

TITLE: Screening Tools to Identify Adults with Mild Cognitive Impairment Not Associated with Dementia: A Review of Diagnostic Accuracy, Effectiveness and Guidelines

DATE: 29 August 2013

CONTEXT AND POLICY ISSUES

Mild cognitive impairment is a heterogeneous condition in which patients present with variable, subtle cognitive changes. The different subtypes of MCI reflect the different patterns of cognitive domain impairments, which may presage different prognosis. The condition can be broadly categorized into amnesic MCI (aMCI) or non-amnesic MCI (naMCI). The amnesic arm further divides into single domain aMCI (aMCI-sd) characterized by isolated memory dysfunction, and multiple domain aMCI (aMCI-md) in which impairments occur in multiple cognitive domains besides memory. The naMCI also has subcategories of single domain (naMCI-sd) manifested as single non-memory MCI impairment, and multiple domain naMCI (naMCI-md) characterized by multiple non-memory cognitive impairment.¹ It has been reported that aMCI progresses preferentially to Alzheimer-type dementia and naMCI corresponding to isolated impairment of cognitive domain other than memory are associated with preferential progression to non-Alzheimer-type dementia.² However, some MCI patients regain cognitive function; some others remain stable, while others experience rapid symptom progression.² It is important to differentiate MCI from dementia because treatment choices differ.³ Petersen et al. were the first to propose the concept of MCI, and it was meant to fill the gap between normal and dementia-type pathological aging.² There is variability in diagnostic criteria used for the condition. A screening instrument with robust sensitivity and specificity to impairments in all domains, without restricted focus on memory, which is able to distinguish between the subtypes and provide reliable positive predictive value may be ideal. At the moment, there is no instrument for cognitive screening which is singularly suitable for global use. The MCI Working group of the European Consortium on Alzheimer's Disease (EADC) advises for diagnosis of MCI to be made by specific neuropsychological evaluation which may be consolidated by paraclinical investigation, laboratory testing, and brain imaging.² The EADC proposed criteria for differentiation of mild cognitive impairment as follows:

- Cognition complaints coming from the patients or their families

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material and may contain material in which a third party owns copyright. **This report may be used for the purposes of research or private study only.** It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

- The reporting of a decline in cognitive functioning relative to previous abilities during the past year by the patient or family
- Cognitive disorders as evidenced by the clinical evaluation (impairment in memory or in another cognitive domain)
- Absence of major repercussions on the daily life (the patient may, however, report difficulties concerning complex day-to-day activities)
- Absence of dementia

Most screening tools for MCI focus on patients with Alzheimer's disease or other forms of dementia and may not be sensitive to MCI patients whose conditions are caused by other factors such as fetal alcohol exposure, acquired brain injury, learning disabilities, and/or those with slow processing speed. This report aims to identify screening measures that can classify MCI patients who are not necessarily pre-dementia or suffering from early AD. Thus it is focused on tools which can distinguish MCI from cognitively normal controls and/or dementia, and further delineate non-dementia MCI subtypes.

RESEARCH QUESTIONS

1. What is the diagnostic accuracy of screening tools to identify adults with mild cognitive impairment not associated with dementia?
2. What is the clinical effectiveness of screening tools to identify adults with mild cognitive impairment not associated with dementia?
3. What are the evidence-based guidelines for the screening of adults with mild cognitive impairment not associated with dementia?

KEY FINDINGS

Screening tools may be classified as comprehensive or non-comprehensive. Comprehensive tools evaluate all primary domains of cognitive function, namely memory, language, visuospatial/perceptual processing, attention, and executive functioning. They are reported to be suitable for more specialist level of care. ACE-R and MoCA are two comprehensive tests found to have high accuracies in differentiating mild cognitive impairment from normal controls. However, their ability to distinguish MCI from early Alzheimer's dementia was not examined. Non-comprehensive screens examine only a limited number of domains and may be more suited to general practice. In this report, DemTect and M@T are as examples of non-comprehensive tools that can differentiate MCI from NC. M@T, but not DemTect, has the additional ability to differentiate MCI from AD with high accuracy. Both the *Qmci* and QCST are reported to require a very short time to administer and score. They have the ability to differentiate between MCI and NC as well as between MCI and mild AD. Currently there is no consensus on a single most accurate screening tool for MCI.

METHODS

Literature Search Strategy

A focused search (with main concepts appearing in title or major subject heading) was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2003 and July 31, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Adults with mild cognitive impairment not associated with dementia (e.g. resulting from fetal alcohol exposure, acquired brain injury, injury, learning disabilities or slow processing speed)
Intervention	Screening tools to identify mild cognitive impairment
Comparator	Screening tools compared to each other Clinician diagnosis
Outcomes	Diagnostic accuracy (e.g. sensitivity, specificity, AUROC, successful diagnosis) Clinical Effectiveness (e.g. Ease of use, length of time to administer) Evidence-based Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analysis, randomized controlled trials (RCTs), non-RCTs

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they did not have a comparator group, if they were published prior to 2003, if they were duplicate publications of the same study, or if they were referenced in the selected systematic review.

Critical Appraisal of Individual Studies

The systematic review was assessed using AMSTAR⁴ tool, and the diagnostic accuracy studies were appraised using the QUADAS checklist.⁵ Numerical scores were not calculated. Instead, the strength and limitations of individual studies are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 708 citations of which 25 potentially relevant studies were selected upon screening for articles for full-text review. Fourteen additional papers were identified through grey literature search. Of these 39 articles, 35 were excluded because they did not meet inclusion criteria. Thus four studies were included in this review, made up of one systematic review⁶ and three non-RCT studies.^{1,3,7} The PRISMA flow chart in Appendix 1 outlines the selection process.

Summary of Study Characteristics

Appendix 2 provides details on the study characteristics.

Country of origin

The systematic review⁶ was conducted by a group the United Kingdom and includes 30 studies from many different countries. One non-RCT study was from Canada³ and the remaining two^{1,7} were from China.

Study setting

The systematic review⁶ included 30 studies, comprising a total of 3284 participants, from various settings including memory clinics, university outpatient memory clinics, and community clinics. Also included were patients from secondary referral clinic neurologist and geriatrician specialists, and community dwelling volunteers. In the non-RCT study conducted with patients from Canada,³ participants were referred for the investigation from four memory clinics in Ontario, Canada between 2004 and 2010. One study from China¹ recruited patient participants from the Memory Clinic of Huashan Hospital in China between August 2008 and May 2009, and the other study⁷ recruited patients from the same memory clinic from June 2009 to October 2011. Assessment and cognitive evaluations in all the non-RCT studies were done in clinics/physician offices.

Patient Population

All the studies included a mix of adult mild cognitive impairment (MCI) patients, cognitively normal controls (NC) and/or patients diagnosed as having mild Alzheimer's disease (AD). The screening tools were assessed for their accuracy to distinguish MCI from NC and/or mild AD. MCI was diagnosed using comprehensive neuropsychological assessment, while diagnoses of mild AD were made based on National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Associations (NINCIDS-ADRDA) criteria. Studies included in the systematic review⁶ involved patients of various ages with mean age per study ranging from 66.6 (± 7.1) years to 79.5 (± 7.2) years. One non-RCT study¹ involved patients aged 55 to 85 years old, and another study⁷ involved patients aged between 50 and 90 years old. The third study³ included participants 55 years or older. In all the non-RCT studies, patients were matched in age, gender and education level by respective cognitively normal control participants. The control group for both studies from China also underwent neuropsychological evaluation.

Interventions and comparators

The systematic review separated screening methods into comprehensive and non-comprehensive based on extent of coverage of cognitive domains and examined the sensitivity and specificity of the tests to distinguish MCI from NC, and in some, also from mild AD patients. Comprehensive tests cover each of the primary domains (i.e. memory, language, visuospatial/perceptual processing, attention and executive functioning) of cognitive function.⁶ Non-comprehensive tests identify clinically significant levels of impairment across a limited range of cognitive abilities.⁶ In one non-RCT study,¹ the Quick Cognitive Screening Test (QCST) was compared to Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) tests to distinguish MCI from NC patients and from mild AD. In a second study,⁷ the sensitivity and specificity of the Memory and Executive Screening (MES) tool to delineate subtypes of MCI from NC was evaluated, but its ability to segregate MCI from AD was not assessed. In the study in Canada,³ the Quick mild cognitive impairment (*Qmci*) screen was evaluated for its sensitivity and specificity to differentiate MCI from NC and dementia, as compared to Standardized Mini-mental State Examination (SMMSE) and AB Cognitive Screen (ABCS) 135.

Outcomes measure

All the studies evaluated the sensitivity and specificity of the tests under investigation to detect MCI patients and distinguish them from age, gender, and education appropriate cognitively normal controls, and/or from mild AD patients all of whom had already been classified by neuropsychological tests. Findings were reported as sensitivity and specificity, and/or these were used in receiver operating characteristic curve (ROC) analysis. ROC curve analysis is used to evaluate the diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from normal cases. When the test perfectly separates the two groups of interest without any overlap, the area under the ROC curve (AUROC) equals 1. When the test cannot distinguish between the two groups, thus suggesting there is no difference between diseased group and normal group, the area will be equal to 0.5. In the systematic review,⁶ outcomes measures were limited to sensitivity and specificity without ROC curve analysis. Two non-RCT studies^{1,7} used sensitivity, specificity, and AUROC as outcome measures, while a third³ reported only AUROC without details on sensitivity and specificity.

Summary of Critical Appraisal

Appendix 3 provides details on critical appraisal.

In the studies included in this report, patients were pre-diagnosed and classified (independent of the screening tools being tested) using standard comprehensive neuropsychological assessment and the various screens tools were evaluated for their ability to differentiate patient classes. One systematic review and three non-RCT studies were appraised. The systematic review⁶ was based on a comprehensive literature search. In total, 21 articles selected from the literature search results and 9 others retrieved from reference lists and the authors' personal records were included. Sample sizes of the included studies were reported to be generally small ($n \leq 100$). A table listing included studies and detailing their characteristics was provided, but a list or link to excluded studies was not given. Besides the general statement on sample sizes, there is no discussion of the quality of the included studies nor was there an investigation of publication bias reported.

The non-RCT studies clearly described the characteristics of the patients and the interventions (screening tools) of interest as well as the main findings and outcomes to be measured. Participant sourcing, diagnosis and classification have been clearly described. In two of the non-RCT studies,^{1,7} all participants received the same reference standard assessment leading to minimized differential verification bias. The other non-RCT study selected the cognitively normal control group by a convenience method instead of the neurophysiological assessment used to classify patients thereby inclining the study to verification bias. Patients groups in two studies,^{1,7} were matched in demographics to each other and to the cognitively normal controls. Grouping patients with similar clinical features and ensuring that participants have comparable demographic to patients likely to receive the index test in practice helps to minimize spectrum bias. In the other non-RCT study,³ there were significant differences in age among patient groups and the cognitively normal group heightening the probability of spectrum bias and reducing generalizability of findings. In this study impaired patients were diagnosed and classified through neuropsychological assessment but the NC group was recruited from among caregivers on their own self-assessed absence of memory impairment. Thus, it is uncertain whether all the participants in this group truly had normal cognitive abilities. Rater blinding to diagnosis was used in one study⁷ as a measure to reduce bias. The two other studies^{1,3} did not discuss knowledge of raters with regards to diagnosis so it is uncertain how that could have

influenced assessments and measured outcomes. Two studies^{1,3} described the index tests in sufficient details to permit replication.

Summary of Findings

Appendix 4 provides further details on the study findings and authors' conclusions.

1. What is the diagnostic accuracy of screening tools to identify adults with mild cognitive impairment not associated with dementia?

The systematic review⁶ identified two comprehensive screening tools, Addenbrooke's Cognitive Examination Revised (ACE-R) and MoCA, which can differentiate MCI patients from cognitively normal controls with high sensitivity and specificity scores of 84% and 100%; and 90% and 87%, respectively. However, their ability to distinguish MCI from AD was not reported. The study also reported high accuracy for two non-comprehensive cognitive screening tools, DemTect and Memory Alteration Test (M@T), which had sensitivity scores of 80% and 79% and specificity scores of 92% and 79%, respectively. M@T also showed high accuracy to distinguish MCI from mild AD but the ability of the DemTect tool to make this distinction was not evaluated in this pair of conditions.⁶ In the non-RCT studies,^{1,3,7} all the tools reported high accuracy outcomes in differentiating MCI from NC with greater sensitivities than their comparators. Appendix 4 provides details of accuracy outcome measures for the tools covered in this report. Two studies^{1,3} also evaluated ability of screening tools to discriminate between MCI and mild AD/dementia and reported high accuracy scores for both QCST and *Qmci*.

2. What is the clinical effectiveness of screening tools to identify adults with mild cognitive impairment not associated with dementia?

From the systematic review,⁶ the comprehensive tools ACE-R and MoCA cover all the primary cognitive domains important in MCI, and the non-comprehensive tools DemTect and M@T, cover a limited range of domains.⁶ Therefore, while the former screens are expected to be effective in a variety of settings including the more specialist level of screening, the effectiveness of the latter may be more suited to general clinical use.⁶

All the non-RCT studies^{1,3,7} reported that the screening measures evaluated are simple and easy to administer and score. Average administration time for ACE-R and MoCA was 15 minutes or less, and it took between 5 and 10 minutes to administer DemTect and M@T.⁶ QCST has administration time of 8-15 minutes,¹ and *Qmci* can be administered in 5 minutes.³ The MES requires a total of approximately 7 minutes to administer and score.⁷

3. What are the evidence-based guidelines for the screening of adults with mild cognitive impairment not associated with dementia?

There was no evidence-based guideline found for screening adults with mild cognitive impairment not associated with dementia.

Limitations

The studies included in the report were generally non-randomized studies, and the systematic review did not discuss the scientific quality of the included studies, so it is not clear if quality was assessed or considered in its conclusions. None of the studies had a power calculation to determine appropriate sample sizes. In addition, it is unclear the extent to which test results may be subject to significant age differences and levels of education.

Among the high-scoring tests in the systematic review,⁶ only M@T was assessed for ability to differentiate between MCI and both NC and mild AD. Therefore, one is unable to determine with certainty whether MCI patients detected by screening with ACE-R, MoCA, or DemTect from NC could have cognitive impairment beyond MCI. Studies investigating the more comprehensive screening measures were drawn from specialist university or hospital clinics. Therefore their utility in community or primary care settings is unknown. In addition, none of the high scoring screens in the systematic review⁶ was investigated for the ability to detect non-amnestic or any other subtypes of MCI.

In one of the non-RCT studies,³ cognitively normal controls were recruited from caregivers based on their own self-assessed absence of memory impairment, which makes the propriety of this classification uncertain. Even though widely accepted protocols were applied in the two studies^{1,7} done in China, it is unclear if the findings are given language and cross-cultural differences. For all the studies the participants were relatively elderly. Therefore, the applicability of findings to a younger population is uncertain. Similarly indeterminate is the applicability of findings to populations with significantly different education levels. None of the studies included in this report examined potential causal disorders or etiological origins of MCI. Therefore, there is no discussion of MCI as a consequence of fetal alcohol exposure, acquired brain injury, learning disabilities or slow processing speed.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The selected studies for this review investigated screening measures to distinguish MCI from either NC or dementia including mild AD. The systematic review⁶ provided no information on quality of included studies. Four scoring tools (ACE-R, MoCA, Demtect and M@T) with high accuracies for distinguishing MCI from NC did not investigate subtypes of MCI so one is unable to determine if the MCIs investigated in the study were associated with dementia. M@T is able to differentiate MCI from AD with high accuracy but the remaining three were not investigated in this respect. The non-RCT studies were generally of high quality for their class. One of them¹ demonstrated the ability of the QCST tool to discriminate MCI from NC and also from mild AD. In addition, it reported that QCST is effective in differentiating amnestic and non-amnestic subtypes of MCI. In a second non-RCT study³ the *Qmci* screening tool was better than SMMSE and ABCS 135 at selecting NC from MCI and differentiating MCI from mild dementia. Finally a third study⁷ showed high accuracy at delineating the various subtypes of aMCI and distinguishing them from NC and from AD. All the tools can be administered within short periods of time and are reported to be simple to apply. However, the studies may be limited in their generalizability to younger populations or populations with specific causes for MCI. In addition, none of the tests have been independently validated in other populations. Taken together, conclusions cannot be drawn on the generalizability of findings of studies employed in this appraisal.

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

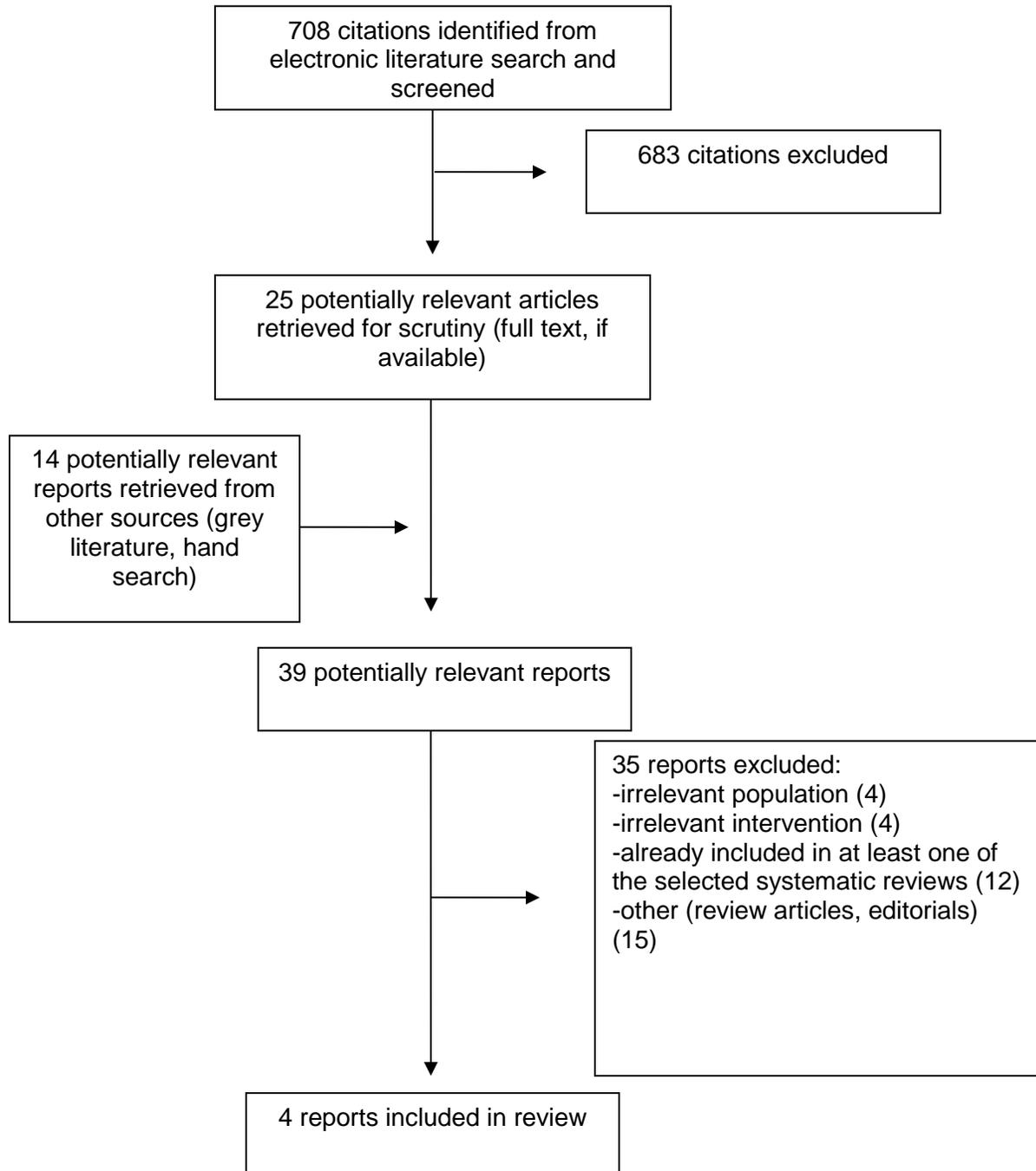
Tel: 1-866-898-8439

www.cadth.ca

REFERENCES

1. Guo QH, Cao XY, Zhou Y, Zhao QH, Ding D, Hong Z. Application study of quick cognitive screening test in identifying mild cognitive impairment. *Neurosci Bull.* 2010 Feb;26(1):47-54.
2. Portet F, Ousset PJ, Visser PJ, Frisoni GB, Nobili F, Scheltens P, et al. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. *J Neurol Neurosurg Psychiatry* [Internet]. 2006 Jun [cited 2013 Aug 26];77(6):714-8. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2077456>
3. O'Caomh R, Gao Y, McGlade C, Healy L, Gallagher P, Timmons S, et al. Comparison of the quick mild cognitive impairment (Qmci) screen and the SMMSE in screening for mild cognitive impairment. *Age Ageing* [Internet]. 2012 Sep [cited 2013 Aug 8];41(5):624-9. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3424052/pdf/afs059.pdf>
4. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* [Internet]. 2007 [cited 2013 Aug 8];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>
5. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* [Internet]. 2003 Nov 10 [cited 2013 Aug 8];3(25). Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC305345>
6. Lonie JA, Tierney KM, Ebmeier KP. Screening for mild cognitive impairment: a systematic review. *Int J Geriatr Psychiatry.* 2009 Sep;24(9):902-15.
7. Guo QH, Zhou B, Zhao QH, Wang B, Hong Z. Memory and Executive Screening (MES): a brief cognitive test for detecting mild cognitive impairment. *BMC Neurol* [Internet]. 2012 [cited 2013 Aug 8];12:119. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3492138/pdf/1471-2377-12-119.pdf>

APPENDIX 1: SELECTION OF INCLUDED STUDIES



APPENDIX 2: CHARACTERISTICS OF INCLUDED STUDIES

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Lonie ⁶ 2009 United Kingdom	Systematic Review	3284 patients with various subtypes of MCIs and mild AD from 30 studies since 1999	Various Screening tools to identify MCI	Screening tools compared to each other and clinical diagnosis	Sensitivity, specificity,
Guo ⁷ 2012 China	NON-RCT	736 adult participants including 197 NC from two communities, 116 aMCI-sd, 195 aMCI-md and 228 AD from a Memory Clinic	MES	Comprehensive neuropsychological tests	Sensitivity, specificity, and AUROC
O’Caoimh ³ 2012 Canada	NON-RCT	965 subjects ≥ 55 yrs., made up of 154 with MCI, 181 with dementia drawn from four memory clinics in Ontario, and 630 cognitively normal control	<i>Qmci</i>	ABCS 135, SMMSE	Sensitivity, specificity, and AUROC
Guo ¹ 2010 China	NON-RCT	386 patients 55-85 years old, including 121 with MCI and 79 with mild AD chosen from the Memory Clinic, and 186 cognitively normal elderly control from two communities.	QCST	Full set of standardized Neuropsychological tests, including MMSE and MoCA	Sensitivity, specificity, and AUROC

ABCS135=AB Cognitive Screen 135; ACE-R=Addenbrooke’s Cognitive Examination Revised; AD=Alzheimer’s Disease; aMCI=amnesic MCI; AUROC=area under the receiver operator curve; CI=confidence interval; M@T=Memory Alteration Test; MCI=mild cognitive impairment; MES=Memory and Executive Screening; MMSE=Mini-mental state examination MoCA=Montreal Cognitive Assessment; NC=normal control; QCST=Quick Cognitive Screening Test; *Qmci*=Quick mild cognitive impairment screen; RCT=randomized controlled trial; SMMSE=Standardized mini-mental state examination

APPENDIX 3: SUMMARY OF CRITICAL APPRAISAL OF INCLUDED STUDIES

First Author, Publication Year,	Strengths	Limitations
Lonie ⁶ 2009 Systematic Review	<ul style="list-style-type: none"> Comprehensive literature search based on pre-defined criteria. Comprehensive literature search was performed 	<ul style="list-style-type: none"> The scientific quality of the included study was not documented so it is not clear if was assessed. The likelihood of publication bias was not assessed
Guo ⁷ 2012	<ul style="list-style-type: none"> Demographically well matched test and control groups Same independent standard reference used to classify patients. Rigorous statistical analysis to minimize confounders Selection criteria is clearly stated Index test described in detail to allow replication 	<ul style="list-style-type: none"> No randomization Test results may be subject to level of education and generalizability difficulties. Time between assessments of reference and index tests is not stated
O’Caoimh ³ 2012	<ul style="list-style-type: none"> Clearly stated inclusion and exclusion criteria Rater was blinded to diagnosis to minimize bias Test procedure has been provided in detail (in a supplemental document) to permit replication A large sample size and comprehensive assessment 	<ul style="list-style-type: none"> A convenience method was used to select NC group predisposing data to verification bias. Unmatched demographics among test groups are likely to introduce spectrum bias. Description of execution of reference standard is not detailed enough. No randomization Time between assessments and index administration is not stated
Guo ¹ 2010	<ul style="list-style-type: none"> Matched test groups in terms of age, gender distribution, and educational level. Same independent standard reference used to classify patients. Rigorous statistical analysis to minimize confounders Selection criteria is clearly stated Index test described in detail to allow replication. Designed to distinguish MCI subtypes including amnesic and non-amnesic MCI. 	<ul style="list-style-type: none"> No randomization Small sample size and no power calculation to determine appropriate size to validate conclusions. Test results may be subject to spectrum bias in the general population owing to level of education, and cultural differences. Time between assessments and index administration is not stated

APPENDIX 4: MAIN STUDY FINDINGS AND AUTHORS' CONCLUSIONS

First Author, Publication Year,	Main Study Findings	Authors' Conclusions
<p>Lonie⁶ 2009 Systematic Review</p>	<p>ACE-R and MoCA were identified as comprehensive tests with high screening accuracies to differentiate MCI from NC</p> <p>ACE-R</p> <ul style="list-style-type: none"> • Sensitivity: 84.0%, • Specificity: 100% • Administration time: 12 to 20 minutes <p>MoCA</p> <ul style="list-style-type: none"> • Sensitivity: 90.0%, • Specificity: 87.0% • Administration time: 10 to 12 minutes <p>DemTect and M@T were high scoring screening tools identified as non-comprehensive test with accuracies to differentiate MCI from NC as follows:</p> <p>DemTect</p> <ul style="list-style-type: none"> • Sensitivity: 80.0%, • Specificity: 92.0% • Administration time: 8 to 10 minutes <p>M@T</p> <ul style="list-style-type: none"> • Sensitivity: 96.0%, • Specificity: 79.0% • Administration time: 5 minutes <p>M@T also has accuracy of differentiating between MCI and AD of:</p> <ul style="list-style-type: none"> • Sensitivity: 87.0%, • Specificity: 82.0% • Administration time: 5 minutes <p>The abilities of the other tests</p>	<p>Four comprehensive screening tools report adequate sensitivity to MCI and early AD. "However, without exception, there is an absence of reliability data for elderly persons who are not cognitively impaired and of the predictive validity of cut-off scores." Pg 913 "None of the identified cognitive screening measures wholly fulfills all of the criteria we have identified as being important in MCI screening." Pg 914</p>

First Author, Publication Year,	Main Study Findings	Authors' Conclusions
	<p>to make this distinction were not examined in this systematic review.</p> <p>Combinations of two or more cognitive screening instruments afforded improved sensitivity at the expense of other outcome parameters in some cases, while in others the results were inconclusive.</p>	
<p>Guo⁷ 2012</p>	<p>Ability of MES to differentiate NC from aMCI single domain</p> <ul style="list-style-type: none"> • Sensitivity: 79.5%, • Specificity: 82.8% • AUROC: 0.893 (95% CI: 0.858-0.928); • Administration time: 7 minutes <p>Ability to differentiate NC from aMCI multiple domain</p> <ul style="list-style-type: none"> • Sensitivity: 87.5%, • Specificity: 91.3% • AUROC: 0.956 (95% CI: 0.938-0.974) • Administration time: 7 minutes 	<p>“The MES may be a highly sensitive and specific cognitive screening tool that is valid, easy to administer, and minimally time-consuming. Because the score range and gradient change of test difficulty are large enough, it may be suitable to evaluate cognitive changes during therapy for outpatients.” Pg 7</p>
<p>O’Caoimh³ 2012</p>	<p>The <i>Qmci</i> demonstrated better ability to distinguish MCI from NC than ABCS 135 and SMMSE with AUROC scores of:</p> <ul style="list-style-type: none"> • <i>Qmci</i> = 0.86 (95% CI: 0.83-0.89); • ABCS 135 = 0.83 (95% CI: 0.79-0.86); • SMMSE = 0.67 (95% CI: 0.62-0.72). <p>AUROC scores for differentiating MCI from dementia are;</p> <ul style="list-style-type: none"> • <i>Qmci</i> = 0.92 (95% CI: 0.89-0.95); • ABCS 135 = 0.91 (95% CI: 0.88 to 0.94); • SMMSE = 0.91 (95% CI: 	<p>The results presented here show that the <i>Qmci</i> is more sensitive than the SMMSE and the ABCS 135 in differentiating MCI from NC. Whereas all three are able to distinguish NC from dementia, the <i>Qmci</i> had a wider and more clinically significant percentage difference in median scores to help discriminate MCI from dementia.</p>

First Author, Publication Year,	Main Study Findings	Authors' Conclusions
	<p>0.88 to 0.94)</p> <p>Administration time: <i>Qmci</i>: 5 minutes SMMSE: NR ABCS 135: 3 to 5 minutes</p>	
<p>Guo¹ 2010</p>	<p>To differentiate MCI from NC QCST showed higher accuracy than MoCA and MMSE with score as follows;</p> <p>QCST</p> <ul style="list-style-type: none"> • Sensitivity: 87.6%, • Specificity: 84.3% • AUROC: 0.923 (95% CI: 0.892 to 0.953) • Administration time: 8 to 15 minutes <p>MoCA</p> <ul style="list-style-type: none"> • Sensitivity: 79.6%, • Specificity: 72.7% • AUROC: 0.856 (95% CI: 0.814 to 0.898); • Administration time: NR <p>MMSE</p> <ul style="list-style-type: none"> • Sensitivity: 83.3%, • Specificity: 38.3% • AUROC: 0.670 (95% CI: 0.608 to 0.731); • Administration time: NR <p>The sensitivity and specificity of QCST to distinguish MCI from mild AD is 75.0% and 78.2%.</p>	<p>“The QCST has shown high test-retest reliability and a content validity. More importantly, QCST has excellent sensitivity in detecting naMCI. Therefore QCST as a screening tool should provide quick guidance for referral and further investigation.” Pg 52</p>

ABCS135=AB Cognitive Screen 135; ACE-R=Addenbrooke's Cognitive Examination Revised; AD=Alzheimer's Disease; aMCI=amnestic MCI; AUROC=area under the receiver operator curve; CI=confidence interval; M@T=Memory Alteration Test; MCI=mild cognitive impairment; MES=Memory and Executive Screening; MMSE=Mini-mental state examination MoCA=Montreal Cognitive Assessment; naMCI=non-amnestic MCI; NC=normal control; NR=Not Reported; QCST=Quick Cognitive Screening Test; *Qmci*=Quick mild cognitive impairment screen; SMMSE=Standardized mini-mental state examination