination (including neurological, mental state and cognitive examinations); laboratory tests such as thyroid-stimulating hormone, serum folic acid, serum vitamin B_{12} and blood count; an interview with a relative or other informant; and neuroradiological evaluation (Feldman 2008; Hort 2010). Before dementia is diagnosed, other physical and mental disorders (for example hypothyroidism, depression) that might be contributing to cognitive impairment should be excluded or treated. Neuropsychological examination includes full assessment of major cognitive domains, including memory, executive functions, language, attention and visuospatial skills. A neuroradiological examination (computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain) is also recommended in most recent consensus guidelines (McKhann 2011), although the use of cerebrospinal fluid (CSF) biomarkers is controversial (Dubois 2010). Sometimes the diagnosis is made on the basis of history and presentation alone.

Prior test(s)

Most tests (for example neuroimaging, CSF analysis) are usually performed after a cognitive deficit has been identified. However, it is conceivable that patients with abnormalities on brain imaging, performed for any number of reasons, are likely to be tested subsequently for cognitive deficits.

Role of index test(s)

Accurate diagnosis leads to opportunities for treatment. At the present time, no 'cure' for dementia is known but some treatments can slow cognitive and functional decline or reduce associated behavioural and psychiatric symptoms of dementia (Birks 2006; Clare 2003; McShane 2006). Furthermore, diagnosis of ADD (and other dementias) at an early stage will help people with dementia, their families and potential carers in making timely plans for the future. Coupled with appropriate contingency planning, proper recognition of the disease may help to prevent inappropriate and potentially harmful admissions to hospital or institutional care. In addition, accurate early identification of dementia may increase opportunities for the use of newly evolving interventions designed to delay or prevent progression to more debilitating stages of dementia.

Alternative test(s)

The Cochrane Dementia and Cognitive Improvement Group is undertaking a series of DTA systematic reviews, including a full investigation of other short cognitive tests like the Montreal Cognitive Assessment (Davis 2013a) and the Mini-Cog test (Chan 2014; Fage 2013; Seitz 2014).

Rationale

The public health burden of cognitive and functional impairment due to dementia is of growing concern. With the changing age structure of populations in both high- and low-income countries, the prevalence of dementia is increasing (Ferri 2005; Prince 2013). At the population level, this has major implications for service provision and planning given that the condition leads to progressive functional dependence over several years. Accurate diagnosis leads to opportunities for treatment and appropriate care, but it is also crucial to identify participants for clinical trials of sufficient power to demonstrate the effectiveness of potential treatments.

At the present time, no 'cure' for dementia is known, but some treatments can slow cognitive and functional decline or reduce associated behavioural and psychiatric symptoms of dementia (Birks 2006; Clare 2003; McShane 2006). Furthermore, diagnosis of ADD (and other dementias) at an early stage (that is MCI) will help people with dementia, their families and potential carers in making timely plans for the future. Coupled with appropriate contingency planning, proper recognition of the disease may help prevent inappropriate and potentially harmful admissions to hospital or institutional care. In addition, accurate early identification of dementia may increase opportunities for the use of newly evolving interventions designed to delay or prevent progression to more debilitating stages of disease.

The Cochrane Dementia and Cognitive Improvement Group is undertaking a series of DTA systematic reviews, including three on the accuracy of the MMSE for diagnosing dementia. This review will be focused on evaluation of the MMSE and delayed-verification studies for assessment of conversion from MCI to dementia.

OBJECTIVES

To determine the diagnostic accuracy of the MMSE at various thresholds for detecting individuals with MCI at baseline who would clinically convert to all-cause dementia, Alzheimer's disease dementia or other forms of dementia at follow-up.

Secondary objectives

To assess the heterogeneity of test accuracy by population (for example memory clinics, community settings) and MMSE thresholds, amongst other factors.

METHODS

Criteria for considering studies for this review

Types of studies

We considered longitudinal studies in which results of the MMSE administered to MCI participants were obtained at baseline and the reference standard was obtained by follow-up over time (at least 12 months). We excluded cross-sectional studies, before-after studies and case reports.

Participants

We included participants recruited from community, primary care and secondary care settings and clinically classified as individuals with MCI at baseline. We established the diagnosis of MCI using Petersen and revised Petersen criteria (Petersen 1999; Petersen 2004), Matthews criteria (Matthews 2008) or Clinical Dementia Rating (CDR) = 0.5 (Morris 1993). These criteria include subjective complaints, decline in memory objectively verified by neuropsychological testing in combination with patient history, decline in other cognitive domains, minimal or no impairment in activities of daily living and not meeting the criteria for dementia. We included all subtypes of MCI participants (amnestic single domain, amnestic multiple domain, non-amnestic single domain and non-amnestic multiple domain). We excluded studies of participants with a secondary cause of cognitive impairment, namely current or past alcohol or drug abuse, central nervous system (CNS) trauma (for example subdural haematoma), tumour and infection, amongst others.

Index tests

The Mini-Mental State Examination (Folstein 1975), or MMSE, is a simple pen-and-paper test of cognitive function based on a total possible score of 30 points; it includes tests of orientation, concentration, attention, verbal memory, naming and visuospatial skills. In follow-up studies, participants with MCI are evaluated by the MMSE to obtain a baseline score and then are followed for several months to allow identification of new cases of dementia. Its utility as a predictive factor could be evaluated for several thresholds, some of them previously specified or otherwise obtained from statistical methods (for example logistic regression); optimal cut-offs are established according to sensitivity and specificity figures, amongst others.

Target conditions

The target condition was conversion at follow-up from MCI to all-cause dementia, Alzheimer's disease dementia (ADD) or other forms of dementia. We expected to find most studies focused on

ADD, vascular dementia, Lewy body dementia and frontotemporal dementia.

Reference standards

Currently, no in vivo gold standard is used for the diagnosis of dementia, and even the value of diagnoses based on neuropathological criteria has been questioned (Scheltens 2011). However, we used acceptable and commonly used reference standards. Clinical diagnosis after follow-up includes all-cause (unspecified) dementia, according to recognised diagnostic criteria for example the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the International Classification of Diseases, 10th Revision (ICD-10). National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)-Alzheimer Disease and Related Disorders Association (ADRDA) criteria (McKhann 1984; McKhann 2011) are the best antemortem clinical consensus gold standard for ADD, defining three antemortem groups: probable, possible and unlikely ADD. DSM and ICD definitions are also acceptable classifications for diagnosis of eventual ADD. The reference standard for Lewy body dementia was the McKeith criteria (McKeith 1996; McKeith 2005), for frontotemporal dementia the Lund-Manchester criteria (Lund and Manchester Groups 1994) and for vascular dementia the National Institute of Neurological Disorders and Stroke (NINDS)-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria (Roman 1993).

Search methods for identification of studies

Electronic searches

We searched ALOIS (Cochrane Dementia and Cognitive Improvement Specialized Register of diagnostic and intervention studies (inception to May 2014), MEDLINE (OvidSP) (1946 to May 2014), EMBASE (OvidSP) (1980 to May 2014), BIOSIS (Web of Science) (inception to May 2014), Web of Science Core Collection including the Conference Proceedings Citation Index (ISI Web of Science) (inception to May 2014), PsycINFO (OvidSP) (inception to May 2014) and LILACS (BIREME) (1982 to May 2014). We identified grey literature in the form of conference abstracts in a number of our database searches, especially in EMBASE and the Web of Science Core Collection, which includes the Conference Proceedings Citation Index. We designed similarly structured search strategies using search terms appropriate for each database (see Appendix 1 for all the search strategies). We used standardized database subject headings such as MeSH terms (in MEDLINE) and Emtree (in EMBASE) and other standardized headings (controlled vocabulary) in other databases, as appropriate. We did not use search filters designed to retrieve diagnostic test accuracy studies (collections of terms aimed at reducing the number needed to screen by filtering out irrelevant records and retaining only those that are relevant) as a method to restrict the search overall because available filters have not yet proved sensitive enough for systematic review searches (Whiting 2011). We did not apply any language restriction to the electronic searches. We requested a search of the Cochrane Register of Diagnostic Test Accuracy Studies (hosted and maintained by the Cochrane Renal Group) and the specialised register of the Cochrane Dementia and Cognitive Improvement Group, ALOIS, which includes both intervention and diagnostic test accuracy studies in dementia. A single researcher with extensive experience of systematic reviewing performed the initial searches.

Searching other resources

We checked the reference lists of all relevant papers for additional studies. We also searched:

- MEDION database (Meta-analyses van Diagnostisch Onderzoek), www.mediondatabase.nl;
- DARE (Database of Abstracts of Reviews of Effects), http://www.crd.york.ac.uk/CRDWeb/;
- HTA Database (Health Technology Assessment Database, the Cochrane Library),
- ARIF database (Aggressive Research Intelligence Facility), www.arif.bham.ac.uk.

Through PubMed, relevant studies were used to search for additional studies using the 'Related Articles' feature. We tracked key studies in citation databases such as the Science Citation Index and Scopus to ascertain further relevant studies. We identified grey literature in the form of conference abstracts in a number of our database searches, especially in EMBASE and the Web of Science Core Collection, which includes the Conference Proceedings Citation Index. We also attempted to contact researchers involved in studies with possibly relevant but unpublished data. We did not perform handsearching as the evidence for the benefits of handsearching is not certain. The findings of a recent study investigating handsearching as a method for identifying diagnostic test accuracy studies suggested little additional benefit for handsearching above a robust initial search strategy in a well-indexed and clearly defined subject area (Glanville 2012).

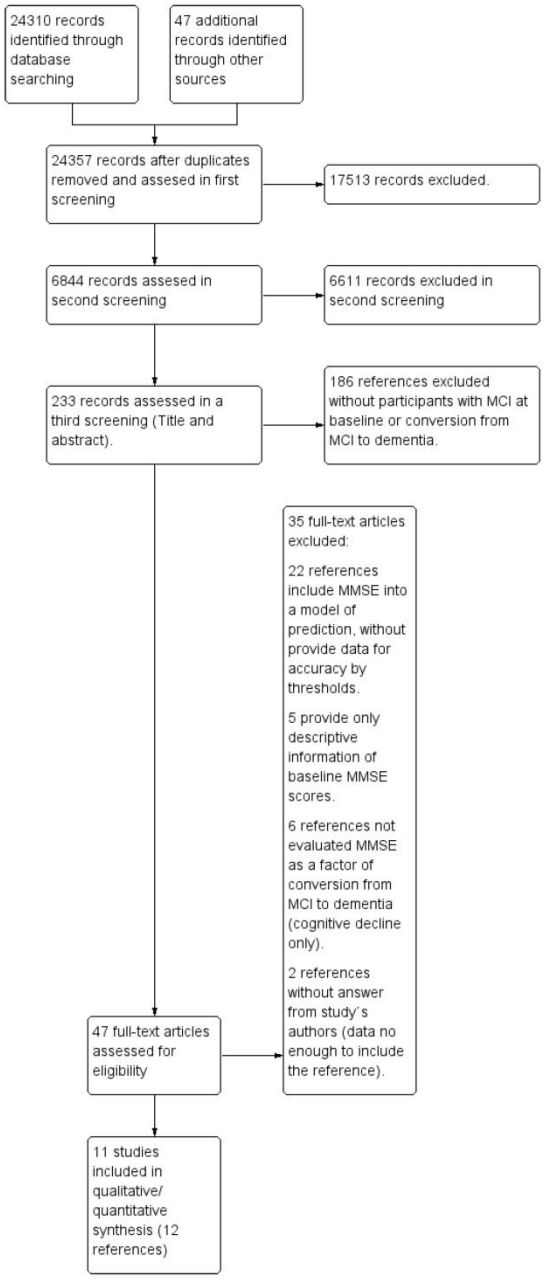
Data collection and analysis

Selection of studies

We selected studies on the basis of title and abstract screening undertaken by the review authors or by teams of experienced assessors. We then located the full paper for each potentially eligible study identified by the search, and two review authors independently evaluated each study for inclusion or exclusion. We resolved disagreements by discussion. If this did not prove conclusive, the

of excluded studies). We contacted nine authors to request useable data, of which six responded. Two studies with insufficient data were therefore excluded (Li 2011; Mauri 2012). One study retrieved in abstract form was classified as an 'ongoing study' because the authors presented a protocol in progress but without information about the accuracy of MMSE scores (Hall 2012). The review included 12 references representing 11 datasets with a total of 1569 participants (Summary of findings 2).

Figure 1. Study flow diagram.



Methodological quality of included studies

We assessed the risk of bias using the QUADAS-2 tool (Appendix 3; Appendix 4). The main results are summarized below (Figure 2; Figure 3).

Figure 2. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

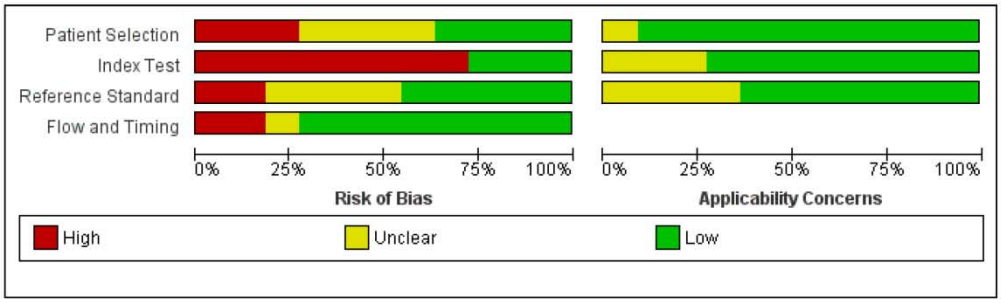
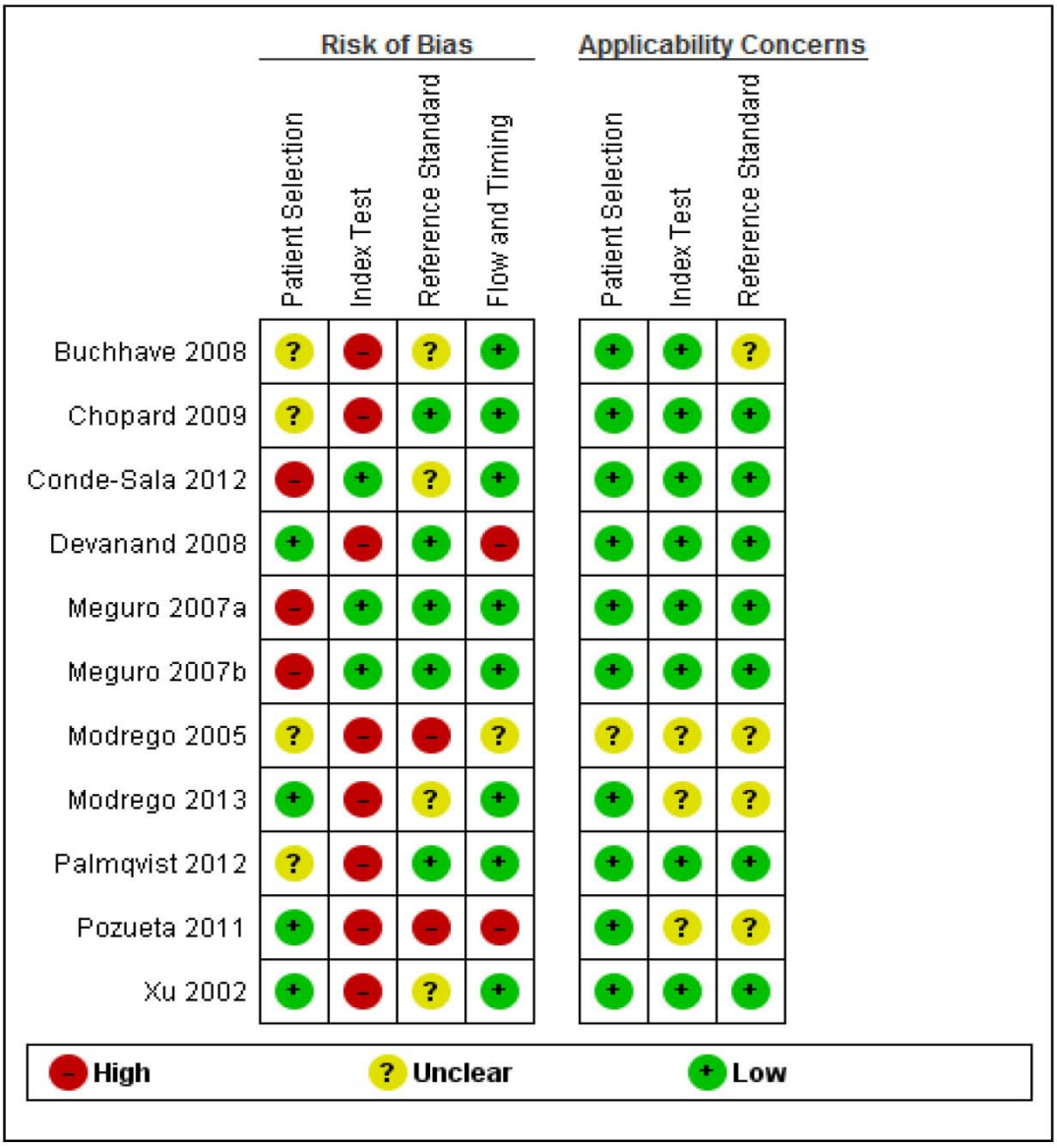


Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



In the patient selection domain we judged three studies (Conde-Sala 2012; Meguro 2007a; Meguro 2007b) to be at high risk of bias due to poor reporting of both the sampling procedure and exclusion criteria. We considered four studies (Buchhave 2008; Chopard 2009; Modrego 2005; Palmqvist 2012) to be at unclear risk of bias because they did not report whether the participants were systematically enrolled. We considered the remaining four studies (Devanand 2008; Modrego 2013; Pozueta 2011; Xu 2002) to be at low risk of bias. We stated that all included studies avoided a case-control design because we only considered data on the performance of the index test to discriminate between patients with MCI who converted to dementia and those who remained stable (that is delayed verification cohort studies).

In the index test domain we considered eight studies (Buchhave 2008; Chopard 2009; Devanand 2008; Modrego 2005; Modrego 2013; Palmqvist 2012; Pozueta 2011; Xu 2002) to be at high risk of bias because the threshold used was not pre-specified and the optimal cut-off level was determined from ROC analyses; therefore, the accuracy of the MMSE reported in these studies appeared to be overestimated. Some studies reported poorly which MMSE version was used and who administered and interpreted the test. We judged the remaining three studies (Conde-Sala 2012; Meguro 2007a; Meguro 2007b) to be at low risk of bias.

In the references´ standard domain we considered four studies (Buchhave 2008; Conde-Sala 2012; Modrego 2013; Xu 2002) to be at 'unclear' risk of bias and two more at high risk (Modrego 2005; Pozueta 2011) because they did not provide enough information about independence and blinding between baseline MMSE scores and the final diagnosis of dementia. These last studies also did not provide enough information about the criteria to establish the conversion from MCI to dementia at follow-up.

In the flow and timing domain we considered the majority of studies (eight) to be at low risk of bias. We judged two (Devanand 2008; Pozueta 2011) to be at high risk of bias and one (Modrego 2005) to be at unclear risk of bias due to loss to follow-up (5% to 15% of losses at follow-up) or poor reporting, or both.

For assessment of applicability concerns, for the majority of the studies (seven) there was no concern that the included patients and setting, the conduct and interpretation of the index test, and the target condition (as defined by the reference standard) did not match the review question. We judged that there was unclear concern about applicability for Modrego 2005 regarding all three domains and for Buchhave 2008, Modrego 2013 and Pozueta 2011 regarding the reference standard domain. It should be noted that the lack of concern about applicability of the three domains mentioned above was based on the inclusion criteria set in the review.

Findings

Included studies are detailed in Characteristics of included studies and Summary of findings 2 and Summary of findings 3. The total number of participants across all included studies was 1569 (median = 109; inter-quartile range (IQR) = 105 to 140). The maximum percentage of losses to follow-up was 15% (Devanand 2008).

One of the references (Meguro 2007a; Meguro 2007b) contained two independent datasets with different follow-ups and we included these as separate entries. Another reference had a single population followed in two different time frames and thresholds (Modrego 2005). We included the information from the longest follow-up (three years) in general analysis. Finally, one of the studies showed information about the accuracy of the Orientation and Recall MMSE subscales (Palmqvist 2012) but this information was not included in our analysis.

More than half of the studies were developed with patients from memory clinics (Buchhave 2008; Chopard 2009; Conde-Sala 2012; Devanand 2008; Palmqvist 2012; Pozueta 2011) with average ages greater than 60 years. In all studies, between 36.3% and 70% of participants were women. Few studies provided descriptive information about social class, years of education, MMSE version used, comorbidities or APOE-ϵ4 status. No study provided information about pharmacological or non-pharmacological interventions for MCI during the follow-up.

Four different diagnostic thresholds were used to define a positive MMSE ($\leq$ 21, $\leq$ 26, $\leq$ 28, $\leq$ 29). Two additional datasets (Meguro 2007a and Meguro 2007b) considered cut-offs according to individual years of education ($\leq$ 17 for less or equal to 6 years of education, $\leq$ 20 for 7 to 8 years of education, and $\leq$ 23 for 10 or more years of education). One additional study provided accuracy for a predicted risk of 0.5 derived from a univariate logistic regression model, instead of a MMSE threshold (Devanand 2008).

Average follow-up times ranged from 15 months to seven years. Median incidence of all-cause dementia in general was 36.5% (4 datasets; IQR = 32.9 to 37.8), while the median incidence of ADD was 39.4% (8 datasets; IQR = 13.3 to 54.2). Only one study provided data for vascular dementia (VaD) incidence (Xu 2002, 6.26%). The scope of the studies included data from five different countries: four studies from Spain; two from Japan, Switzerland and USA; and one from France. In general, sensitivity and specificity figures ranged between 23% and 88% and 32% and 94%, respectively (Summary of findings 3).

Baseline MMSE scores for conversion from MCI to all-cause dementia

Three studies provided numerical data for conversion from MCI to all-cause dementia, with four datasets (n = 792). Sensitivity ranged from 23% to 76% and specificity ranged from 40% to 94% (Figure 4). Figure 5 shows the accuracy estimations of in-

cluded studies in ROC space along with the SROC curve fitted by the model. We noticed a large lack of precision represented by the 95% confidence interval around the pooled estimates as well as a wide region of prediction, showing a high degree of influence of heterogeneity in this analysis. Under these conditions, there was considerable uncertainty regarding the combination of results from these studies, and the pooled results derived from this model need to be interpreted with caution. The degree of heterogeneity as well as the quality of evidence lowers the level of confidence in the strength of the results. To translate the meta-analysis results into absolute effects, at the median specificity of 88%, we estimated the sensitivity to be 40%. In a hypothetical cohort of 100 MCI patients with a 36.5% incidence of dementia, the number of missed cases would be 18 patients, while 8 MCI patients would be overdiagnosed.

Figure 4. Forest plot of 1 MMSE conversion to all-cause dementia.

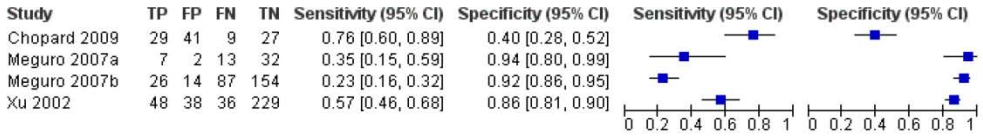


Figure 5. Baseline MMSE scores - conversion from MCI to all-cause dementia.

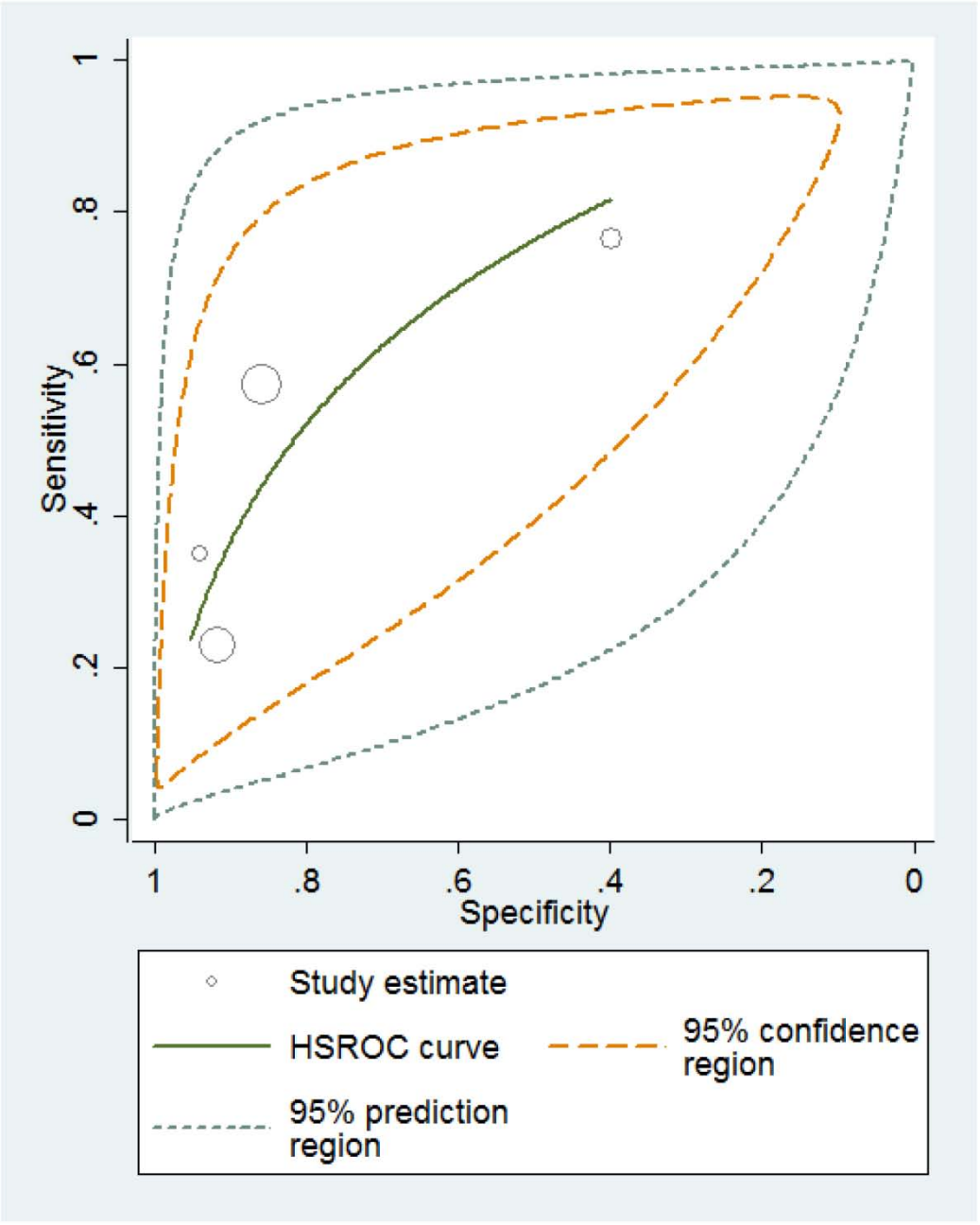
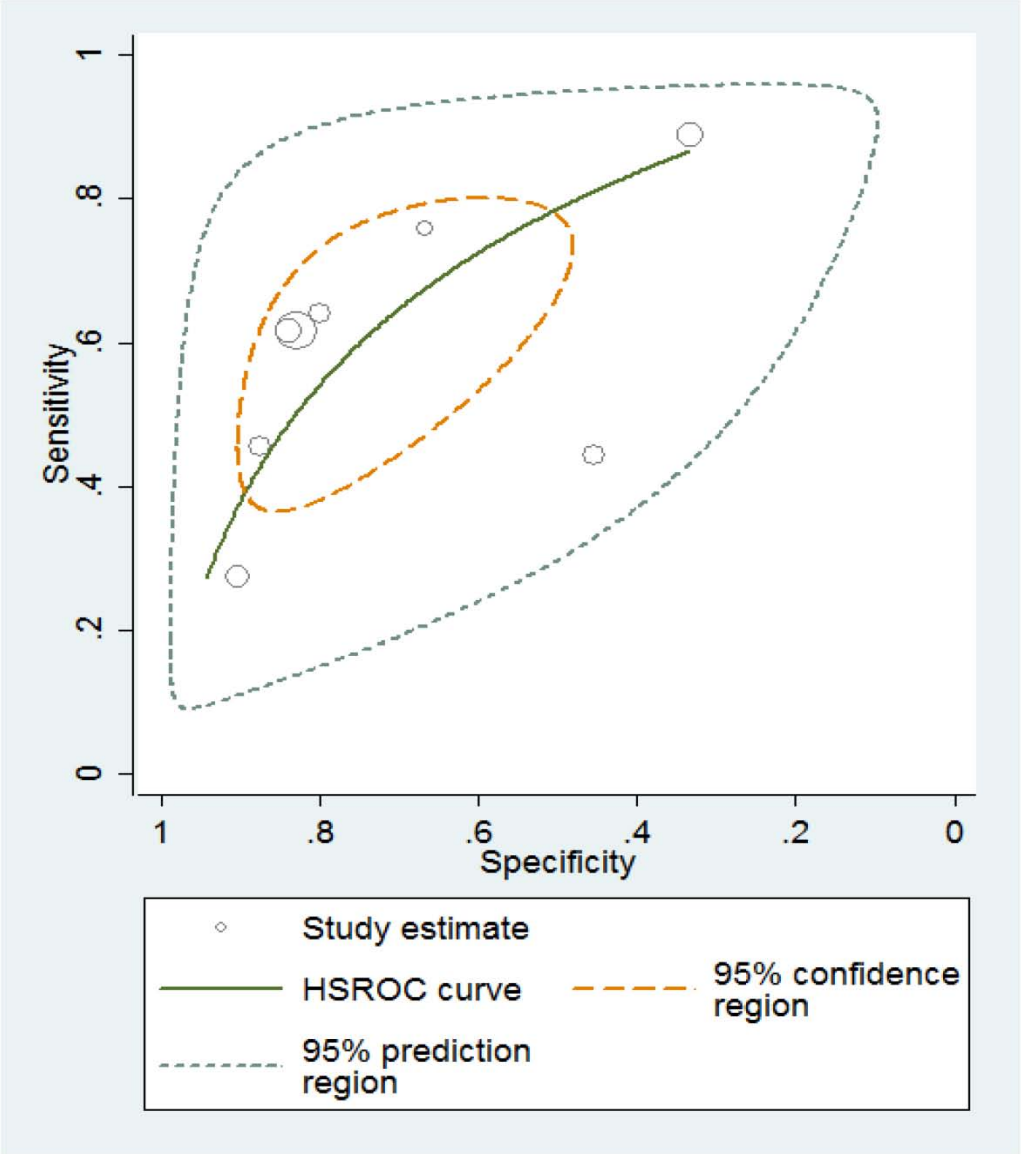


Figure 7. MMSE scores conversion from MCI to ADD.



Baseline MMSE scores for conversion from MCI to vascular dementia (VaD)

Only one study provided information about conversion from MCI to VaD (Xu 2002). This study presented a sensitivity of 36% and a specificity of 80% with an incidence of VaD of 6.2%. In a hypothetical cohort of 100 MCI patients the number of missed cases would be 5 patients, and 19 MCI patients would be overdiagnosed.

Analysis of heterogeneity and sensitivity analysis

Although we had planned to explore possible sources of heterogeneity through meta-regression, including several pre-specified variables, this was not undertaken due to the scarcity of studies included in our meta-analysis. In a narrative description, we noticed that the index test threshold was one of the main sources of variability between included studies. Only five studies (two for conversion to all-cause dementia, three for conversion to ADD and one for conversion to VaD) shared a common threshold (26/27 points), the remaining studies used other cut-offs to classify converters.

We also noticed an important variability in the estimated incidence of dementia. For instance, the incidence for ADD varied between 13% and 54% in MCI samples analysed. The influence of factors such as training of evaluators, education, presence of APOE-4 or onset of medical management was not assessed due to lack of reporting of these variables in the included studies. Related to version of MMSE used, we performed a sensitivity analysis for conversion from MCI to ADD. We removed the data of Modrego 2005 and Modrego 2013 because these studies used a MMSE version with a different scale (35 points). We did not find a significant difference in test accuracy or in perception of heterogeneity when these studies were removed.

Given the modest number of papers and the clinical heterogeneity registered, we did not perform any further sensitivity analysis by risk of bias measured with QUADAS-II items.

Summary of findings

What is the diagnostic accuracy of MMSE scores at baseline for identifying those MCI participants who would convert to dementia, Alzheimer´ s disease dementia or other forms of dementia over time?							
Patient population	Participants diagnosed with MCI at baseline using Petersen and revised Petersen criteria (Petersen 1999; Petersen 2004), Matthews criteria (Matthews 2008) or Clinical Dementia Rating (CDR) = 0.5 (Morris 1993)						
Prior testing	Most tests are usually performed after a cognitive deficit has been identified						
Settings	Participants were recruited from: i) secondary care - outpatient clinic (n = 3); ii) secondary care - memory clinics (n = 6) and iii) populational sources (n = 2)						
Index tests	MMSE scores at baseline						
Reference standard	NINCDS-ADRDA or DSM or ICD criteria for Alzheimer's disease dementia; McKeith criteria for Lewy body dementia; Lund criteria for frontotemporal dementia; and NINDS-AIREN criteria for vascular dementia						
Target condition	Dementia in general (defined by studies), Alzheimer's disease dementia or other forms of dementia						
Included studies	11 studies (1569 participants) of prospectively cohorts with any accepted definition of MCI were included						
Quality concerns	Patient selection and index test domains were insufficiently reported. Seven studies have not pre-specified thresholds Regarding the reference standard domain, a significant number of studies did not have enough information about the independent interpretation between the MMSE scores and the final diagnosis There were not important concerns about applicability domains in general						
Limitations	Limited investigation of heterogeneity due to insufficient number of studies						
Test	**Studies**	**Cases/participants**	**Median specificity from included studies**	**Sensitivity at median specificity (1)**	**Consequences in a cohort of 100**		
					Median percentage converting (range) (2)	**Missed cases (3)**	**Overdiagnosed**
All-cause dementia							
MMSE scores at baseline	4	255/792	88%	40%	36.5 (23.9 to 40.2)	22	8
Alzheimer's disease dementia							
MMSE scores at baseline	8	374/1128	80%	54%	39.1 (13.3 to 47.6)	18	12
Non-Alzheimer's disease dementia (vascular dementia)							
MMSE scores at baseline	1	22/351	80%	36%	6.26	5	19
Investigation of heterogeneity	The planned investigations were not possible due to the limited number of studies available for each analysis						
Conclusions	Our review did not find the evidence for supporting a substantial role of MMSE test in identifying those MCI patients who would develop dementia. The information included in this review is heterogeneous and does not present a definitive answer about critical issues such as an optimal cut-off, the influence of educational background or even the effects of literacy in the accuracy of MMSE						

(1) Meta-analytic estimate of sensitivity derived from the HSROC model at the median value of specificity computed from the included studies. Summary estimates of sensitivity and specificity were not computed due to high heterogeneity derived from included studies
(2) The median percentage of conversion and range were computed using all the studies included in the analysis for each target condition
(3) Missed (false negative) and overdiagnosed (false positive) numbers were computed using the median percentage of conversion for each target condition

DISCUSSION

Summary of main results

In this review we included 11 heterogeneous studies with a total number of 1569 MCI patients followed for conversion to dementia. Four studies assessed the role of baseline scores of MMSE in conversion from MCI to all-cause dementia (defined by the authors of each study) and eight studies assessed this test in conversion from MCI to Alzheimer´ s disease dementia (ADD). Only one study provided information about MMSE and conversion from MCI to vascular dementia (VaD). Other dementias, such as frontotemporal dementia or Lewy body dementia, were not assessed by any study. Due to the high heterogeneity and the scarcity of data we could not formally evaluate the influence of factors such as the threshold, the follow-up times, or even the incidence of dementia in the accuracy of this test.

For conversion from MCI to all-cause dementia, we included information from 792 patients (Chopard 2009; Meguro 2007a; Modrego 2005; Xu 2002), 255 of whom developed dementia. Two out of four included studies used CDR scores of 0.5 as the definition of cognitive impairment without dementia. The follow-up time frames were wider in comparison with the rest of studies included in this review (from 14 months to 7 years). Only two studies shared a common cut-off to define dementia (scores $\leq$ 26) and showed higher specificities and lower sensitivities in comparison with the rest of studies in this group. The accuracy of baseline MMSE scores ranged from sensitivities of 23% (Meguro 2007b) to 76% (Chopard 2009) and specificities from 40% (Chopard 2009) to 94% (Meguro 2007a). We obtained a summary sensitivity of 40% from the SROC curve at the median specificity of 88%. According to this information, MMSE scores appear to have a modest specificity but without the capacity to detect more than half of the MCI converters.

Related to conversion from MCI to ADD, we included information from 1128 patients (Buchhave 2008; Conde-Sala 2012; Devanand 2008; Modrego 2005; Modrego 2013; Palmqvist 2012; Pozueta 2011; Xu 2002) 374 of whom developed ADD. Five out of eight included studies used the Petersen diagnostic criteria (Petersen 1999; Petersen 2004) for defining MCI. The follow-up times in this group of studies were between two and six years. Only three studies (Modrego 2005; Pozueta 2011; Xu 2002) shared a common threshold (scores $\leq$ 26). The accuracy of baseline MMSE scores ranged from sensitivities of 27% (Devanand 2008) to 89% (Buchhave 2008) and specificities from 32% (Buchhave 2008) to 90% (Devanand 2008). We obtained a summary sensitivity of 54% from the SROC curve at the median specificity of 80%. Again, MMSE scores appear to have a modest specificity but without the capacity to detect near to half of MCI-converters.

Strengths and weaknesses of the review

Our review is part of a series of diagnostic test accuracy (DTA) reviews related to neuropsychological tests on dementia, for which a generic protocol was developed. This protocol identified a priori the best methodology in order to assess the accuracy of cognitive tests in the identification or conversion to any type of dementia (Davis 2013).

This review is the first Cochrane DTA review to assess the role of a well-known paper-and-pencil test (MMSE) in the evaluation of people in the early dementia stage, an entity recently recognized as an important frontier for successful management of this condition. We were challenged in the selection of studies for the research question because we shared a search strategy designed to cover all the DTA reviews related to MMSE and its accuracy in different settings (that is in people over 65 years within a secondary healthcare setting, and asymptomatic and previously clinically unevaluated people aged over 65 years in community and primary care populations). At the same time, with the use of such an exhaustive search strategy we could be sure we included all possible studies, even those with smaller sample sizes, to determine the accuracy of MMSE in predicting conversion from MCI to full dementia.

Although the MMSE is a cognitive test with more than 40 years of use, we only identified studies published since 2002 to answer our research question, possibly due to our specific baseline population (MCI). Also, the review only included studies with a delayed verification of the diagnosis, in contrast to the classic cross-sectional assessment of test accuracy. Such a combination of inclusion criteria had a direct influence on the number of retrieved and included studies in our review. For instance, a considerable number of studies with potential information were excluded because MMSE scores were evaluated as a part of prediction models without providing information about the accuracy of a specified threshold. We hope that in the future we can update our review with information provided by the contacted authors of excluded studies as well as ongoing studies.

We noticed that most of the included studies did not have the assessment of baseline MMSE scores as a main purpose. In most studies the MMSE was included as part of the usual diagnostic pathway for MCI patients and a common comparator for the principal test assessed. This directly affected the reporting quality and, most importantly, the methodological evaluation of included studies. Our results showed that the index test domain had the greater risk of bias, in most of the cases due to lack of reporting related to administration of MMSE as well as the absence of pre-specified thresholds. We think that the lack of pre-specified thresholds partially explained the high level of heterogeneity among the included studies. The scarcity of information did not allow us to formally assess the influence of this factor in the accuracy of MMSE, but the differences are easily noticed in the analysis of SROC curves. Additional factors that could affect the operative characteristics of MMSE, such as APOE status, the duration of MCI stage at the beginning of the study or even the administration of pharmaco-

logical or non-pharmacological interventions were not reported in a consistent way to be considered in our analyses.

Applicability of findings to the review question

Although the MMSE is a test with quick and easy administration, needs few resources and covers multiple cognitive domains at once, it is necessary to remark that this test was not developed to identify the early stages of dementia or even to predict the development of dementia in the long term. In our review, although it was not possible to estimate in a valid way the pooled operating characteristics, the descriptive data provided by the studies showed that neither the sensitivity nor specificity exceeded 80% at the same time. Only one study (Modrego 2005) shows a balance between accuracy figures, estimating a sensitivity of 76% and a specificity of 67% for the conversion of MCI to ADD, but derived from information with a high risk of bias. Our results suggest that MMSE may be of value to decrease the post-test probability of progression to dementia in the presence of normal test scores that confirm the possible conversion. These results may show that the items of the MMSE are insufficient to detect the change from mild to advanced cognitive decline, or even that some factors such as age, education and literacy must be taken into account to determine its true value in MCI patients. Likewise, this brief cognitive test may be more useful to document cognitive changes over time rather than to predict future progression with a single measurement. The verification of this hypothesis requires the assessment of evidence not presented in this review.

AUTHORS' CONCLUSIONS

Implications for practice

At present, there is consensus about the clinical relevance of MCI because this stage represents an opportunity to prevent or delay progression to dementia through modifications of risk factors such as depression and hypertension. The identification of diagnostic tools to predict which patients may progress to more severe stages of the disease has become a priority. The role of cognitive tests in the diagnosis of dementia is not questioned,because they show the clinical decline in areas like speed of information processing, executive functions and reasoning (Sperling 2011), while the role of biomarkers remains under evaluation (Kokkinou 2014; Ritchie 2014; Vacante 2013; Zhang 2014).

The Mini-Mental State Examination (MMSE) is a brief neuropsychological test that provides an overview of cognitive function which, in the setting of patients with MCI, is supplemented with more specialized neuropsychological tests for other domains of language, praxis and executive functions, among others. MMSE advantages reside in the easy way of administration (especially in terms of time and resources) without direct harmful effects, as well as a high acceptability by the health professionals involved in the management of people with dementia. In fact this popular test is frequently administered by clinicians to MCI patients and our review could help them to interpret the results of MMSE of their patients. Ideally, this brief cognitive test could be used for initial classification of MCI patients in order to determine their needs in a further and comprehensive assessment. However, there might be occasions where an extensive and formal neuropsychological evaluation is not available. In both cases it is important that clinicians know the limitations related to the use of this test in the prediction of dementia for MCI patients.

Our review did not find evidence supporting a substantial role of MMSE as a stand-alone single-administration test in the identification of MCI patients who may develop dementia. For example, a MCI patient with a baseline probability of 39% to develop ADD in the next three to four years (median incidence of ADD in our studies) only increases his or her post-test probability to 63% (95% CI 49 to 75) using a MMSE score indicator of progression (LR+ = 2.67), while a negative MMSE score for progression only decreases his or her post-test probability to 27% (LR - = 0.58, 95% CI 20 to 34). In the case of progression to dementia in general we found similar results. In all cases, clinicians would prefer to request additional and extensive tests to be sure about the management of these patients. Also, the review has not been able to address some critical issues such as an optimal cut-off, the influence of educational background, or even the effects of literacy in the accuracy of MMSE.

We think that MMSE items, despite the fact that they cover several cognitive domains, are insufficient for registering subtle cognition changes in MCI patients, especially for detecting those dementias without an important decline in the memory domain (such as frontotemporal dementia and primary progressive apraxia). It is important that clinicians are aware of the limitations related to the use of MMSE as a stand-alone single-administration test and seek to either use MMSE as a follow-up to detect changes in time, or to use it in the context of comprehensive assessments with more specialized neuropsychological tests for other domains of language, praxis and executive functions.

Implications for research

At present, the identification of useful cognitive tests that are able to detect subtle cognitive changes in people at different stages of dementia has become an important challenge. Although the information included in this review does not support the extended use of the MMSE in the stage of progression of MCI to dementia, we should not forget that this kind of test could be useful in settings where formal neuropsychological assessment is not available. In order to determine, with more information, the true operative characteristics of this test future research could focus on the evaluation of unique and pre-specified diagnostic thresholds, as well

5. DISCUSION

Esta tesis ha integrado tres trabajos de investigación con objetivos independientes, pero unidos por aspectos clínicos y metodológicos comunes. El aspecto clínico común en este trabajo fue el diagnóstico de la demencia, especialmente la demencia por enfermedad de Alzheimer, la cual resulta de marcada importancia para la oportuna identificación y clasificación de pacientes que pueden beneficiarse de las alternativas de manejo disponibles para esta condición. Como en otras patologías, se han sugerido diferentes herramientas diagnósticas para esta tarea, las cuales evidencian el entendimiento de las características de la condición a nivel clínico y biológico. En general, para que la práctica clínica sea efectiva, debe contarse con la evidencia suficiente para que los elementos empleados en la identificación de estos pacientes puedan realizarse con la máxima validez posible.

En este contexto, la pregunta de investigación planteada fue: ¿Cuál es la calidad de la evidencia referente a las herramientas diagnósticas empleadas en la actualidad para el abordaje de los pacientes con demencia por Enfermedad de Alzheimer y otras demencias?, la cual fue abordada por medio de tres objetivos:

a. Evaluar la calidad de las guías de práctica clínica publicadas a nivel mundial, que aborden el diagnóstico de la demencia de tipo Alzheimer y otras demencias.
b. Evaluar la calidad de las revisiones sistemáticas de las características operativas de los instrumentos para el diagnóstico de demencia por EA y otras demencias.
c. Determinar la exactitud diagnóstica del MMSE para la detección de sujetos con DCL quienes pueden progresar a demencia por cualquier causa, demencia por EA y otras formas de demencia.

Como resultado del primer trabajo se determinó que la calidad de las GPCs que abordan el diagnóstico de demencia por EA y otras demencias es heterogénea en su calidad metodológica, y las recomendaciones dirigidas al diagnóstico varían ampliamente en términos de la valoración de la calidad de la evidencia subyacente y la confianza en la misma.

En el segundo trabajo se encontró que las revisiones sistemáticas de las herramientas diagnósticas en demencia publicadas hasta 2013 presentan deficiencias metodológicas importantes, que impiden en su mayoría la diseminación de sus conclusiones en la práctica clínica.

En el tercer trabajo, referente a la evaluación de una de las pruebas cognitivas más tradicionales en demencia como es el MMSE, mostramos que no existe evidencia que apoye el uso extendido de dicha herramienta para determinar la posible conversión de los pacientes con DCL a demencia. Asimismo, para responder todos los objetivos se hizo uso de toda la metodología indicada para las revisiones sistemáticas, realizando la búsqueda sistemática de todos los estudios que respondiesen cada una de las preguntas de investigación específicas, e incorporando en cada uno la valoración de la calidad de la evidencia por medio de instrumentos ampliamente difundidos y validados para esta tarea.

Respecto a los resultados específicos de la primera investigación (Alzheimer's Disease Dementia Guidelines for Diagnostic Testing: A Systematic Review), un aspecto fundamental fue el rigor en el desarrollo de la GPC, en el cual se encontró alta variabilidad en el uso de los sistemas para la graduación de la evidencia y la fuerza de las recomendaciones. En nuestro estudio encontramos que un considerable número de guías no emplearon un sistema para expresar la confianza otorgada a la evidencia valorada y a los posibles beneficios con la implementación de la recomendación presentada, y aun en aquellas que emplearon un sistema, este fue incapaz de reconocer la naturaleza de la evidencia diagnóstica, que es claramente diferente a la evidencia de efectividad de una intervención (67, 124). En general, los usuarios de las GPC deben conocer no sólo las directrices principales sugeridas por los expertos, sino también conocer el grado de certeza de validez de la información empleada, así como el grado de certeza para proyectar que la recomendación conlleva más beneficios que daños (125).

El uso de sistemas genéricos conlleva dificultades en entender por qué una recomendación varía dependiendo de la GPC, lo cual confunde a los lectores respecto a si la conducta recomendada debe realizarse o no. Un ejemplo en nuestro caso estuvo relacionado con el uso de pruebas neuropsicológicas, siendo la calidad de la evidencia y la fuerza de la recomendación ejemplo de completa variabilidad en las GPC evaluadas en el presente estudio, aún en aquellas calificadas

como de alta calidad. Las recomendaciones relacionadas con el uso de pruebas cognitivas breves tuvo un comportamiento similar, mostrando una alta incertidumbre respecto a la prueba cognitiva a usar para el tamizaje de adultos con sospecha de demencia (35). Estos resultados nos muestran que actualmente la evidencia no se aprecia como definitiva para resolver estos importantes temas, lo cual puede denotar que las investigaciones pueden ser insuficientes para responder temas básicos para el diagnóstico de esta patología.

Asimismo, para el tema de las nuevas herramientas diagnósticas sugeridas para demencia, las cuales se han sugerido sólo para escenarios de investigación, no se encontraron recomendaciones que promovieran su uso explícito en la práctica clínica. Creemos que este punto refleja de manera adecuada la incertidumbre que aún se tiene con respecto a estas herramientas. Se conoce que para el adecuado uso de dichos elementos diagnósticos, se debe contar con información referentes a la estandarización local, puntos de corte adecuados para todos los estadios de la condición, y entrenamiento de personal para su implementación, entre otros aspectos (126). Las nuevas guías de práctica clínica de publicación reciente reconocen que el diagnóstico de demencia aún es esencialmente clínico. Por ejemplo, Moore y colaboradores actualizan las recomendaciones del Consenso Canadiense para el diagnóstico y tratamiento de la demencia, enfatizando que el uso de marcadores biológicos y neuroimágenes aún debe permanecer en los escenarios de investigación mientras más datos clínicos válidos son recolectados (127). Asimismo, el panel desestimula el diagnóstico de DCL teniendo en cuenta resultados aislados de niveles de depósito de amiloide, y recomienda que los pacientes deben ser igualmente informados de los inconvenientes de estas pruebas diagnósticas.

Una de las principales fortalezas de este trabajo fue la búsqueda e identificación amplia de la evidencia, complementando diferentes estrategias para incluir todas las posibles GPCs en el diagnóstico de demencia. Sin embargo, debido a limitaciones del idioma, tuvieron que ser excluidas seis referencias en idiomas como alemán o chino. Asimismo, la búsqueda sólo se limitó a un rango de tiempo de seis años (2005-2011), lo cual se realizó para garantizar que las GPC analizadas fuesen aún vigentes para la comunidad científica. Recientemente se han publicado nuevos reportes referentes a la evaluación de la calidad de las GPC en demencia que corroboran nuestros hallazgos. En 2014 Damiani realizó una evaluación de la calidad de la GCP para el manejo

de demencia, incluyendo GPC enfocadas en tratamiento y diagnóstico, publicadas en idioma inglés y limitadas a aquellas producidas por asociaciones de Europa y Norteamérica (128). En su evaluación realizada por dos pares evaluadores, los autores encontraron que los dominios de Aplicabilidad e Independencia Editorial fueron los más afectados en la evaluación bajo los criterios del AGREE-II. Asimismo, Damiani y colaboradores encuentran deficiencias en el dominio de Rigor en el desarrollo (Media (DE)= 54; 23 vs. Mediana (RIQ)= 55.3; 16-92).

En relación al segundo trabajo de esta tesis (Diagnostic tools for alzheimer's disease dementia and other dementias: an overview of diagnostic test accuracy (DTA) systematic reviews), nuestra revisión encontró que un número significativo de referencias en diagnóstico de demencia aluden a investigaciones que reportan diferencias entre grupos respecto a valores cuantitativos diagnósticos (por ejemplo, diferencias promedio entre casos y controles), en vez de información relacionada con las características operativas en comparación con un patrón de referencia (129). Si bien dichos estudios resultan esenciales en las primeras etapas de desarrollo de una prueba diagnóstica, son marcadamente insuficientes para determinar si es capaz de distinguir a los enfermos de los sanos, y por tanto no permiten la toma de decisiones respecto al uso de una herramienta diagnóstica en un determinado contexto clínico.

La evaluación de la calidad de las revisiones identificadas mostró diferentes deficiencias en su desarrollo. Más de la mitad de las mismas no presentan una evaluación de la calidad de la evidencia recopilada, por tanto se analiza de manera conjunta información de desconocida validez, y el valor resultante puede llegar a ser no-interpretable (130). Asimismo, es de anotar que 16% de las revisiones hubiesen realizado una valoración de la calidad de la evidencia por medio de instrumentos desarrollados para valorar la calidad del reporte (STARD). Debe destacarse que solo cerca de la mitad de las revisiones presentan las limitaciones de la información que han recopilado, y la emplean para contextualizar sus conclusiones, lo cual resulta fundamental para saber si los resultados numéricos, sean cuales fueren, pueden ser modificados o resultan datos confiables para la toma de decisiones.

Respecto a la metodología para obtener estimaciones conjuntas de las características operativas, se encontró que algunos autores usaron métodos que fueron desarrollados para revisiones de

intervenciones, en las cuales se requiere una sola estimación (por ejemplo, el RR), mientras que en diagnóstico siempre es necesario obtener pares de estimaciones (por ejemplo, la sensibilidad y la especificidad). En la actualidad existen diferentes modelos estadísticos que son adecuados para dichas estimaciones y que evitan un inadecuado manejo de los datos diagnósticos (77, 131-133). Si bien la evaluación de la heterogeneidad no tiene una prueba estadística ampliamente aceptada en el campo diagnóstico, debe evitarse el uso de medidas como el I-cuadrado, ya que resultan deficientes para el manejo de datos en esta área (134).

Creemos que una de las principales limitaciones en este trabajo fue el uso de herramientas como el PRISMA o el AMSTAR, las cuales fueron claramente desarrolladas para valorar revisiones de intervenciones; para tal fin tuvieron que realizarse definiciones operativas que cubrieran las particularidades en este tema. En la actualidad se vienen desarrollando diferentes herramientas que pueden cubrir estas deficiencias, y que permitirán valorar de manera adecuada este tipo de revisiones, existiendo diferentes reportes recientes respecto a este tema. Por ejemplo, Ferreira y colaboradores presentaron los resultados de las siete revisiones con metanálisis relacionadas con biomarcadores en relación a los ítems del PRISMA (135), encontrando que estas revisiones poseen deficiencias en áreas como la disponibilidad de protocolos y el reporte de sesgo de publicación, tal como lo habíamos señalado en nuestra evaluación de este mismo tema (136). Sin embargo, los autores interpretan la calidad de las RSL seleccionadas como optima, ofreciendo una recomendación positiva para el uso de estos biomarcadores en el contexto clínico. En un estudio similar, Gaugler y colaboradores reunieron la evidencia relacionada con la sensibilidad y especificidad estimada de biomarcadores en EA, identificando en la literatura revisiones con/sin metanálisis de datos, publicadas al 2012 (137). Los autores no realizan ninguna evaluación de la calidad de las revisiones identificadas, e incluso identifican que una alta proporción de ellas no presenta un patrón de referencia para las estimaciones de las características operativas de las pruebas evaluadas. Este reporte concluye que existen beneficios clínicos con el uso de biomarcadores en EA, aunque se trata de un estudio financiado por la industria.

Respecto al tercer trabajo de esta tesis (Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI)), se identificaron 11 estudios altamente heterogéneos con 1569 pacientes con DCL, seguidos

para su posible conversión a demencia. La evidencia fue más amplia para la conversión a demencia por EA; sin embargo, en todos los subgrupos evaluados se presentaron diferencias en los puntos de corte sugeridos para la conversión, lo cual repercutió en la alta variabilidad de la información recopilada y en la imposibilidad de estimar de manera confiable y válida las características operativas de la prueba evaluada.

Nuestro trabajo es una de las primeras revisiones Cochrane en evaluar de manera sistemática el papel del MMSE como una de las pruebas más reconocidas en demencia. Esta revisión se realizó en el contexto del DCL, para el cual identificamos un número discreto de referencias que abordaban la pregunta de investigación. En la evaluación de la calidad notamos que el dominio relacionado con la prueba fue uno de los más afectados, debido a que en muchos casos la evaluación del MMSE fue realizada de manera secundaria, mientras otras herramientas diagnósticas (como los biomarcadores) eran descritas de manera más adecuada. Si bien todas estas deficiencias pudieron afectar este reporte, en la información no se pudo identificar evidencia de estimaciones de características operativas iguales o superiores a 80%. Sólo un estudio con alto riesgo de sesgo, presenta cifras cercanas a la anteriormente expuesto (Sens= 76% y Esp= 67%). Es de anotar que el MMSE no fue desarrollado para ser usado en el escenario del DCL, por tanto, sus ítems pueden ser insuficientes para detectar los cambios de la cognición en presencia de factores como la edad, la educación y el analfabetismo conocidos factores de reconocida influencia en el MMSE. Algunos autores han postulado que los resultados individuales en esta prueba pueden no ser suficientes para detectar el deterioro cognitivo, pero sí que evaluaciones seriadas podrían ayudar al clínico en determinar la conversión a demencia de pacientes con DCL.

Es de anotar que en la actualidad se ha realizado una extensa evaluación de diferentes herramientas diagnósticas asociadas a demencia en general, especialmente para la demencia por EA. En relación a la evaluación de la cognición reportada por informantes, Harrison y colaboradores sólo encontraron un estudio que evaluara las características operativas del IQCODE en pacientes atendidos en cuidado primario, siendo necesario ampliar las investigaciones en este escenario para dar recomendaciones definitivas respecto al uso de este instrumento (138). Asimismo, en la evaluación de la evidencia relacionada con el β Amiloide en plasma y liquido cefalorraquídeo, Ritchie y colaboradores encontraron información heterogénea respecto a

sensibilidad y especificidad de la conversión de DCL a demencia por EA, concluyendo que la utilización de este biomarcador no debe ser empleada de manera indiscriminada para el diagnóstico de EA a nivel poblacional hasta que mejore la calidad de la evidencia (139). En la misma línea de biomarcadores, Zhang y colaboradores obtuvieron resultados igualmente heterogéneos respecto a las características operativas del 11-C- PIB- PET SCAN en pacientes con DCL y posterior conversión a demencia por EA u otras demencias, desestimulando su uso y teniendo en cuenta su alto costo (140). La evaluación de otros biomarcadores, como la presencia de APOE-4 y el uso de RM están en proceso de publicación.

6. CONCLUSIONES

Debido al incremento en la prevalencia de la demencia, se hace necesario que el personal clínico cuente con la mejor evidencia para la toma de decisiones diagnosticasen este tipo de pacientes. Esto implica que los documentos que resumen la evidencia disponible, así como aquellos que presentan recomendaciones para la práctica cotidiana, sean de la mejor calidad y reflejen de manera adecuada las verdaderas capacidades de las herramientas diagnósticas en demencia.

El desarrollo de guías de práctica clínica en demencia pueden mejorar en la medida en que usen las directrices más actualizadas para su realización, de tal manera que puedan valorar la mejor evidencia diagnóstica , y presenten recomendaciones que no generen dudas al personal que las utilice. En un futuro se debe promover el desarrollo de revisiones sistemáticas de alta calidad, las cuales puedan reflejar la extensión y calidad de la evidencia de las diferentes pruebas diagnósticas en ésta área. En la actualidad existen diferentes iniciativas que pueden asegurar que estos documentos sean realizados con la mayor validez posible (63, 131, 141). Por tanto, el papel de todas las herramientas diagnósticas empleadas en demencia, incluso de aquellas que se presentan como novedosas (142, 143), debe ser valorado de manera sistemática, tal como se realizó para el MMSE en el campo de DCL, a fin de determinar su verdadero papel y alcance en los nuevos escenarios que el clínico enfrenta en la actualidad.

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